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NEUROLOGY AND NEUROSURGERY

Papers in Medicine

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NEUROLOGY AND NEUROSURGERY

Papers in Medicine

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Editorial Board: M. Mägi (editor), T. Asser, A. Tikk, T. Tomberg,
M. Roose.

In this volume of "Acta et commentationes Universitatis Tartuensis" the papers of the coworkers of the Department of Neurology and Neurosurgery, University of Tartu, are published. The volume continues the series of publications of the University of Tartu and the Estonian Ludvig Puusepp Society of Neurologists, Neurosurgeons and Psychiatrists "Voprosy klinicheskoi nevrologii i psihiatrii" (Problems in Clinical Neurology and Psychiatry, in Russian), vol. 1-10 in 1961-1975 and volumes of "Acta et commentationes Universitatis Tartuensis" No. 589 (1981), No. 749 (1986) and No. 901 (1990). This volume includes papers on actual problems of clinical neurology and neurosurgery, as, e.g., disturbances of cerebral blood flow and metabolism in cerebrovascular diseases, head injury, intoxications, treatment of diseases of the nervous system, etc.

This volume is dedicated to 60th birthday of Professor Ain-Elmar Kaasik, M.D., Ph.D., D.h.c. (Uppsala), Chairman of the Department of Neurology and Neurosurgery, University of Tartu, Member of the Estonian Academy of Sciences.

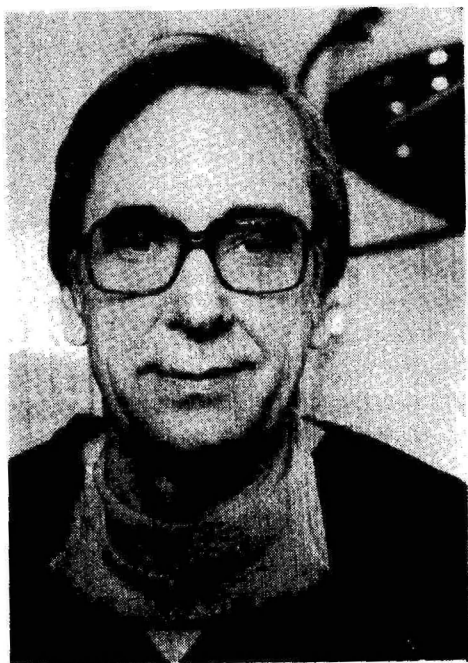
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CONTENTS

Ain - Elmar Kaasik. On the occasion of his 60th birthday.....	5
A.-E. Kaasik, M. Mägi. Development of neurology and neurosurgery in Estonia.....	9
A. Tikk, E. Kross, U. Rink (Noormaa), M. Mägi, J. Eelmäe, M. Kuklane, M. Heinsoo. Neurological and neurosurgical intensive care in Tartu	16
J. Kõrv, M. Roose, A.-E. Kaasik. Stroke in Estonia: first-year results of a stroke register.....	34
J. Kõrv, M. Roose, A.-E. Kaasik. Is there a regional variation in the stroke incidence in Estonia?	44
K. Gross, K. Kisand, S.-M. Lüüs, A. Kokk, A.-E. Kaasik. Diagnosis of tick-born encephalitis in South Estonia (1988-1993)	53
K. Gross, A. Kokk, A.-E. Kaasik. Disability and multiple sclerosis.	61
M. Roose, A.-E. Kaasik, T. Tomberg. CSF metabolic alterations in ischemic-hypoxic brain tissue damage.....	68
I. Lutsar, S. Haldre, M. Topman, T. Talvik. Diagnostic value of intracellular enzymes in the cerebrospinal fluid in patients with infections of the central nervous system.....	75
T. Talvik, A. Sööt, S. Haldre, A. Piirsoo, A.-E. Kaasik. Creatine kinase isoenzyme BB concentrations in hypoxic-ischemic encephalopathy.....	85
L. Kõiv, E. Merisalu, K. Zilmer, T. Tomberg, A.-E. Kaasik. The levels of catecholamines, ACTH and cortisol in plasma as prognostic factors of severe head injury.....	92
U. Rink, H. Vadi, A. Tikk. Haemostasis in brain tumours.....	102
M. Kuklane, J. Eelmäe, M. Roose, A.-E. Kaasik. Changes in brain metabolism and craniospinal system viscoelastic parameters after intrathecal administration of THAM	114
M. Heinsoo, J. Eelmäe, M. Kuklane, T. Tomberg, A. Tikk. ICP and craniospinal dynamics in the acute stage of aneurysmatic SAH patients.	121
J. Eelmäe, M. Kuklane, M. Heinsoo, A. Tikk. Argued approach to surgical treatment of hydrocephalus.	131
A. Kalda. Stimulation of the septal complex increases local cerebral blood flow in the hippocampus in unanesthetized rabbits.....	145
T. Tomberg, M. Mägi, T. Kauba. Hemodynamic effects of calcium antagonists in stroke patients	152

T. Tomborg, M. Mägi. Effect of Sermion on cerebral blood flow in patients with brain infarction	160
Ü. Linnamägi. Neurotoxicity of lead: alteration in neural transmission and cerebral microvasculature	166
Ü. Linnamägi, A. Schotter, A.-E. Kaasik. Changes of local cerebral blood flow and cerebrovascular reactivity caused by lead exposure in adult rabbits	176
Ü. Linnamägi, K. Zilmer, M. Zilmer. Is lead-induced excessive lipid peroxidation implicated in alteration of local cerebral blood flow and vascular reactivity?.....	187
T. Asser, P. Mustafin. Quantitative determination of muscle tone in spinal cord lesions.....	193
T. Asser, P. Eelmäe, J. Eelmäe. Computerized quantitation of muscle tone in lumbar disc radiculopathy.....	204
A. Kulla, T. Asser, A. Önn, M. Ulst, S. Kruup, K. Pöldvere. Morphological changes after destruction of rabbit intervertebral disc	214
R. Zupping, A. Ellamaa. Cervicogenic headache.....	222
L. Luts, I. Kalbe. Optimization of microwave therapy	228



AIN-ELMAR KAASIK

On the occasion of his 60th birthday

On the 2nd of August, 1994 Estonian neurologists and neurosurgeons celebrate the 60th birthday of the Chairman of the Department of Neurology and Neurosurgery, University of Tartu, Professor Ain-Elmar Kaasik, M. D., Ph. D., Dr. h.c. (Uppsala), Member of the Estonian Academy of Sciences.

Ain-Elmar Kaasik was born on August 2, 1934 in Tallinn in the family of a book-keeper. In 1953 he graduated from the Tallinn 10th High School and entered the Medical Faculty of the University of Tartu. He became interested in neurology already during his student years and performed his first research work under the guidance of Professor Ernst Raudam (1915–1992), Chairman of the Department of Neurology and Neurosurgery during many years. A.-E. Kaasik graduated from the Medical Faculty in 1959 and started his professional career at the Põltsamaa Hospital in Jõgeva District. In 1961 he continued his work at the neuro-intensive care unit of the Tartu University Hospital and at the same time started his neurosurgical training. In 1962–1964 he was the head of the neuro-ICU. In 1964–1967 he was a Ph. D. student at the Department of Neurology and Neurosurgery, University of Tartu. In January, 1968 he joined the teaching staff of the Department, first as an Assistant Professor, from 1972 as an Associate Professor (Docent) and in 1973 he was elected for the position of Professor of Neurology. Since 1984 he has been Chairman of the Department of Neurology and Neurosurgery, University of Tartu.

Ain-Elmar Kaasik started his career as a neurologist, thereafter he specialized in the intensive care and neurosurgery. His main neurosurgical training was performed at the Tartu University Hospital under the guidance of Professor E. Raudam and Dr. R. Paimre. In 1964 he attended a training course at the Central Postgraduate Training Institute of Physicians in Moscow. In 1980 he spent some sabbatical months at the N. N. Burdenko Neurosurgical Institute in Moscow. An important part of his postgraduate training passed at the Brain Research Laboratory of the Department of Neurosurgery, University of Lund — 11 months in 1967/1968, 3 months in 1975. In 1987 he spent 4 months as a Fulbright lecturer (Visiting Professor) at the University of Pennsylvania, Philadelphia, where he delivered a series of lectures on cerebral circulatory and metabolic disorders, supervised practical work and acquainted himself with the organization of the medical education in the USA. In September–October, 1989 he was a Visiting Professor at the University of Uppsala, and in 1990 the invited lecturer at the College of Surgeons, Jackson, Wyoming, USA. He also has repeatedly visited Finnish and Danish centres of neurology and neurosurgery. During many years he was a member of the cooperative work group of neurologists and neurosurgeons of the Universities of Tartu and Helsinki.

A.-E. Kaasik has operated in all areas of neurosurgery, except endovascular procedures. Most remarkable results were achieved in stereotaxic neurosurgery and in microsurgical operations in the sellar

region. A.-E. Kaasik has also acted as a consultant neurologist, e.g. in the areas of cerebrovascular diseases, neuroinfections and neuromuscular disorders.

The first scientific publications of Professor A.-E. Kaasik date back to the student years. Now the list of his publications consists of more than 260 references, among them 3 monographs, a textbook, 3 monograph-type practice guidances and 120 scientific papers. According to the Citation Index, his publications were the most cited articles among the Estonian medical researchers, at least in 1976–1980 (H. Martinson, *Nõuk. Eesti Tervishoid* 1982, 1, 33–39).

In 1967 he commenced his Ph. D. (Cand. Med. Sci) dissertation "Cerebral gas exchange in the acute stage of cerebrovascular disorders". Some of the results of this study were cited by the well-known Danish researcher N. A. Lassen when he formulated his famous concept of luxury-perfusion syndrome (*Lancet* 1966, 7473, 1113–1115).

A.-E. Kaasik's second dissertation (Dr. Med. Sci) "Brain extracellular acidosis and its pathophysiological meaning (Experimental and clinical-biochemical study)" was defended in 1972. The main topics of his research were the disorders of cerebral blood flow and metabolism in acute cerebral disorders. He has introduced several methods of basic research, viz. biochemistry and clinical chemistry, into clinical research. In 1972 he received (as a member of the research group headed by E. Raudam together with M. Mägi, R. Paimre and R. Zupping) the Soviet Estonia Award for the research of pathogenic mechanisms and introduction of new treatment principles of cerebrovascular diseases. In 1982 he published together with R. Zupping the monograph "Cerebrovascular Diseases" (in Estonian). In the manual "Clinical Pharmacology" (edited by L. Allikmets) he wrote the chapter "Pharmacotherapy of Neurological Diseases" and in 1991 in the textbook "Reanimatology" (edited by R. Talvik) the chapter on acute cerebral catastrophies. A.-E. Kaasik has also written an extensive chapter "Motorics" in the textbook "Clinical Investigation of Nervous System" (1982, 1987). He has been the scientific advisor of 12 dissertations which were performed to achieve the former Cand. Med. Sci. or Dr. Med. Sci. degrees.

When the Estonian medical science was evaluated by the Swedish Medical Research Council in 1992 the project supervised by A.-E. Kaasik "Research of the mechanisms of development of focal brain damage" received a high opinion. The methods were considered adequate and relevant, the investigators highly competent and the results valuable. The project was considered to belong to the first category.

In 1991 Professor Ain-Elmar Kaasik was elected Honorary Doctor (*dr. med. honoris causa*) of the University of Uppsala. In 1993 he was elected Member of the Estonian Academy of Sciences.

A.-E. Kaasik is a member of numerous scientific organizations. At present he is the Vice Chairman of the Estonian L. Puusepp Society of Neurologists and Neurosurgeons and also the Vice President of the Baltic Neurosurgical Association. He is a member of the Estonian Medical Research Board, Council of the University of Tartu, Council of the Medical Faculty, Council of the University Hospitals. Recently he was a member of the Estonian Council of Science and the Estonian Scientific Fund Council. He was the Vice Chairman of the All-Union Society of Neurosurgeons, member of the Board of the All-Union Society of Neurologists. At present he is a member of the editorial boards of the scientific journals "Eesti Arst" and "Voprosi Neurochirurgii" (Moscow). A.-E. Kaasik is the Estonian National Delegate to the World Federation of Neurology, a corresponding fellow of the American Academy of Neurology (from 1994), a corresponding member of the Scandinavian Neurosurgical Society (from 1973).

Professor Kaasik has held several administrative posts. In 1975–1980 he was the Dean of the Faculty of Postgraduate Studies of Doctors and Pharmacists; in 1981 Associate Dean of the Medical Faculty and in 1984–1989 Dean of the Medical Faculty, University of Tartu.

Ain-Elmar Kaasik meets his 60th birthday in active work and in good physical shape which has been achieved by cross-country skiing and cycling from schoolyears until present time, working at his summer place in free time. His associates in the Department of Neurology and Neurosurgery, numerous pupils and colleagues throughout Estonia, also his patients congratulate him and wish him good health and new success in his beloved work as a doctor, researcher and teacher.

DEVELOPMENT OF NEUROLOGY AND NEUROSURGERY IN ESTONIA

A.-E. Kaasik, M. Mägi

More than a hundred years ago, in 1891 Heinrich Unverricht (1853–1912) described a new familial neurological disease which was characterized by the combination of myoclonias and epileptic seizures. Now the disease has been given the name of progressive myoclonus epilepsy of the Baltic type or the Unverricht-Lundborg disease.

Heinrich Unverricht was born on September 18, 1853 in Breslau (now Wrocław in Poland). In 1877 he graduated from the Medical Faculty, University of Breslau. His doctoral dissertation concerned inflammatory diseases of the lungs (Lungenentzündung) [1]. In 1883 he was appointed Docent (Associate Professor) in the Department of Internal Medicine of the same university. In 1886 he was elected Extraordinary of Internal Medicine and Director of the Polyclinic in the University of Jena. During his Breslau and Jena period H. Unverricht's scientific interests were mainly concentrated on pulmonary diseases. His interest in neurological problems was reflected in an experimental study of the innervation of respiratory movements [2].

In 1889 H. Unverricht was elected Ordinary Professor of Special Pathology and Director of the Medical Clinic of the University of Derpt (Dorpat), which is now known under the name of Tartu.

In spite of the short duration of his work in Tartu H. Unverricht won popularity among his colleagues, pupils and patients. A year after Koch's fundamental work he published a paper on tuberculin treatment [3]. He also investigated the Cheyne-Stokes type of respiration disorder, and clonic and tonic seizures [4].

In 1891 his famous monograph "Die Myklonie" was published [5]. In this book he described a new familial progressive neurological disease which he had observed in a family in the town of Paide (then: Weissenstein) in the center of Estonia. Two of these patients were later investigated by Lundborg [6]. As Unverricht described a family in Estonia it has been suggested that the Unverricht-Lundborg disease is a typical familial disease among Estonians and Finns [7]. However, the original case records indicate that the family described by Unverricht was most likely of Baltic German origin [8].

In 1892 Heinrich Unverricht moved to Magdeburg where he was appointed Director of the Hospital and in 1894 he was nominated Medical Counsellor. He died in Magdeburg in 1912 [9].

Professor H. Unverricht was definitely not a founder of neurology in Estonia. However, his scientific and personal impact allows us start the early history of Estonian neurology from his heritage.

One of the most distinguished surgeons of the second half of the 19th century was Ernst Gustav Benjamin von Bergman (1836–1907), Professor of Surgery in Tartu (Dorpat) (1871–1878). He participated in three wars and acquired much experience in field surgery. The papers on skull injuries published during his Tartu period were fundamental in the development of neurosurgery as a new independent medical discipline. In 1907 Ernst von Bergmann moved to Würzburg and became one of the founders of German neurosurgery [9].

Another former scholar of Tartu University who became a pioneer neurosurgeon was Nikolai Nilovich Burdenko (1876–1946). He belonged to the pleiad of highly-qualified surgeons who were brought up by Professor Maximilian Friedrich Werner Zoege von Mannteuffel (1857–1926), a surgeon of great compass and exceptional skill. Nikolai Burdenko graduated from Tartu University in 1906 and in 1917 he was elected Professor of Surgery. However, his neurosurgical career did not start before he left Estonia — first he went to Voronezh, and thereafter to Moscow where he founded a large school of neurosurgery [10]. The speciality of neurosurgery in Estonia was actually established by Professor Ludvig Puusepp (1875–1942) who had received his medical education at the St. Petersburg Military Academy (1894–1899), where he had begun his training in neurology under the guidance of Professor Vladimir Bechterew (1857–1927). In 1907 the Petersburg Psycho-Neurological Institute established a Chair of Surgical Neurology and Puusepp was appointed its first head. In 1920 he moved to his father's native country of Estonia and on December 2, 1920, he was appointed Professor of Neurology at Tartu University and Director of the Hospital of Nervous Diseases. There he separated the teaching of neurology from the teaching of psychiatry and created a strong neurological unit that included an operating room as well as neuroradiology, physical therapy, and laboratory services. Until 1940, Puusepp's hospital in Tartu was the only highly specialized center of neurology and neurosurgery in the Baltic States. Numerous patients from Latvia, Lithuania, and also from Finland were treated in Tartu between 1920 and 1940. In the course of 22 years at the University of Tartu, Professor Puusepp enlisted trainee neurosurgeons from various countries, including Spain and Yugoslavia [11].

Professor Ludvig Puusepp created a school of surgical neurology. As early as 1897, his teacher, Professor Vladimir Bechterew had established a special operating room for the surgical treatment of his patients

from the Department of Nervous and Mental Diseases at the St. Petersburg Medical Academy. Most of the prominent surgeons of St. Petersburg operated there, but Professor Bechterew was far from satisfied with their surgical results. Already at the inauguration of the operating room, Bechterew had formulated his creed: "If today's neurologists must still request the help of surgeons, the coming generation will no longer need to do so, for they have seized the scalpel to perform what legitimately belongs to their realm". Puusepp himself described the period: "In contemporary medical science there is a tendency to develop specialists for various parts of the body; each area of specialisation covers all methods of treatment including surgery. Only such combination of treatment methods in any branch of medicine will give us a perfect speciality. Today nobody is surprised at the gynecologist performing operations in his own field, the ophthalmologist in his own: only the neurologist is still on the sidelines, he treats but does not perform operations. If an operation in his field is necessary, the neurologist asks for the assistance of a general surgeon, as was the case formerly with eye, ear and gynecological patients. For example, nobody asks a surgeon to remove a cataract from such a small an organ as the eye; how can we then insist on the surgeon having detailed knowledge of so complicated a structure as the nervous system? Therefore it is obvious that it is time for neurologists to become surgeons in their field, and treat disorders of the nervous system not only with drugs and physical therapy, but also with the scalpel" [12].

This creed remained Puusepp's foremost objective throughout medical and academic career. Ever since, the effectiveness of both neurology and neurosurgery has greatly increased. However, Estonian neurosurgery is still based on neurology. This is particularly reflected in the medical education and, especially, in the planning and realisation of research projects.

When Puusepp came to Tartu, he was already a distinguished neurologist and neurosurgeon who had also been highly successful in the field of research. However, his best articles and books were written in Tartu, such as the monograph, *Die Tumoren des Gehirns*, published in 1929. This voluminous work (726 pages) was soon translated into Spanish and printed in Barcelona in 1931. During 1932 to 1939, two and a half volumes of Puusepp's *Chirurgische Neuropathologie* came out in Tartu. In 1932 he started publication of *Folia Neuropathologica Estoniana*. Puusepp was the founder and editor of the journal. In the course of 17 years 17 volumes were printed, which first and foremost contained articles by Tartu scientists, but also published papers by numerous foreign contributors, including such outstanding scholars as

Bechterew and Polenov (Leningrad), Rossolimo (Moscow), Mingazzini (Rome), Marburg (Vienna), Freeman (Philadelphia), Van Bogaert (Brussels), Guillain and Alajouanine (Paris), Marinesco (Bucharest), Dandy (Baltimore), Walker (Chicago), and Ley (Barcelona). The papers issued in Tartu reflect a high level of research, publishing important contributions to the diagnosis and treatment of brain tumors. In 1929, a modification of ventriculography was described. In 1932, fresh data on vertebral discogenic damage to the cauda equina were presented. In 1939, an extensive review of cerebral angiography and surgical treatment of cerebral aneurysms was published. Several papers were devoted to various nervous diseases and new surgical approaches, such as the Puusepp sign of the fifth toe and the Puusepp syringomyelia operation [13].

Professor Puusepp's health worsened considerably toward the end of 1940, and on October 19, 1942, he died in Tartu of carcinoma of the stomach. His successor was Professor Johannes Riives (1895–1971) who for many years had been the closest colleague of Professor Puusepp. However, his chairmanship (1942–1944) was short. The activities of the unit were depressed by the Nazi occupation of Estonia and the conversion of most of the service into a German military hospital. In autumn 1944, when many Estonians fled to the West, Professor Riives left first to Sweden where he worked with Professor Olivecrona, and thereafter to Canada [14].

The next Chairman and Director of the Hospital of Nervous Diseases was Professor Voldemar Üprus (1902–1956). Since 1928 he had been a pupil and fellow of Professor Puusepp. In 1933–1934 Dr. Üprus was trained in London on the grounds of the Rockefeller Fellowship. In the economically and politically very complicated postwar period Professor Üprus succeeded in restoring the Hospital's activities, teaching process and even some research projects. However, in 1948 he was accused of being a "bourgeois nationalist" and was dismissed from the university. He was, however, allowed to work in the industrial town of Kohtla-Järve, where he died in 1956 [15].

Contemporary Estonian neurology and neurosurgery has been mostly influenced by Professor Ernst Raudam (1915–1992), who was the Chairman of the Department of Neurology and Neurosurgery of Tartu for a very long period (1948–1984). He graduated from the University of Tartu in 1940 and had also been pupil of Professor Puusepp. Another pupil of Puusepp, Dr. Felix Raudkepp moved to Tallinn in 1940 and established there also a service for neurosurgery (at present the Department of Neurosurgery, Tallinn Mustamäe Hospital). Since 1940 several other departments of neurology have been set up in Esto-

nia, but the Department Neurology and Neurosurgery of Tartu has remained the main centre of clinical work and research. In 1978 the service was considerably expanded, and in 1988 a thoroughly reconstructed intensive care unit and a new operating theatre were opened. Today the service in Tartu functions as a part of a 1100-bed University Hospital and is relatively autonomous. It consists of three subunits, i.e. the Department of Neurology (60 beds), the Department of Neurosurgery (50) and the Neuro Intensive Care Unit (10 beds). There are 120 neurosurgical and neurotraumatological beds in Tallinn, as part of the 900-bed municipal general hospital. The Department of Neurology in the Kohtla-Järve Emergency Aid Hospital has a section of neurotraumatology which consists of 20 beds. Hence the general number of neurosurgical and neurotraumatological beds in Estonia is 200, i.e. 1.31 per 10.000 (the population of Estonia is 1.543.000). This capacity understandably corresponds to long treatment periods — the average hospitalisation time in Estonian neurosurgical wards was recently 14–16 days. The transfer from the state fixed hospital budget to insurance medicine has considerably shortened hospital days. The average hospital stay in 1993 was 10.4 days. In Estonia all patients with discogenic radiculopathies and other peripheral nerve compression syndromes are treated by neurosurgeons. The same concerns spinal and peripheral nerve injuries. Orthopedic surgery is relatively underdeveloped and specialized hand surgery is non-existent in Estonia. Therefore, even the patients with cervical fractures and luxations who have no spinal cord lesions are operated on by neurosurgeons. Insufficient facilities for the rehabilitation and/or long-time treatment in Estonia are also the reasons for fairly long hospital days in virtually all specialized departments.

In spite of the difficult economic situation, insufficient investments, and lack of adequately trained auxiliary personnel, Estonian neurosurgery has managed to meet most of the established Western standards. The services in Tartu and in Tallinn are equipped with CT scanners, operating microscopes, monitoring systems, etc, as a rule of Western manufacture. This enables to perform virtually all categories of neurosurgical procedures, except endovascular operations and radiosurgical manipulation

A short review of the development of various neurosurgical procedures in Tartu may illustrate the state of the speciality in Estonia. In 1957 the surgical evacuation of spontaneous intracerebral hematomas was started. Although cerebral angiography in Tartu had been introduced already in 1936 it was not restarted until 1957, after contrast media had become available. In 1959 stereotaxic surgery was instituted;

1962 denotes the introduction of electrocorticography and planned surgery for epilepsy. In 1963 the first reconstructive operations were performed on patients with cerebral ischemia for the carotid artery and in 1981 the first extra-intracranial microvascular anastomoses were carried out. In 1965 Professor Arvo Tikk performed the first spinal fusions in the patients with spinal cord injuries and 1974 he started to operate peripheral compression neuropathies. Ventriculo-atrial shunting operations were introduced by Dr. Jaan Eelmäe in 1981. In general, in the late 70s and early 80s various microsurgical methods in all kinds of operations were introduced, e.g. disc surgery, neurooncology, vascular surgery, and also peripheral nerve surgery which today includes nerve autotransplantation procedures [16].

In research projects preference has been given to the study of craniocerebral injuries, peripheral nervous disorder and cerebrovascular disease. The studies of craniocerebral traumas involve epidemiology, prolonged unconsciousness, metabolic and blood coagulation disorders. The cerebrovascular research has been aimed at determining general metabolic disorders, brain gas exchange and CSF acid-base parameters, and also at ascertaining the epidemiology and risk factors of stroke. One of the aims of these studies has been to reveal the biochemical markers of the brain tissue damage in CSF and in cerebral venous blood, and to correlate these findings to the pathologic changes on CT. The influence of some treatment procedures on these changes are being investigated. Several studies have been aimed to investigate CSF hydrodynamics in the development of intracranial hypertension and in subsequent pathologic changes in the brain.

On the initiative of Professor Raudam, already in the late 60s important international relations were established. In 1973 a special agreement on cooperation was signed with the Departments of Neurology and Neurosurgery, University of Helsinki. From 1967 most of the University staff members have participated in postdoctoral fellowship programmes in Sweden, Germany, USA, Japan and Austria.

Although the publishing of *Folia Neuropathologica Estoniana* was stopped by World War II, it is appropriate to make a reference to the 10 volumes of "*Problems of Clinical Neurology and Psychiatry*" which were more or less regularly published in Tartu in the period of 1961–1975. As a sequel to these proceedings were special volumes of *Acta et Commentationes Universitatis Tartuensis*, viz. vol 589, 1981; vol. 749, 1986; and vol. 901, 1990.

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NEUROLOGICAL AND NEUROSURGICAL INTENSIVE CARE IN TARTU

A. Tikk, E. Kross, U. Rink (Noormaa), M. Mägi, J. Eelmäe,
M. Kuklane, M. Heinsoo

An overview of the history of the neurological/neurosurgical intensive care unit (NNICU) in 1958–1993 and the most important modern problems of neuro-intensive care in Tartu are provided. The experience shows that 17 per cent of neurosurgical patients and 8 per cent of neurological patients need intensive care. The basic groups are patients with severe head injury (32.0 per cent), cerebro-vascular diseases (19.6 per cent), brain tumours (19.2 per cent) etc. About 20 per cent of patients needed artificial ventilation in 1958 and over 80 per cent in 1993. From 1958 to 1973 the emergency call team played an important role in intensive care in Estonia. Later the transportation of patients was transferred to the multidisciplinary intensive care unit of the Tartu Clinical Hospital and to local anaesthesiologists. The main problems concerning the diagnostics of disorders of consciousness, prognostic value of the biochemical markers, the outcome and the quality of life of the neuro-intensive care patients are discussed.

The evolution of the neurological-neurosurgical intensive care

In the spring of 1958 the Neurological and Neurosurgical Departments of the Tartu University Hospital began to give more attention to patients suffering from paralysis of respiratory muscles. The outbreak of a polio epidemic in the autumn of 1958, which attacked more than 1.000 people in Estonia, demanded urgent measures to stem the disease. 70 patients had severe respiratory disturbances or suffered from bulbar paralysis. Critically ill patients were brought to Tartu, and a Respiratory Care Unit (RCU) with 8–10 beds and the necessary staff and respiratory and medical equipment were rapidly set up. In this way the intensive care principles in the treatment of nervous diseases were introduced in Tartu [1]. After the elimination of the polio epidemic in the spring of 1959, the apparatus and the experience acquired during the intensive care of polio patients were used in the treatment of patients with other severe brain damage. At the same time neuro-

anaesthesiology started developing in Tartu. Intratracheal anaesthesia and controlled hyperventilation were used during neurosurgical operations. Very soon the advantages of the intensive care system became evident in treating patients whose condition earlier had been beyond hope [1, 2, 3].

As in the late 1950s anaesthesiology as a speciality only began to develop in this country, the recently founded RCU became a leading centre of intensive care in Estonia with its 1.5 million population. Here patients were admitted mainly in comatose state of various etiology and who suffered from paralysis of respiratory muscles and were in need of mechanical ventilation. But treatment was also given to critical chest injuries, tetanus, poisonings, etc. and to other non-neurological intensive care patients of other specialities (internal medicine, etc.). The Tartu RCU, which had been set up to treat the polio epidemic, developed into one of the first multi-disciplinary intensive care units in the then Soviet Union.

By the end of the 1960s there was already a fully developed anaesthesiological service in Estonia [3]. In this connection the RCU became a pure Neurological-Neurosurgical Intensive Care Unit (NNICU) that concentrated only on the treatment of nervous system diseases and from this time the NNICU also served as the only place for long-term respiratory treatment in our country [4].

From the very beginning of our activity arose the need for creating an emergency call team (ECT), a team which was called in to render medical assistance in other local hospitals all over Estonia and which also transported the patients needing intensive care to Tartu. It should be pointed out that the Respiratory Center's ECT, often using intubation, tracheostomy, mechanical ventilation and infusion therapy during transportation, has played an important role in introducing the principles of intensive care to the medical staff of different local hospitals in Estonia [2, 3, 4, 5].

The radius of activities of our ECT extends to 200 km with an average population density of 30 persons per 1 sq km.

In the first ten years of our activity ECT made 793 trips to the local hospitals or to the scene of accident. In these cases the ECT arrived within 2 hours of the onset of illness or the accident in 10.3 per cent of cases, within 2-6 hours in 26.2 per cent, within 7-24 hours in 37.2 per cent and within more than 24 hours in 26.1 per cent of cases [5].

Of these 793 cases 480 (60.5 per cent) were in life-threatening conditions and were transported to the NNICU by the team, 313 cases (39.5 per cent) were kept in intensive care without removal from the local hospital. 92 cases of them (29.4 per cent) proved to be incurable

and died either on the scene of accident or during the initial stage of treatment. Only 28 per cent of the calls in 1959-1968 occurred between 8 a.m. and 2 p.m., 36 per cent of the calls falling on the hours between 2 p.m. and 8 p.m. and 36 per cent on the hours from 8 p.m. to 8 a.m., i.e. on night hours. We mainly used an ambulance car, adapted for the ECT needs, the use of air transport in that period did not exceed 15 per cent of the total number of trips.

In the 1970s, after the rapid development of the anaesthesiological service, the anaesthesiologists of local hospitals started transporting their critical patients to our centre. In 1976 a surgical ICU was set up at the Tartu University Hospital and in 1981 an ECT was created at this unit. The surgical ECT was equipped with a modern reanimation car, and it rendered medical aid also outside Tartu. In the last years 10 per cent of the patients treated at our NNICU have been transported here by the ECT.

At the very beginning of our activity, at the time of the polio outbreak when the respiratory centre was rapidly organized we started with two doctors trained to a certain extent to work in this field, A. Veldi and A. Tikk, the latter had attended a two-week course at the Moscow polio-center dealing with problems of respiratory treatment.

The introduced methods of intensive care opened up new horizons for effective treatment of severe cases. This attracted many young neurologists and neurosurgeons to work at our ICU, especially in the first decade of the existence of the NNICU. In the 1970s and 1980s a specialized neuro-anaesthesiological service was developed in our department. In the last decade the neuro-anesthesiologists ran the around-the-clock service both at the operation theatre and at the NNICU. The neurologists and neurosurgeons cooperate with them only if special problems of treatment spring up.

Treatment of patients at the Neurological/Neurosurgical ICU

In the years 1958-1993 9068 patients were treated at the NNICU in Tartu. Our experience shows that up to 17 per cent of neurosurgical patients need the assistance of NNICU (including post-operative care), and on average about 8 per cent of neurological patients are in need of intensive care.

Table 1. Main data about Neurological/Neurosurgical ICU (1958–1993)

Diagnosis	Number of patients	Percent	Mechanical ventilation	Percent	Case fatality per cent
Head injuries	2938	32.3	1508	51.3	28.0
Spinal cord injuries	359	4.0	148	41.2	26.1
Cerebrovascular diseases	1910	21.1	951	49.8	42.5
Brain tumors	1763	19.5	1142	64.8	18.9
Meningitis and encephalitis	481	5.3	152	31.6	28.3
Polynuropathies	148	1.6	71	48.0	24.3
Status epilepticus	267	3.0	62	23.2	10.9
Poisonings (1958–1976)	373	4.1	51	13.7	9.0
Poliomyelitis(1958–1959)	70	0.8	35	50.0	28.6
Tetanus(1956–1976)	40	0.4	18	45.0	45.0
Other diseases	719	7.9	318	44.2	20.3
Total	9068	100	4456	49.1	26.9

During 1960–1975 the number of patients in NNICU fluctuated between 184 and 222 patients per year. During the last period (1982–1993) the number of patients in the neurointensive care remarkably increased. In 1993, there was an abrupt increase in the number of patients to 447, which means one fifth, compared with the previous period. We think that this fact is typical of contemporary trends in this field of activity. The average time of treatment at the NNICU has been from 7.4 to 10.4 days. Of all the patients treated at the NNICU children up to the age of 14 constitute 10 per cent.

The basic group that needs intensive care is the patients with severe head injuries (32.6 per cent). The increase in the total number of patients was due to trauma patients mainly victims of violent assaults (an increase of 30% in 1993 in comparison with 1992). 15 per cent of the patients hospitalised in the department of neurosurgery with brain traumas have been treated at the NNICU. This group consists mainly of patients with severe consciousness disorders. Spinal cord traumas with severe neurological deficit amounted to 359 (4.1 per cent). In the case of patients with tetraparesis or tetraplegia in cervical spinal cord injury 412 per cent have been in need of long term artificial ventilation. Other bigger groups are patients with vascular diseases and brain tumours, 20.1 and 19.6 of all the patients, respectively. Postoperative mechanical ventilation was used in patients with brain tumours who were somnolent preoperatively or who appeared to develop significant brain swelling as a result of tumour expansion. Weaning from respirators and extubation took place under careful monitoring of arterial blood gases and pulse oximetry, when the patient was awake, breathed adequately and was able to follow commands. Specific cases at the NNICU are patients with the paralysis of respiratory muscles (Guillain-Barré syndrome, polyneuropathies, myasthenia, cervical spinal cord injuries, etc.). Such patients are relatively few but they need long-term respiratory care and special attention. The high mortality rate of the polyneuropathy patients is due to the fact that the group included also cases of polyneuropathic syndromes in combination with carcinomas, collagenous diseases and poisonings. The longest period of assistant ventilation was 3 years in the case of a myasthenia patient who began to recover satisfactorily after thymectomy.

Figure 1 provides the mean numbers of patients undergoing respiratory treatment in the NNICU and the data of respiratory treatment (intubation, tracheostomy and mechanical ventilation) in different periods of the NNICU evolution during 35 years. As can be seen the number of patients at the NNICU has increased almost three times since the beginning of the team-work, especially in 1993. At the same

the treatment of respiratory insufficiency has also increased up to 80 per cent of the patients treated. This is connected with the remarkable increase in severe head injuries in the last years. From the end of the 1970s mechanical ventilation was more extensively used. For instance, in the case of head injuries at the NNICU 23 per cent of the patients used mechanical ventilation until 1970. In the years 1971–1980 it was used by 60 per cent of the patients, and from 1981 in 85 per cent of the head injury patients the mechanical ventilation and ventilatory support was combined with other methods of treatment.

At the end of 1970, as result of the effective support given by the English firm "Portex" it was possible to introduce tubes for longterm intubation at the NNICU. From this time the number of tracheostomy diminished, especially in the case of children. Nevertheless, during the whole period of the NNICU activity tracheostomy has been performed in 1.631 patients (18.0 per cent).

The application of computerized tomography, long-term ICP monitoring (from 1981), the complete monitoring system (the German firm Hellige) (from 1984), and pulse oxymetry (from 1991) has helped us obtain more accurate indications for controlled hyperventilation.

A serious problem in the case of comatose patients is the avoidance of lung complications and their treatment. The NNICU has been dealing with these problems since its very beginning. Already in 1959, in collaboration with the physicists of Tartu University the first aerosol and electroaerosol apparatus were created to be used together with the apparatus of artificial respiration. Aerosol treatment has considerably diminished the occurrence of lung complications [4, 6, 7, 8, 9].

Patients with severe brain damage may have noticeable systemic and local metabolic disturbances of the brain. A central problem here is monitoring the metabolic data and their correction which is an essential precondition in successful intensive care. At our NNICU these questions have been important in scientific research. Our research into several aspects of homeostasis has changed in the course of the last 30 years. At the beginning main attention was devoted to gas exchange and water-electrolyte metabolism [10, 11, 12, 13, 14, 15]. The dynamics of gas exchange was in close correlation with the disorders of water-electrolyte metabolism. The body water compartments were established in detail. The most severe decompensation in the development of water-electrolyte disorders took place at the end of the first week of the illness. The main problem in all brain damaged patients was severe hypovolemia and extracellular water deficit, which in severe cases was even up to 1/3 of the normal values [14, 15]. The systemic disorders of water-electrolyte metabolism correlated well with the metabolic shifts

of the brain. This was found out on the basis of cerebral venous blood (CVB) and cerebrospinal fluid (CSF) studies. From brain tissue hypoxia lactic acidosis develops in most frequent brain diseases (trauma, tumours, stroke).

Pathophysiological and prognostic evaluation of this phenomenon has been one of the most important problems of the metabolic studies in this group of patients [16–27].

In 1974 it was proposed that the blood derived from the damaged brain and cerebrospinal haemostatic properties would better measure local cerebral haemostasis in comparison with data from systemic circulation. The haemostatic abnormalities in CVB prevailed over those of systemic circulation — local cerebral disseminated intravascular coagulation was diagnosed in head injury [28], cerebrovascular disease [29, 30], brain tumours [31] and in meningitis and meningoencephalitis. High fibrinogen consumption in the severely damaged brain on the basis of the 125-iodine labelled fibrinogen degradation was established [32]. Haemostatic properties of CSF were worked out [32]. Haemostatic balance in the brain was impaired because of the deadlock in different mechanisms (primary haemostasis, enzymatic coagulation and fibrinolysis) of the haemostatic system. It leads to haemostatic breakdown in local cerebral blood, thrombin inhibition pathways with high fibrinolysis in CSF and extensive haemorrhagic complications in the case of severe brain damage [33]. Increased platelet aggregation and antithrombin III deficiency correlated well with thromboembolic phenomena in stroke, and in brain tumours in the postoperative period [35, 36, 37]. Recent data show that haemostatic abnormalities are also closely related to a wider problem — pathological peptide degradation proteolysis and endogenous intoxication [35].

Of great significance has been the intracranial pressure (ICP) recording in the NNICU. It is interesting to note that ICP was recorded in Tartu University as early as the 1860s by E. Bergmann [36]. Before World War II elevated ICP and lowered craniospinal system (CSS) volume parameters were studied by several researchers [37, 38, 39]. Routine ICP recording in the NNICU was introduced by A. Tikk in 1976 in order to evaluate ICP changes in patients with severe head injury [40]. From the end of the last decade, ICP research together with recording CSS viscoelastic parameters during the bolus infusion test [41, 42, 43] and pathophysiological changes in traumatic hydrocephalus have been the major tasks in our NNICU. On the basis of these studies we have concluded that posttraumatic ventriculomegaly is caused mainly by posttraumatic brain atrophy and the impairment of CSF resorption is not common in patients with severe head injury [44,

45]. As several metabolic factors can affect CSS equilibrium, brain damage markers and acid-base balance concurrently with ICP have been analysed by several researchers [46]. In order to obtain full time recording and to perform the bolus infusion test recurrently at the bedside, a personal computer software (NEUROMON) was worked out. On this basis new tasks of determining the genesis of hydrocephalus after spontaneous subarachnoid hemorrhage (SAH) were set.

Complications may threaten aneurysm patients by increasing ICP and worsening CSS viscoelastic parameters with concomitant brain metabolic changes. In SAH patients, in addition to the above mentioned parameters, ICP amplitude (A mmHg) and resistance to resorption of CSF will be useful records [43, 47]. It was also established that a reliable indication for shunting operation in hydrocephalus patients is significantly elevated resistance to resorption — $R > 10 \text{ mmHg/ml per min}$ [48].

Prior to the era of intensive care a patient with prolonged unconsciousness was described only as a casuistic case. With everyday use of intensive care prolonged unconsciousness became a daily occurrence. At the Tartu NNICU the occurrence of prolonged coma has been studied in detail [16, 25, 49, 50, 51]. It was found that coming out of coma has regular phases and starts with the restoration of the functions of phylogenetically older parts of the brain. Evolutionally most of the new cortical functions are reintegrated last of all. Phases of recovery from prolonged unconsciousness described by M. Mägi are given in Table 2.

In case of complications (infections, etc.) the process of recovery may stop or even reversal to previous phases may take place.

We have also elaborated criteria for an irreversible comatose state. Out of severe brain traumas at our NNICU 5 per cent of the patients irreversibly stabilized at a vegetative state level [25]. A lot of attention has been give to rendering the clinical and biochemical criteria for prognoses more precise [16, 21, 23, 25, 27, 49, 50].

Intensive care often poses problems concerning brain death diagnosis. In the papers published in Tartu this question was brought out for the first time in the then Soviet Union [52, 53]. Besides clinical evaluation special attention was paid to the precision of the biochemical criteria for irreversible brain damage.

Apart from the task of saving the patient's life, intensive care plays an important part in maintaining the quality of life after patients leave the ICU. After a long term coma recovery is also very slow, at least two or three years are required for vital recovery of the patients' neurological and mental state.

Table 2. Phases of recovery from prolonged unconsciousness

Coma dépassé	↑	Total irreversible loss of all cerebral function, i.e. brain death
Acute coma with severe disturbances of autonomic functions and metabolism	↓	Severe disturbance of all cerebral function
Coma with partial stabilisation of autonomic functions	↓	Restoration and stabilisation of pontobulbar functions
Apallic syndrome	↓	Restoration of the mesencephalic reticular activating system functions and improvement of the descending reticular system functions
Akinetic mutism	↓	Restoration of the thalamic reticular activating system and the thalamo-cortical unspecific projection system functions and of the diencephalic inhibiting mechanisms
Phase of reestablishment of verbal contact with the patient	↓	First signs of restoring of neocortical functions at the insufficient level of unspecific activation
Phase of severe dementia and prevalence of hypothalamic and limbic disturbances in clinical picture	↓	Insufficient restoration of limbic, hypothalamic and neocortical functions at the increased level of the unspecific activation mechanism
Phase of the integration of higher psychic and somatic functions	↓	Restoration and refixation of connections between cortical areas, neocortex and other brain functional systems

At the NNICU severe head injury treatment was evaluated in 76 patients from the point of view of their post-injury quality of life. They were admitted in a deep comatose state. 69 per cent of cases were operated on for intercranial haematomas. Controlled hyperventilation with intratracheal intubation was used in 64 per cent of cases and with tracheostomy in 36 per cent of cases. After the treatment at the NNICU all these cases needed long-term rehabilitation in psychiatric and other hospitals. Two or three years after a severe head injury almost all the patients were discharged. According to our data in 63 per cent of cases the quality of life was relatively good, including the cognitive and behavioural functions. Severe psychological and physical defects were found in 10 per cent of cases. In general the results of treatment were better in children [54].

Discussion

In spite of the fact that intensive care is expensive, consuming 0.8 per cent of the gross national product, it has, on the whole, proved its usefulness in clinical practice and is rapidly developing [55].

Specialized neuro-intensive care units for treatment of patients with severe nervous system diseases prove to be beneficial [56, 57, 58]. Most of the modern well-known NNICUs were founded, also like our centre, 30–35 years ago and experienced almost the same evolution — from poliomyelitis wards to specialized NNICUs [57, 58, 59]. Technical progress and understanding of prognostic aspects of patients with critical brain damage gradually reduced initial mortality compared to the results before the intensive care period and gave a better quality of life for thousands of aggressively treated patients [58, 60]. These reports confirm our recent data about the decrease in mortality and increase in the quality of life after severe head injury, especially in children.

After a short period of activity as a polio respiratory centre it rapidly developed into a multidisciplinary ICU with a substantial number of patients with severe nervous system diseases. Compared with many European and North-American countries the beginning of intensive care and specialization in neuro-intensive care in our clinic was about 10 years earlier [57, 58, 61]. The use of the modern methods of anaesthesia and intensive care in Estonia began in Tartu already in the 1950s. However, our local hospitals did not have sufficient understanding and experience of anaesthesia and intensive care, to say nothing of a regular anaesthesiological service for patients in life-threatening conditions all over Estonia [3]. In this situation the only right way for proper treatment of these critical patients was to transfer all the prob-

lems of diagnosis, treatment and transportation to our relatively well-equipped emergency call team [4, 5]. Other authors have also shown that they could be highly effective in quick and safe transportation of patients with the help of an intensive care unit team [62, 63]. There are certainly possibilities of improving the results of treatment, for instance, some therapeutic problems of prehospital emergency medicine have not been completely solved in Estonia.

Our data — 17 per cent of neurosurgical and 8 per cent of neurological patients needing intensive active monitoring and care in the NNICU — are similar to those of many other countries [56, 64]. The tendency to an increasing number of treated patients in our centre during the last five years is concomitant with trends all over the world [57, 58]. In the USA the number of ICU beds which have been projected for 2000 is already 24 per cent of all hospital beds [55].

The average time of treatment at our NNICU has been from 7.4 to 10.4 days. It seems to be quite near to the experience of other hospitals [57, 64].

Patients with critical brain damage have also their special problems. In general, severe brain damage in almost all cases is connected with cerebral hypoxia from local and systemic circulatory disorders. Important factors in the progression of brain hypoxia and hypoperfusion are the obstruction of the upper respiratory tract and other interconnected factors, which lead to secondary brain damage and irreversibility and poor outcome in the treatment of the disease. This basic knowledge has been taken into account during many years of our activity (Fig. 1). The technical progress of ventilators has given us the possibility of long-term artificial ventilation. In the recent period the use of servo-ventilators has enabled us to reach a new stage of treating and weaning from respirators patients having problems of respiratory insufficiency. The diagnosis and treatment efficiency of the new ventilatory equipment and long-time ventilation in the management of brain and systemic hypoxia have been stressed by other authors [59, 64, 65]. The new promising advances with the use of ICP control provides a new approach and better treatment and outcome in neuro-intensive care [43, 47].

Our experience in all aspects of prolonged unconsciousness (the dynamics of recovery through several phases, prognostic criteria, electroencephalographic and biochemical changes, etc.) are in good correlation with the data of other specialists in this field [66]. The prevalence of vegetative state (apallic syndrome) in our centre (5 per cent of all severe head injury cases) is similar to the figures of other authors [60, 64]. Unfortunately, the irreversible vegetative state has become a burden to society since the introduction of intensive care methods.

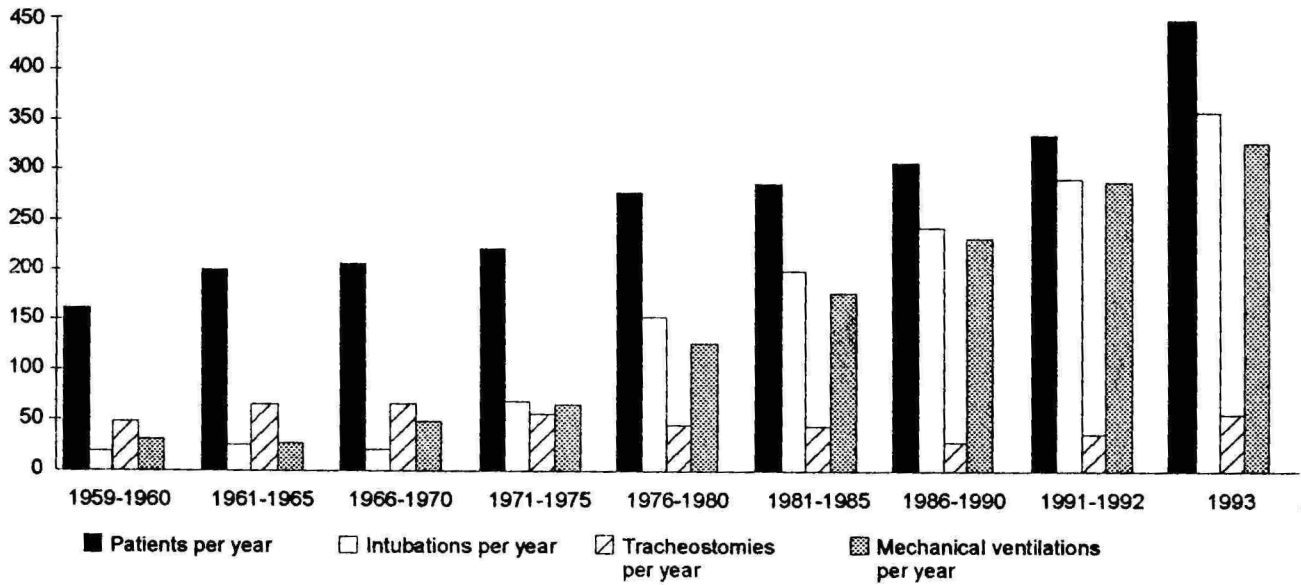


Fig. 1. Respiratory treatment in NNICU

Careful examination with parallel biochemical monitoring (main data of homeostasis — water and electrolyte balance, acid-base equilibrium hormonal state, osmolality, haemostasis, pathological protein degradation, etc.) have given us clearer understanding of the problems and a more scientific basis for the early prognosis of outcome. Although the problems related to brain death were published by us already in the 1960s and 70s [52, 53], the official guidelines for determining brain death were established and accepted in Estonia quite recently [67]. The actual problems of neuro-intensive care — high untreatable ICP, local haemostatic breakdown with frequent haemorrhagic complications and not always understandable quick cerebral death — have not been solved as yet. We hope that the new automated data collection in our unit with careful examination of intracranial pressure-volume relationship will soon give us early daily clinical prediction in individual cases and provide new and better treatment trends for the patients.

Interhospital comparisons with other authors [68, 69] have shown that the quality of life for long-term survivors after neuro-intensive care are relatively good in our ICU. In this aspect, intensive neurologic rehabilitation confirms a major beneficial effect [60, 70]. A rehabilitation centre for these patients is badly needed for the whole of Estonia.

In this review, the authors have attempted to give a survey of the history, present state and place of neurological and neurosurgical intensive care in neurology and neurosurgery. The advance of technology is so rapid that we cannot predict future developments but must bear in mind the words of William James [71]: “We have to live today by what truth we can get today and be ready tomorrow to call it a falsehood.”

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STROKE IN TARTU, ESTONIA: FIRST YEAR RESULTS OF A STROKE REGISTER

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A population based stroke register was set up on January 1, 1991. Herein, the first year results of the whole study period, 1991–1993, are presented. All medical records of suspected first-ever stroke in the Outpatient Clinic of Tartu, few other hospitals of Tartu, in the departments of the Tartu University Hospital were reviewed with the help of computerised data for the health statistics, and the patients admitted to the Department of Neurology and Neurosurgery were prospectively recorded by the members of our study group and followed during their hospitalisation. The stroke patients in the nursing home of Tartu were currently evaluated by a member of our study group. There were 233 cases of first-ever stroke occurring between Jan. 1, 1991 and Dec. 31, 1991. The total crude incidence of first-ever stroke was 204. After adjustment by age and sex to the 1990 Estonian population significant men's predominance became evident. The age-specific incidence rates rose with age, only for the oldest women surprisingly a decreasing tendency appeared. Compared to other studies in Europe, the age-specific incidence for younger and middle ages was rather high, probably due to the higher prevalence of several risk factors in Estonia. The comparatively lower numbers for the oldest women were likely associated with better controlled hypertension or just because they died at home before the visit of a physician without a perfect description in the outpatient's card, and the cases were excluded. Since the first epidemiological study on stroke (1970–1973), the total crude incidence has somewhat increased, after adjustment by age and sex it has increased for men and decreased for women. The total incidence rates for stroke subtypes were in accordance with other studies. Thirty-day case fatality rate (29%) was moderately higher than that in other regions of Europe. In conclusion, the data obtained during the study show higher rates of stroke in the younger and middle ages compared to the other population based studies in Europe and Estonia (1970–1973). Some increase of the total crude incidence and significant decrease of the case fatality has likely taken place in Estonia over 20 years. The data for the whole study period, 1991–1993, will probably show if these tendencies are real and provide valuable material for health care planning.

Acute cerebrovascular diseases are one of the most frequent causes of death in the Western countries [1]. Although the case fatality of stroke has fallen [2, 3], the decline in the incidence of stroke has stopped and even some increase became evident in Rochester, Minnesota [2], in Denmark [4] and Sweden [5] in the 1980s. The incidence of first-ever stroke between countries varies widely, in Europe it ranges from 93 [6] to 389 [5] per 100000 annually, in Estonia it is moderately high according to the first study from 1970 to 1973 [7]. To evaluate the possible temporal changes in Estonia and to obtain the material for health care planning, a community-based register was set up on January 1, 1991 in Tartu. In this paper, the first-year results of the whole registration period of 1991–1993 are presented.

Patients and methods

Tartu, a good representative of the Estonian population is a university town, situated in the Eastern part of Estonia. According to the official statistics [8], the population of Tartu was 114243 in 1991, consisting of 52389 (46%) men and 61854 (54%) women. The older age group (over 65 years) constituted 12 per cents of the whole population.

Table 1. Age and sex structure of the study population in 1991

Age	Men	Women	Total
0–54	43150	45581	88731
55–64	5232	7022	12254
65–74	2513	4937	7450
75–84	1267	3328	4595
≥85	227	986	1213
Total	52389	61854	114243

The study area is served by the Department of Neurology and Neurosurgery of the University Hospital of Tartu, by few other specialised hospitals, by an outpatient clinic and a nursing home. In our experience most stroke cases in Tartu are treated in the Department of Neurology and Neurosurgery. All first-ever stroke patients admitted to the Department of Neurology and Neurosurgery were prospectively recorded by the members of our study group and followed during their hospitalisation. All outpatients' records of suspected first-ever stroke

were monthly checked with the help of computerised data for health statistics kept in the Outpatient Clinic of Tartu. Hospital records for patients, who developed a stroke while inpatients in other departments of the Tartu University Hospital and other hospitals of Tartu, were reviewed at regular intervals. The information was achieved from the computerised data files or just by reviewing the hospital records. All stroke patients from the nursing home were currently evaluated by one of the authors. Death certificates for fatal cases outside the hospital were regularly checked, in the case of a clinical diagnosis of stroke clinical records were examined. Some stroke patients may be missing among those cases, as only the ones with a certain diagnosis of stroke were included. The patients were followed by sending them a questionnaire after 6 months and by checking their data from the Address Bureau of Estonia at 2 years.

The diagnosis of stroke was based on clinical evaluation, using the WHO criteria. The subtyping of stroke is reported elsewhere [9]. **Cerebral infarction (CI)**: the cases with the clinical diagnosis of cerebral infarction admitted to the Department of Neurology and Neurosurgery of the Tartu University Hospital and followed by the members of the study group during the hospitalisation. Computed tomography (CT), when performed, did not show intracerebral hemorrhage. **Intracerebral hemorrhage (ICH)**: clinically focal neurologic deficit, associated with signs of bleeding in the cerebrospinal fluid; intracerebral hemorrhage was demonstrated in autopsy or CT. **Subarachnoid hemorrhage (SAH)**: lacking focal neurologic deficit with hemorrhagic cerebrospinal fluid, or blood in the subarachnoid space at CT or autopsy. **Unspecified stroke (US)**: the cases, not meeting the criteria for CI, ICH, and SAH.

The incidence rates were age and sex adjusted by the direct method. Confidence intervals were calculated by the standard method. The two-tailed T test was used, when analysing the difference between groups, and $p < 0.05$ was considered as significant.

Results

There were 233 cases of first-ever stroke occurring between January 1, 1991 and December 31, 1991. The mean age of stroke patients was 69.9 years for all, 65.0 for men and 73.9 for women. The youngest patient was a 15-year-old male, who suffered from CI evaluated by CT. The diagnostic methods used are shown in Table 2.

Table 2. Diagnostic methods performed during the study

	CI	SAH	ICH	US	Total
Treated at home	0	0	0	23	23 (10%)
Hospitalised	171	12	21	6	210 (90%)
Seen by a neurologist	171	12	20	18	221 (95%)
Treated at the Dept of Neurol. & Neurosurg.	167	11	20	0	198 (85%)
Lumbar puncture	129	10	18	1	158 (68%)
CT scan	4	0	2	0	6 (3%)
Angiography	11	3	4	0	18 (8%)
Brain autopsy	20	3	6	0	29 (12%)
Total	171	12	21	29	233
per cents	73.4	5.2	9.0	12.4	100

In 86 per cent of cases cerebral infarction was diagnosed on clinical grounds. These patients were evaluated and followed by the authors at the Department of Neurology and Neurosurgery, and in 76% of cases the diagnosis was supported by lumbar puncture. The remaining part of CI was verified either at autopsy (12%) or on CT (3%). Twenty five per cent of SAH cases were recognised at autopsy, in 75% cases the clinical diagnosis of SAH was supported by lumbar puncture. The diagnosis of ICH was based on autopsy in 29% of cases, on CT in 10%, and on hemorrhagic lumbar puncture associated with focal neurologic deficit in 62%. The admission per cent at the acute stage was 86, 9 patients (4%) developed a stroke while inpatients.

The total crude incidence rate of stroke was 204 per 100000 annually (Table 3). The crude rate for women was higher than that for men due to the women's excess in older age groups. After adjustment by age and sex differences to the 1990 Estonian population significantly higher rate was found for men. Men's predominance was apparent in all ages, except for those 75-84. In younger and middle ages the higher rates for men were statistically significant. The age specific incidence rates increased with age, comparatively lower rates were found for the oldest women.

Table 3. Crude age-specific incidence rates of stroke per 100000 annually

Ages (years)	Men		Women		Total	
	Cases	Rate	Cases	Rate	Cases	Rate
0-54	21	49 a	7 a	15	28	32
55-64	33	631 b	15 b	214	48	392
65-74	21	836	32	648	53	711
75-84	23	1815	63	1893	86	1872
≥85	6	2643	12	1217	18	1484
Total	104	199	129	209	233	204
1991*		267 c		168 c		207
1970-1973*		253 d		192 d		212

* Adjusted by age and sex to the 1990 Estonian population
a, b, c, d p < 0.05

Table 4. Age specific incidence rates for different pathological types of stroke per 100000 annually

Ages (years)	CI		ICH		SAH		US	
	M	F	M	F	M	F	M	F
0-54	35	13	9	2	2	0	2	0
55-64	573 a	157 a	38	28	0	14	19	14
65-74	637	446	80	81	0	81	119	41
75-84	1184	1412	0	180	79	150	552	150
≥85	881	710	0	0	0	0	1763	507
Total	149	150	15	21	4	16	31	21
*	195 b	122 b	18	18	5	13	51 c	15 c
CFR	21%		50%		62%		41%	

* Adjusted by age and sex to the 1990 Estonian population
CFR: case fatality rate on the 30th day
a, b, c p < 0.05

Of 233 stroke patients 171 (73.4%) suffered from CI (84% in the carotid and 16% in the vertebrobasilar territory), 21 (9%) ICH (81% supratentorial and 19% infratentorial) and 12 (5.2%) SAH. Unspecified stroke was diagnosed in 29 cases (12.4%).

The crude age-specific incidence rates for CI were higher than those for other subtypes of stroke in all age classes, except for the older ones, where unspecified stroke was more frequent (Table 4). Age specific rates for CI were somewhat higher for men, after adjustment by

age and sex, the predominance of the total rate of CI for men was statistically significant. The diagnosis of unspecified stroke was more common in older ages and statistically higher figures for men were found in comparison with the total rates for US. A slight increasing tendency with age became evident in other pathological types of stroke, ICH and SAH. No cases of ICH and SAH were registered for the oldest.

The total case fatality of first-ever stroke by the 30th day was 29%. Early mortality was highest for those who suffered from ICH (62%) and lowest for the CI patients (21%) (Table 4).

Discussion

According to the national census [8] the age and sex structure of Tartu was similar to that of Estonia. The influence of Tartu University with its hospitals on the whole health care system of Tartu and readily available computerised system for health statistics makes case finding easy and the whole region suitable for epidemiological studies. The proportion of neurologists in Tartu is high and qualified medical care is easily available to the local population. Hence, the possibility that some acute stroke cases are treated in other hospitals is minimal. Most stroke patients in Tartu are admitted to the Department of Neurology and Neurosurgery, few of them were treated in other hospitals and at home. Therefore, we presumably could assure an almost complete case finding system for all first-ever stroke cases in Tartu.

It is widely known that a population based study is the only possibility of obtaining plausible results of the incidence of stroke. To compare the incidence rates between countries, the criteria for a study setup must be uniform [10]. The incidence rates should be presented for standard age groups and for first-ever strokes. These aforementioned differences between studies make it difficult to compare the figures with each other. We could probably overcome these points, but there are some other shortcomings, as the subtyping of stroke, which does not meet the criteria for an ideal study, defined by Malmgren [10]. There are probably some cases of ICH misdiagnosed as CI, because of the small number of cases verified by CT or autopsy in our study. The recognition of small hemorrhages by CT has likely increased the incidence and improved the survivorship of intracerebral hemorrhage [11]. According to the WHO criteria, the diagnosis of stroke as a whole is based on clinical evaluation, which enables us to compare the rates with other studies, especially with those performed before the era of CT.

Table 5. Crude incidence rates of stroke in some study centres per 100000 annually

Study	0-54	55-64	65-74	75-84	≥ 85	Total
Valle d'Aosta, Italy 1989 [15]	23	234	729	1642	3236	223
Frederiksberg, Denmark 1989-1990 [4]	21	306	702	1310	1600	306
Oxfordshire, UK 1981-1986 [15]	...	291	690	1434	1987	160
Malmö, Sweden 1989 [12]	...	183	546	1100	1719	225
Tilburg, the Netherlands 1978-1980 [14]	20	201	688	1609		145
Espoo-Kauniainen Finland 1978-1980 [6]	...	241	647	1347		93
Söderhamn, Sweden 1983-1986 [5]	...	315	912	2341	3968	389
Tartu, Estonia 1970-1973 [7]	(50-59) 158	(60-69) 445	(70-79) 1329	(80-89) 2839	(90-99) 3950	184
Tartu, Estonia 1991	32	392	711	1872	1484	204

A slight increasing tendency in the total crude incidence of stroke was found in Estonia comparing the numbers with those reported by the previous study 1970-1973 (204 and 184, respectively). Somewhat higher figures in 1991 became apparent for middle aged men and lower for the older ages, particularly for women. The total age and sex adjusted incidence rate for men increased and in women decreased, but the changes were nonsignificant. The incidence figures of the present study are closer to that in Malmö [12] and Valle d'Aosta [13] (Table 5). Higher rates are shown in Scandinavia [4, 5], lower in the Netherlands [14], UK [15], and Finland [6]. The increasing trend of age-specific

incidence with age found by all stroke studies, was confirmed by our data as well. It is not easy to explain the higher rates for the younger and middle age classes compared to others. We suppose that this appeared due to the higher prevalence of risk factors (undetected and untreated hypertension, smoking, unsatisfactory diet habits, heavy alcohol use) in Estonia than among the Western populations. The lower incidence for the oldest group can be explained by more adequately controlled hypertension in older women than in younger ages. This speculation coincides with the finding of the greatest reduction in the prevalence of hypertension through better treatment of mild hypertension in Rochester, Minnesota, USA [16], where the age specific incidence rates decreased more rapidly in the older ages, particularly in the women over 75. Another explanation is possibly associated with our methodology, which was similar to the records linkage system used in Rochester, Minnesota, USA [2]. We included only the cases with perfect clinical diagnosis of first-ever stroke. The excluded patients probably belonged to the older ages, who remained at home and perhaps died before the visit of a physician and in whom definite clinical symptoms of stroke missed in the outpatient's card. We suggest that not more than about 5% of the total number of first-ever strokes were excluded. Similar difficulties are shown by the study in Malmö [12]. Perhaps the few possibly undetected cases affected the rates in the oldest age group, more unlikely the total results.

The case fatality by the 30th day is moderately high. The figures for immediate mortality stated by other study centres are 23% in Söderhamn [10], 19% in Oxfordshire [17], 15% from Malmö [12], 31% in Valle d'Aosta [13]. The higher case fatality for cerebral hemorrhage and for the uncertain type found by several authors is confirmed by our study. The latter subtype of stroke concern predominantly older persons, who are not admitted and whose pathological type of stroke remains undetermined. These undetermined cases are more likely occurred due to cerebral hemorrhage than to cerebral infarction, because of the higher case fatality for US resembling that of ICH [17].

The early mortality of stroke depends predominantly on the prevention of the secondary complications of stroke, which are better avoided by intensive care during the acute period of stroke, rather than on the direct therapeutic effect on acute brain damage [2, 15]. The significant decrease of the 30-day mortality since the 1970s in Estonia (from 49% to 29%) is probably associated with a greater number of stroke patients admitted to the Department of Neurology and Neurosurgery (34% in 1970–1973 and 85% in 1991). In Europe the hospitali-

sation proportion of stroke patients varies from 54% in Oxfordshire [18] to 80–90% in Scandinavia [4, 5, 12].

In conclusion, the data obtained during the study show higher rates of stroke in the younger and middle ages compared to other population based studies in Europe and Estonia (1970–1973). Some increase of the total crude incidence and significant decrease of case fatality has likewise taken place in Estonia over 20 years. The data for the whole study period, 1991–1993, will certainly show if these tendencies are real and provide a valuable material for health care planning. Nevertheless, no data about the true prevalence of risk factors for stroke are available in Estonia, the figures in this study prove the need for effective primary prevention of stroke, especially in the young.

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IS THERE A REGIONAL VARIATION IN THE STROKE INCIDENCE IN ESTONIA?

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The present study was undertaken to assess the differences in stroke incidence between an urban and semirural community of Estonia. For this purpose a community based epidemiological study was performed in Tartu from Jan. 1. 1991 to Dec. 31. 1991. Using retrospective methods, a similar study was carried out in Viljandi District (VD) from Jan. 1. 1990 to Dec. 31. 1990. All medical records of suspected first-ever stroke and TIA were reviewed and those meeting the diagnostic criteria were registered. The crude annual incidence rate of stroke was slightly higher in VD than in Tartu, i.e. 232 and 204, respectively. After adjustment to the 1990 Estonian population by age and sex, all rates were somewhat lower in VD, and a significant men's prevalence became evident among both populations. The incidence rates increased with age, but in Tartu comparatively low rate was found for the oldest age group, particularly in women. The rates for stroke subtypes and for TIA were without significant differences between the regions. 30-day case fatality was nonsignificantly higher in VD, reaching the level of 40% after 6 months. In conclusion, no regional variation in the incidence of first-ever TIA and stroke became evident between these two regions in Estonia.

Acute cerebrovascular diseases are still a subject of great interest because of their central role in disability and mortality. The differences in incidence rates of stroke reported from many countries suggest the existence of a real geographical variation in the morbidity of stroke [1, 2]. Several stroke studies confirm about differences in the incidence of stroke between regions in the same country [3, 4, 5, 6]. However, no data about regional variation of stroke incidence are available in Estonia. The only epidemiological study on stroke incidence in Estonia was carried out in Tartu in 1970–1973 [7].

The present study was undertaken to assess the differences in stroke incidence between an urban and a semirural community of Estonia. For this purpose a stroke registry was started in Tartu in 1991 and simultaneously, using retrospective methods, a study was carried out in the Viljandi District for the year 1990.

Patients and methods

Tartu is a university town, situated in the eastern part of Estonia with a population of 114243 in 1991 [8]. Viljandi District (VD) lies in the central part of Estonia and its population was 65176 in 1990. The main town in VD is Viljandi. In VD 65 per cent of the population reside in the rural area and in 5 small towns. In Tartu 17 per cent and in VD 20 per cent of the population were over the age of 60, with the female to male ratio of 2 : 1 in this age group.

A community based epidemiological study on stroke incidence was performed in Tartu from Jan. 1. 1991 to Dec. 31. 1991. Using retrospective methods, a similar study was carried out in VD from Jan. 1. 1990 to Dec. 31. 1990. In Tartu all first-ever stroke and TIA cases, admitted to the Department of Neurology and Neurosurgery of the Tartu University Hospital, were daily evaluated and recorded by the members of the study group and followed during their hospitalisation. All outpatients' records and hospital records of suspected stroke and TIA in other departments and hospitals in Tartu were monthly checked and registered. A general practitioner in the nursing home of Tartu reported currently about their stroke cases. In VD 11 general practitioners in the rural area were interviewed and a neurologist in the Outpatient Clinic of Viljandi reported their first-ever stroke and TIA cases. All hospital records of suspected stroke and TIA in 3 small general hospitals, in 2 wards of neurology in the rural area, in the Department of Neurology and other departments of the Central Hospital of Viljandi were reviewed. To obtain information about fatal stroke cases outside the hospitals, all death certificates in both regions were checked, and if there was a clinical diagnosis of stroke, clinical records were looked through. Only the cases with the certain diagnosis of stroke were included, using similar exclusion criteria as J. P. Broderick et al. [9]. The stroke patients were followed by checking their data in the Address Bureau of Estonia after 1 year.

The diagnosis of stroke and TIA was based on clinical evaluation, using the WHO criteria. Stroke was defined as rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than vascular origin. The subgrouping of stroke was based mostly on clinical evaluation. The patients with clinical diagnoses of cerebral infarction, admitted to the Department of Neurology and Neurosurgery of the Tartu University Hospital and to the wards of neurology in VD, and followed by a neurologist during hospitalisation, were subtype as cerebral infarction (CI). Computed tomography (CT) and autopsy,

when performed, did not show intracerebral hemorrhage. Intracerebral hemorrhage (ICH) was diagnosed, if clinically focal neurologic deficit was associated with signs of bleeding in the cerebrospinal fluid, or an intracerebral hemorrhage was demonstrated by autopsy or CT. The diagnosis of subarachnoid hemorrhage (SAH) was established, when the stroke patient lacked focal neurologic deficit and the cerebrospinal fluid was hemorrhagic, or blood was found in the subarachnoid space on CT or at autopsy. The cases with a clinical diagnosis of stroke, not meeting the criteria for CI, ICH and SAH, were subtype as unspecified stroke (US). TIA was defined as rapidly developing clinical signs of focal cerebral dysfunction of presumed vascular origin lasting less than 24 hours. Only first cases in lifetime (first-ever strokes and TIAs) were considered, when calculating the incidence. The incidence figures were age and sex adjusted by the direct method. Confidence intervals (CI) were calculated by the standard method. The two-tailed T test was used, when analyzing the difference between groups, and $p < 0.05$ was considered as significant.

Results

A total of 151 first-ever stroke cases were identified in the VD in 1990 and 233 cases in Tartu in 1991. Fifty five patients (36%), among them 24 (34%) men and 31 (38%) women, resided in Viljandi. The mean age of stroke patients was 69.0 years in the VD and 69.9 years in Tartu. The mean age for women was 71.8 years in VD and 73.9 years in Tartu, of men 65.7 years in the VD and 65.0 years in Tartu. The youngest stroke patient in Tartu was a 15-year-old male, in the VD a 20-years-old female, both subtype as cerebral infarction on CT. The age groups where stroke became a problem, were 35–39 years in men and 45–49 in women.

In the VD 134 (89%) and in Tartu 221 stroke patients (95%) were evaluated by a neurologist, 198 stroke cases (85%) in Tartu were followed by the members of the study group during their hospitalization in the Department of Neurology and Neurosurgery of the Tartu University Hospital. In Tartu 90% and in the VD 91% of stroke patients were admitted to hospital. Lumbar puncture was performed on 79 stroke patients (52%) in VD and on 158 stroke patients (68%) in Tartu, autopsy data were available for 16 stroke cases (11%) in the VD and for 29 stroke cases (12%) in Tartu. In 12 stroke cases (8%) in VD and 6 stroke cases (3%) in Tartu the diagnoses were verified by CT. Cerebral angiography was performed on 4 stroke patients (3%) in VD and on 18 stroke patients (8%) in Tartu.

Table 1. Crude age specific incidence rates of stroke (per 100000 annually) in Tartu in 1991 and Viljandi District in 1990

Age (yr)	Tartu			Viljandi District		
	Men	Women	Total	Men	Women	Total
0-54	49 a	15 a	32	54	29	41
55-64	631 b	214 b	392	755 d	187 d	429
65-74	836	648	711	651	874	798
75-84	1815	1893	1872	1610	1139	1277
≥ 85	2643	1217	1484	2825	1192	1533
Total	199	209	204	232	232	232
*	268 c	168 c	208	263 e	157 e	199

a, b, c, d, e $p < 0.05$

* Age and sex adjusted to the 1990 Estonian population

The crude annual incidence rate of stroke was slightly higher in the VD (Table 1). In the VD the male and female crude incidence rates of stroke coincided and nonsignificantly exceeded the rates for Tartu. After adjustment by age and sex to the 1990 Estonian population, all rates were somewhat lower in VD. Comparing the crude rates for men and women, no significant differences were found among these populations, but after adjustment by age and sex differences, a significant predominance of men became evident. This was especially significant in the age groups 0-54 and 55-64 in Tartu and 55-64 in VD. In all age classes, except 65-74 in the VD and 75-84 in Tartu, somewhat higher rates for men were apparent. Comparing the age specific incidence rates of stroke, no significant difference between these regions was found. The incidence rates of stroke increased with age, but comparatively low rates were observed in the older age groups. The rate for women ≥ 85 in Tartu was lower than for those aged 75-84, lowering the total rate in this age group. In the VD, the incidence rate for men 65-74 years old was somewhat lower than that for the former and for women of the same age group.

Table 2. Total incidence (per 100000 annually) of different types of stroke; age and sex adjusted to the 1990 population of Estonia

Subtype	Tartu			Viljandi District		
	Men	Women	Total	Men	Women	Total
CI	195 a	122 a	153	208 d	116 d	157
ICH	18	18	19	16	32	19
SAH	5	13	11	–	3	2
US	51 b	15 b	25	39	15	22
US+CI	246 c	137 c	178	247 e	132 e	179

a, b, c, d, e $p < 0.05$

In Tartu 171 (73%) and in VD 117 cases (78%) were subgrouped as cerebral infarction. The total age adjusted incidence rates for CI nearly coincided in these regions (Table 2). The age and sex adjusted incidence rate for CI in men was significantly higher than the women's rate among both populations, but no significant differences between the regions were found.

The diagnosis of unspecified stroke was established in 19 cases (13%) in VD and in 29 cases (12%) in Tartu. This subtype predominated in the older age groups, without remarkable differences between these regions.

The total incidence rate of ICH was equal and diagnosed in 9% patients in both regions. The rate for ICH in women in VD was slightly higher than that in Tartu, but nearly coincided in men. This diagnosis was more represented in middle and older age groups.

The only SAH case (1% of cases) in VD occurred in a 50-year-old woman, the total rate was nonsignificantly lower than the rate for SAH (5% cases) in Tartu. In Tartu, the age specific rates for SAH increased with age, the women's rates were slightly higher, and the SAH patients belonged to the ages 45–84.

30-day case fatality in the VD was somewhat higher than in Tartu, reaching the level of 40% after 6 months in both regions (Table 3). Case fatality was higher for the patients with ICH in both regions. In VD case fatality for unspecified stroke was the highest.

Table 3. Case fatality after different types of stroke in Tartu and in Viljandi District (in per cent)

Subtype	Tartu		Viljandi District	
	30 days	6 months	30 days	6 months
CI	21	32	20	28
ICH	62	71	71	79
SAH	50	50	—	—
US	41	66	79	84
US+CI	24	37	28	36
Total	29	40	32	40

Table 4. Crude age and sex specific incidence rates for TIA (per 100000 annually) in Tartu and in Viljandi District

Age (yr)	Tartu			Viljandi District		
	Men	Women	Total	Men	Women	Total
0-54	9	2	6	0	12	6
55-64	57	85	73	126	70	94
65-74	40	81	67	177	90	120
75-84	395	180	239	95	39	56
≥85	0	0	0	565	0	118
Total	25	28	26	30	29	29
*	34	25	27	36	24	27

* Age and sex adjusted to the 1990 Estonian population

The rate for first-ever TIA for both sexes was 29 in the VD and 26 in Tartu (Table 4). Neither in the crude nor in the age and sex adjusted total rates significant differences were found between the populations. In the oldest age group in Tartu and in the age class 0-54 of men and ≥ 85 of women in the VD no cases of TIA were registered.

Discussion

The regions are well suited for epidemiological studies, as the rates of hospitalization and the number of neurologists are high, medical care is available to everyone. In Tartu, computerized medical records for health statistics, kept in the Outpatient Clinic and in the Tartu University Hospital, were available for the study. The assumption

is that the results were validly comparable as the record retrieval system was similar, resembling the previous study in Estonia [7]. The cases of stroke in VD were homogeneously distributed throughout the rural and urban area without noteworthy differences in the frequency between the rural and urban populations. Therefore, we did not calculate the incidence rates of stroke for the rural population, as the confidence intervals would have been too wide.

The main shortcoming of the study, which prevents it from meeting the criteria defined by Malmgren et al. [2] for an ideal study, is the subtyping of stroke. In Tartu only 3% and in VD 8% of the cases were evaluated by CT, autopsy data were available in 12% in Tartu and in 11% in VD. The pathological type of stroke was not precisely differentiated before the era of CT [10], and the incidence of ICH has risen with the introduction of the CT scan due to the detection of small hemorrhages by CT. Hence, in this study the number of ICH could have been somewhat underestimated.

The significant men's preponderance found among both populations is in accordance with other studies [1, 7]. The comparatively low rates in older age groups, especially for women, is a surprising finding. As an explanation we venture three possible reasons. Firstly, one can speculate that this decline resulted from the treatment of hypertension, which may be somewhat better controlled in older women than in younger age groups and men. This suggestion agrees with the finding of the reduction of prevalence of hypertension in the persons aged ≥ 75 (particularly women) in Rochester, Minnesota, USA from 1950 to 1979 [11]. Another study from the same centre reported about a decline in the 1970s and a recent increase in the 1980s, which was most prominent in the older age group [9]. We suppose that some similar changes may have taken place in the older age groups in Estonia. Secondly, we suggest this finding and the lower rate for 65–74-year old men in VD is casual, as the confidence intervals were wide. The third, and the most plausible explanation is that the stroke patients, mostly in older age groups, who stayed at home and died before the visit of the physician, not having perfect clinical data, were excluded, according to the methodology used in the study in Rochester, Minnesota, USA [9]. Furthermore, the incidence rate for SAH in the VD may be underestimated. We also excluded some probable SAH cases, who died before admission and perfect clinical or autopsy data were not available.

The incidence rate for TIA in both regions was similar and rather low. These rates are comparable to the 31 TIA cases in Rochester [12] and 33 in Tartu in 1970–1973 [7]. The mentioned study from

Rochester [12] suggests that there are some persons in the community who had TIA and did not report these symptoms to the physician either at the time of the symptoms during the subsequent visit. The real number of persons with TIA does not exceed 10% of the total number of persons with identified TIA. The authors have found that about 9% of first-ever stroke patients had a preceding history of TIA. V. V. Hachinsky [13] supposes that this must be an underestimation as the real number of persons who have suffered from TIA may even be greater. Some patients may be forgetful, senile, aphasic, seriously ill or die before stating about the history of their past health. The low figures for TIA in this study may be explained similarly. Some TIA cases were missed as the stroke patient was not able to state about the preceding TIA during the evaluation of a subsequent stroke, some persons probably did not report about their TIA to the physician at all.

The figures of 30-day and 6-month total case-fatality for the study regions nearly coincided. High case-fatality of ICH, reported by several authors, was confirmed by this study. The highest early mortality from unspecified stroke in VD may be due to the cases of intracranial hemorrhage, which lacked perfect clinical or autopsy data, and therefore was classified as unspecified stroke.

Some authors have referred to geographical differences in the incidence of stroke. The results of a community based stroke register in Finland from 1983 to 1985 shows a higher incidence of stroke in East Finland than in the southwestern part of the country [4]. The large variation in the incidence of nonfatal stroke may partly depend on the differences in levels and trends in risk factors and partly on different technological support for a perfect diagnosis and methodological differences, not on the early treatment of acute cerebrovascular accidents, which is uniform throughout Finland [14]. A noteworthy difference in the incidence of stroke between regions was found in Sweden [3]. In Malmö, the rates were markedly lower than these in the Lund-Örup district, which lies in the neighbourhood. The authors suggest active intervention and preventive measures as a result of the results from screening programs in Malmö. Differences in stroke incidence between regions became evident in a large-scale population study in China [6]. The incidence of stroke differed significantly in various topographic areas and was much higher in the cities. The recent study from Taiwan [5] shows that in rural areas stroke incidence rates are higher than in the cities, it was explained by the lower educational level in the countryside. In rural areas the people are not sufficiently educated to avoid the risk factors of the cerebrovascular disease. In Estonia medical care is available to everybody, the system is uniform all over the

country, the educational level is rather high, living conditions are similar in the city and in the rural area, and probably, there are no differences in the prevalence of risk factors. In conclusion, no regional variation in stroke incidence became evident between these regions in Estonia. To overcome the limitations, such as small subgroups, as for example in VD, and in order to use CT for verification of the diagnosis, the study in the urban region of Tartu, which is a good representative of the Estonian population was carried out in the course of 3 years, to obtain a more reliable overview of stroke incidence in Estonia.

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DIAGNOSIS OF TICK BORN ENCEPHALITIS IN SOUTH ESTONIA (1988–1993)

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Several investigations have demonstrated that the incidence of tick-born encephalitis (TBE) in South Estonia is high. However, the diagnostic criteria used in the studies are unclear. This study was conducted to evaluate the diagnostic criteria of TBE in Estonia. The case histories of all patients with the final diagnosis of TBE and of all patients whose sera were tested with complement fixation (CF) and hemagglutination (HI) for tick transmitted diseases from 1988 to 1993 were examined. In addition all sera examined in the Laboratory of the Hospital of Infectious Diseases were tested with ELISA for IgM antibodies against TBE virus (Immunozyzm FSME IgM, Immuno AG, Austria).

The results demonstrated that the most important prerequisites for the diagnosis of TBE were the presence of meningitis and the fact of the tick bite. The results of the serological analyses (CF, HI) did not influence the diagnosis. On the other hand the comparison of TBE-IgM ELISA results with HI and CF titres revealed no statistically significant correlation between TBE-IgM ELISA and HI results or between HI and CF titres. Spearman rank correlation revealed a weak but significant correlation with CF.

Our results demonstrate that the diagnostic methods and criteria used to diagnose TBE are inadequate and therefore it is impossible to determine the real incidence rate of TBE in Estonia.

The history of tick born encephalitis (TBE) in Estonia long and well studied. The first diagnosed patients with TBE in Estonia were noted in 1950. A special study was conducted in the area to confirm that there had been no cases of TBE before 1950 [1]. In the next research E. Raudam and colleagues analysed retrospectively all 46 TBE cases diagnosed during the next 22 years, demonstrating that there was a significant increase in the incidence of TBE in Estonia [2]. Thus, it has been concluded that certain parts of Estonia belong to the high risk area of TBE infection. One of the high risk areas is South Estonia with the distribution of two main types of tick born encephalitis virus (TBEV) infected ticks *Ixodes ricinus* and *Ixodes persulcatus*. The number of *I. persulcatus* is the largest in April and May and *I. ricinus* ticks are active in May, June and August [3, 4]. However, existing data about the used diagnostic criteria are insufficient. The first clinical

diagnosis [2] was typically based on the bite of the tick, characteristic two temperature curves, meningeal signs, pleocytosis and increased protein content in cerebrospinal fluid (CSF). Additionally in many cases the tremor of the tongue, asymmetry of the tendon reflexes and pain in the hands were described. Also, the laboratory tests were used, particularly, the complement fixation (CF) and/or hemagglutination inhibition (HI) tests [2]. Some epidemiological studies have recently been based on the estimation of antibody titres with CF, HI and IgM antibodies to TBEV by ELISA [3]. Unfortunately, there was no explanation of the diagnostic criteria of TBE. Hence, the aim of the present study was to examine the currently used diagnostic criteria and to evaluate the value of each criteria used.

TBE is usually considered a mild disease and complications are observed seldom 10 to 15% of all patients [2, 5, 6]. The patients are usually treated in the Department of Infectious Diseases [7]. Exceptionally, in the Tartu University Hospital all suspected neuroinfections, including TBE are referred to and treated in the Department of Neurology. Thus the other hypotheses tested was if there are more diagnosed severe cases of TBE (with focal neurological signs) if the patients are under the supervision of neurologists who are trained to find focal neurological signs, compared to the patients treated by specialists of infectious diseases as it is common elsewhere. For these purposes we evaluated the clinical and serological data of patients with TBE.

Methods

TBE infection is traditionally treated in the Department of Neurology of the Tartu University Hospital. The Tartu University Hospital is a central hospital in Estonia, therefore all complicated TBE patients are transferred here. On the other hand, the department treats all neurological patients (including all patients with suspected meningitis or encephalitis) from the town of Tartu and Tartu district.

TBE is clinically diagnosed (CTBE) in the Department of Neurology of the University Hospital if meningitis or encephalitis follows a tick bite (14 days before the second phase), occurs in spring, summer or autumn and has a typical clinical picture (typical biphasic course with moderate fever, myalgia, headache).

All case histories from 1988 to 1993 with the clinical (final) diagnoses of TBE were selected. In addition, all patients whose sera were tested for antibodies to TBE were included and the case histories of these persons were checked to determine the final diagnosis.

Serological tests of TBE were performed in the Laboratory of the Hospital of Infectious Diseases by CF and HI reactions (Tomsk, Russia) and sera with titre 1 : 20 or higher were evaluated as positive. 28 sera of patients were proved retrospectively with ELISA for the determination of IgM antibodies against TBE-virus (Immunozyzm FSME IgM, Immuno AG, Austria) and TBE-IgM ELISA results were compared with the HI and CF data obtained by Spearman rank correlation and Chi-square tests. Statistical analysis was carried out using the Statgraphics 4.0 statistical package (STSC and Statistical Corporation).

According to all the collected data, all TBE cases were divided into clinically (CTBE) or serologically proved TBE. According to the results of CF and/or HI tests the patients were divided as follows: serologically supported (SSTBE) cases — all patients with even minimal changes in antibody titres, and serologically confirmed (SCTBE) cases — patients with the four-time change of antibody titres of paired sera.

Results

Altogether 52 patients (14 female and 38 male) with TBE were admitted to the Department of Neurology. 17 of them were hospitalised from Tartu and 12 from Tartu district. The peak of the admission was in June with 18 patients and in August with 13 patients (Fig.1). The tick bite was noted in the case histories of 51 (98%) of patients. One patient without a documented tick bite was a Latvian from Riga who had gone for a walk in the woods near the city and he developed peripheral palsy predominantly in the cervical region.

The incubation period of TBE was from 2 to 45 days, most often 14 to 21 days (22.7). CSF was investigated in all patients and in 51 (98%) of the patients mononuclear pleocytoses was demonstrated. Elevated protein account was present in 45 (86%) patients (over 0.3 g/l). The meningeal form of TBE was demonstrated in 46 (88%) patients.

Altogether six patients (12%) had serious complications: three of them had peripheral paresis, one had spastic hemiparesis, one spastic paraparesis, one patient had diplopia, nystagmus and positive Babinski sign on the left. Three patients were from Eastern Estonia, one was a Latvian who was visiting relatives in Estonia when he was admitted during the second phase of TBE, one was the resident of Tartu town (1/17) and one from county (1/12). That is 6.9% of all patients admitted from the town of Tartu and district. In five patients neurological symptoms persisted after the discharge from the hospital, one patient with diplopia and Babinski sign was cured. All but one patients were male. All patients with complications were febrile before or at admission.

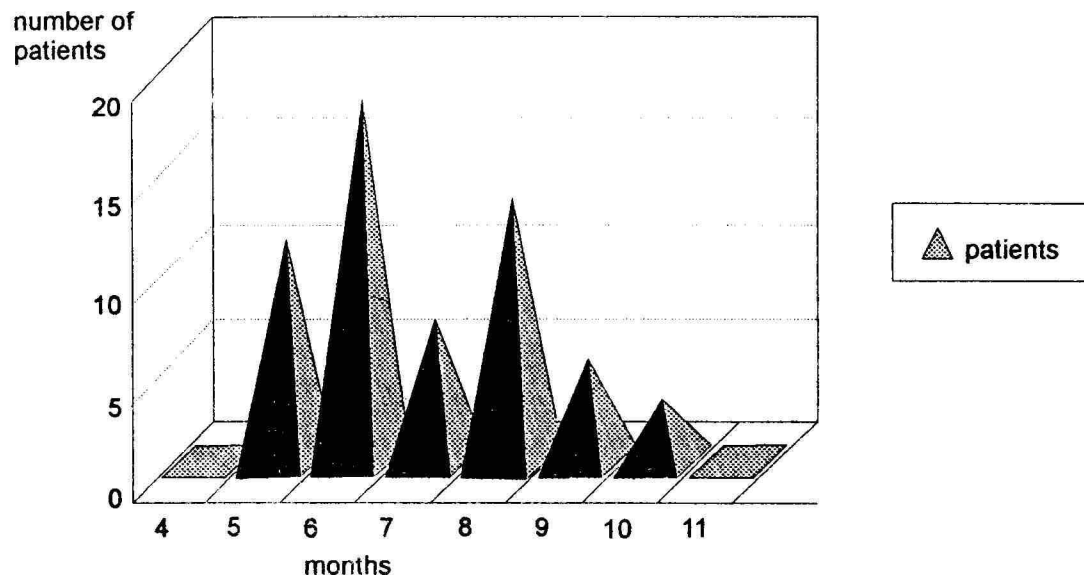


Fig. 1. Seasonal variability of TBE in South Estonia (1988-1993)

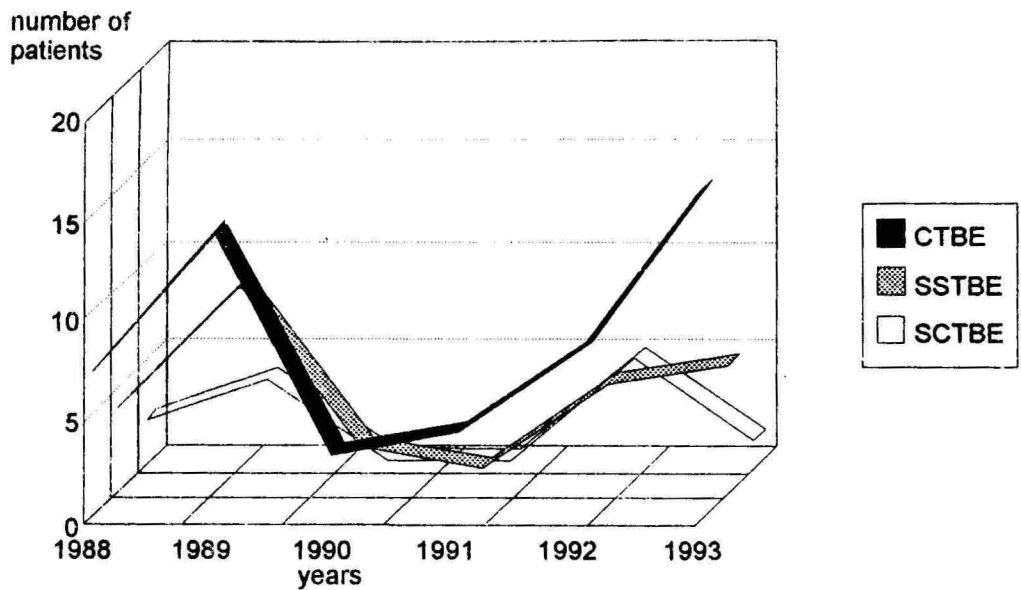


Fig. 2. Diagnosis of TBE

The incidence rate of TBE according to different diagnostic criteria was analysed (Fig. 2). So, of 52 patients with CTBE 28 had only minimal changes in the titres of antibodies (SSTBE group) and 12 had a four-fold change accepted universally as positive for TBE (SCTBE group). There were no patients with TBE diagnosed only on the bases of the laboratory information.

The comparison of TBE-IgM ELISA results with HI and CF titres revealed no statistically significant correlation between TBE-IgM ELISA and HI results or between HI and CF titres. However, the Spearman rank correlation analysis showed that between TBE-IgM ELISA values and CF titres existed a significant but weak monotonic dependence ($r = 0.389$, $p < 0.05$). Of 28 studied sera 23 gave positive results by CF, 20 by HI and 9 by ELISA. The proportion of positive cases proved to be significantly lower using ELISA (Chi-square 8.65, $p < 0.01$ with HI and 14.29, $p < 0.001$ with CF).

Discussion

Our study demonstrated that although Estonia is considered a high risk area for TBE the criteria used to diagnose TBE are insufficiently valid.

It is widely accepted that TBE is usually a mild disease and the recorded incidence rate depends on the extent how often and how thoroughly the diagnosis is sought [7, 8]. Since the problem of TBE has been investigated and vaccinations have been performed in Estonia, the awareness of the population and physicians of TBE is at a level. It is common to suspect TBE if temperature appears some weeks after a tick bite. Thus we conclude that more or less all TBE patients in the town of Tartu and district are consulted by a neurologist and lumbar puncture is performed. Hence, the major variable influencing the incidence rate of TBE are diagnostic criteria. The clinical and laboratory findings of the group do not differ from those described in literature [8, 2]. The incubation period from 2 to 45 days and mostly meningeal signs on admission are commonly observed. Pleocytosis and elevated protein account are usual laboratory findings. We could demonstrate that the peak of admission was in June (Fig. 1) this coincides with the large number of both tick types prevalent in South Estonia

The present study demonstrates that the CTBE is very common (Fig. 2). Neurologists consider the most important prerequisites for the diagnosis of TBE diagnosed meningitis and the fact of a tick bite. Only one patient did not have a known tick bite and serological tests were

performed when the patient deteriorated rapidly due to progressive peripheral palsy affecting mostly the cervical region. Serologically he belonged to the SCTBE group. On the other hand all patients with meningitis and known tick bites were serologically tested. The epidemiology of TBE is well studied in many countries and only serologically confirmed cases are taken into account [8]. Serological tests have been widely used in the everyday practice of the hospital and also in the research work since 1972 [3, 4]. However, it was possible to demonstrate that the final diagnosis in the group of patients studied was not influenced by the results of the serological tests. There were no cases of TBE that were diagnosed only on bases of the laboratory data. One possible explanation is the fact that as TBE is in 93.1% of cases a very mild disease, the condition of the patients allows them to be sent home in about ten days and therefore the serological data that come too late cannot influence the final diagnosis because it is already concluded and the case history is already sent to archives of the hospital. In any case, the co-operation between laboratory and department should be improved.

On the other hand according to our data CF and HI kits produced in Tomsk (Russia) and used in our study gave more positive cases than TBE-IgM ELISA widely used in Europe. It is important to stress that there was no correlation between HI values and established antibody titres with ELISA and the relation was weak for CF and ELISA results. Hence, to avoid the serological hyperdiagnosis of TBE infection in Estonia, it is important to stop using any kits in our laboratories without strict quality control.

The number of patients with serious complications was six, i.e. 12% of all the admitted cases. Yet the Tartu University Hospital is a central hospital in Estonia and the increased frequency of complicated cases was to be expected. It is also important that neurological complications were observed only in 6.9% of all the cases admitted from Tartu and district. We can conclude that TBE is really a mild disease.

The data presented by Raudam et al. [2] based on the clinical picture of Estonian patients demonstrated focal neurological symptoms that disappeared by the time of discharge. We could demonstrate the phenomena of quick recovery only in one patient who was admitted with diplopia and positive Babinski reflex. Other five patients were discharged with serious neurological residua. On the other hand our data does not confirm that afebrility is correlated with serious complications as mentioned elsewhere [2], all our patients with complicated forms were febrile.

In conclusion we can say that TBE is usually a mild disease, but according to the existing data it is not possible to say whether there is TBE in Estonia and if there is we are unaware of the morbidity. Taking into account the observed high rate of TBEV infected ticks in South Estonia [3] it is possible though that TBE is present in the region but probably it is much less common than suspected previously.

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DISABILITY AND MULTIPLE SCLEROSIS

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The problems concerning disability were studied in a comprehensive group of prevalent multiple sclerosis (MS) patients in South Estonia as a part of an epidemiological study.

The number of MS patients rapidly decreases in the age groups exceeding 49 years. Thus the life span of Estonian MS patients is considerably shorter if compared to other countries. On the basis of one research we can confirm that there is no difference in the availability of the medical service in different regions in Estonia, neither is there any difference compared to other countries. 55% of the Estonian MS population has retired because of the handicap. The mean time from the onset to the retirement was 5.4 years (SD 6.9). 21% of prevalent patients retire during the first five years after the onset. The factors prolonging the time of being employed were as follows: higher education, physically undemanding jobs, place of residence in a town. Higher age at onset determined higher age at retiring. 23.8% of Estonian MS patients are divorced or separated. 68.3% divorce after the onset of MS and only 4.9 after retiring because of the handicap. The leading cause of divorce was MS as determined by the patients.

Multiple sclerosis is a disease of the young adulthood. About 90% of the affected are in the productive years between ages 15 and 55. So, it affects young people who otherwise would be healthy labour force. Because of the long life expectancy associated with the disease there are few conditions that have a greater socio-economic impact.

According to available data, the incidence rate of MS in Estonia has been stable over the years [1]. The incidence rate is about 2 persons per 100 000 population, thus affecting approximately 30 men and women yearly in addition to about 500 to 600 MS patients.

The disability of MS patients has been evaluated in many studies [2, 3, 4, 5, 6]. Basically the development of disability depends on medical, individual and social parameters [7].

The social conditions are different in Western and Eastern Europe, especially in post communist countries. Therefore it is important to study the situation in the Eastern countries to understand the rehabilitation goals and pitfalls.

Methods

The present study was conducted in South Estonia from 1987 to 1989, according to the methods described by Gross and colleagues [8]. All the data were based on the prevalent patients of South Estonia collected retrospectively. Disability was evaluated according to the contemporary official system concerning pensions. All the patients who were unable to work were divided into two groups of handicap. The person with the first group of handicap was determined as being unable to work and he needed permanent personal help in everyday life. The second group was determined as being unable to work but able to manage at home alone.

Results

The mean age of the MS population was 44 (SD 21.9) for male and 44.9 (SD 11.5) years for female patients. The number of MS patients quickly decreased in the age groups exceeding 49 years (fig. 1).

The time of onset ranged from 6 to 49 years, mean 27.6 years. The symptoms at onset did not differ from the generally suggested.

The availability of medical services was evaluated to compare the condition in Estonia and in other countries. The time from the onset to the first visit to the physician was 1.1 years (SD 3.2) for ethnic Estonians and 2.42 (SD 6.1) for migrant population. The mean time from the first visit to the diagnosis was 3.9 (SD 5.7) and 4.1 (SD 5.9) years respectively for ethnic Estonians and migrant population. When the patients visited the doctor in 32.3% the first diagnosis made was MS, in addition in 21% of patients the first diagnosis was paraparesis or optic neuritis. The first diagnosis were not different in Estonians and representatives of other nationalities.

There are 55% of the patients who have retired because of their handicap. The mean time from the onset before the patients retired was 5.4 years (SD 6.9). The patients who in addition needed permanent personal assistance became so disabled in 3.1 years (SD 5.3).

According to a self report questionnaire about the necessity of permanent personal help, 53.7% of patients with the second group of handicap and 51% with the first group need help in their everyday life.

21% of prevalent patients retire during the first five years after the onset. 18.8% of prevalent patients are still working after having MS for 20 years. On the other hand the per cent of employed MS patients in the groups of patients with different durations of the disease remains stable.

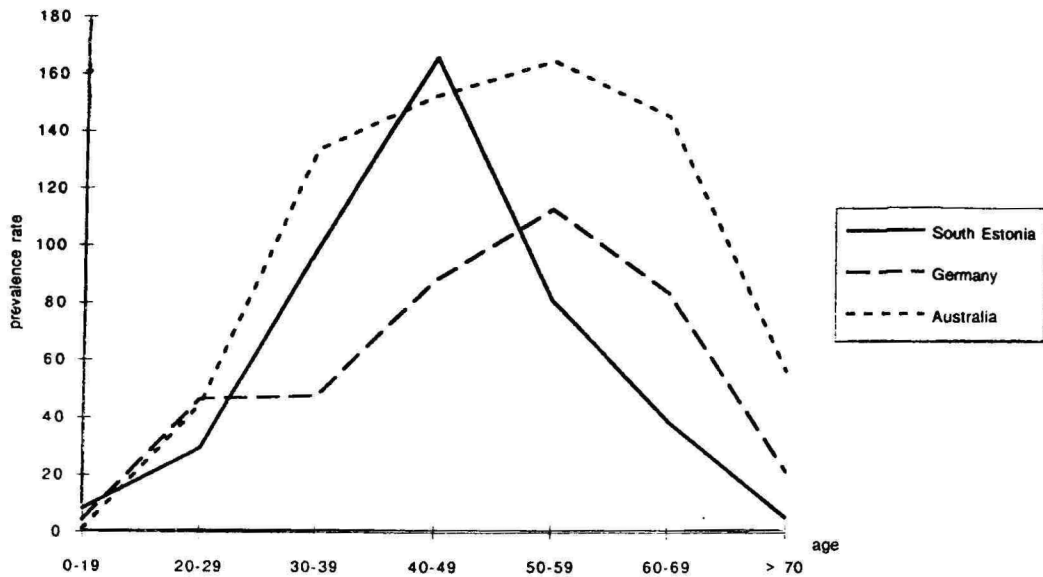


Fig. 1. Age specific prevalence rate of MS patients in different countries

Multiple regression of factors influencing the duration of being employed determined the importance of education, profession and the place of residence. 32% of patients with 8 year general school education and 10% with higher education lose their job in 5 years after the onset of MS. The job is also retained significantly longer by patients with secondary or technical education. Statistically significant differences exist up to the 15 years of duration of MS (fig. 2). Additional analyses reveal that especially physically demanding jobs cause earlier unemployment.

Table 1. Relations between the age at retiring and the age at onset of MS

Age at onset	Number of patients	Age at retiring	CD	p
20-29	44	31.9	6.4	
30-39	35	41.6	5.9	0.001
40-	9	48.6	4.98	0.003

Older age at onset determined older age at retiring (table 1).

The duration of being employed is not influenced by MS in relatives, by the number or time of birth of children.

2 patients i.e. 1% of all MS patients and 6.7% of patients who need permanent personal assistance live in institutions, one of them is severely disabled, the other is a fully ambulatory patient.

In all Estonian MS population 15% are single, 23.8% divorced or separated, 60.5% are married. Of the divorced or separated patients 31% were divorced before the initial symptoms, 68.3% divorce after the onset of MS and only 4.9% retire after they have retired because of their handicap.

One third considers MS the leading cause for divorce and it was the most important reason for male patients. 28% considered the alcohol abuse of the spouse the reason for divorce. 20.5% mentioned the unfaithfulness of the spouse.

Discussion

According to our data the life of a person is considerably changed in Estonia when he or she has MS.

In the first place, the comparison of age specific prevalence rates of MS patients in Estonia and in Germany and Australia (fig. 1) reveals

that the duration of life of Estonian MS patients is much shorter if compared to Estonian population in general and even to MS patients in other countries. This may be due to the medical problems or to the inadequacy in the rehabilitation or to the more severe course of MS in Estonia.

The availability of medical services is quite similar to that in other countries and there is no treatment that alters the course of the disease, not in Estonia and not in the West [9]. So, about a year after the patient has mentioned some vague symptoms, he goes to a doctor, who probably is a neurologist. It is probable because the availability of the consultation of a neurologist is very good with 1.06 neurologists per 10 000. Nearly half of them were given a diagnosis suggesting possible MS during a first visit. MS is diagnosed according to the criteria of Schumacher et al. [10] in four years after the first visit. The age specific prevalence rate also demonstrates that there is only a little delay in diagnosis, probably due to the absence of good imaging methods up to very recently. Thus we can conclude that Estonian MS patients consult the physician in time and the diagnosis is not significantly delayed.

In the meantime, the instability of the marriage increases. As suggested by the patients, in most families the cause of the divorce was MS. Hence, MS has negative influence on marriage. We could demonstrate that it is not the physical workload but emotional stress that breaks the family because most families break before the spouse develops disability.

Disability is a very important problem in patients with MS. In Estonia 55% of prevalent patients have retired because of their handicap. It is less than in Siberia (there it is 75%) [11]. The speed of retiring because of the handicap is the same as in Germany [4] but slower than in the Ukraine (there about 39–50% retire during the first year [5]).

Developing disability affects the working abilities differently. The educational level of the patient is of utmost importance. While of the patients with only 8 year education 32% have to retire in 5 years after the onset, of patients with higher education only 10% have lost their job. So, it is of great importance to encourage patients to get higher education.

Age at onset as a prognostic variable has been thoroughly studied. Most authors agree that if MS starts in the age range from 20 to 30 years the prognosis better than in patients with later onset [12, 13]. However the social prognosis seems to be better if the first symptoms appear later. Our analysis demonstrates that patients having initial symptoms before the age of 30 retire at the age of 31 versus patients

retiring at 42 and 48 if they exhibit the first symptoms before or after the age of 40 respectively.

The place of residence i.e. small towns like Põlva or Jõgeva have negative influence on employment. The reason is that small places have limited number of physically undemanding jobs and probably there are also fewer places that require higher education.

Basically, the % of the employed after 20 years of MS is practically the same as in other countries 18,6% [2, 3].

We conclude that the overall prognosis is not markedly worse than in other countries. The per cent of benign cases is the same as in other countries.

As everywhere else there is no treatment altering the prognosis. Therefore it is vital to increase the quality of life. It is possible to counsel the patients with newly diagnosed MS to help to understand their personal problems and the problems of their family and to try to assist in finding solutions. It is vital to stress the importance of education and to support by all means every possibility to go out to work, even the job at home is of great importance.

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CSF METABOLIC ALTERATIONS IN ISCHEMIC-HYPOXIC BRAIN TISSUE DAMAGE

M. Roose, A.-E. Kaasik, T. Tomberg

The activity of lactate dehydrogenase (LD), its first isoenzyme (LD1), aspartate-aminotransferase (AST), alanine aminotransferase (ALT), creatine kinase (CK), gamma-glutamyl transpeptidase (GGT) and alkaline phosphatase (ALP) in CSF were examined in 99 patients and compared to brain CT findings in 52 patients with ischemic stroke. The kinetic method by means of reaction velocity analyser and kits from Boehringer were used for the measurement of the activity of the enzymes (I.U.). The activity of LD, LD1, AST and GGT in CSF was significantly increased after brain infarction, especially in nonsurvivors. The activity of LD, LD1 and GGT in CSF was in correlation with the extent of brain damage on CT.

Ischemic-hypoxic damage causes different metabolic changes in brain tissue, first of all disturbances of energy, protein and glucose metabolism. All these metabolic changes are reflected in extracellular fluid biochemistry including the activity of the enzymes of blood and cerebrospinal fluid (CSF). The estimation of several tissue-specific enzymes such as brain type of creatine kinase isoenzyme in serum, for ascertaining heart muscle damage [1] has become routine during the last 20 years. Similar investigations of blood and CSF in the diagnostics of neurological diseases have been less successful [2]. Therefore the diagnostic value of the enzymatic changes of blood and CSF in neurology has either been ignored [3] or CSF enzymes have been considered nonspecific for brain tissue [4]. Only during the last years certain relationship between the activity of several enzymes [5, 6], e.g. lactic dehydrogenase [7, 8], creatine kinase [8, 9], aspartate aminotransferase [10] and gamma-glutamyltranspeptidase [11, 12] in plasma and disorders of the central nervous system have been described. However, the data about the release of the enzymes into CSF and blood during nervous system impairment have been contradictory and need further investigation.

The purpose of the present study is to estimate the alterations of CSF enzymatic activity depending on the severity of the clinical picture, on the outcome of the disease and on the extent of brain tissue damage on CT.

Material and methods

The study group consisted of 99 patients with brain infarction (BI), among them 60 women and 39 men with the mean age 67 ± 4 years. Most of the patients (89 ± 2 per cent) suffered from hemispheric infarction and only 11 ± 3 per cent from infarction in the vertebrobasilar system. Hypertension (56 ± 5 per cent) and several heart disorders (67 ± 3 per cent) were the most important risk factors of stroke in these patients. In 19 patients an angiographic investigation of cervical arteries was performed, while in 17 cases an atherosclerotic damage of the vessels was discovered.

The control group consisted of 40 patients of the same age without any signs of central nervous system disorders.

All patients were divided into three groups according to the severity of the clinical picture. The first "mild" group consisted of 47 patients with a mild neurological deficit and usually with total recovery and the second, "moderate" group of 23 patients with hemiparesis and partial speech disturbances. The third, "severe" group included 29 patients with hemiplegia, expressive or total aphasia and disturbances of consciousness.

All patients were also divided into two groups according to the outcome of the disease. The patients of the first group recovered without neurological defects or with a mild neurological deficit. The second group included patients with a poor or fatal outcome.

CT investigations were performed in 52 patients. According to the extent of brain tissue damage on CT these patients were divided into 3 groups: the patients without hypodensive changes on CT, the ones with a hypodensive area in the territory of one artery and the ones with large hypodensive changes in the territories of several arteries. According to the signs of brain edema formation on CT the same cases were divided into 3 groups: the patients without, with moderate and severe brain swelling.

The activity of following enzymes in the CSF was measured: lactic dehydrogenase (LD), its first isoenzyme (LD₁), creatine kinase (CK), aspartate-aminotransferase (AST), alanineaminotransferase (ALT), gamma-glutamyl transpeptidase (GGT) and alkaline phosphatase (ALP), and compared with the severity of cerebral tissue damage and the prognosis of the disease.

The kinetic method by means of the reaction speed analyser (SPECOL) and suitable kits from Boehringer were applied for the determination of enzymatic activity. The samples were drawn on the first days during the second week after the stroke. The analysis of variance was used for the statistical analysis of CSF enzymes activity.

Results

The mean activity of LD, LD, AST, CK and GGT in CSF after ischemic stroke significantly exceeded the activity of the enzymes of the control group ($p < 0.05$), (Table 1).

Table 1. Enzymatic activity of CSF in 99 patients with cerebral infarction. ($\bar{x} \pm m$ I.U.)

Enzyme	Control	Cerebral infarction
LD	28.0 \pm 2.9	75.7 \pm 10.8*
LD	13.0 \pm 1.4	45.5 \pm 6.0*
AST	10.6 \pm 2.8	21.5 \pm 2.5*
ALT	5.0 \pm 1.4	5.4 \pm 0.8
CK	0	13.7 \pm 3.9*
ALP	10.7 \pm 6.8	10.7 \pm 2.2
GGT	0	3.1 \pm 2.0*

* $p < 0.05$ compared to control

The values of LD, AST and GGT in CSF were especially high in "severe" strokes ($p < 0.05$) compared with the insignificant increase of enzymatic activity in the groups of "moderate" and "mild" stroke patients ($p < 0.05$), (Table 2).

Table 2. CSF enzymatic activity in patients with cerebral infarction depending on the severity of clinical findings ($\bar{x} \pm m$ I.U.)

Enzyme	Control (n = 40)	Cerebral infarction		
		mild (n = 47)	moderate (n = 23)	severe (n = 29)
LD	28.0 \pm 2.9*	54.3 \pm 7.2	67.4 \pm 17.7	186.0 \pm 80.0
LD	13.0 \pm 1.4	36.2 \pm 5.4*	52.0 \pm 14.8*	49.9 \pm 11.6*
AST	10.6 \pm 2.8	16.6 \pm 1.18*	18.0 \pm 2.2*	32.0 \pm 7.6*
ALT	5.0 \pm 1.4	4.3 \pm 1.2	5.1 \pm 1.4	6.1 \pm 2.0
CK	0	10.2 \pm 3.4*	8.1 \pm 1.3*	20.5 \pm 9.0*
ALP	10.7 \pm 6.8	12.5 \pm 2.5	9.1 \pm 1.6	10.9 \pm 5.8
GGT	0	0	0.94 \pm 0.41*	8.1 \pm 5.7*

* $p < 0.05$ compared to the control

The enzymatic activity of CSF was in correlation with the outcome of the disease (Table 3). The unfavourable outcome of the disease was accompanied by a significantly higher mean activity of LD,

LD CK and GGT in CSF during the first week. In these patients enzymatic activity remained on a high level or even increased during the second week of the disease. For example, the mean activity of LD in these patients increased two fold during the second week (Table 3). In patients with a favourable outcome the release of the enzymes into CSF was moderately increased in the first week and then revealed a tendency to decrease.

Table 3. CSF enzymatic activity in patients with cerebral infarction depending on the outcome of the disease ($\bar{x} \pm m$ I.U.)

Enzyme	Control	Cerebral infarction			
		favourable outcome		unfavourable outcome	
		1st week	2nd week	1st week	2nd week
LD	28.0 ± 2.9	54.3 ± 7.2*	50.5 ± 11.2*	143.0 ± 52.4*	141.0 ± 31.0*
LD	13.0 ± 1.4	36.2 ± 5.4*	27.6 ± 6.4*	51.9 ± 9.2*	107.0 ± 34.5*
AST	10.6 ± 2.8	16.6 ± 1.2*	17.0 ± 1.3*	26.5 ± 4.8*	24.0 ± 2.2*
ALT	5.0 ± 1.4	4.3 ± 1.2	3.6 ± 0.3	6.4 ± 1.4	3.7 ± 0.6
CK	0	10.2 ± 3.4*	2.2 ± 2.5*	15.6 ± 5.6*	4.6 ± 4.6
GGT	0	0	0	3.8 ± 2.4*	28.8 ± 20.0*
ALP	10.7 ± 6.8	12.5 ± 2.5	9.8 ± 5.8	10.0 ± 3.1	9.7 ± 9.7

* $p < 0.05$ compared to the control

To estimate the relationship between CSF enzymatic activity and the severity of brain tissue damage, and edema formation, we correlated the activity of two enzymes, i.e. LD and GGT, which were in the best correlation with the outcome of ischemic stroke, with the extent of brain damage and brain edema on CT. The mean activity of LD in CSF after cerebral infarction was in a good correlation with the extent of brain damage (Table 4). In the patients with extensive brain damage on CT, e.g. with large hypodensive changes in the territories of several arteries, a considerably higher LD activity in CSF was disclosed ($p = 0.05$). On the other hand the increased activity of GGT in CSF did not correlate with the severity of brain damage. LD release into the extracellular space increased with the formation of brain edema ($p = 0.05$) whereas the concentration of GGT in CSF did not correlate with the cerebral tissue swelling, on the contrary, it showed even a tendency to decrease.

Table 4. The activity of LD and GGT in CSF depending on the severity of brain damage and brain edema formation ($\bar{x} \pm m$ I.U.)

Group of patients	LD	GGT
Control	28.0 \pm 2.9	0
Extent of brain damage on CT		
without CT finding	19.5 \pm 6.8	6.3 \pm 5.6*
one artery	34.3 \pm 13.3	2.1 \pm 0.6**
multiple arteries	142.7 \pm 60.2*	3.1 \pm 1.2**
Edema cerebri		
without	23.3 \pm 4.6	5.9 \pm 2.9**
mild	62.7 \pm 22.6*	2.5 \pm 1.0**
severe	188.5 \pm 104.8	1.3 \pm 0.4

* p = 0.05 compared to the control

** p < 0.05 compared to the control

Discussion

Compared with the controls markedly increased CSF enzymatic activity was detected in the patients with ischemic stroke. Most expressive changes were discovered in the activity of the enzymes regulating glycolytic processes (LD, LD1) [6, 13], energetic metabolism (CK) [6] and transamination (AST, GGT) [6, 12]. The increased activity of LD and LD1 in CSF after ischemic brain tissue damage reflects the activation of oxydative-reductive processes in hypoxic and anaerobic conditions. Increased anaerobic glycolysis leads to the accumulation of lactate in the brain tissue and to a longlasting metabolic acidosis of CSF [14]. The anaerobic isoenzymes of LD (LD4, LD5) are preferably activated and released into CSF in anaerobic conditions [15]. Increased enzymatic activity of CSF in patients with ischemic stroke demonstrates the increased leakiness of the plasma membranes of affected brain cells due to ischemia. The release of enzymes into the extracellular space is related to the prognosis of the disease [16], to the severity and the extent of brain tissue damage and also to the edema formation in the patients with cerebral infarction [17]. The larger is the number of brain cells involved, the higher is LD activity in CSF [18]. The activation of GGT as a cell membrane enzyme is especially closely connected with the impairment of cell membranes.

According to our data ischemic-hypoxic brain tissue damage is connected with significant changes in glucose metabolism. Increased

activity of LD in CSF is also a specific marker of cerebral tissue damage and LD is a good prognostic predictor of the clinical outcome of cerebral infarction. In the recent years investigations have discovered that ischemic-hypoxic lactic acidosis is accompanied by pronounced secondary biochemical processes in the ischemic area which are mainly connected with the metabolic derivatives of arachidonic acid [19, 20, 21]. The so-called ischemic biochemical cascade of arachidonic acid in the tissue damaged by ischemia may have a significant influence on the activation of enzymes in CSF and blood and most likely is a decisive factor in the final outcome of the disease. It stands to reason that the regional differences in brain enzyme activity affecting the amount of enzyme release should be considered [22].

The recent investigations have revealed that a significant role in ischemic-hypoxic processes is played by lipid peroxidation generated by free radical reactions deliberated during the ischemic biochemical reactions in cell membranes [23, 24].

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DIAGNOSTIC VALUE OF INTRACELLULAR ENZYMES IN THE CEREBROSPINAL FLUID IN PATIENTS WITH INFECTIONS OF THE CENTRAL NERVOUS SYSTEM

I. Lutsar, S. Haldre, M. Topman, T. Talvik

The determination of aspartataminotransferase (AST), lactic dehydrogenase (LDH), gammaglutamyltranspeptitase (GGT), creatine phosphokinase (CPK) and creatine kinase BB (CK-BB) in cerebrospinal fluid (CSF) was performed in 16 patients with viral meningitis and encephalitis (VM), in 25 children with bacterial meningitis (BM) and in 15 patients with meningismus. The activity of AST and GGT was significantly higher in patients with BM on admission if compared to those with viral meningitis and meningismus ($p < 0.05$ and $p < 0.005$ resp.) and decreased with the therapy. The highest concentration of AST and LDH appeared in patients with poor outcome as well as in those with ventriculomegaly on the neurosonography ($p < 0.05$). The concentration of CK-BB increased in all patient groups on admission and remained higher on the termination of therapy. The present study confirms the high activity of AST and GGT in CSF of BM patients, whereas the increased activity of AST and LDH reflects the extent of brain injury. However, the prognosis for individual patients can not be established on the basis of enzyme activity alone and depends on several factors. *Aspartataminotransferase, creatine kinase, lactic dehydrogenase, gammaglutamyl transpeptitase, bacterial meningitis, viral meningitis, cerebrospinal fluid.*

Introduction

Disturbances of the enzymatic system are caused by several pathologic processes. Estimation of serum aspartate aminotransferase (AST, EC 2.6.1.1), lactate dehydrogenase (LDH, EC 1.1.1.27), gamma glutamyltranspeptitase (GGT, EC 2.3.2.2) and creatine kinase (CPK, EC 2.7.3.2) are widely employed as valuable diagnostic aids in diseases involving necrosis or damage of tissues characteristically rich in these enzymes. The activities of these enzymes have been measured in the cerebrospinal fluid (CSF) of patients with a variety of

neurological disorders [1-16]. The results obtained, however, are controversial.

The purpose of the present study was to measure the activity of AST, LDH, GGT, CPK and the concentration of its brain type isoenzyme CK-BB in the CSF of patients with bacterial and viral meningitis and encephalitis as well as in patients with meningismus to establish whether any of these enzymes would correlate with brain damage of different etiology and to assess their usefulness in clinical investigations and prognosis.

Materials and Methods

The patients studied included 16 children with viral meningitis and encephalitis (VM), 25 children with bacterial meningitis (BM) and 15 patients having no infection of the central nervous system, whom lumbar puncture was performed due to meningeal syndrome. The first sample of CSF was collected on the 1st-3rd day of the disease and from those with bacterial meningitis the second sample was collected on the 6-10 day of the treatment. The CSF was sampled by lumbar puncture, centrifuged immediately. Samples were frozen to -20°C and stored up three months before analysis. In all cases routine laboratory investigations i.e. CSF protein, sugar, cell count and bacterial cultures were examined. The activity of CPK, LDH, AST and GGT was measured by photocolorimetric assay using commercial kits (Labsystem FP-900). The immunoenzymatic technique type "Sandwich" described by S. Haldre [10] was used for the measurement of CK-BB concentration. The normal values of the discussed enzymes have been found in the literature and are shown in Table 1.

Table 1. Control values of CK-BB, CPK, LDH, AST and GGT in CSF in the literature

Enzyme	Activity	Author
CPK (U/l)	0.4 - 6.3	A. Pasaglu et al. 1989 [12]
AST (U/l)	0 - 12	M. Agrawal et al. 1989 [11]
LDH (U/l)	3 - 17	P.V. Nelson et al. 1975 [3]
GGT (U/l)	0	T.G. Radzavil et al. 1986 [7]
CK-BB(ng/l)	5.3 ± 1.2	S. Haldre 1988 [10]

Outcome of the survivors was assessed by multidisciplinary team (pediatrician, child neurologist, speech therapist, psychologist) 12 months after the acute period.

Statistical analysis: the results are given as median \pm confidence interval. A computerised statistical package was used. This included nonparametric Mann-Whitney U test for unpaired samples, the Wilcoxon test for paired samples, Spearman's rank test for nonparametric regression analysis.

Results

The activity of the AST, CPK, LDH, GGT and CK-BB in 16 patients with viral meningitis (VM), 25 children with bacterial meningitis (BM) and 15 patients with meningismus were measured.

Table 2. Activity of AST, CKP, LDH, GGT and CK-BB in CSF in patients on admission

Enzyme (range)	Viral meningitis n = 16	Bacterial meningitis n = 25	Meningismus n = 15
CK-BB (ng/l)	37.5 (24.0-43.0)	31.0 (15.0-59.0)	39.0 (34.0-46.0)
CPK (U/l)	4.3 (2.0-9.0)	4.2 (2.6-5.5)	3.3 (2.6-5.3)
AST (U/l)	4.0 (3.6-7.3)	8.8* (6.1-11.0)	4.7 (3.5-6.3)
LDH (U/l)	28.1 (4.8-52.2)	33.8 (19.7-70.2)	15.4 (7.6-20.6)
GGT (U/l)	1.67 (0.6-4.45)	5.3** (2.1-8.7)	1.5 (1.0-2.0)

* $p < 0.05$ in comparison with patients without BM

** $p < 0.005$ in comparison with patients without BM

Table 2 shows the results of CSF enzyme determinations on admission. An equal diagnosis independent increase of CK-BB concentration was noted in all patient groups. The activity of AST was two fold higher in patients with BM compared with those without it ($p < 0.05$), nevertheless, it did not exceed the normal value found out

from the literature. The median value of the activity of LDH (33.8 U/l) was the highest in patients with BM and the lowest in those with meningismus, but statistically significant differences did not exist. All patients had the raised activity of GGT in the CSF. A statistically significant increase ($p < 0.005$) of it was noted in patients with BM on admission in comparison with those with VM and meningismus.

Table 3. Activity of AST, CPK, LDH, GGT and concentration of CK-BB in CSF in patients with BM on admission and on the 6th–10th day of therapy

Enzyme	CK-BB	CPK	AST	LDH	GGT
Time of measurement (range)	ng/l	U/l	U/l	U/l	U/l
On admission	31.0 (15.0–59)	4.2 (2.5–5.5)	8.8 (6.1–11.3)	33.8 (19.7–42.7)	5.3 (2.1–8.7)
On the 6–10 day of therapy	34.0 (19–38)	4.3 (2.8–8.2)	5.6 (3.1–8.3)	27.3 (12.1–42.7)	1.6 (1.1–8.2)

The activity of intracellular enzymes after the treatment was estimated only in patients with BM. Table 3 demonstrates that the activity of AST, LDH and GGT decreased with the treatment, but that of CPK and the concentration of CK-BB remained the same. The activity of the AST was simultaneously estimated in the CSF and blood serum in 40 patients. No correlation were found between the levels of AST in the CSF and in the serum ($r = -0.362$). The activity of LDH correlated with the count of polymorfonuclear leucocytes (PMNL) in CSF on admission ($r = 0.538$), but no correlation was found on the 6th–10th day of therapy ($r = -0.224$). There were 3 patients with the *E.coli meningitis* having more than 1000 PMNL in CSF on the 10th day of therapy, but the activity of LDH was 2.5; 4.3 and 91.5 U/l resp.

The relationship between the enzymatic determinations and the outcome are shown in Table 4. 37 out of 41 children with the infections of the central nervous system survived and 4 died during the acute period. There were 32 patients who recovered completely or had mild impairments and 5 children had severe disturbances at the time of the follow up examination.

As shown in table 4 the patients of ICNS who died or recovered with residual lesions had significantly higher median CSF AST and LDH activity ($p < 0.05$) as compared to those with good recovery. Although the concentration of CK-BB was higher in patients with good a prognosis, difference was not statistically significant.

Table 4. Enzymes data on admission in relation with outcome of ICNS

Outcome (range)	CK-BB ng/l	CPK U/l	AST U/l	LDH U/l	GGT U/l
Dead/ severely disabled n = 9	9.5 (2-37)	3.8 (2.6-4.5)	12.1* (5.0-17.4)	60.5* (37.1-235.4)	2.7 (1.8-11.4)
Good recovery n = 32	38.0 (30-49)	4.5 (1.7-6.5)	6.7 (4.0-9.0)	27.5 (15.2-46.3)	2.9 (0.9-8.1)

* p < 0.05

Table 5. Enzyme data in relation to neurosonographic findings in patients with BM

Neurosonographic finding (range)	CPK U/l	AST U/l	LDH U/l	GGT U/l
Ventriculomegaly n = 7	4.5 (3.2-7.7)	12.1* (10.5-15.1)	71.1* (69.7-235.4)	2.7 (2.6-7.2)
Normal n = 8	3.5 (2.7-5.4)	8.0 (7.4-8.9)	23.4 (18.7-27.5)	2.5 (1.1-5.2)

* p < 0.05

Table 5 shows the results of CSF enzyme determination according to the neurosonographic findings. The patients were grouped according to the most common finding as the presence or absence of enlargement of the lateral ventricles. There were 7 patients who developed ventriculomegaly after BM and 8 infants had normal findings.

Table 5 demonstrates that the CSF activity of AST and LDH was significantly higher in patients who developed ventriculomegaly in comparison to those having normal neurosonographic findings (p < 0.05). The highest value of AST and LDH activity 211.3 U/l and 14.1 U/l resp. was seen in patients with VM developing hydrocephalus.

Discussion

In this study our aim was to estimate the value of some intracellular enzymes by different infections of the central nervous system and to

establish whether any of the measured enzyme levels correlates with CNS dysfunction thus assessing their prognostic value and determining their usefulness in clinical practice. An elevation of AST, LDH and GGT activity in patients with BM on admission demonstrating neuronal cell injury as well as altered permeability of blood-brain barrier has been reported by several authors (3.5–7.16). The increased activity of AST and GGT in BM patients was also registered in this study, but no statistically significant increase of the median value of LDH activity was observed, although some patients with BM had very high levels. The data of AST activity in CSF in patients with viral meningitis are controversial. In the study of S. I. Sirkis [5] was shown 2.2–2.6 fold elevation of AST in 264 patients with viral meningitis in comparison with the control group, but no elevation of AST activity in viral meningitis was found in some other studies [6, 14]. Our data revealed a statistically significant increase in AST activity in CSF in patients with BM in comparison with those with viral meningitis and meningismus and pointed its prognostic value. The patients who either expired or recovered with residual complications had significantly higher AST activity than in cases with complete recovery. Similar correlation of enzyme activity in acute illness with extensive damage of tissues and prognosis has been reported [11, 14, 21, 22]. Although the activity of AST in patients with poor prognosis rose rapidly in CSF and blood serum also we as the other authors could not find any correlation between AST activity in the serum and the activity of the same enzyme in CSF ($r = -0.362$) [5, 7]. We can assume that the main source of AST activity in CSF is brain tissue, although we cannot exclude, that in a patient severe ill an enzyme can cross it due to the raised permeability of blood-brain barrier.

The benefit of the measuring of the activity of LDH was very small in our material as found by S.Landaas et al [6]. This is in contrast to others [23–25] who have claimed significantly higher concentration of LDH by BM. We also found the activity of LDH higher by BM if compare to VM and meningismus- 33.8, 28.1 and 15.4 U/l respectively, but the differences are not statistically significant. The good correlation ($r = 0.538$) between CSF PMNL and the activity of LDH confirms the opinion of several studies that PMNL are the main sources of LDH activity in CSF in BM patients [2, 3, 14], although the exact origin of the enzymes may be differentiated only by isoenzyme studies. However, good correlation was found only during the acute period of BM. The low activity of LDH on the 6th–10th day of therapy, despite the high amount of PMNL in CSF, also suggests a cerebral origin of LDH in the acute period of brain injury. The present study like the previous

ones [21, 26] establishes a definite relation between CSF AST and LDH activity and the extent of the brain injury. The significantly higher activity of AST and LDH in the CSF ($p < 0.05$) was found in the patients who died or were severe impaired as well as in those having enlargement of the side ventricles during the acute period. Simultaneous finding of ventriculomegaly in the ultrasonography and raised activity of LDH and AST in CSF strongly suggests that one of the reasons of the enlargement of side ventricles after BM is also brain atrophy developing after necrosis of brain tissue.

The present study as well as previous ones [27-29] indicates, that CSF CPK activity is not reliable in differentiating between the bacterial and nonbacterial CNS infections. The three-fold increased activity of CPK shows the disturbances of the energy balance in the brain tissue in patients with bacterial and viral meningitis as well as with meningismus. The high concentration of isoenzyme CK-BB in the CSF seems to be the best predicting a bad prognosis in head injured patients in several studies [10, 15, 30-32]. High level of CK-BB is found in the brain and its concentration in other organs, such as pancreas, uterus, liver and spleen, is too low as to be of any practical significance [17-20]. The highest tissular CK-BB content was found in the brain cortex and capsula interna, while only limited amounts were measured in the pons, cerebellum and medulla oblongata [33]. CK-BB is localized in astrocytes [34] as well as in neurons [35] and cytolysis of these tissues results in the elevation of this enzyme. It was a surprise to find that the concentration of CK-BB in patients with bad prognosis was even lower (9.5 ng/l) comparing to those with good outcome (38.0 ng/l). The fact that some patients with bad prognosis did not have an increase of CK-BB concentration in CSF was also shown in the previous studies [12, 36]. The variable increase in CK-BB concentration in different patients is not completely understood. The concentration CK-BB in the CSF changes rapidly especially during the first hours of brain injury [29, 36], that is way the results depend on the time of collecting CSF. In this study the wide time spectrum from 1 to 3 days of the illness could account for that. The various regional distribution of CK-BB in the brain and it has also been reported [26, 37] the fact that small focal lesion in functionally important regions of the brain may cause severe defects with minimal enzyme release. Raised concentration of CK-BB in patients with meningismus was an unpredictable finding and shows that even in those cases the hypoxic-ischaemic damage of the brain tissue may occur.

Conclusions. A significant rise of AST and GGT activity in CSF was found in patients with bacterial meningitis during the first days of

brain injury. The remarkably increased activity of AST and LDH in the acute phase of the brain injury may therefore be valued as an indicator of the extent of brain damage and so it is prognostically important. A definite prognosis for the individual patient cannot be established on the basis of the enzyme activity alone and it depends on several factors.

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CREATINE KINASE ISOENZYME BB CONCENTRATIONS IN HYPOXIC-ISCHEMIC ENCEPHALOPATHY

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Creatine kinase isoenzyme BB (CK-BB) was determined in cerebrospinal fluid of 169 (90 fullterm and 79 preterm) neonates by using an original method of enzyme linked immunosorbent assay. The control group (n = 30) includes healthy adult persons. CK-BB was significantly elevated in all preterm newborns with hypoxic-ischemic encephalopathy (HIE). The correlation between concentration of CK-BB and severity of HIE, also between many clinical symptoms was established. High concentrations of CK-BB in the neonatal period correlated with severity of HIE and were followed by poor outcome at the age of one year.

Creatine kinase isoenzyme-BB (CK-BB) is considered a relatively specific protein for neural tissue [1] and its elevated levels in serum and cerebrospinal fluid (CSF) are usually associated with brain damage [2, 3, 4, 5, 6]. Increased concentration of CK-BB in umbilical cord blood [7] is probably a marker of intracerebral hemorrhage. V. Ruth [8] showed that substantially elevated serum CK-BB activity indicates a high risk of neonatal death. B. Dalens et al [9] showed that neurologic abnormalities in infants 12 months of age correlated with high CK concentrations in CSF obtained on the third day of life. Later investigations [10, 11] demonstrated a direct correlation between high CK-BB levels and poor short-term outcome in newborn who had intraventricular hemorrhage (IVH) or central nervous system (CNS) infection. The study of M. Amato et al [12] also confirms that the quantity of CK-BB in neonatal serum correlates with the severity of brain tissue damage. Because of the relatively few data concerning CK-BB in CSF of neonates the aim of this study was to assess

– the value of CK-BB level in CSF during the first week of life as a marker of brain damage;

– the value of CK-BB as a biochemical marker for outcome at the age of one year.

Patients

The study included 169 liveborn (90 term and 79 preterm) neonates who were born in the Maternity Hospital of Tartu University. The criterion for inclusion was Apgar score 7 or less at the fifth minute of life. All babies had documented neurological symptoms of hypoxic-ischemic encephalopathy (HIE) according to the criteria by H. B. Sarnat and M. Sarnat [13] which was the indication for lumbar puncture (LP).

HIE was graded as

– mild (I) — minor disturbances of tone, hyperalertness, hyperreflexia, tachycardia with recovery in 72 hours,

– moderate (II) — lethargy, hypotonia, hyporeflexia, occasionally seizures, with recovery in 7 days,

– severe (III) stage — coma, respiratory failure (assisted ventilation), profound hypotonia, seizures.

Neurological examination [14, 15] was performed on the 2nd and 5th day of life using the unified assessment cards for newborn. CSF was obtained the same days. LP was performed in 99 newborns on the 2nd day and in 71 newborns on the 5th day of life (one baby with severe HIE and periventricular hemorrhage had LP on the 2nd and 5th day of life). In all cases, the parents were informed and their consent to investigation and participation in the follow-up study was obtained. All children were examined in the 3rd, 6th, 9th and 12th month of life. The first final protocol of motor, mental and speech development was obtained at the age of 12 months. All children were divided into 4 groups: 1) normal, 2) slight impairment, 3) moderate impairment (disability), 4) severe disability (handicap). The child was regarded having slight impairment if the delay in motor development was noted at the age of 12 mo/or if the I or II stage of cerebral palsy (CP) was diagnosed.

Moderate impairment was diagnosed when the child had CP (III stage) with spastic diplegia, spastic hemiparesis II–III stage, seizures and/or mental and/or speech delay. Severe impairment (handicap) was diagnosed if CP with spastic diplegia, spastic tetraplegia was of the IV grade and/or speech and/or mental delay was present. The severity of CP (I–IV grade) was estimated according to the modified classification of Mincar [16] and described by us earlier [17]:

I – slight neurological symptoms without motor impairment,

II – moderate — motor impairment, walking independently,

III – severe — walking with support,

IV – motor handicap. For children with hemiparesis the severity of disability was estimated according to the hand function by the same scale.

The control group consists of 30 adult persons without symptoms of pathology of CNS.

Methods

The data were automatically analysed by the Apple II micro-computer, using the methods of linear or logistic regression analysis. For use in linear regression analysis, the data had to be transformed into logit units. The computer, working according to the original program, printed out the results of the regression analysis of the standard curve (data table and regression graph) and MAB content in ng/ml of individual serum samples determined on the basis of standard curve regression.

Data analysis was performed in the Statistical Center of the Tartu University using IBM EC-1060. The software of the Laboratory of Applied Mathematics of the Tartu University (1984) was used.

Results

CK-BB was elevated in all newborns with HIE. Concentration of CK-BB is given in Table 1.

CK-BB concentration was increased in all babies, but significantly elevated in preterm babies. A correlation between the concentration of CK-BB on the 2nd day of life and severity of HIE was established (Table 2). There was a significant elevation of CK-BB concentration in CSF on the 2nd day of life (Table 3). The correlation was statistically significant between the concentration of CK-BB and the stage of HIE. However, the correlation between the severity stages of HIE and CK-BB on the 5th day of life was not significant, but a clear tendency of increase in the concentration of CK-BB according to the severity of HIE could be demonstrated. The baby who had LP twice had extremely high concentration of CK-BB on the 2nd day of life (272.3 ng/ml) with significant decrease of the concentration of CK-BB on the 5th day of life (72.1 ng/ml).

In spite of the small number of patients with the III stage of HIE, the correlation between CK-BB and severity of clinical symptoms was

significant. The same correlation was present in babies on the fifth day of life (Table 3).

A correlation was established between the increased concentration of CK-BB on the 2nd day of life and the gestational age ($r = -0.590$), birthweight ($r = -0.560$), 5th minute Apgar score (-0.230), and also between many clinical symptoms: abnormal muscle tone ($r = 0.448$), absence or weak sucking reflex ($r = 0.629$), absence of reflexes of placing (supporting) ($r = 0.648$), seizures ($r = 0.310$). It is interesting to note the correlation between weak (or absence of) cry and CK-BB ($r = 0.230$).

The follow-up study at the age of 12 mo shows that of 169 babies 65 were normal (38%), 30 (18%) were minimally (mildly) impaired, 57 (34%) moderately impaired and 17 (10%) were severely impaired (handicap). Significant correlation between poor outcome and concentration of CK-BB was established.

Discussion

According to our data we were able to demonstrate that CK-BB concentration in CSF was increased in all newborns with HIE and correlated with severity of the stages of HIE, especially on the 2nd day of life. CK-BB has been considered relatively specific for neural tissue, but there is evidence that its concentration is different in different parts of the brain. P. Urdal [18] and K. Kato et al. [19] have demonstrated the highest concentration of CK-BB in the cerebellum. Several studies have demonstrated high CK-BB levels in cord blood of high risk preterm babies. M. Amato et al [7] suggested it may be a marker of cerebral hemorrhage. Other studies [8, 20] conclude that high concentrations of CK-BB correlate with neonatal death, but not with neurological damage in survivors of asphyxia.

In our study we were able to demonstrate that CK-BB level was remarkably higher in preterm babies with HIE which can be explained by greater vulnerability of their brain cell membranes. We could also demonstrate a significant correlation between severity of stages of HIE and poor outcome. Thus, CSF CK-BB concentration appears to be a sensitive biochemical parameter for detection of acquired perinatal brain injury from various causes. Newborns with HIE II and III have significantly more adverse outcomes than babies with HIE I. An extremely high concentration of CK-BB in preterm babies and less severe outcome (2 cases) may be the result of cerebral oedema causing

release of CK-BB from glial cells. For more definite information of these patients a long-term (4–6 years old) follow-up is in progress.

According to our data and some controversial background information, elevated serum CK-BB in high risk babies during the first day of life reflects brain damage immediately before and during the delivery and therefore can be a good marker only for short-term outcome (neonatal death).

The increase of CK-BB in CSF on the 2nd and 5th day of life may indicate perinatally acquired structural neurological disorders. Our data suggest that determination of the CK-BB concentration in CSF is a clinically useful test for identification of risk-group babies for CP.

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Table 1. Concentration of CK-BB in CSF

	Number of cases	Concentration of CK-BB ng / ml
Fullterm babies	90	29.0 ± 3.1*
Preterm babies	79	168.0 ± 22.2*
Control group	30	5.3 ± 1.2

* $p < 0.005$

Table 2. Concentration of CK-BB in CSF (on the 2nd day of life) and the severity of HIE ($\bar{x} \pm m$)

	HIE I	HIE II	HIE III	Control group
Concentration of CK-BB (ng/ml)	97.6 ± 18.5*	132.0 ± 23.5*	272.3 ± 78.8*	5.3 ± 1.2
Number of cases	49	45	5	30

* ... $p < 0.0005$ in comparison with control group

HIE III > I $p < 0.005$

HIE III > HIE II $p < 0.005$

Table 3. Concentration of CK-BB in CSF (on the 5th day of life) and the severity of HIE ($\bar{x} \pm m$)

	HIE I	HIE II	HIE III	Control group
Concentration of CK-BB (ng/ml)	38.1 \pm 15.9*	58.4 \pm 10.6*	88.0 \pm 32.7*	5.3 \pm 1.2
Number of cases	21	42	8	30

* $p < 0.05$ in comparison with control group

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THE LEVELS OF CATECHOLAMINES, ACTH AND CORTISOL IN PLASMA AS PROGNOSTIC FACTORS OF SEVERE HEAD INJURY

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Plasma epinephrine, norepinephrine, ACTH and cortisol determination and CT scans were performed in 22 patients with severe head injury on the first day after the injury. These data were compared with the outcome of the patients.

The results of the study revealed a considerable increase of the catecholamine and cortisol levels in plasma in all patients with severe head injury. Maximal high levels of cortisol in connection with relatively low catecholamine levels in plasma turned out to be prognostically bad. Such hormonal changes occurred in the patients with mesencephalic-diencephalic pathology detected by CT of the brain.

The high rate of mortality and long time of morbidity in severe head injury is caused by the fact that the primary destructive injury to the brain cannot be repaired and secondary processes could be hardly prevented, reversed, or halted [1, 2, 3]. Many different forms of surgical therapy, including control of intracranial pressure and medical therapy including the use of osmotic agents, controlled ventilation, hypothermia, barbiturates, can positively influence the outcome.

However, little attention has been given to hormonal response, especially regulatory mechanism of stress reaction in the prognosis in severe brain injury. Common response to all traumas appear to be the activation of the sympathetic nervous system and the hypothalamus-hypophyseal-adrenocortical axis. This results in the elevation of the plasma level of epinephrine (E), norepinephrine (NE) as well as adrenocorticotrophine (ACTH) and glyocorticoids [4, 5, 6]. Activation of these two systems comprises the core of the stress response [7]. Nevertheless, it should be mentioned that in head injury, one of the main chains of this reaction — brain — is impaired and relationships between affected hormone secretion and prognosis of the patient need further investigation [8, 9].

Clinical material and methods

Patient selection and clinical assessment. Twenty-two patients with acute isolated and closed severe head injury were studied. All patients were men in the age from 18 to 60. The median elapsed time between accident and the first examination was 4.3 hours (1 to 14 hours). After the initial assessment of injury, attention to respiratory and cardiovascular function was given and endotracheal intubation was performed if needed. The neurological status was evaluated by the Glasgow Coma Scale (GCS) [2]. The criteria for including into the group of severely injured patients was scale value from 3 to 7. This basic neurologic evaluation was repeated several times every day throughout the hospital stay, but in this paper we correlated only the neurological status on admission and its relation to outcome. All patients were divided into two groups: survived and nonsurvived (dead) patients. Their general data are given in Tables 1, 2, 3, 4.

Table 1. Glasgow Coma Scale on admission

GCS score	No. of survived	No. of nonsurvived
3&4	2	7
5	2	2
6	3	2
7	3	1
Total	10	12

Table 2. Mortality related to surgical treatment

Outcome	Surgical cases	Nonsurgical cases
survived	5	5
nonsurvived	3	9
Total	8	14

Table 3. Outcome of survivors related to GCS score on admission

GCS score	Good recovery	Moderate disability	Severe disability	Persistent vegetative state
3&4	—	1	—	—
5	—	—	2	1
6	1	—	2	—
7	1	1	1	—

Table 4. Day of death in cases with lethal outcome

Day of death	No. of cases
1	1
2	2
3	1
6	3
7	1
8	2
13	1
14	1

Computerized tomography scans. Computerized tomography (CT) of the brain was performed in all patients on hospital admission, and repeated when clinically indicated. In all patients focal findings on the CT scan were revealed, consisting of hematomas (subdural, intracerebral, epidural) and/or hemorrhagic contusions and areas of oedema. Special attention was paid to the detection of changes in the mesencephalic-diencephalic area as an essential regulatory center of endocrine activity [10, 11]. Therefore a complex of linear and volumetric measurements of CT was performed: volume of hematoma (H), volume of oedema (O), width of III ventricle (IIIv), width of pontine cistern (PC), index of dislocation of medial line (IDML) (Fig. 1.). Normal linear measures of the brain structures were found on the basis of CT-scans of 16 persons (median age: 34 years) without any cerebral or/and head diseases and skull anomalies.

Laboratory findings of hormones. In all patients venous blood samples were taken on the first day after injury. Hormone levels were measured by two methods: E and NE by the fluorometrical technique, ACTH and cortisol by immunoassay. The control group consisted of 15 men – blood donors, 20 to 46 years of age (median 31.3 years).

The statistical calculations were carried out by using Student's unpaired t-test and p-value of less than 0.05 was considered significant.

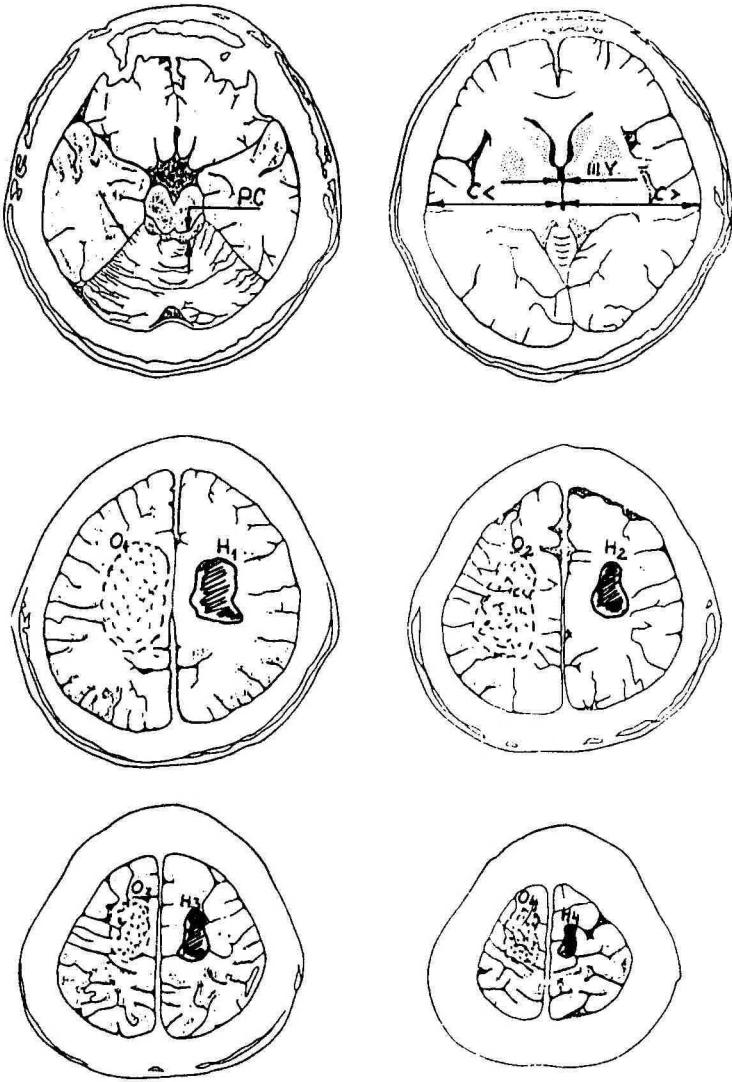


Fig. 1. Linear and volumetric measurements of CT:

PC = pontine cistern, III V = III ventricle, IMLD = C < C >, volume of H = H1 + H2 + H3 + H4, volume of O = O1 + O2 + O3 + O4

Results

In all cases of severe head injury, the CT scan demonstrated oedema and/or hematoma areas of variable size and shape in involved cerebral hemisphere with a shift of midline structures toward contralateral side and distortion of the supra and infratentorial cerebro-spinal fluid rooms. Generally, after severe injuries local lesions have been observed more frequently in the frontotemporal regions. CT signs of the primary lesions of the brain stem and mesencephalic-diencephalic area were not revealed.

The data of cranial CT are listed in Table 5.

Table 5. Summary of data of cranial CT parameters in cases with severe head injury and in control group

Parameter of CT	Control group	Survived	Nonsurvived
Volume of hematoma \pm m (cm ³)	0	81.0 \pm 18.5*	103.8 \pm 17.8*
Volume of oedema \pm m (cm ³)	0	251.3 \pm 40.3*	314.5 \pm 25.6*
Width of III ventricle \pm m (mm)	5.0 \pm 0.52	2.00 \pm 0.68*	1.17 \pm 0.36*
Width of pontine cystem \pm m (mm)	3.5 \pm 0.41	1.14 \pm 0.31*	1.33 \pm 0.23*
IDML \pm m	0.98 \pm 0.002	0.916 \pm 0.011*	0.897 \pm 0.009*

* significant difference ($p < 0.05$) between groups of examined patients and control group.

Severe head injury caused statistically significant changes in CT parameters. Volume of H made up about 7%, volume of O – about 20% of the whole intracranial space. The width of the IIIV and PC lessened more than twice. The reduction of IDML in severe head injury was also significant. In spite of the tendency that patients with bad prognosis had more severe changes in parameters of CT, there were no significant differences of CT data between groups of survivors and nonsurvivors.

In Table 6 the plasma levels of investigated hormones are presented.

Table 6. Epinephrine, norepinephrine, ACTH and cortisol plasma levels in patients with severe head injury (survived and nonsurvived) and in control group

Hormone	Control group	Survived	Nonsurvived
EPINEPHRINE (ng/ml)			
Mean	0.92	2.79*	1.86**
Median	0.80	2.85	1.69
St. deviation	0.34	1.29	0.91
St. error	0.08	0.41	0.26
Minimum	0.40	0.90	0.59
Maximum	1.80	4.63	3.30
NOREPINEPHRINE (ng/ml)			
Mean	2.18	4.81*	2.97**
Median	2.10	4.35	2.80
St. deviation	0.64	2.56	1.31
St. error	0.16	0.81	0.38
Minimum	1.30	1.80	1.10
Maximum	4.00	10.60	5.50
ACTH (nmol/l)			
Mean	21.0	26.2	37.0
Median	15.0	10.0	30.5
St. deviation	12.8	21.6	30.1
St. error	3.3	6.8	8.7
Minimum	10.0	10.0	10.0
Maximum	49.0	60.0	86.0
CORTISOL (nmol/l)			
Mean	273	628.5*	1129.9**
Median	240	597.2	1129.7
St. deviation	89	316.6	386.5
St. error	23	100.1	111.6
Minimum	130	220.0	572.0
Maximum	485	1143.0	1746.0

* significant difference ($p < 0.05$) between groups of examined patients and control group.

** significant difference ($p < 0.05$) between groups of survivors and nonsurvivors.

The analysis revealed significant differences of values E, NE and cortisol between various groups of examined persons. The levels of catecholamines in all patients with severe head injury significantly exceeded normal ranges. However, in nonsurvived patients the amount of E and NE in plasma was significantly lower than in survivors. Cortisol level was also significantly higher in all severely injured patients, especially in the group of nonsurvivors. There was no significant difference between the levels of ACTH in various groups of examined persons.

Discussion

Most authors base the prognosis of traumatic brain-injured patients mainly on symptoms indicating the state of the brain stem [12, 13]. The most common prognostic evaluation is based on GCS values [2]. The high mortality rate occurs in patients with GCS score less than 8 on admission [12]. In our studies the mortality among the patients with GCS from 3 to 7 was 54.5%. Of 10 survived patients with severe head injury only two had a good recovery.

CT-scanning has not only high diagnostic value, but also some prognostic significance. The compression of the IIIIV and PC, dislocation of the medial line associated with the formation of areas O and/or H occurred in all cases of severe head injury. The mortality in patients with severe midline dislocation was higher than in those in whom IMLD was lower. Becker et al. [13] found also such difference in mortality between patients who had a shift of the midline measured on ventriculograms. These observations suggest that patients with mass lesion have a poor prognosis. However, in our study there were no statistically significant differences in the values of CT parameters between survived and nonsurvived patients. Although we did not find direct lesions in the mesencephalic-diencephalic area, diffusely involved or normal CT scans do not necessarily imply lack of brain damage in this region. Lesions of the mesencephalic-diencephalic area were demonstrated by indirect changes on CT, moreover they may be visible with an alternative technique such as magnetic resonance imaging or microscopically [14, 15]. It was proved by Crompton et al. [16] who found hypothalamic lesions in 42% of autopsies in patients who died due to brain trauma (histologically — shearing of the stalk axons and spasm of regional vessels).

Brain injury not only results in damage to structures of the central nervous system causing neurological impairments, but also activates the

sympathoadrenal and hypothalamo-hypophyseal-adrenocortical axis and causes changes of the levels of their hormones in blood. There have been a considerable number of reports on the hormonal abnormalities in head injury [9, 17]. Recent studies have shown directly or indirectly that the degree of sympathetic activation correlates with the extent of brain injury [6, 18, 19, 20]. Our study confirms the concept of activation of the sympathoadrenal system caused by brain injury. However, in patients who died the levels of catecholamines in plasma were statistically lower than in survived severely injured patients. The mechanism of this abnormality is probably that nonsurvivors have more extensive brain lesion in the mesencephalic-diencephalic area which is known to be abundant in catecholaminergic receptors and as a pathway of the sympathoadrenal axis [11, 21, 22]. From this point of view Lindvall et al [11] suggested that the decrease of the levels of catecholamines was caused by brain tissue destruction in the hypothalamic area due to traumatic brain compression. Levati et al. [12] showed the correlation between arterial hypotension and mortality, arterial hypotension was present in 57.6% of died head injured patients. It is our impression as well as of other authors that such kind of arterial hypotension might be caused by a low level of catecholamines in circulating blood.

High levels of circulating cortisol have been demonstrated after head injury. This has been shown to correlate with low values of GCS and bad outcome of traumatic brain injury [4, 21]. Although plasma cortisol levels in severe head injury must reflect elevated ACTH levels, in our investigation there was dissonance between levels of ACTH and cortisol. Only a slight increase of ACTH may be caused by a lesion in the mesencephalic-diencephalic area (incl. pituitary gland) [23, 24]. Another possibility is that high cortisol levels cause a decrease of ACTH production by feedback mechanism. In spite of the insignificant increase of ACTH level the cortisol level was five time higher than in the control group. It is possible that this is connected with the fact that the bowling out of catecholamines from the adrenal medulla causes directly a more intensive biosynthesis and excretion of corticosteroids in the adrenal cortex. As is shown by our investigation the high level of cortisol in plasma in connection with not very high levels of catecholamines is a sign of an unfavourable outcome in severe head injury.

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HAEMOSTASIS IN BRAIN TUMOURS

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The present study evaluates the functional activity of the haemostatic system in 42 patients with brain tumours (BT) in the pre- and postoperative period. Primary haemostasis, antithrombin III, fibrinolysis and fibrinogen catabolism on the basis of the 125-iodine labelled fibrinogen degradation were studied in cerebral venous blood (CVB) in comparison with the data from systemic arterial blood samples and controls. CVB was obtained by puncture of the superior bulb of the internal jugular vein. CSF thromboplastic, antithrombin and fibrinolytic activity and FDP were also estimated. Haemostatic abnormalities in CVB prevailed over those of systemic circulation. In the first week after the operation the platelet count fell more in CVB compared with the samples from systemic venous and arterial blood. Severe thrombocytopenia in fatal cases of BT correlated with the high number of circulating platelet aggregates. CVB antithrombin III deficiency, CVB increased radiofibrinogen consumption, CVB high FDP and fibrinogen arterio-venous differences were also established. CVB hemostatic breakdown in large and malignant BT occurred. Inhibition of CSF thromboplastic and increased fibrinolytic activity prevailed in non-survivors compared to patients with good outcome.

Consequently, different local haemostatic mechanisms and thrombo-haemorrhagic balances in patients with operated brain tumours were observed. Therefore, haemostatically different active treatment has to be used. The role of haemostatic abnormalities as mediators of secondary brain injury, mainly thrombo-haemorrhagic complications after the operation of brain tumours are stressed.

The complex nature of the haemostatic system and the multiple complications of its abnormalities, mainly the disseminated intravascular coagulation (DIC) syndrome, represent a difficult problem for neurosurgeons and for neurointensive care doctors. Different patterns of thrombohaemorrhagic balance in brain tumours may occur [1]. The aim of the present study was to investigate the functional activity of the haemostatic system in local cerebral venous blood (CVB) and in systemic arterial blood and also cerebral extracellular fluid — cerebrospinal fluid (CSF) haemostatic properties in pre- and postoperative period of brain tumours. One of the most important tasks of the study was to determine the significance of haemostatic abnormalities and their possible effect on thrombo-haemorrhagic complications, on the prognosis and on the outcome of the patients.

Material and methods

The study comprises 42 consecutive patients with brain tumours (mean age 48 years). The histological diagnosis according to the histological international classification of brain tumours [2] was as follows: meningioma - 9, acoustic neuroma - 6, pituitary adenoma - 5, glioblastoma - 16, astrocytoma - 3, oligodendroglioma - 1, and metastatic carcinoma of the brain - 2 patients. In 35 patients brain tumour was located supratentorially and in 7 patients - infratentorially. The patients were postoperatively usually placed in a neuro-intensive care unit, where all intensive-care measures were used [3, 4]. The data of haemostasis were studied prior surgery and thereafter within 2-3 weeks. The methods used in this research were published earlier [3, 4, 5, 6]. CVB was obtained by the puncture of the superior bulb of the internal jugular vein (JV).

Results

1. Primary haemostasis

As can be seen, in the first postoperative week in platelet count fell more in CVB samples compared to the arterial ones in cases of brain tumours. At the same time the percentage of circulating platelet aggregates (CPA) increased more in JV blood samples and correlated well with the clinical outcome. The mean values of CPA were more pronounced in patients with lethal outcome than in recovered ones (Table 3).

Table 1. Fibrinogen catabolism in arterial blood and CVB in the first postoperative week in brain tumours

X ± mt 5%

Whole radioactivity	Controls(I)arterial blood (per cent of initial 100 per cent) n = 8	Controls(II) CVB (per cent of initial 100 per cent) n = 8	Brain tumours arterial blood (III) (per cent of initial 100 per cent) n=19	Brain tumours CVB(IV) (per cent of initial 100 per cent) n = 19
1st day	73.9 ± 5.3	73.0 ± 1.3	65.5 ± 3.7*	50.4 ± 2.4**
2nd day	27.2 ± 2.7	27.5 ± 1.2	21.8 ± 3.4*	16.0 ± 1.8**
3rd day	16.2 ± 1.4	16.2 ± 1.2	10.6 ± 2.1*	6.2 ± 1.2**

* I > III, $p < 0.05$

** III > IV, $p < 0.05$

2. Fibrin formation and fibrinolysis (Figure 1, Table 1, 2, 3).

According to our data the clearance of 125-iodine labelled fibrinogen and fibrin-monomer from arterial blood and CVB in cases of brain

tumours is more rapid than in controls ($p < 0.05$). The rapid increase of non-clottable radioactivity in cases of brain damage compared to controls is caused by accelerated fibrinolysis ($p < 0.05$). The fibrinogen catabolism is more pronounced in CVB compared to arterial blood. Radioactivity was revealed in CSF in patients with brain tumours but not in control subjects. According to our previous data, radioactivity in CSF increased more in cases of BT than in those of head injury and stroke*. Fibrinogen level in brain damage increased in arterial blood in the first week of the illness. In cases of lethal BT fibrinogen concentration diminished more in CVB samples than in arterial ones. In individual cases of BT transient fibrinogen fall occurred in CVB, compared to arterial ones in the first or second week of the postoperative period. As a rule, soluble fibrin was postoperatively detectable in all patients with brain tumours. In the first postoperative week there were periods of its prevalence in CVB, fibrinogen and fibrin degradation products (FDP) were elevated, but prevailed shortly in CVB during 1-2 weeks of the postoperative period in all the patients studied. Factor XIII activity decreased postoperatively more in JV blood samples as compared with systemic ones, especially in non-survivors. There was more frequent decrease of fibrinolytic activity (FA) in cases of BT. Tromboelastographic (TEG) studies showed phasic changes in haemostasis: hypercoagulation, hypocoagulation and hypocoagulation with increased FA in JV blood samples, mainly in cases of severe brain damage with lethal outcome (Table 3). Reduction of the elasticity of the coagulum was seen as a decrease of the maximum amplitude (MA) of thromboelastogram, mainly in patients with great neurological deficit. A good relationship was found between the severity of the haemostatic abnormalities and the severity of disorders of consciousness in patients with brain tumours: haemostatic breakdown prevailed in deeply comatose patients. It is known that severe hypocoagulation and increased FA correlate with more severe morphological haemorrhagic and necrotic lesions in the autopsy of the brain in BT [8].

Coagulation inhibitors

Antithrombin III (AT III) was detected in arterial blood and CVB in the pre- and postoperative period (Table 3). As can be seen, there is AT III deficit and it decreased promptly in the first postoperative week mainly in CVB. AT III was the lowest in cases of BT, complicated with thromboembolic phenomena. According to our previous data the estimation of AT III preoperatively can be used for prediction of pulmonary embolism [9].

* Author's certificate

Table 2. Fibrinogen degradation in arterial blood in the first postoperative week in brain tumours

x ± m

Parameter		Control group (I)	Brain tumours (II)
Total radioactivity (imp/min/1ml)	Initial radioactivity	6245 ± 223	1678 ± 316 ^x
	1st day	4639 ± 155	1678 ± 316 ^x
	2nd day	1292 ± 475	664 ± 160 ^x
	3rd day	773 ± 259	380 ± 105 ^x
Clottable radioactivity (imp/min/1ml)	Initial radioactivity	5953 ± 111	2043 ± 158 ^x
	1st day	3143 ± 117	1363 ± 321 ^x
	2nd day	1265 ± 290	511 ± 165 ^x
	3rd day	753 ± 151	281 ± 91 ^x
Radioactivity of protamine sulfate precipitate (imp/min/1ml)	Initial radioactivity	5080 ± 926	2035 ± 370 ^x
	1st day	3650 ± 812	1109 ± 240 ^x
	2nd day	1042 ± 339	445 ± 118 ^x
	3rd day	507 ± 138	212 ± 63 ^x
Radioactivity of trichloroacetic acid (TCA) precipitation (imp/min/1ml)	Initial radioactivity	6216 ± 117	2548 ± 459 ^x
	1st day	4618 ± 941	1545 ± 294 ^x
	2nd day	1068 ± 316	644 ± 153 ^x
	3rd day	517 ± 150	303 ± 88 ^x
Non-clottable radioactivity (imp/min/1ml)	Initial radioactivity	29 ± 24	530 ± 45 ^x
	1st day	21 ± 10	315 ± 20 ^x
	2nd day	27 ± 18	163 ± 16 ^x
	3rd day	20 ± 24	99 ± 9 ^x

X-I > II, p < 0.005

Table 3. Haemostatic parameters in patients with brain tumours in the first postoperative week

X ± 2 S.D.

Parameter	Controls (I)	1st week	2nd week
Platelets 10 ⁹ · (A)	240.0 ± 4.1	140.8 ± 9.0	164.2 ± 9.9 ^{xv}
Platelets 10 ⁹ · (CVB)	241.0 ± 4.2	120.7 ± 12.8	120.4 ± 8.8 ^{xo}
Platelet aggregation per cent (A)	9.0 ± 1.8	30.7 ± 3.8	42.4 ± 3.2 ^{xo}
Platelet aggregation per cent (CVB)	8.8 ± 1.8	50.0 ± 2.4	64.2 ± 3.6 ^{xov}
Antithrombin III per cent (A)	100.0 ± 7.0	62.0 ± 8.8	54.0 ± 10.4 ^{xo}
Antithrombin III per cent (CVB)	100.0 ± 7.0	46.0 ± 8.4	28.4 ± 6.0 ^{xov}
Fibrinogen (A) g/l	3.3 ± 0.2	4.1 ± 0.2	3.0 ± 0.1 ^{xo}
Fibrinogen (CVB) g/l	3.2 ± 0.2	2.4 ± 0.1	2.1 ± 0.1 ^{xov}
β-naphtol (A) r.u.	0	2.4 ± 0.2	3.2 ± 0.2 ^{xo}
β-naphtol (CVB) r.u.	0	3.4 ± 0.1	3.8 ± 0.1 ^{xov}
Ethanol test positive per cent (A)	0	64.4 ± 4.2	72.4 ± 6.2 ^{xo}
Ethanol test positive per cent (CVB)	0	90.1 ± 3.2	98.8 ± 2.1 ^{xov}
FDP positive per cent (A) (> 40μ/ml)	0	68.4 ± 3.8	82.4 ± 2.4 ^{xo}
FDP positive per cent (CVB) (> 40μg/ml)	0	100.0 ± 7	100.0 ± 7.0 ^{xo}
Fibrinolytic activity per cent (A)	13.8 ± 0.1	12.0 ± 0.2	11.0 ± 0.1 ^{xo}
Fibrinolytic activity per cent (CVB)	13.9 ± 0.1	14.2 ± 0.1	15.4 ± 0.1 ^{xov}
MA of TEG (A) mm	45.8 ± 1.2	54.2 ± 7.8	32.0 ± 6.4 ^{xov}
MA of TEG (CVB) mm	45.8 ± 1.1	30.2 ± 1.8	18.8 ± 3.2 ^{xov}

x – different from controls, p < 0.05

o – cerebral venous blood different from arterial blood, p < 0.05

v – 1st week different from 2nd week

Table 4. Cerebrospinal fluid haemostatic properties in patients with brain tumours

X ± 2S.D.

Parameter	Controls (n = 35)	Brain tumours (n = 30)	
		Survivors (n = 21)	Non-survivors (n = 9)
CSF thromboplastic activity 1st day elevated (per cent)	0	54.8 ± 4.6	30.4 ± 2.8 ^{1,2}
3rd day decreased (per cent)	0	33.6 ± 1.2	62.4 ± 4.2 ^{1,2}
CSF fibrinolytic activity elevated (per cent of studied cases)	0	36.4 ± 4.8	96.4 ± 2.0 ^{1,2}
CSF FDP elevated (per cent of studied cases)	0	58.4 ± 4.8	100.0 ± 7.0 ^{1,2}
Index of thromboplastic activity (ITA)	1.5 ± 0.5	3.4 ± 1.4	1.2 ± 1.2 ^{1,2}
Antithrombin activity	0.2 ± 0.5	-3.2 ± 0.8	-6.8 ± 2.0 ^{1,2}
Activity of plasminogen activator (per cent of studied cases)	0	42 ± 12	58 ± 16 ^{1,2}
Activity of plasmin (per cent of studied cases)	0	0	100.0 ± 7.0 ^{1,2}

1 - p < 0.05 versus controls

2 - p < 0.05 non-survivors versus survivors

CSF haemostatic properties

The results are given in Table 4. A mean high thromboplastic activity of CSF in patients with brain tumours was detected. There was a difference in the index of thromboplastic activity (ITA) in survived

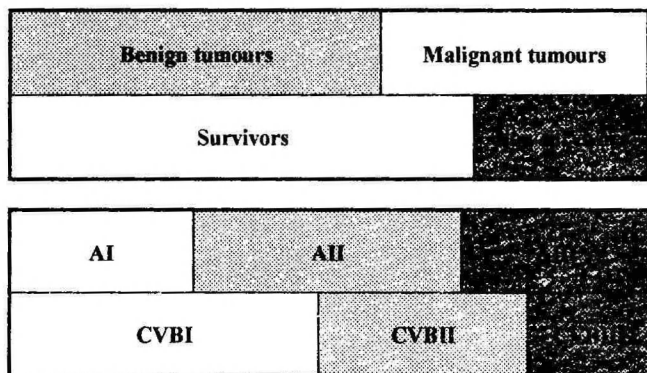
and lethal cases. It increased in fatal outcome. In different cases of brain tumours there was also inhibition of ITA in up to one third of the patients. This occurred in all cases of BT, with brain haemorrhagic complications in the second postoperative week [8]. The mean value of the anticoagulative potential of CSF decreased and showed that CSF ability to inhibit fibrinogen degradation was reduced in BT. Increased FA of CSF was detected mainly in lethal cases. The high activity of the plasminogen activator was present in survived and also in non-survived cases. Also a high level of FDP in CSF in brain tumours was present. The higher levels were detected in patients with greater neurological deficit and in comatose patients. The increase of non-clottable radioactivity in CSF was also found at the same time.

DIC syndrome in brain tumours (Figure 1).

The chronic DIC syndrome was frequently diagnosed in systemic arterial blood and predominantly in CVB already before the patient was operated on. Extensive operation on the brain as a rule lead to severer haemostatic abnormalities and the subacute or acute DIC syndrome. Severe hypocoagulation with increased fibrinolysis was detected in lethal cases of advanced brain tumours (glioblastomas, melanomas and in brain metastases of cancer). It caused haemorrhagic complications in the brain and also multiorgan failure (heart, lungs, liver and kidney damage) was diagnosed in these patients [10].

Discussion

According to our data there are well-known general pathogenetic mechanisms of the disease — disseminated intravascular coagulation and increased platelet aggregation (development of circulating platelet aggregates) in patients with brain tumours. This pathology prevails in CVB in comparison with arterial blood. The phenomenon of predominance of DIC in the local cerebral vasculature was diagnosed as a local cerebral disseminated intravascular coagulation syndrome by us already in 1975–1979 (Noormaa and Tikk – 3). As can be judged from our data, DIC may appear as an acute or mainly chronic process, the clinical manifestations of DIC are haemorrhagic, thrombotic or both and are associated with a high mortality. The decompensated haemostatic system in the condition of breakdown loses its working ability because of the falling out or permanent loss of the components and/or mechanisms of several haemostatic functions and is not able to fulfill the task of tissue repair and healing. So the damaging effect of haemostatic abnormalities on intracranial dynamics and thrombo-haemorrhagic fatal complications in patients with brain tumours occur.



- I - Hypercoagulation
- II - Hypocoagulation
- III - Hypocoagulation with increased FA

Fig.1. Systemic arterial (A) and cerebral venous blood (CVB) haemostasis in patients of brain tumours (1st postoperative week) n = 14

A number of previously reported studies have documented changes of haemostatic parameters in brain tumours [1, 11, 12]. These studies, however, have not analyzed haemostatic abnormalities in the different parts of the vascular system (in systemic venous and arterial blood and in the blood derived from the damaged brain — cerebral venous blood). There are only a few cases described in the literature, which are concerned with the diagnostics of DIC in brain tumours and the complications, probably connected with severe intravascular coagulation [13, 14]. The haemostatic breakdown in cerebral local vasculature has been reported by us as an index of brain damage severity [3]. The deadlock in biological systems is one of the reasons for death [15, 16]. This theory can be used also for the decompensation mechanisms and for the breakdown mechanisms of haemostasis in severe brain diseases with lethal outcome.

Microcirculatory haemostasis showed decreased platelet count and intravascular platelet aggregation in BT, which were more severe in CVB compared to arterial blood. The question remains whether platelet aggregates exacerbate damage in the cerebral microvessels in BT. In cerebrovascular diseases it is shown that the recruited mass of platelets enhances the degree of endothelial injury by releasing damaging mediators from activated platelets. In this case there is a permanent

vascular occlusion at the site of the brain tumour and its surroundings, which increase the brain damage [17, 18]. Experimental data show a significant correlation between the duration and a number of activated platelets and their aggregation and the underlying endothelial damage. The aggregating platelets may lead to a long-lasting thrombus and permanent neurological damage [19]. Precisely how the platelets contribute to the progression of endothelial damage and neurological deficit remains unclear, but thromboxane A_2 and serotonin, and toxic substances released by platelets are firmly involved [20]. The role of platelet aggregation factor (PAF) is also under study [21].

Our data confirm that there is activated coagulation present in both systemic arterial and CVB blood samples, but it is more pronounced in the local cerebral vasculature in BT. The same disorders have previously been pointed out in patients with head injury, in cerebral infarction and in brain haemorrhage [22, 23]. Thus, intravascular coagulation is a common phenomenon occurring in severe brain damage and is connected with the release of thromboplastin from the parenchymal tissue of the damaged brain, which may lead to enhanced thrombin activity mainly in the local cerebral vasculature. When the extent of brain damage has reached the critical volume, it reflects also on the systemic circulation [23].

We have also documented abnormal fibrinolytic activity in patients with brain tumours, thus confirming previous studies that have established that thrombin activity outweighs fibrinolytic activity in systemic blood samples [24]. However, in contrast to previously reported results, we have found increased fibrinolytic activity in CVB samples compared to arterial ones. The increased fibrinolytic activity in local cerebral vessels is, according to our previous data [10], a risk factor of haemorrhagic complications — mainly subdural haematomas — in head injury [25]. According to our data the high fibrinolytic activity is also connected with postoperative haemorrhagic complications in cases of malignant brain tumors [10]. Low fibrinolytic activity was previously attributed either to the deficient level of plasminogen activator or to the presence of plasminogen activator inhibitors, but without clear confirmatory evidence [1, 13, 14]. According to our results the haemostatic function changes after the removal of the brain tumour, leading to a severe DIC syndrome in the postoperative period. These data are analyzed more closely in our other papers [8]. The operation on the brain is always connected with anticoagulative protein-antithrombin III deficiency, which may be one of the factors why low-grade preoperative intravascular coagulation can lead to the fulminant DIC syndrome with

all to ischemic and haemorrhagic consequences in the brain and other organ systems [8, 26].

Our data show also abnormalities of CSF haemostatic properties in brain tumours. According to our previous results and the data of this paper, the prognostic significance of different haemostatic parameters in CSF may vary and the changes are rather similar to those which occur in other cases of brain damage with different etiology, as in head injury and stroke [5]. High fibrinolytic activity of CSF is a poor prognostic marker in all patients with severe brain damage, among them also in those with brain tumours [5]. It should be underlined that there is different time-dependent dynamics of thromboplastic and antithrombin activity in patients with brain tumours and the main factor it depends on is the severity of brain damage.

Our previous data show the significance of thromboembolic phenomena in the prognosis of BT. Determination of the low antithrombin III activity before brain tumour operations is one of the possibilities of predicting thromboembolic phenomena and also fulminant DIC in these patients [10].

In conclusion, the findings in the present paper unquestionably have a therapeutic significance for patients with brain tumours. The appropriate therapy of the pharmacological intervention in brain tumours requires an understanding of the pathogenesis and the diagnostics of haemostatic abnormalities in various types and various situations in the treatment of brain tumours (preoperative and postoperative period). Thus, we recommend a further study of haemostatic parameters in brain tumours for a better treatment of patients. The problem of tumour invasiveness and metastases and other tumour-host interaction mechanisms has been extensively studied [27]. Perhaps the rapid development in the field of oncohaemostaseology will give an answer in the future [28]. The haemostatic function is related also to the process of proteolysis which extensively affects homeostasis [29]. It confirms our latest results about significance of proteolysis in the prognosis of brain tumours, and the data which are closely related to haemostatic disorders, mainly the DIC syndrome in brain damage [30].

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CHANGES IN BRAIN METABOLISM AND CRANIOSPINAL SYSTEM VISCOELASTIC PARAMETERS AFTER INTRATHECAL ADMINISTRATION OF THAM

M. Kuklane, J. Elmäe, M. Roose, A.-E. Kaasik

The presence of lactic acidosis in the cerebrospinal fluid (CSF) of patients with head injury and brain infarction has been well documented. The authors studied the effect of intrathecal THAM on the craniospinal system (CSS) viscoelastic parameters and cerebral markers in 26 patients with severe CSF lactic acidosis. The results indicated that the decrease of CSF pH and PVI, with concomitant increase of lactate and pyruvate levels and brain elastance are related to the severity of injury. Close correlations were found between CSF acidosis and measured CT parameters. The most significant effect of THAM after bolus were the increase of CSF pH and the decrease of CSF $p\text{CO}_2$. 24 hours after THAM administration increased CSF pH and lactate values, more expressed in the severely injured group, were detected. The most remarkable effect on CSS viscoelastic parameters was expressed as a decrease of elastance and increase of PVI. The authors theorised that elevated lactate in CSF after the intrathecal THAM administration appears due to the lactate efflux from the cells to the extracellular space.

Introduction

Cerebral ischemia and severe head injuries are associated with an enhanced stimulation of anaerobic metabolism and, there by, development of intra- and extracellular lactacidosis [1]. Lactacidosis is thought to be an important factor which enhances brain damage under these conditions, *e.g.* leading to the formation of cytotoxic brain edema and, eventually irreversible death of nerve cells [2]. Lactic acid formed in the intracellular compartment may leak from damaged cells of an ischemic or traumatic focus, resulting in an extracellular acidosis in the lesion proper and surrounding perifocal brain tissue. Amelioration of brain acidosis and increased ICP by systemic buffering agents has been proposed as a method of treatment by several authors [3, 4, 5]. Although mortality and morbidity rates of brain injury have been reduced

substantially by improved prehospital interventions, intensive care, aggressive management of ICP and successful treatment of the primary brain injury have been elusive. In experimental models THAM (tris-hydroxyaminomethane = tromethamine) has been effective in treating brain injury, reducing cerebral acidosis and ICP, and reversing the adverse effects of prophylactic hyperventilation on early recovery [6]. As was presumed by B. K. Siesjö [7], administration of base via the CSF route may also ameliorate CSF and cellular acidosis and so improve the condition for survival or revival of cell function and structure.

The aim of the present study was to investigate the possibility of correction of CSF acidosis and craniospinal system (CSS) viscoelastic parameters with intrathecal administration of THAM.

Material and Methods

The study was carried out on 26 patients after severe head injury and brain infarction (Reaction Level Scale - RLS85 > 3) during the first 36 hours after admission to the Neurosurgical ICU of the Tartu University Hospital. Mean age of patients was 49.2 ± 18.7 years and score of RLS85 6.0 ± 1.3 . All patients were managed by a standard protocol that emphasised early surgical evacuation of intracranial hematomas, controlled ventilation and monitoring of CSF pressure. The arterial PaO_2 was kept above 80 mmHg by increasing positive-end expiratory pressure from 0 to 20 cm H_2O , increasing the fraction of inhaled O_2 from 0.3 to 1.0 as required, and using paralysing agents.

CT scans were performed as soon as possible after stabilisation. The volume of brain edema was estimated on CT by tomodensitometry (16–22 HU) and the volume of edema per slice of 10 mm (VEI - volumetric edema index) together with midline shift and the Evans index.

In lumbar CSF, internal jugular venous and arterial blood samples pH, pCO_2 , pO_2 , BE, lactate, pyruvate, lactic dehydrogenase (LDH), gammaglutamyltranspeptidase (GGT) were analysed before, one and 24 hours after intrathecal administration of 5 ml 0.3 M THAM. Enzymatic activity was recorded using photocolormeter Spekol and the suitable kits from Boehringer. Acid-base parameters were determined with a Radiometer.

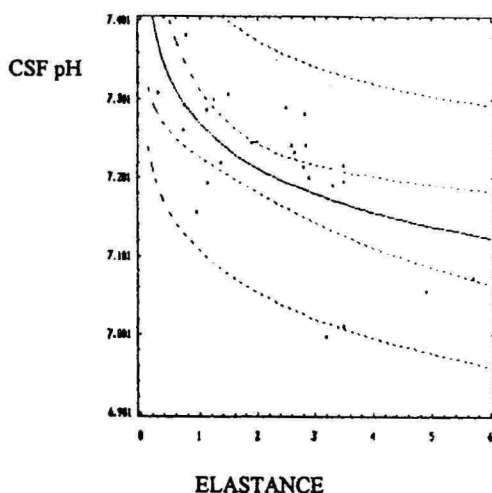


Fig. 1. Correlation between CSF pH and craniospinal system elastance mmHg/ml ($r = -0.63$)

Table 1. Changes in CSF, internal jugular venous (V) and arterial (A) blood pH, pCO₂ (mmHg), lactate, CSF lactic dehydrogenase (LDH) and gammaglutamyltranspeptidase (GGT) activity (I.U.), CSF pressure (mmHg), elastance E mmHg/ml, pressure-volume index (PVI ml) before, one and 24 hours after intrathecal THAM administration (M ± SD)

		Before THAM	Time (hours) post THAM	
			1	24
CSF	pH	7.217 ± 0.093	7.636 ± 0.113	7.351 ± 0.084
V blood	pH	7.344 ± 0.074	7.384 ± 0.053	7.366 ± 0.064
A blood	pH	7.400 ± 0.094	7.422 ± 0.081	7.420 ± 0.072
CSF	pCO ₂	36.2 ± 3.1	16.0 ± 4.8	35.3 ± 3.9
V blood	pCO ₂	34.8 ± 2.8	34.3 ± 2.4	35.4 ± 2.8
A blood	pCO ₂	28.5 ± 2.7	28.7 ± 2.2	29.4 ± 2.7
CSF	lactate	3.8 ± 1.4	4.0 ± 1.5	4.9 ± 1.8
V blood	lactate	1.8 ± 0.5	2.0 ± 0.4	1.8 ± 0.7
A blood	lactate	1.7 ± 0.5	1.8 ± 0.4	1.6 ± 0.6
CSF	LDH	146 ± 55	148 ± 50	167 ± 62
CSF	GGT	3.3 ± 0.6	3.5 ± 1.0	4.0 ± 0.9
CSF	pressure	11.5 ± 6.1		12.5 ± 7.4
	E	2.3 ± 1.3		2.0 ± 1.4
	PVI	11.3 ± 4.5		12.4 ± 5.9

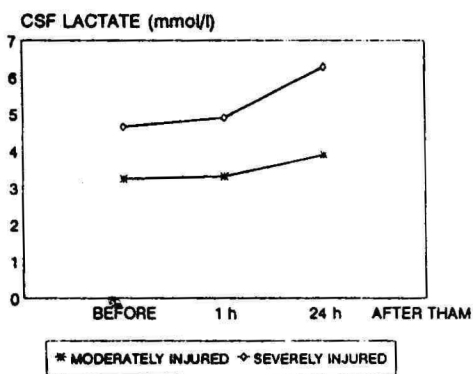


Fig. 2. Changes in CSF and arterial blood pH, pCO₂ after THAM administration

* $p < 0.01$

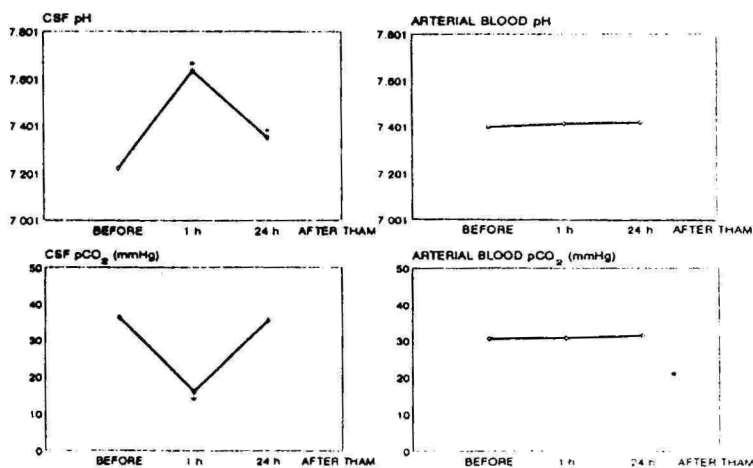


Fig. 3. CSF lactate dynamics before, 1 and 24 hours after THAM administration

CSF pressure was measured through a lumbar catheter by the registration system (Transducer MP-4, Amplifier RP-3, both of them Nihon-Kohden; Hellige Servomed with transducers Bell-Howell). Using the repeated bolus infusion test method by Eelmäe [7] the craniospinal system (CSS) viscoelastic parameters were calculated: elastance (E mmHg/ml), pressure-volume index (PVI ml), compliance (C ml/mmHg) and resistance to resorption (R mmHg/ml/min). After exclusion of treatable causes of elevated ICP, such as hypoxia, low blood pressure, or mass lesions, attempts were made to keep CSF pressure below 20 mmHg by the following intervention sequences: skeletal muscle paralysis with pancuronium, sedation with morphine and benzodiazepins, intravenous infusion of mannitol, hyperventilation to PaCO₂ levels of 28 to 30 mmHg, and CSF drainage. Barbiturate coma was not included.

Results

Table 1 shows the changes in monitored physiological variables one and 24 hours after intrathecal administration of THAM.

The results of the study indicated that the decrease of the CSF pH and PVI, with a concomitant increase of lactate and pyruvate levels and E were highly related to the severity of injury. Regression analysis showed close correlation between CSF acidosis and CT parameters (with Evans index $r = 0.420$, midline shift index $r = 0.680$, VEI $r = 0.447$) together with CSS viscoelastic properties (Fig. 1).

Before the THAM administration severe CSF acidosis was observed; the most effect of THAM 1 hour after bolus were the increase of CSF pH and the decrease of CSF pCO₂. 24 hours after the THAM administration a significantly higher CSF pH ($p < 0.01$) and lactate increase, more expressed in the severely injured group (RLS85 > 5), were detected (Fig. 2, 3). However, no significant changes were observed in arterial and internal jugular venous blood acid-base balance and enzymes activity.

The most remarkable effect on CSS viscoelastic parameters was expressed as a decrease of elastance and increase of PVI.

Discussion and conclusions

A number of pathological conditions affecting the brain tissue are accompanied by changes in intra- and extracellular pH, reflecting disturbances in the normal pH regulation. The major cause of the reduction of pHi (intracellular pH) and pHe (extracellular pH) during ischemia and injury is a mismatch between glycolysis and oxidative

phosphorylation. Thus, under anaerobic conditions the normal glycolytic pathways are blocked at the stage of pyruvate oxidation, and leads to the reduction of pyruvate to lactate [2]. The amount of H^+ generated during the injury corresponds to the amount of lactate accumulated, plus the H^+ released from hydrolyzation of ATP stores. As is proved, cerebral acidosis is more pronounced during conditions where the substrate for lactate production is more readily available, i.e. during hyperglycemia [8] or when a trickle of blood flow remains [9]. Lactic acid contributes to brain tissue swelling by two different mechanisms. One is dissociation in the cell and exchange of H^+ ions against Na^+ , the other accumulation of lactate anions, which cannot leave the cell as charged molecules [10]. This process continues in pathology and leads to an irreversible damage of nerve cells.

As has been demonstrated [11, 12], raising extracellular pH may enhance lactic acid efflux from cells. Since 30% of THAM is in non-ionized form, it can cross the plasma membrane and directly affect intracellular acidosis [13]. Our study showed that intrathecal administration of THAM causes CSF pH alkaline shift and normalisation of BE. As THAM accepts hydrogen, it shifts the $CO_2-HCO_3^-$ equilibrium toward bicarbonate and lowers pCO_2 . In addition, we found CSF pH to be higher even 24 hours after THAM administration. At the same time a decrease in CSS elastance, together with increased lactate values, higher in the more injured group were detected. From the above facts we can conclude that elevated lactate in CSF after THAM administration appears due to the lactate efflux from the cells to the extracellular space.

Hence, it seems probable that intrathecal administration of THAM may ameliorate CSF and cellular acidosis due to persisting ischemia, e.g. due to stroke or trauma with cellular edema, and thus improve conditions for survival of cell function and structure.

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ICP AND CRANIOSPINAL DYNAMICS IN THE ACUTE STAGE OF ANEURYSMATIC SAH PATIENTS

M. Heinsoo, J. Eelmäe, M. Kuklane, T. Tomberg, A. Tikik

The craniospinal system (CSS) viscoelastic parameters, ICP and CT investigations were performed in 13 patients with ruptured saccular aneurysms. The results of this study prove that ICP and CSS viscoelastic parameters were more abnormal by the seventh day after SAH. Patients with a low PVI, compliance and high elastance (independent of their ICP level) should be carefully monitored and these parameters should be frequently determined to track intracranial buffering capacity. Enlargement of cerebral ventricles together with the decrease of R by the end of the second week after SAH indicates brain tissue damage due to oedema and ischaemia.

Introduction

Since the introduction of intracranial pressure (ICP) measurement by Guillaume and Janny [1] and Lundberg [2], ICP monitoring has been a useful adjunct in the management of patients with aneurysmatic subarachnoid haemorrhage (SAH). When an intracranial saccular aneurysm ruptures, the ICP rises abruptly and almost reaches the magnitude of arterial blood pressure. Unless a cerebral hematoma is formed, ICP will rapidly drop to a lower level [3, 4]. The clinical course in the days following the rupture is of prognostic significance, and several pathological factors can increase ICP. Obstruction of cerebrospinal fluid (CSF) flow from the basal cisterns due to clot formation [5] or impairment of the absorption of CSF by blockage of the arachnoid villi by red blood cells [6] are responsible for "acute" hydrocephalus [7].

Disturbances of cerebral autoregulation and damage of the brain tissue in direct contact with blood [8, 9], together with hypotensive-hypoxic episodes related to surgical or anaesthesiological intervention and vasospasm are the most important pathogenetic factors leading to cerebral ischemia and edema after subarachnoid haemorrhage. Singly or together, these complications may threaten the aneurysm patient by increasing ICP and worsening craniospinal system (CSS) viscoelastic parameters with concomitant brain metabolic changes. The importance of CSS viscoelastic parameters in understanding the pathophysiology of raised ICP and brain edema has been clearly demonstrated in the

laboratory [10, 11] and a number of clinical studies have focused on the correlation of brain compliance and ICP following traumatic brain injury [12, 13, 14]. An elevated ICP has been found in patients with poor clinical condition [4, 15] and drainage of CSF has resulted in clinical improvement [16]. On the other hand, continuous CSF drainage should be not performed too readily in patients with SAH, because the removal of a large amount of CSF can induce cerebral vasospasm as well as hydrocephalus [17].

The aim of the present study was to observe dynamically CSS viscoelastic parameters and on this basis determine the need of ventricular drainage and permanence of ICP recording in patients with aneurysmatic subarachnoid haemorrhage. In addition, dynamical CT investigations were performed to evaluate CSF compartment size and using CSS viscoelastic parameters, decide the indication for the shunting operation.

Clinical material and methods

The series included 13 patients with ruptured saccular aneurysms admitted to the Neurological and Neurosurgical Intensive Care Unit of the Tartu University Hospital between September 1993 and February 1994. The mean age of the patients was 48 years (range 36 to 63 years). There were 7 females and 6 males. Clinical grading of the patients was performed according to the classification of Hunt and Hess: Grade I comprised 3, Grade II 6, Grade III 3 patients and Grade IV 1 patient. In all cases early diagnostic clarification including CT, cerebral angiography and surgical treatment were performed. Ruptured aneurysms were located in the following arteries: 5 anterior communicating, 3 internal carotid, 2 middle cerebral and 2 anterior cerebral. The ventricular catheter was placed via right frontal burrhole into the right frontal horn before craniotomy (2 cases) or after the operation. In the case of right-sided aneurysms, on the left side, a thin ventricular catheter was inserted into the frontal horn of the lateral ventricle. The external Belle-Howell transducers were used for continuous ICP recording. Using the repeated bolus infusion test by J. Eelmäe [18], the following CSS viscoelastic parameters were dynamically calculated after a 4 ml saline bolus: pressure-volume index (PVI), elastance (E), compliance (C) and resistance to CSF resorption (R).

Recurrent CT investigations were performed to evaluate ventricular size, periventricular oedema, midline shift and hypodense areas.

All patients studied were in the intensive care unit under continuous observation. Direct blood pressure, pulse, respiratory rate, temperature and pupillary reactions were recorded in connection with the measurement of mean ICP. Five postoperatively unconscious patients were subjected to volume-control ventilation with moderate hypocapnia (PaCO_2 30–35 mmHg).

Results

Relation between clinical grades, ICP and CSS dynamics

Differences between clinical grades are presented in Table 1. Normal or slightly elevated ICP was recorded in patients with grade I–II and IV. Higher ICP was measured in patients with grade III. Concomitant changes were observed in CSS elastance and compliance. PVI was clearly decreased in more severe groups (Fig. 1.).

Temporal course of ICP and CSS dynamics

The temporal course of ICP, CSS elastance, compliance and pressure volume index are presented in Table 2. ICP increased during the first seven days, whereupon decreased to the normal level. Elevation of CSS elastance and decrease of compliance were more expressed by the seventh day after SAH. Concomitant changes were observed in PVI records, however, slight increase in values by the ninth day was admitted (Fig. 2.).

Comparison between CSS dynamics

Close correlation was found between ICP, elastance, compliance and resistance to absorption (Fig. 3.). No correlation was observed between ICP and PVI in this group of aneurysmatic SAH patients.

CT

During the acute stage the Evans index decreased, two months after SAH enlarged ventricles were observed (Fig. 1.).

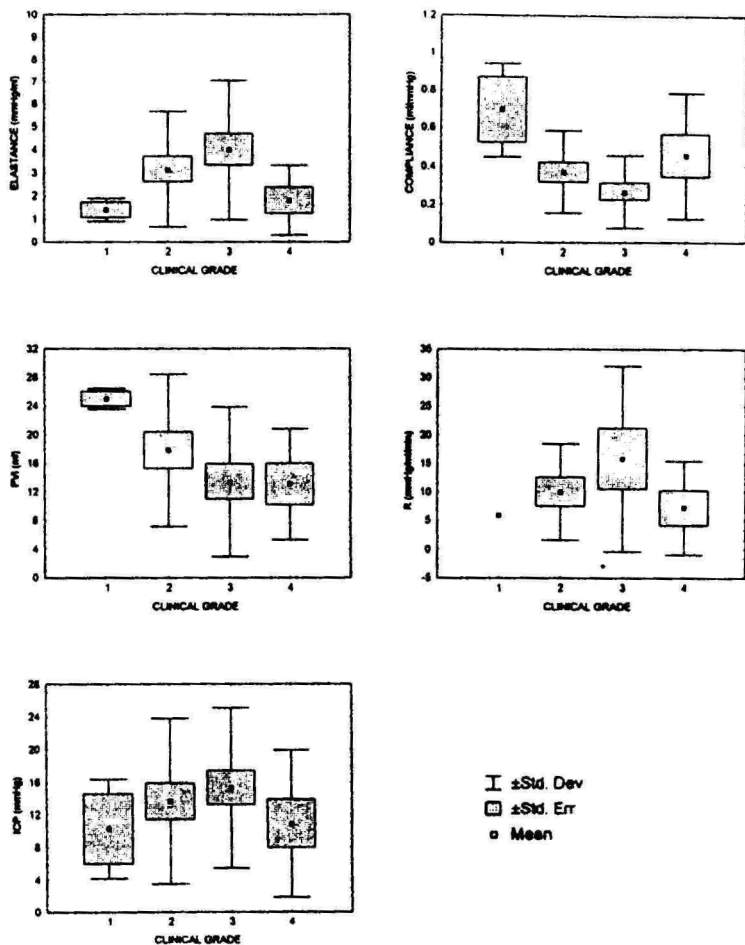


Fig. 1. Differences of craniospinal system elastance, compliance, pressure-volume index (PVI), resistance to resorption (R) and ICP between clinical grades (Hunt and Hess)

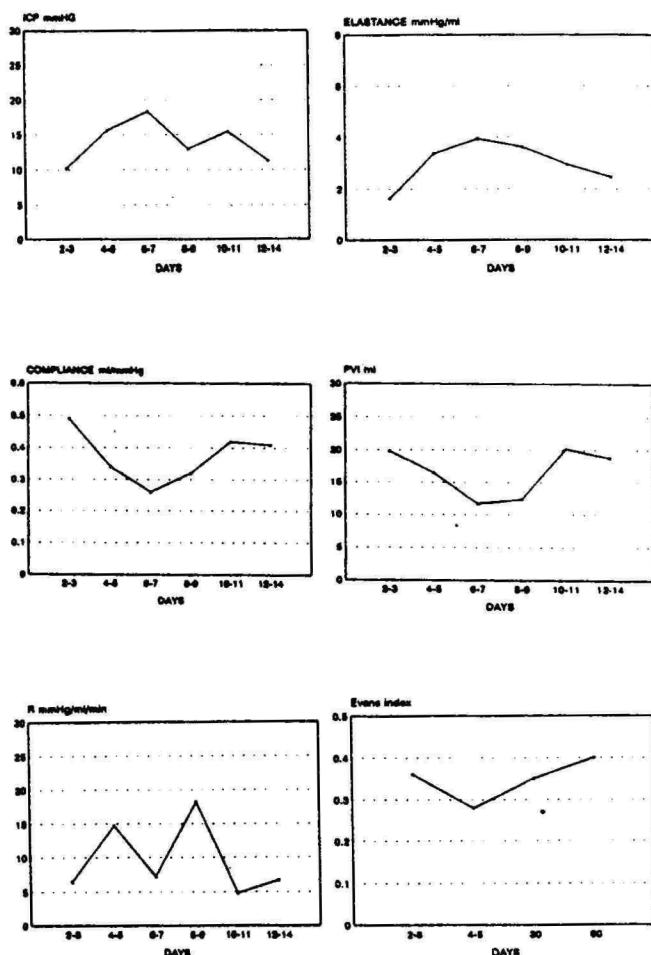


Fig. 2. Changes in ICP, craniospinal system elastance, compliance, pressure-volume index (PVI), resistance to reabsorption (R) and Evans index in the acute stage after rupture of saccular aneurysm

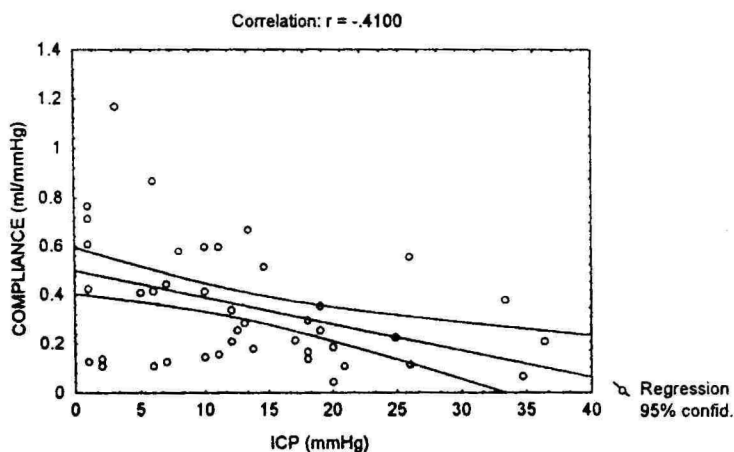
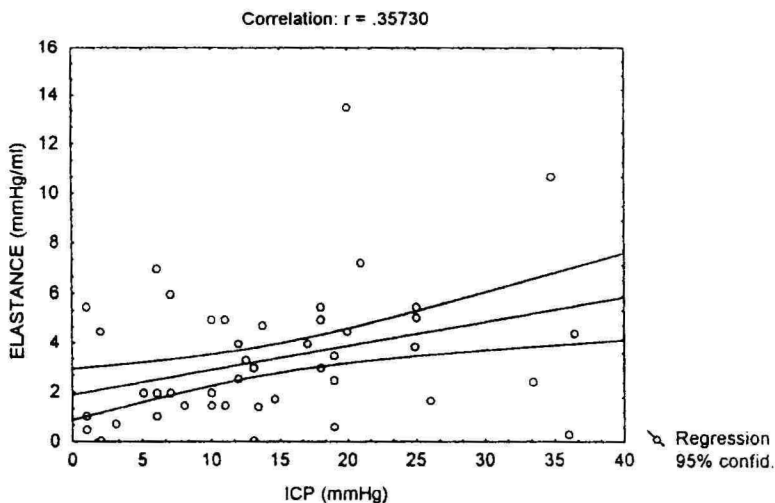


Fig. 3. Correlation between ICP and craniospinal system elasteance, compliance.

Table 1. Normal values and differences of ICP, pressure-volume index (PVI), elastance (E), compliance (C) between clinical grades (Hunt and Hess)

	Norm	I	II	III	IV
ICP mmHg	15	10.3 ± 4.3	13.7 ± 2.3	15.3 ± 2.1	10.9 ± 3.0
PVI ml	> 12	25.0 ± 1.1	17.8 ± 2.6	13.4 ± 2.5	13.0 ± 2.9
E mmHg/ml	2-3	1.4 ± 0.35	3.2 ± 0.56	4.0 ± 0.68	1.8 ± 0.57
C ml/mmHg	0.2-0.3	0.70 ± 0.18	0.37 ± 0.05	0.27 ± 0.19	0.45 ± 0.11
R mmHg/ml/min	< 10	5.9 ± 0.0	10.1 ± 2.7	15.9 ± 5.4	7.3 ± 3.1

Table 2. The course of mean intracranial pressure (ICP), pressure-volume index (PVI), elastance (E), compliance (C) and resistance to CSF resorption in the acute stage after aneurysmatic SAH

Days	2-3	4-5	6-7	8-9	10-11	12-14
ICP mmHg	10.2 ± 4.3	15.6 ± 4.5	18.4 ± 4.5	12.9 ± 3.3	15.5 ± 5.2	11.3 ± 2.8
E mmHg/ml	1.6 ± 0.6	3.4 ± 0.6	3.9 ± 1.2	3.6 ± 0.7	2.9 ± 1.1	2.5 ± 0.7
C ml/mmHg	0.5 ± 0.09	0.3 ± 0.07	0.26 ± 0.06	0.3 ± 0.1	0.4 ± 0.09	0.4 ± 0.09
PVI ml	19.8 ± 7.9	16.5 ± 2.9	11.7 ± 2.7	12.4 ± 1.3	20.2 ± 5.6	18.8 ± 5.8
R mmHg/ml/min	6.5 ± 4.0	14.7 ± 8.4	7.2 ± 4.5	18.2 ± 6.8	4.8 ± 1.3	6.7 ± 1.5

Discussion

Continuous measurement of ICP in aneurysmatic SAH patients is getting more widely used in neurosurgical intensive care units in order to guarantee reliable monitoring of CSS dynamics. However, still controversies exist in the management of these patients postoperatively.

Our data show a steadily increasing ICP, being highest on the seventh day. However, only in the period between 4 and 7 days abnormal ICP was recorded in this study. The dependence of ICP on clinical grading was obvious. Lower ICP and close to normal values of CSS viscoelastic parameters (except PVI) in patients of grade IV can be explained by aggressive therapeutic intervention, including drainage, and controlled ventilation. One can infer from these data that ICP may be lowered but the effect is transient since the brain remains tight.

Thus, with the return of small increment of blood volume or oedema, pressure increases rapidly. This suggests that therapies should be directed to increasing PVI as well as reducing ICP, as has been demonstrated by Shapiro and Marmarou [19].

More clearly expressed changes concomitantly with ICP increase were recorded in PVI, elastance and compliance dynamics. From this point of view, formation of brain oedema of aneurysmatic SAH patients is most expressed on the seventh day after bleeding. Disturbances of cerebral autoregulation together with vasospasm, incomplete regional re-circulation after ischemia, raised ICP, blockage of CSF passage and metabolic changes are all responsible for the occurrence of cerebral oedema or hypoxia.

Unlikely, in head injury, the most "critical" period follows after 3-5 days [20].

This demands a longer recording of ICP and CSS dynamics in order to prevent unexpected worsening of the clinical status. Although, prolonged use of the ventricular catheter increases the rate of CSF infection [21], no complications were observed in the study group. It should be taken into account, that postoperative extensive CSF drainage may increase the incidence of shunt-dependent hydrocephalus [17, 22]. In this study, no clear dynamics and relationships were found in the analysis of resistance to resorption. This can be explained with the small group of patients and by the need of longer investigations.

Enlargement of cerebral ventricles together with the decrease of R by the end of the second week after SAH indicates brain tissue damage due to oedema and ischaemia.

In conclusion the results of this study prove that ICP and CSS viscoelastic parameters were more abnormal by the seventh day after SAH. Patients with a low PVI, compliance and high elastance (independent of their ICP level) should be carefully monitored and these parameters should be frequently determined to track intracranial buffering capacity.

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ARGUMENTED APPROACH TO SURGICAL TREATMENT OF HYDROCEPHALUS

J. Eelmäe, M. Kuklane, M. Heinsoo, A. Tikk

In conclusion, the indications for shunting in different types of hydrocephalus are based on the type of infusion test curve and on CSF dynamics parameters. The hydrocephalic patients selected must be operated on as early as possible before ventricular enlargement ($EI > 0.45$) develops.

Introduction

No doubt we have reached a turning point in the history of hydrocephalus. Most of the 20th century was devoted to studying the altered physiology of CSF. As the 21st century approaches, the recognition of hydrocephalus as a brain disease should be re-emphasised, which should lead to new treatment methods. Updating early work should be done with this in mind. Rapidly advancing technology, including positron emission CT, magnetic resonance imaging, spectroscopy, and other sophisticated methods, should provide more advanced knowledge of the pathophysiology of the brain and should open a new era in the management of hydrocephalus. There are many promising data already. For instance, increased knowledge of nerve regeneration and remyelination may lead to drug therapy aimed at regrowth with functional recovery. The extravillous drainage mechanism, as represented by the supposed lymphatic route, and further clarification of the intraparenchymal absorption mechanism may lead to new methods that will reduce outflow resistance. Moreover, advanced research into the interaction of the brain-CSF interface should demand a changes more physiological procedures that will allow CSF to maintain its role as a biological fluid. Furthermore, in the near future the concept of the isolated cerebrospinal fluid space, based on a pressure-difference mechanism, may prompt the invention of new treatments. We have already waited too long for the advent of more appropriate treatments to replace shunting. Future treatment of hydrocephalus should be aimed at including effective functional recovery, and not simply at producing a surgically arrested state with brain damage [16]. Dilatated cerebrospi-

nal fluid (CSF) spaces can be found by pneumoencephalography (PEG), computed tomography (CT), sonography, and magnetic resonance imaging. The pathogenesis of ventriculomegaly needs to be specifically determined in each individual patient, so that the most appropriate treatment method can be selected.

Patients with hydrocephalus of primary atrophic genesis cannot be improved after shunting procedures. Patients with ventriculomegaly of secondary genesis, caused by disturbances of the CSF circulation, usually improve after correction of the CSF circulation. The results of shunting procedures depend upon the timing and the indications of the operation. Especially important is the fact that sometimes in hydrocephalus of secondary genesis one can be faced with a situation in which the ventricular system is enlarging but the intracranial pressure (ICP) does not increase [2]; shunting procedures are not indicated in such cases.

In the last 10–20 years many investigations reporting successful shunting of patients with hydrocephalus of primary atrophic genesis have been published. One can presume that among these patients were cases with concealed CSF circulation disturbances [7, 8, 9].

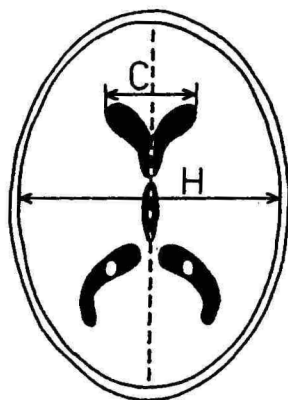
For the successful treatment of hydrocephalus a complete investigation, both of the CSF volume and of pressure-volume response compensation mechanisms in the craniospinal system (CSS), must be performed. Such investigations involve the measurement of ventricular system size and the quantitative analysis of CSF dynamics [3–6, 13–15, 17, 20–22].

Clinical Material and Methods

This prospective study was carried out in two different groups of patients. The first group consisted of 184 patients with several different types of hydrocephalus. The second group consisted of 64 persons who underwent shunting procedures. All of them were treated either in the intensive care unit or in the neurosurgical and neurological departments of Tartu University Hospital.

Table 1. Mean value of of pressure (P), pulsatile amplitude (A), elastance (E), pressure-volume index (PVI), compliance (C) and resistance to cerebrospinal fluid absorption (R) at various stages of the infusion test ($\bar{x} \pm \delta$)

Stage of investigation	P ₁ (mmHg)	P ₂ (mmHg)	A (mmHg)	E (ml/mmHg)	PVI (ml)	C (mmHg/ml)	R (mmHg/ml per min)
Opening values (P _o , A _o)	10.5 ± 7.4	-	1.6 ± 1.6	-	-	-	-
Parameters after withdrawal of CSF (P ₁ , A ₁ , E ₁ , PVI ₁ , C ₁)	8.2 ± 6.0	-	1.2 ± 1.4	2.4 ± 2.3	18.7 ± 20.8	0.19 ± 0.23	-
During injection of saline:							
2 ml	11.7 ± 7.8	11.3 ± 7.7	1.6 ± 1.7	1.8 ± 1.6	10.2 ± 11.7	0.45 ± 0.56	31.4 ± 418.0
4 ml	13.6 ± 8.7	12.6 ± 7.8	1.8 ± 1.8	1.3 ± 1.6	13.1 ± 15.7	0.53 ± 0.63	8.7 ± 34.1
6 ml	15.2 ± 8.5	13.8 ± 7.6	2.0 ± 1.7	1.4 ± 1.9	12.6 ± 13.1	0.48 ± 0.67	9.8 ± 28.0
8 ml	17.3 ± 9.8	15.4 ± 8.4	2.3 ± 1.8	1.8 ± 1.9	12.1 ± 13.0	0.37 ± 0.45	97 ± 23.2
10 ml	20.0 ± 10.9	17.0 ± 9.2	2.6 ± 1.9	2.3 ± 2.5	10.0 ± 11.2	0.28 ± 0.38	17.7 ± 65.6
12 ml	21.3 ± 10.7	18.3 ± 9.6	3.1 ± 2.5	2.1 ± 1.7	9.7 ± 15.7	0.30 ± 0.46	9.5 ± 26.7
14 ml	23.1 ± 11.7	18.4 ± 8.6	3.4 ± 2.5	2.5 ± 2.3	11.0 ± 11.2	0.32 ± 0.34	10.0 ± 17.0
16 ml	23.6 ± 11.0	19.4 ± 9.1	3.5 ± 2.4	2.8 ± 2.1	10.5 ± 11.4	0.30 ± 0.42	15.1 ± 31.5
18 ml	25.1 ± 11.7	20.9 ± 12.7	3.8 ± 2.6	2.8 ± 2.1	10.1 ± 7.9	0.25 ± 0.26	15.1 ± 31.5
20 ml	25.7 ± 12.1	-	3.9 ± 2.6	2.4 ± 5.0	11.8 ± 10.4	0.25 ± 0.36	-
I Queckenstedt's probe							
II — —	34 ± 13.4	-	3.7 ± 2.1	-	-	-	-
III — —	32.8 ± 13.5	-	3.3 ± 2.0	-	-	-	-
III — —	42.2 ± 12.2	-	4.9 ± 2.4	-	-	-	-
After injection of saline:							
1 min	23.5 ± 12.9	-	3.5 ± 2.6	-	-	-	9.6 ± 37.3
2 min	21.3 ± 12.1	-	3.0 ± 2.4	-	-	-	12.2 ± 60.3
3 min	20.2 ± 11.2	-	2.6 ± 2.2	-	-	-	21.9 ± 122.6
4 min	20.1 ± 11.6	-	2.7 ± 2.1	-	-	-	19.3 ± 52.8
5 min	19.7 ± 11.3	-	2.6 ± 2.2	-	-	-	19.1 ± 55.0



$$\text{Evans Index} = C/H$$

Fig. 1. Measurement of ventricular size by Evans

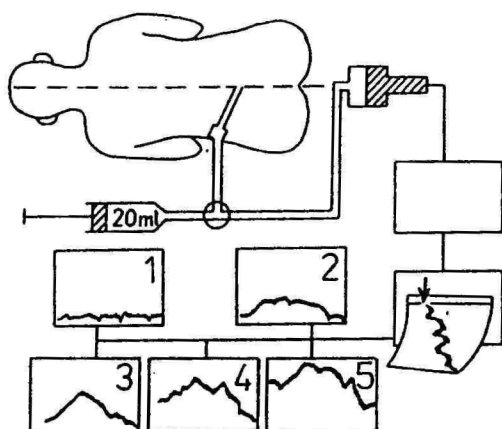


Fig. 2. Scheme of infusion test and types of pressure curves. 1, atrophic curve; 2, normal curve; 3, compensated curve; 4, decompensated curve; 5, hypertensive curve

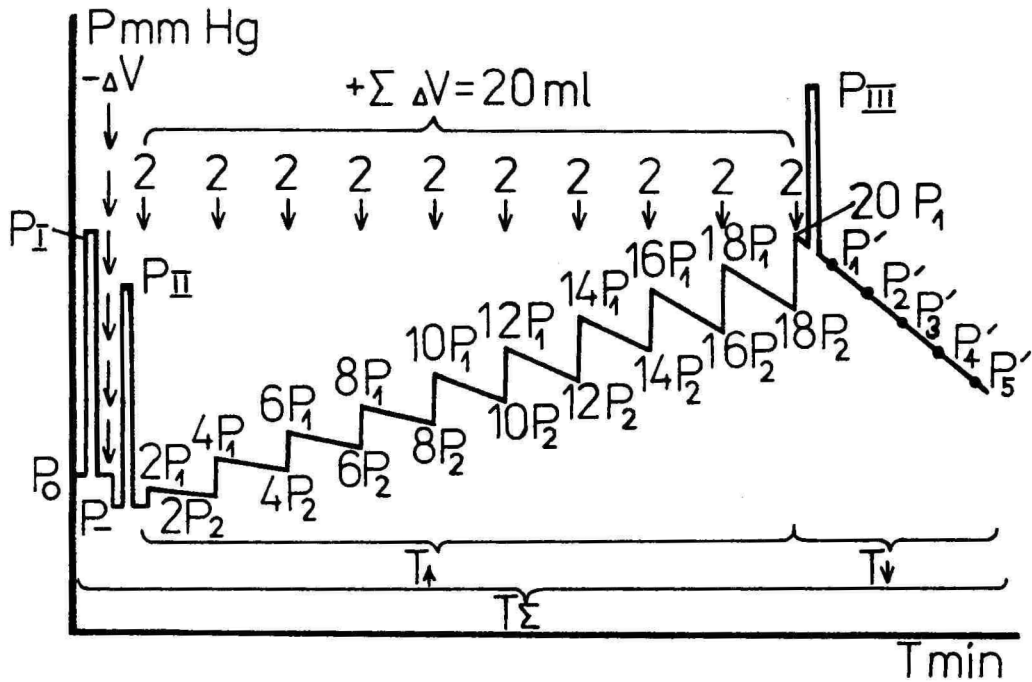


Fig. 3. Schematic representation of resultant curve during infusion test

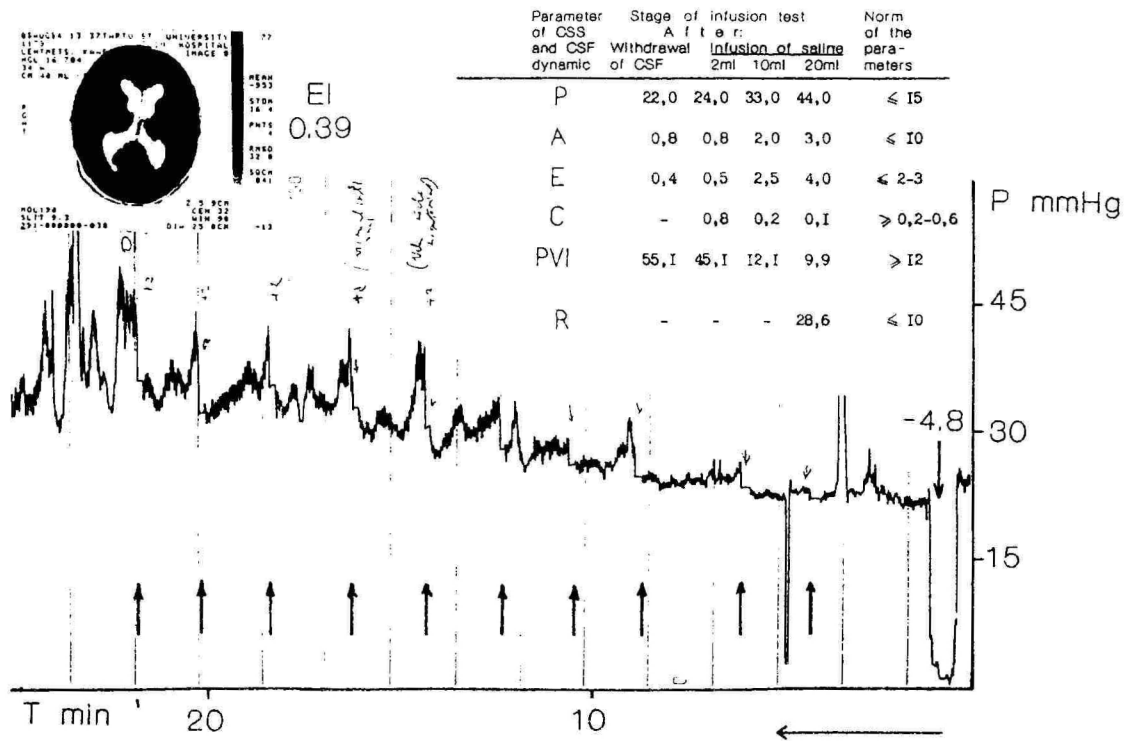


Fig. 4. Preoperative hypertensive type of pressure curve during infusion test and quantitative parameters of CSF dynamics in a 39-year-old patient with communicative hydrocephalus of unknown etiology. Evans index (EI) 0.39. P, pressure; A, pulsatile amplitude; E, elastance; C, compliance, PVI, pressure-volume index; R, resistance to cerebrospinal fluid absorption

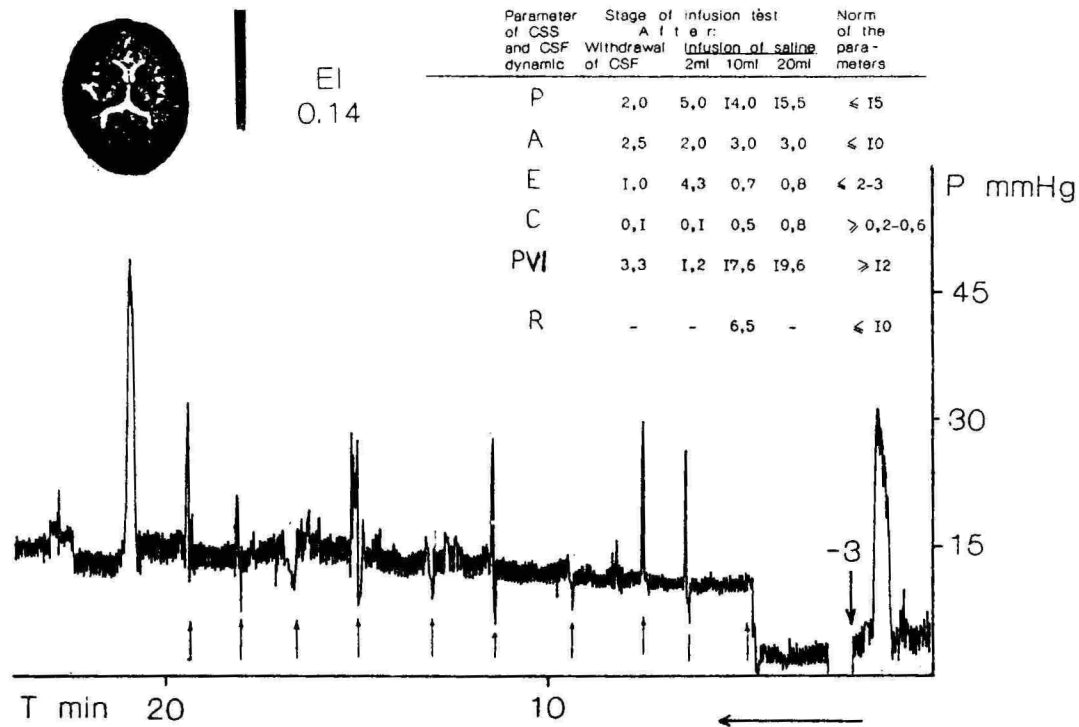


Fig. 5. Normal type of pressure curve during infusion test and quantitative parameters of CSF dynamics after shutting procedure in the patient presented in Fig. 4. Evans index (EI) 0.14. Definitions of parameters as in Fig. 4

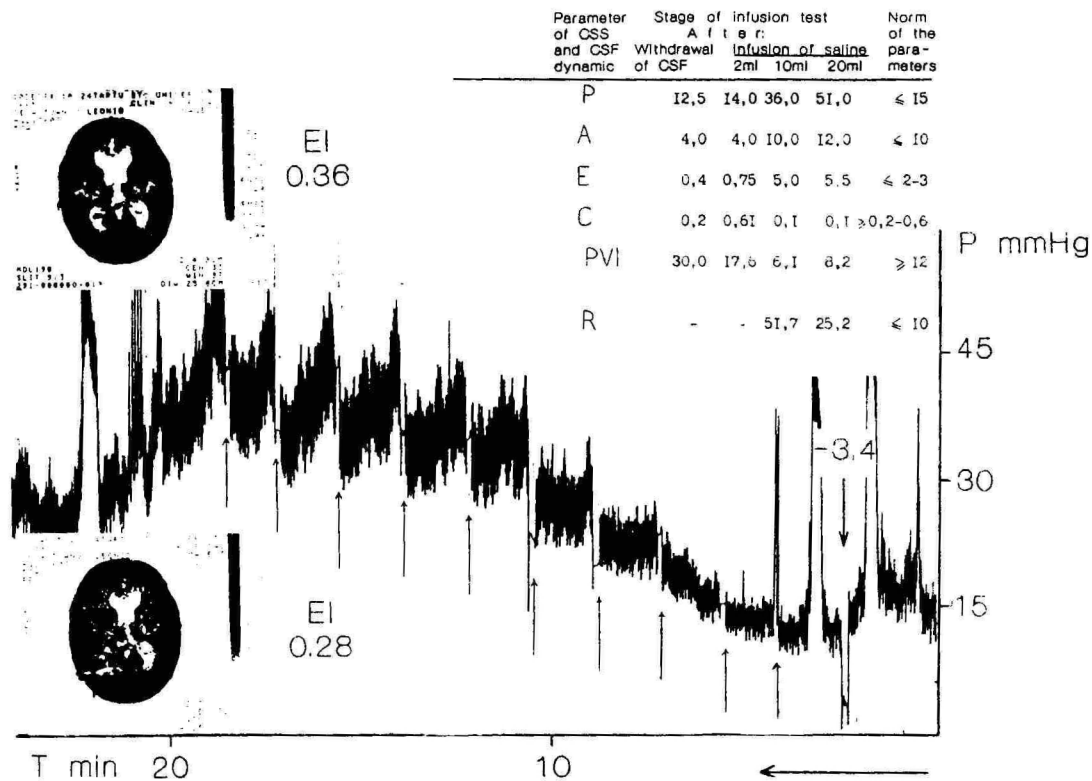


Fig. 6. Preoperative decompenated type of pressure curve during infusion test and quantitative parameters of CSF dynamics in a normal pressure hydrocephalus patient. Ventricular size dynamics according to Evans index (EI) before and after operation were EI = 0.36 and EI = 0.28, respectively. Definitions of parameters as in Fig. 4.

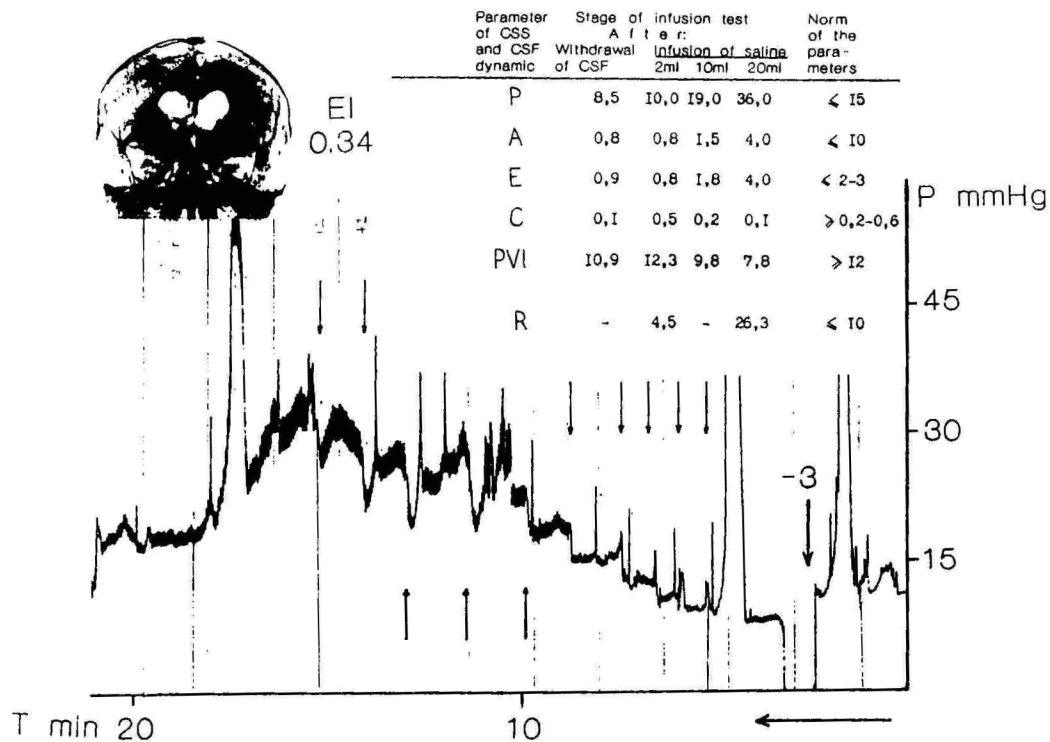


Fig. 7. Compensated type of pressure curve during infusion test and quantitative parameters of CSF dynamics in a patient with mental disorders. Evans index (EI) 0.34. Definitions of parameters as in Fig. 4.

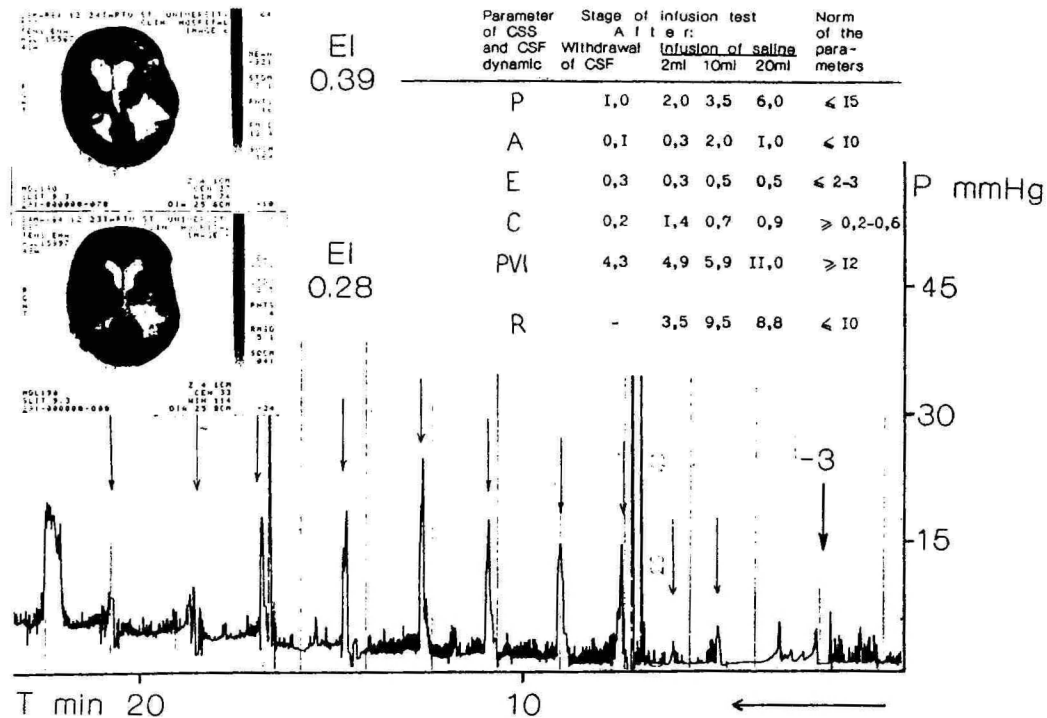


Fig. 8. Atrophic type of pressure curve during infusion test and quantitative parameters of CSF dynamics in a patient with hemispheric glioma. Ventricular size by Evans index (EI) was 0.39 before shunting. After operation size had reduced to EI = 0.28. Definitions of parameters as in Fig. 4.

Table 2. Correlation matrix of ventricular size and CSF dynamics parameters

* - $p < 0.05$

ICP	-0.160					
A	-0.065	0.990*				
E	-0.232	0.874*	0.869*			
PVI	0.094	-0.388	-0.370	-0.667		
C	0.300*	-0.908*	-0.973*	-0.896*	0.645	
R	-0.074	-0.433	-0.429	0.481	-0.413	0.228
	EI	ICP	A	E	PVI	C

EI, Evans index; ICP, initial intracranial pressure; A, pulsatile amplitude; E, elastance; PVI, pressure-volume index; C, compliance; R, resistance to cerebrospinal fluid absorption

Computed tomography studies (CT) were performed on the "Delta-Scan-190" (Ohio Nuclear, USA). The thickness of the slices was 10 mm. To achieve maximum objectivity, a modified Evans index (EI) was used for the evaluation of ventricular dimensions (Fig. 1). Four groups were formed according to the enlargement of ventricular size: hydrocephalus - $EI > 0.3$; encephalopathy - $EI = 0.2-0.3$; normal size - $EI 0.1-0.2$; brain oedema - $EI < 0.1$.

The investigation of CSF dynamics by the repeated bolus injection technique was carried out as follows (Fig. 2). After inserting a spinal needle into the lumbar subarachnoid space the CSF pressure was measured by a registering system (Transducer MP-4 and Amplifier RP-3, Nihon-Kohden, Japan, and chart writer PS-1-02, USSR). Then 20 ml of saline was injected in 2 ml boluses (mean injection rate was $1.7 + 0.2$ ml/min). After every bolus the pressure was measured. CSF pathway obstruction was excluded by the Queckenstedt manoeuvre. The mean test time was $24.0 + 5.9$ min. From the curves obtained (Fig. 3) a complex of CSF dynamics parameters was calculated: initial intracranial pressure (ICP), pulsate amplitude (A), elastance (E), pressure-volume index (PVI), resistance to CSF absorption (R), and Ayala index (AI). Curves of the infusion test were divided into five types: (1) atrophic, (2) normal, (3) compensated, (4) decompensated, and (5) hypertensive (see Figs. 4, 5, 6, 7 and 8).

Results

CSF dynamic parameters after every bolus injection were calculated in the first group (Table 1). The normal values of CSF dynamic parameters were: $ICP < 15$ mmHg, $A < 10$ mmHg, $E = 2-3$ mmHg/ml,

C = 0.2–0.3 ml/mmHg, PVI > 12 ml, R < 10 mmHg/ml per min, and AI > 2.3 ml/mmHg. These data correspond to values published by other authors. A correlation matrix of these CSF dynamics' parameters and ventricular size was composed (Table 2). A positive correlation between ventricular size and C was found ($r = 0.300$). A tendency to negative correlation between EI and E was observed ($r = -0.232$).

The criteria for shunting procedures on the infusion test were decompensated or hypertensive curves. The preoperative quantitative parameters for a 34-year-old patient with communicative hydrocephalus of unknown aetiology can be seen in Fig. 4. This patient had an EI of 0.39 and a hypertensive type of infusion test curve. His ICP, E, and R values were higher than normal, but PVI and C values were lower than normal. The postoperative infusion test curve and CSF dynamic parameters are shown in Fig. 5. A normal type of curve was found and all the CSS visco-elastic property values were normalized. Figure 6 shows the correct indications for shunting. The curve was decompensated and CSF dynamics parameters had abnormal values after the last 2 ml bolus injection; ICP (51 mmHg), A (12 mmHg), E (5.5 mmHg/ml) and R (25.2 mmHg/ml per min) were increased, but C (0.1 ml/mmHg) and PVI (8.2 ml) were decreased. After shunting, the headache and gait disturbances disappeared and, on CT investigation, EI was found to have decreased from 0.36 to 0.28. The compensated curve (Fig. 7) of a patient with mental disorders and large ventricles on PEG did not justify shunting, as 5 min after the last injection ICP decreased to normal values (16 mmHg). The infusion test was also used for detecting shunt function (Fig. 8). A patient with a cyst after the removal of hemispheric glioma was shunted as she showed CSF circulation disturbances, based on clinical and CT signs (large ventricles and midline shift). The infusion test was not performed. The patient improved initially after shunting, but two months later mental disorders, vomiting, and stupor developed. As the curve of the infusion test was of the artificial type and quite normal ventricular size without midline shift was found on CT, the worsening of the patients' condition was probably due to tumour growth, not to shunt occlusion.

Changes in ventricular size before and after the operation were analysed in 31 out of 64 patients. The ventricular size had not decreased in 4 cases (Fig. 9), but in 27 cases a successful result of shunting was observed, together with a decrease of the ventricles. It was found that good results can be obtained in cases with EI > 0.45 before the operation (Fig. 10).

Discussion

Numerous investigations have shown the usefulness of the infusion test in determining indications for shunting operations. Hussey et al. [10] stated that patients with rapid elevation of the CSF curve need shunting procedures, but Alberti [1] was of the opinion that the main importance was the decreasing part of the curve after injection. In our opinion, both parts of the curve are important. The rate of elevation of ICP after injection characterizes the visco-elastic quality of the craniospinal compartment while the decrease of the curve indicates the ability of the craniospinal system (CSS) to absorb CSF. Our data are in accordance with the findings of Lamas and Lobato [12] who, in 92.5% of their cases, found it possible to determine the effectiveness of shunting procedures from the type of infusion test curve. The pressure-volume index (PVI) is one of the main parameters which characterizes the volumic compensation of the CSS [18, 20]. But there are some difficulties in the interpretation of this index, especially regarding its correlation with ventricular size. Shapiro and Marmarou [18] and Kosteljanetz [11] found that PVI depended on the volume of the CSS; however, in a later study Shapiro et al [19] did not find a correlation between PVI and ventricular size. We agree with Tans and Poortvliet [20], who recommended investigating the viscoelastic parameters of the CSS in complex, preferably by the bolus technique.

The real parameter of CSF dynamics is R (resistance to CSF absorption) and there are no problems with its interpretation: patients whose R value is more than 10 mmHg/ml per min need a shunting operation. At the same time, R is more sensitive than PVI because, when $R > 20$ mmHg/mm per min, the decrease in PVI stops [22]. Our data support their opinion.

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STIMULATION OF THE SEPTAL COMPLEX INCREASES LOCAL CEREBRAL BLOOD FLOW IN THE HIPPOCAMPUS IN UNANESTHETIZED RABBITS

A. Kalda

The effect of local electrical stimulation of the septal complex (SC), i.e. the medial septal nucleus and the nucleus of diagonal band, on the local hippocampal blood flow (HBF) measured by the hydrogen clearance technique was examined in 14 unanesthetized rabbits. Out of 9 correctly located sites, 7 gave cerebrovascular responses, without significant hypertension or agitation. Electrical stimulation of SC produces a significant increase in HBF (+ 30%). This evidence supports the point of view that cholinergic projections of SC are in control of HBF since the flow changes observed showed no obvious changes in systemic PaO₂, PaCO₂ and pH, and could not be attributed to hypertension or behavioural changes.

Introduction

The fact that most blood vessels in the brain are innervated by fibers containing noradrenaline, acetylcholine, serotonin and some peptides [1] indicates a functional role of these neurons in the regulation of regional cerebral blood flow (CBF).

The hippocampus receives axonal fibers originating from the cells of the medial septal nucleus and the nucleus of the vertical limb of the diagonal band of the Broca — septal complex (SC), of which 35–45% are cholinergic [2]. It has been reported that focal electrical and chemical stimulation of SC produces an increase of the release of acetylcholine from the dorsal hippocampus in unanesthetized rabbits [3] and an increase in hippocampal blood flow (HBF) in unanesthetized rats [4, 5]. This response is specific of the hippocampus, since CBF in the cortex, caudate nucleus, thalamus, midbrain, pons, medulla oblongata and cerebellum is not altered. HBF responses are elicited whether or not there are changes in systemic arterial blood pressure [6]. Considering the previous finding, there is a possibility that cholinergic septohippocampal nerve fibers act as an intracerebral vasodilator for the hippocampal blood vessels.

Thus, the present pilot study was undertaken to clarify whether or not cholinergic septohippocampal nerve fibers contribute to the neural regulation of HBF in unanesthetized rabbits.

Material and methods

The experiments were performed on 14 rabbits of either sex, weighing between 2.5–3.5 kg.

HBF measurements

HBF was quantitatively estimated by the hydrogen clearance technique [7] by means of an amplifier (Fizioblok – 01, Puls) and monopolar electrodes. Monopolar electrodes were constructed from platinum wire (diameter 150–200 μm), sharpened electrochemically to a tip diameter 20–30 μm . The electrodes were insulated with glass tubing to within 1 mm of the tip. Hydrogen gas was administered via face mask so that the hydrogen concentration of the inhaled gases was 5–10% and oxygen concentration was not altered. Polarisation was at +0,3 V with a reference Ag/AgCl electrode fixed on the left ear.

General surgical and technical procedures

The adopted method was a two steps experimental procedure. The first step consisted of the implantation of the chronic measurement and stimulation electrodes. The second step, 14–21 days later, included experiments on the unanesthetised animal.

The rabbits were anesthetised with ketamine (5 mg/kg i.v.) followed by halothane. A monopolar platinum electrode was stereotaxically (Gyartasi stereotaxic instrument) inserted into the left dorsal hippocampus (CA-1) and a bipolar stainless steel electrode into the SC, according to the co-ordinates of Fikova et al. [8]. The electrodes attached were to the skull by dental cement and a stainless steel screw.

The blood for the Astrup test (PaO_2 , PaCO_2 and pH) was taken from the ear artery and was measured by means of BG-3 Instrumentation Laboratory.

The catheters for the measurement of arterial blood pressure were placed in the femoral artery under short halothane anaesthesia and the incision was infiltrated with 0.5% Novocain. Arterial blood pressure was estimated directly by means of a mercury manometer.

Electrical stimulation of SC

Monophasic pulse of 0.5 m/sec duration and 60 Hz frequency were generated and delivered through an isolation unit. The stimulus current was quantified by an oscilloscope. The stimulus intensity was progressively raised to 100 μ A and then maintained constant during the HBF measurement.

Experimental protocol

Before the experiments were carried out every animal had been accustomed to restraint for several times. The animals were restrained in standard box. They could move their heads but they could not freely move their trunks and limbs. The rabbits did not appear to be distressed by the procedure.

On the day of experiments, the rabbits were placed in standard box at least for 1 hour to adapt them to the environment, with the leads connected to the reference-, measure- and stimulation electrode. The control HBF values were obtained by measuring HBF at the least three times, (at 10–15 minutes intervals), before the stimulation and after it.

Histological location of stimulation sites

To identify the location of the electrode tips an electrolytic lesion was made by passing a direct current of 0.15 mA during 30 s through the electrode. After sacrificing the animal with excess phenobarbital the brain was removed and fixed in paraffin, cut in frontal section of 10 μ m using a microtome and stained by the Nissl method. The position of the marks of the electrode tips were then estimated by a light microscope.

Data analysis

The statistical treatment was applied to the HBF responses of the stimulated sites which fulfilled the following two conditions: 1) the sites were correctly located in or close to SC; 2) the responses were not associated with a general perturbation, i.e. not associated with movements involving the whole body or excitation.

The HBF values were calculated by manual analysis from the initial slope, the mono-exponential part of the desaturation curve was reported on semilogarithmic paper. The data are presented as mean \pm SD. The responses to stimulation were evaluated by comparison with the mean of three control values, was used paired t-test.

Results

Stimulation sites

14 rabbits were investigated and histologically localised. Of these 9 were considered to be correctly located in the SC region, of which 7 fulfilled the criteria for the specific responses defined in Material and methods. The 2 others gave rise to perturbed responses and were excluded from the analysis.

Effects of stimulation of the SC region on the systemic variables and behaviour.

Table 1. Effect the stimulation on the systemic variables

Variables	Control	Stimulation
MaBP mmHg	84-4.2 (3)	86-4.2 (3)
PaCO ₂ mmHg	75-3.8 (5)	37-2.3 (5)
PaO ₂ mmHg	75-3.8 (5)	76-3.0 (5)
pH	7.4-1.7 (5)	7.3-2.1 (5)

MaBP - mean arterial blood pressure, PaCO₂ - arterial CO₂ tension, PaO₂ - arterial O₂ tension. The number in parenthesis is the number of rabbits. All values are expressed as mean \pm SE.

No significant changes in these variables were caused by SC stimulation.

Most of the stimulation's were associated with stereotyped movements of the head such as chewing and vibration of the vibrissae, which ceased as soon as the stimulation was stopped.

Effect of SC stimulation on HBF

The effect of SC stimulation on absolute flow values and on percentage under control conditions are given in Table 2.

Table 2. Effect of SC stimulation on the HBF

Animal No.	Control	Stimulation	%
2	132-4.7	173-3.6	31
3	115-1.4	156-2.9	36
5	61-2.9	83-12.8	37
9	52-5.9	60-4.1	15
12	122-6.1	165-11.6	35
13	69-3.4	89-4.5	28

All values are expressed as mean \pm SE in ml / 100g / min. $p < 0.05$ compared with control level (paired t-test).

The stimulation of SC for a period of 40 s ($< 100 \mu\text{A}$, 60 Hz) in unanesthetized rabbits resulted in an increase of HBF up to about 30% of the control level ($p < 0.05$).

Discussion

The present study shows for the first time that direct activation of SC in the basal forebrain of unanesthetized rabbits induces vasodilatation (30%) in the dorsal hippocampus, which is the densest area of projection of this cholinergic system. These results are in accord with the previous results, which have been achieved using different CBF measurement methods and different laboratory animals [4-6].

Although the mechanism of the stimulation action was not determined in the present study the possible explanation is that stimulation activates the cell bodies of the cholinergic neurones located in these areas, resulting in an increased release of acetylcholine in the hippocampus, and then stimulates the chain of events leading to a rise of HBF. This view is also supported by the findings confirming that electrical stimulation of SC enhances the release of acetylcholine in the hippocampus [3, 9] and stimulates the neuronal activity of the hippocampus [10].

However, the most reasonable explanation is that cholinergic neurons originating in SC are responsible for the vasodilatation of the vessels in the hippocampus. The ability of cerebral vessels to dilate in response to acetylcholine, either exogenously administered or endogenously released, has been extensively documented [11, 12]. Further, there is evidence that cerebral vessels are innervated by cholinergic nerves [13, 14] and an endothelium derived relaxing factor (has since been shown to be nitric oxide) act as vasodilator during acetylcholine induced vasodilatation of blood vessels [15, 16]. Therefore, it is probable that an increase of HBF depends on these potent vasodilator substances, acetylcholine and nitric oxide, but does not depend on an increase in metabolic activation caused by the neuronal activity, as has been proposed [4].

Previously it had been reported that the increase in HBF due to chemical stimulation of neurons in SC with micro injection of L - glutamate is not influenced by i.v. administration of atropine, but almost totally abolished by successive i.v. administration of mecamylamine (n-cholinoblocator) [4]. Such evidence suggests that the central cholinergic system originating in SC contributes to the hippocampal vasodilative response via activation of nicotinic cholinergic receptors. On the

other hand the increase in HBF due to electrical stimulation of SC is not significantly influenced after i.v. injection of atropine alone or after successive i.v. administration of mecamlamine [4]. These results suggest that non-cholinergic fibers, passing through SC contribute to these hippocampal responses induced by electrical stimulation of SC.

In conclusion, there is a possibility that cholinergic septo-hippocampal nerve fibers act as an intracerebral vasodilator system for hippocampal blood vessels. One can suggest the hypothesis that central cholinergic vasoactive fibers function to provide a brief preparatory increase in rCBF prior to the vasodilatory action of local metabolites [17]. Probably the septal cholinergic vasodilative fibers have a role in the preparatory increase in HBF. In regard to enhancement of the HBF a transient activation of this system may be sufficient to oxygenate the tissue, prior to the generation of metabolites.

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HEMODYNAMIC EFFECTS OF CALCIUM ANTAGONISTS IN STROKE PATIENTS

T. Tomberg, M. Mägi, T. Kauba

The changes of regional CBF, EEG, central hemodynamics and arterial pressure after the intravenous injection of verapamil (Finoptin or Isoptin, 5–7.5 mg, 35 cases) or nimodipine (Nimotop, 1–1.5 mg, 18 cases) were investigated and CT was performed in the acute stage of cerebral infarction. According to our data, both drugs caused an increase of the initially decreased rCBF in the low density areas, a moderate shift to faster frequencies in EEG and a slight decrease of arterial pressure without any significant changes of central hemodynamics. The effect was more pronounced after nimodipine. In the hyperemic and non-involved areas the rCBF decreased or did not change. No cerebral steal phenomenon was noticed. It was concluded that in the acute stage of brain infarction calcium antagonists have a favourable effect on the cerebral circulation and functional activity.

The role of calcium ions in the pathogenesis of ischemic brain damage has become increasingly evident during the last decade. Calcium plays an essential role in the regulation of cellular homeostasis controlling the excitability of neuronal and neurochemical events at membrane and cytoplasmic levels [1, 2]. A number of experimental and clinical data have been published about the beneficial action of calcium entry blockers in ischemic brain damage [3, 4]. Two modes of action are attributed to calcium channel blockers: 1) a cytoprotective effect with prevention of calcium overload in the neurons; 2) increase of cerebral blood flow due to the antivasoconstrictive effects through the direct action on the smooth muscle cells and secondarily via the inhibition of vasoconstrictive substances.

In the experimental studies calcium channel blockers lessened the consequences of global cerebral ischemia [5] and resolved vasospasms following subarachnoid haemorrhage [6]. In patients with cerebrovascular disorders they caused an increase of global or regional CBF [7] and dilatation of pial vessels [8]. Calcium antagonists are also able to prevent cerebral vasospasm in cases of subarachnoid haemorrhage [9].

Clinical studies have shown the beneficial effect of calcium antagonists on neurological recovery in patients with focal cerebral ischemia [10, 11, 12]. The aim of the present study was to investigate the acute effects of calcium antagonists of the verapamil and nimodipine type on regional cerebral blood flow (rCBF), cerebral functional

activity (EEG) and central hemodynamics in patients with acute cerebral infarction. This study continues our previous investigations of the effect of vasoactive drugs on rCBF and EEG in patients with cerebral infarction [13, 14].

Methods

rCBF was measured by means of the intracarotid Xenon-133 clearance method using the system "Xenon-1". The calculations of CBF were made on the basis of the height/area method. rCBF has been measured in three relatively large regions — frontal, temporal and parietal regions on the affected side. Two types of Ca entry blocking drugs were used — verapamil (Isoptin, Finoptin) and nimodipine (Nimotop) type. The CBF investigations were made before and after the intravenous administration of 5–7.5 mg Isoptin or Finoptin (Group I, 25 patients) or 1–1.5 mg Nimotop (Group II, 18 patients) in 20 ml of saline. 29 patients were men and 14 women, their age varied from 36 to 87 years, the mean age was 64 years. 36 patients had cerebral infarction in the territory of the middle cerebral artery and 7 patients in the vertebrobasilar system. 18 cases were examined during the first week of the illness, 12 during the second week and 13 during the third week of the illness. Monitoring of arterial blood pressure and heart rate were performed during every investigation. Most patients underwent a computerized tomographic examination (CT) of the brain using the scanner "Delta-scan 190" (Technicare, matrix 256 x 256 elements) and CT-CBF correlations were made. On the CT scans the localization and volume of the lesion and severity of brain edema (ventricular compression and/or mid-line shift) were evaluated. The whole lesion volume was represented by the sum of lesions in different slices.

Before and during 20-30 minutes after the intravenous injection of the investigated drug EEG, ECG and pneumogram were registered by means of a 17-channel "Nihon Kohden" electroencephalograph and frequency analyzer MAF-5. Mean integral values of 2–4, 4–8, 8–12, 12–20 and 20–30 waves per second frequency bands were measured and EEG Integral Index (I.I._{EEG}) was calculated by dividing mean integral values of — and — activities to mean integral values of α , β_1 and β_2 activities. Normal values of this index in older age are 0.68 ± 0.02 in F – O and 0.71 ± 0.02 in C – T recording. Central hemodynamics was investigated by a noninvasive technique, the whole body integral rheography. Heart rate (HR), left ventricular stroke volume and its respiratory changes, cardiac output, left ventricular stroke index (LVS) and cardiac index (CI) were evaluated.

Results

The mean hemispheric rCBF before the drug administration in both groups of patients (Table 1 and 3) was slightly lower as compared with normal CBF values in their age. More marked reduction of rCBF was revealed in the region of infarction, which corresponded to the low density area on CT. rCBF was especially reduced ($p < 0.05$) in patients with a large infarction (volume of the low density area between 140–250 cm³ on CT) and cerebral edema (mass-effect on CT).

After the intravenous injection of isoptin (Group I) the mean rCBF increased in 7 patients, reduced in 13 patients and in 4 patients it did not change. The mean rCBF in Group I reduced by 9%, but this change was statistically not significant (Table 1). Isoptin had also some hypotensive effect on the systolic and diastolic blood pressure, the heart rate decreased slightly.

CBF-CT correlations showed that in the territory of infarction rCBF increased significantly, on average by 19 percent, whereas in the other regions it decreased by 12 percent.

A pronounced increase of rCBF was observed mainly in the regions with marked ischemia before the administration of Isoptin, which took place in the case of a large infarction (+28%), brain edema (+14%) and brain atrophy (+15%). But in the regions of relative or absolute hyperemia a decrease of rCBF was observed (by 17%). No intracerebral steal phenomenon was noticed.

The rCBF changes corresponded well with the shifts of the EEG frequency content. As is demonstrated in table 2, the shift of I.I._{EEG} to normalization can mostly be seen on the side of infarction, especially in the cases of large infarction with severe hemiplegia (from 1.51 ± 0.12 to 1.12 ± 0.18 ; - 26% in C - T recording).

No significant changes of central hemodynamics were observed, except a mild tendency to decrease of the vascular tone.

The results for Group 2 showed that after the intravenous administration of Nimotop the mean rCBF increased in 8 cases, was reduced in 1 case and in 9 cases it did not change. The mean rCBF of all patients increased by 19.6% ($p < 0.05$). There was also a slight decrease of systemic blood pressure and heart rate.

CBF and CT correlations revealed a significant increase of rCBF in the region corresponding to the low density area in CT (+ 20%, $p < 0.05$) without any changes in noninvolved areas. A more marked increase of rCBF was noticed in the regions with severe ischemia before drug administration. In hyperemic areas Nimotop caused a decrease of rCBF ($p < 0.05$).

The effect of Nimotop on rCBF was more pronounced in the first and second week of the illness, in patients with cortical infarctions as compared with patients with subcortical infarctions and in normotensive patients, compared with hypertensive patients. We did not observe such differences using Isoptin.

In one patient Nimotop caused a marked decrease of blood pressure and heart rate accompanied by a decrease of rCBF in all regions. No intracerebral steal phenomenon was noticed in this material.

The changes of EEG and central hemodynamics were similar to those described after the Isoptin or Finoptin administration.

Discussion

During ischemia, the Ca^{++} ion homeostasis is impaired and the intracellular Ca concentration increases. This is an important factor for a number of adverse reactions of cellular metabolism. The accumulation of intracellular Ca in vascular smooth muscle cells produces vasoconstriction which impairs the microcirculation [15]. Calcium entry blockers can modify these processes, but whether calcium antagonists can improve brain perfusion in patients with cerebral infarctions is still unclear.

According to this study the calcium entry blockers of the verapamil and nimodipine type increased rCBF in the ischemic areas (initial rCBF under 40 ml). This effect was more marked using nimodipine, which is a selective cerebrovascular calcium antagonist [3]. The improvement of cerebral perfusion was mostly observed in the regions corresponding to the low density areas on CT, while in noninvolved areas the changes of rCBF were mild. The preference of Nimodipine activity for low perfused areas in stroke patients was also demonstrated by Gaab et al [16]. The increase of blood flow in the ischemic areas is probably due to a certain vasodilating effect on constricted vessels. In the hyperemic areas both drugs led to the reduction of the perfusion. Analogous results have been published in earlier studies [5, 17]. The reduction of CBF in preceding hyperemia may be caused by the redistribution of the flow and certain vasodilatation in the surrounding regions. It seems to be a favourable reaction, which could diminish the development of brain edema in the hyperemic areas.

This study did not reveal any "steal" phenomenon from the ischemic area to the surrounding brain tissue, which is observed using the traditional vasodilators, papaverin or cavinton [13, 14]. These data are in agreement with those presented in the literature: no indication

for a steal effect could be seen by comparing the reaction of the unequally perfused regions [17]. So we can assume that the vasodilating effect of calcium blockers is not limited to regions with normal vascular reactivity, which is important in the clinical use of the drug.

Calcium antagonists of the verapamil and nimodipine type caused also some hypotensive effect on arterial blood pressure (mean decrease 4–12 %), which in a few cases could even cause a decrease of cerebral blood flow.

Quantitative EEG investigations confirmed the most pronounced positive effect of Ca-blockers on brain functional activity in regions with severe brain infarction and large motor deficit. Both rCBF and EEG changes were considerably reduced in noninvolved areas on the side of infarction, the EEG changes were also minimal on the opposite side. In our opinion, these facts confirm the regulatory effect of Ca-blockers on impaired brain perfusion during acute brain infarction. As there were no significant changes of extracellular central hemodynamics, this effect probably was caused by a direct action of Ca-blockers on brain vessels and neurons.

Table 1. Effect of Isoptin on rCBF ($\text{ml} \cdot 100\text{g}^{-1} \cdot \text{min}^{-1}$, $\bar{x} \pm m$) in patients with cerebral infarction

rCBF	Before administration	After administration	(%)
Whole group	42.3 \pm 2.8	38.4 \pm 1.9	-9
Initial rCBF:			
less than 40 ml	24.1 \pm 1.5	27.7 \pm 1.2*	+15
40–55 ml	47.6 \pm 1.3	44.2 \pm 1.2	-7
over 55 ml	69.1 \pm 4.3	56.3 \pm 5.6	-18
Low density area	25.8 \pm 2.3	30.8 \pm 2.1*	+19
Noninvolved area	49.1 \pm 4.9	43.1 \pm 3.9	-12
Brain edema:			
low density area	25.0 \pm 3.1	28.4 \pm 2.2	+14
noninvolved area	48.0 \pm 6.6	40.5 \pm 8.5	-16
Without edema:			
low density area	34.9 \pm 4.6	38.8 \pm 3.3	+5
noninvolved area	50.8 \pm 5.0	41.0 \pm 2.8	-19
Large infarction	20.5 \pm 2.3	26.3 \pm 1.8*	+25
Small infarction	34.8 \pm 4.1	35.0 \pm 3.4	+1

* $p < 0.05$

Table 2. The EEG Integral Index (I.I.EEG) in C - T recording before and after the intravenous administration of 5 mg Finoptin ($\bar{x} \pm m$)

	On side of infarction			On opposite side		
	Before	After	%	Before	After	%
Whole group	1.20 \pm 0.11	1.20 \pm 0.09	-15	0.91 \pm 0.06	0.90 \pm 0.06	-1
Patients:						
-with hemiplegia	1.51 \pm 0.12	1.12 \pm 0.18	-26	0.92 \pm 0.07	0.90 \pm 0.05	-2
-mild hepiparesis	1.05 \pm 0.07	1.00 \pm 0.06	-5	0.92 \pm 0.10	0.95 \pm 0.11	3
-with blood pressure less than 160/95 mmHg1.	47 \pm 0.19	1.16 \pm 0.18	-21	0.96 \pm 0.08	0.92 \pm 0.08	-4
-with blood pressure over 160/95 mmHg	0.95 \pm 0.05	0.89 \pm 0.08	-6	0.85 \pm 0.07	0.78 \pm 0.05	-8

Table 3. Effect of Nimotop on rCBF ($\text{ml} \cdot 100\text{g}^{-1} \cdot \text{min}^{-1}$, $\bar{x} \pm m$) and parameters of central hemodynamics in patients with cerebral infarction

Parameters	Before administration	After administration	(%)
rCBF whole group	34.1 \pm 1.8	40.8 \pm 2.4*	+19.6
Initial rCBF:			
less than 40 ml	28.8 \pm 1.3	36.8 \pm 2.3*	+27.7
40-55 ml	44.3 \pm 1.0	52.9 \pm 3.7*	+19.4
over 55 ml	75.8 \pm 9.8	47.1 \pm 4.5*	-37.8
Low density area	39.4 \pm 3.7	47.3 \pm 3.6*	+20.0
Noninvolved area	34.3 \pm 1.9	34.0 \pm 2.3	-0.8
Cortical infarction	37.6 \pm 3.2	44.3 \pm 4.7	+17.8
Subcortical infarction	36.0 \pm 1.8	35.4 \pm 3.2	-1.6
Hypertensive patients	31.2 \pm 2.4	31.9 \pm 3.5	+2.0
Normotensive patients	35.2 \pm 2.2	44.1 \pm 2.9*	+25.0
Time of investigation:			
I week	32.3 \pm 4.2	42.6 \pm 1.9*	+31.8
II week	28.7 \pm 4.6	37.1 \pm 7.2	+20.0
III week	31.3 \pm 2.8	33.8 \pm 3.3	+7.9
Blood pressure:			
systolic	149 \pm 6.1	141 \pm 6.1	-5.0
diastolic	89 \pm 3.1	78 \pm 3.5*	-12.0
Heart rate	87 \pm 4.0	81 \pm 3.0	-7.0
CI	4.48 \pm 1.8	4.85 \pm 2.14	+8.0
LVSI	0.055 \pm 0.02	0.057 \pm 0.02	+3.6

* $p < 0.05$

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EFFECT OF SERMION ON CEREBRAL BLOOD FLOW IN PATIENTS WITH BRAIN INFARCTION

T. Tomberg, M. Mägi

The effect of Sermion on rCBF, EEG, ECG, respiration and arterial pressure after the intravenous injection of 4mg drug was investigated and CT was performed in 22 patients with ischemic stroke. An increase of the mean rCBF, diminishing of slow activity in EEG and decrease of blood pressure were noticed without any changes of heart and respiration rate. There was some unfavourable hemodynamic effect after using Sermion in some individual cases (intracranial steal phenomenon, systemic hypotension, bradycardia).

Vasodilators are commonly used for the treatment of cerebral vascular disorders. They can improve the collateral circulation in the brain and increase cerebral blood flow (CBF) in critically hypoperfused areas. However, in the acute stage of cerebral infarction unfavourable hemodynamic effects may also occur due to the impairment of CBF autoregulation. The mechanism of action of cerebral vasodilators in cases of acute infarction can differ in various vascular areas depending on the actual hemodynamic situation and the pre-existing state of the vessels [1].

Among the cerebral vasodilating agents Sermion is widely recommended for the treatment of cerebrovascular disorders, but its effect on the cerebral circulation in patients with an acute ischemic stroke is not clear.

Sermion (Nicergoline, Farmitalia Carlo Erba) is a derivative of ergoline, which has alpha-adrenolytic, myogenic vasodilating and metabolic effect on the central nervous system [2]. It decreases cerebral and peripheral vascular resistance, reduces the mean arterial pressure and increases the cerebral blood flow [3]. The platelet antiaggregating action of Sermion as also been demonstrated [4].

The aim of this study was to investigate the acute effect of Sermion on the cerebral circulation, brain functional activity (EEG) and autonomic function in the acute stage of cerebral infarction (CI). The present study continues our previous investigations of the effect of vasoactive drugs on rCBF and EEG in patients with CI [5, 6].

Material and methods

The effect of Sermion was investigated in 22 patients, among them 11 men and 11 women. Their age varied from 42 to 85 years, the mean age was 70 ± 2 years. 20 patients had CI in the territory of the middle cerebral artery, 1 patient in the vertebrobasilar system and 1 patient had a spontaneous subarachnoid hemorrhage. The clinical severity of CI was estimated according to the clinical state of the patients and its dynamics. 12 patients had mild or moderate neurological signs and 10 patients had severe hemiparesis or hemiplegia. 2 patients died during the acute period of CI. Before and after the intravenous administration of Sermion (4 mg in 20 ml of saline) the following investigations were made.

rCBF was measured by means of the intracarotid Xenon-133 clearance method using the system "Xenon-1". The calculation of CBF was made on the basis of the height/area method. rCBF has been measured in three relatively large regions – frontal, temporal and parietal regions on the affected side. 8 patients were examined during the first week of the illness, 6 patients during the second week and 8 during the third week of the illness. Monitoring of arterial blood pressure and heart rate frequency were performed during every investigation.

20 patients underwent a computerized tomographic examination (CT) of the brain using the scanner "Delta-scan 190" (Technicare, matrix 256×256 elements) and CT-CBF correlations were made. On the CT scans the localization and extent of the lesion and severity of brain edema (ventricular compression and midline shift) were evaluated. Quantitatively cella media index in each hemisphere was calculated dividing the width of the brain at the level of cella media to the width of the hemisphere at the same level and interhemispheric ratio of these indices was established (normal value is 1.0 ± 0.02).

The EEG recordings were made using the 17-channel "Nihon Kohden" apparatus with frequency analyzer MAF-5, electrodes were located according to the international "10-20" system.

Results

According to CT examinations the hypodensity areas could be seen in 15 patients: in 6 cases on the whole territory of the middle cerebral artery, in 6 cases in the region of its one or two cortical branches and in 3 cases in the paraventricular deep structures. In 5 patients CI was isodense. There was brain edema in 9 cases (interhemispheric ratio of cella media indices 1.217 ± 0.05) and diffuse brain atrophy in 10 cases.

The mean hemispheric rCBF before the drug administration (Table 1) in all patients was significantly lower as compared with normal CBF values for their age. More marked reduction of rCBF was revealed in the region of infarction, which corresponded to the low density area on CT ($p < 0.05$). rCBF was also significantly reduced ($p < 0.05$) in cases with a large infarction in the whole territory of the middle cerebral artery and in patients with severe clinical state. But there was no correlation between the level of the mean CBF and the extent of CI ($r = -0.179$). A slight adverse correlation between the mean CBF and cella media index on the affected side was revealed ($r = -0.296$).

After the intravenous injection of Sermion the mean rCBF increased in 13 patients, was reduced in 4 cases and in 5 cases it did not change significantly. The mean rCBF increased by 15%, $p < 0.05$, (from 31.5 ± 1.2 to $36.1 \pm 2.2 \text{ ml} \times 100 \text{ g}^{-1} \times \text{min}^{-1}$, Table 1). The number of ischemic regions was reduced after Sermion (from 53 to 44 recordings), the number of normally perfused and hyperemic areas increased (from 6 to 13 and from 3 to 5 recordings, respectively).

A pronounced increase of rCBF was observed mainly in normally perfused areas (+23%), in ischemic and hyperemic areas the effect of Sermion was less (+14% and +18% respectively). rCBF and CT correlations revealed a significant increase of rCBF in the regions corresponding to the low density area on CT (+22%, $p < 0.05$) and relatively small changes in noninvolved areas (+5%). The drug caused also a significant increase of rCBF in cases of brain edema (ventricular compression and midline shift on CT), which was mostly seen in large infarctions (in the whole territory of middle cerebral artery).

The increase of the mean rCBF was higher in patients with arterial hypertension (+31%) than in patients with normal blood pressure (+9%).

The effect of Sermion on rCBF was more pronounced in the first week of the illness (+22%) than in the second (+13%) and third week (+7%), but these differences were statistically not significant.

In 4 patients the administration of Sermion caused a decrease of the mean rCBF: in 1 case from the hyperemic area, but in 3 patients from the ischemic areas. The reduction of the mean rCBF was within the limits from 4 to $15 \text{ ml} \times 100 \text{ g}^{-1} \text{ min}^{-1}$. The small reduction of rCBF in a single registration area was revealed in 6 more cases. In one case the significant decrease of the cerebral perfusion was connected with the development of bradycardia after the administration of Sermion (the decrease of the heart rate from 78 to 54).

Table 1. Effect of Sermion on rCBF ($\text{ml} \times 100\text{g}^{-1} \times \text{min}^{-1}$, $\bar{x} \pm m$) and parameters of central hemodynamics in patients with cerebral infarction

Parameters	Before administration	After administration	%
rCBF whole group	31.5 \pm 1.2	36.1 \pm 2.2*	+15
Initial rCBF:			
less than 40 ml	26.7 \pm 0.9	30.5 \pm 1.3*	+14
40-55 ml	44.1 \pm 1.7	54.3 \pm 3.4*	+23
over 55 ml	73.1 \pm 13.7	86.6 \pm 10.7	+18
Low density area	29.6 \pm 1.9	36.2 \pm 2.6*	+22
Noninvolved area	41.5 \pm 6.8	43.7 \pm 6.1	+ 5
Brain edema	34.3 \pm 1.9	44.8 \pm 3.0*	+31
Without edema	32.2 \pm 3.0	34.7 \pm 3.3	+ 8
Large infarction	29.4 \pm 1.7	36.4 \pm 3.1*	+24
Small infarction	35.1 \pm 3.3	38.7 \pm 3.9	+10
Hypertensive patients	33.3 \pm 3.6	43.7 \pm 3.0*	+31
Normotensive patients	31.0 \pm 2.7	33.8 \pm 3.1	9
Time of investigation:			
I week	31.6 \pm 5.6	38.6 \pm 5.5	+22
II week	29.4 \pm 1.8	33.4 \pm 3.5	+13
III week	32.9 \pm 2.4	35.4 \pm 4.2	+ 7
Blood pressure:			
systolic	159 \pm 6	137 \pm 6*	-15
diastolic	93 \pm 4	79 \pm 4*	-16
Heart rate	84 \pm 3.5	85 \pm 3	1

* $p < 0.05$

Sermion caused a marked hypotensive effect ($p < 0.05$) on systolic (-15%) and diastolic (-16%) blood pressure. There was also a slight increase of the heart rate in connection with carotid artery puncture, without any significant further changes after Sermion.

The EEG changes were not significant. The increase of rCBF in hypoxic areas and in low density areas by CT corresponded to a slight shift to faster frequencies in EEG.

Discussion

A number of factors have been identified following acute cerebral infarction which may result in decreased cerebral blood flow. These include arterial obstruction, increased intracranial pressure due to cerebral edema, systemic hypotension and local factors affecting

vascular tone such as the release of tissue metabolites and biproducts of cellular damage [7-9]. It can lead to a longlasting postischemic hypoperfusion, impaired microcirculation and secondary loss of neuronal tissue [10]. Vascular resistance can be regulated by various types of pharmacological agents, including pre- or postganglionic blockers of the sympathetic nervous system, - adrenoceptor blockers, stimulators of β_2 -adrenergic, histaminergic or dopaminergic receptors in the vessels, blockers of calcium channels in the muscle cell membrane and drugs that relax vascular smooth muscle directly without acting on a specific receptor [1]. Sermion has probably a combined mechanism of action: alpha-adrenolytic and directly vasodilating.

As can be seen in the present study, Sermion caused a significant rise of CBF and a hypotensive effect on arterial blood pressure due to the decrease of cerebral and systemic vascular resistance without any marked changes in cardiac function. These reactions were also demonstrated by other authors [3, 11]. But according to our study, Sermion as a typical vasodilator may cause "steal" phenomenon from the ischemic area to the surrounding brain tissue due to the different vascular reactivity in various areas. It may further impair the perfusion in an ischemic area.

There were some more unfavourable hemodynamic effects of Sermion. The marked increase of CBF not only in hypoperfused and normally perfused areas, but also in hyperemic areas may cause a rise in intracranial pressure due to an increase in the vascular bed [12]. There is also the possibility of producing deficit in cerebral circulation due to a general lowering of blood pressure in some individual cases already having systemic hypotension. According to this study, bradycardia and reduction of CBF are also possible as a consequence of using Sermion. Analogous results have been published in earlier studies [11]. After the administration of Sermion the pronounced increase of rCBF in low density areas (infarction) in cases of cerebral edema, large infarction and in hypertensive patients is probably related to the preexisting raised vascular resistance, which is regulated by local factors, such as adrenergic innervation, vasoactive metabolites, etc. As the influence of Sermion on the cardiac function and respiration according to our data was not significant, then the changes of rCBF were caused by the decrease of cerebrovascular resistance.

It was concluded that although the administration of Sermion can improve critically impaired cerebral perfusion and cerebral functional activity in patients with an acute ischemic stroke, paradoxical reactions of cerebral blood flow must be considered using this drug in clinical practice.

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NEUROTOXICITY OF LEAD: ALTERATION IN NEURAL TRANSMISSION AND CEREBRAL MICROVASCULATURE

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The review paper presents adverse effects of an injurious ecological factor — heavy metal lead — on nervous system. Probable pathogenetic mechanisms of neurotoxicity are altered calcium metabolism, disturbed neural transmission and inadequate cerebral microcirculation.

Introduction

There is ample evidence of real and potential hazards of environmental chemicals to the nervous system function. Changes or disturbances in the central nervous system function, usually manifested by vague complaints and alterations in behaviour, reflect on the quality of life; however, they have not yet received attention. Neurotoxicological assessment is therefore an important area for toxicological research.

It has become evident, particularly in the last decade, that low-level exposure to certain toxic agents can produce deleterious neural effect. While there are still episodes of large-scale poisoning, concern has shifted to the more subtle deficits that reduce functioning of the nervous system in less obvious, but still important ways so that intelligence, memory, and emotion and other complex neural functions are affected [1].

Lead intoxication is one of the most important toxicological problems. Analysis of ice layers belonging to past ages and of human skeletons of the past indicates that lead levels of recent generations of humans are thousands of times higher than those of early human populations [2].

Preliminary studies revealed a severe involvement of the nervous system in lead intoxication [3]. However, more attention was given to the impairment of its peripheral part, alteration of the functions in the central nervous system were not in the centre of interest. Therefore this study was proposed to deal with lead-induced changes in the brain and to analyze their possible mechanisms.

All biochemical effects of lead are undesirable. But this heavy metal is accumulating in our environment: the past decades have seen

an increasing interest in the possible effects of chronic non-occupational low-level intake of lead, as may occurring urban children exposed to dust containing the residuum of organolead petrol additives, or to old house-paint, or to acidic drinking water in old buildings with lead pipework and to residua of industrial pollution. Lead has been accumulating in soils, in waters and water-plants, it is also retained in the human organism (mainly in the skeleton, and in the brain too) [4].

No threshold for toxicity is apparent, suggesting that blood lead levels currently prevalent in industrial societies and previously thought to be safe may signify some degrees of risk of brain injury [5].

Nosological manifestations of lead intoxication

Lead exposure in high doses in humans, especially children, can cause encephalopathy with convulsions, stupor or coma sometimes followed by death [6, 7, 8]. In most countries, the occurrence of lead encephalopathy has progressively decreased due to legal action restraining the use of lead in paints, toys and pipes and as an additive in petrol [9, 10].

The extent to which sub-encephalopathic exposure to lead affects the central nervous system may widely vary. As cited in handbooks, vegeto-vascular disorders, headaches, asthenia, depression can be symptoms of lead-intoxication [11]. This heavy metal has been implicated among the causes of several neurological diseases including motor neuron disease [12, 13], presenile dementia with Alzheimer type changes [14, 15], diffuse demyelination of the cerebral white matter [16] and brain tumors in children [17]. Consequences of continuous low-level lead exposure are difficult to define. In these conditions overt symptoms of disease have not been found, but a deviation from the optimum state is obvious. The latter is expressed primarily by the higher functions of the brain and behavioural deficits [5, 18, 19].

For instance, the minimal brain dysfunction or hyperactivity syndrome is one of such diseases which includes different symptoms and can cause a decrease of a child's adaptation skill [18].

Toxicity of lead: altered neural transmission

Chemical synaptic transmission involves a complex series of events (synthesis and storage, release, reuptake or degradation of neurotransmitters, interaction of transmitters with postsynaptic membrane), any or all of which could be disturbed by neurotoxins [4].

In industrialized societies lead screening assays have shown relatively high lead levels in many children. The main concern is to know, whether these blood levels can produce subtle alterations in the function of the central nervous system. A lead exposure and neuropsychological deficits in children (behavioural and cognitive deficits, altered reaction time patterns) [5, 18, 19]. The latter is due to the fact that a developing nervous system is particularly sensitive to toxic effects of this heavy metal. The more critical period of life is supposed to be the age from 6 months to 3 years in several respects. For instance the organism of a child retains 50% of ingested lead, in adults only 10% [20]. In this period of life a very intensive formation of synaptic connections takes place, due to the increasing experiences of the infant [21, 22]. The efficiency of this processes supposed to be one of the main main targets of lead in the nervous system [23].

The basis of altered synapse formation is supposed to be disturbances in neural transmission. Many of the aberrations produced by lead appear to be related to the ability of this heavy metal to either inhibit or mimic the action of calcium [23 for review]. In the nervous system, calcium ions play a special role in the release of neurotransmitters from presynaptic nerve endings. Many investigators have focused on this aspect of function in describing the neurotoxic actions of lead. At low concentrations, lead enhances the spontaneous or basal release of neurotransmitters from presynaptic nerve-endings [24, 25, 26]. In addition to this effect lead blocks the release of neurotransmitters normally produced by depolarization of nerve endings, blocking voltage-dependent calcium channels [27, 28, 29]. The biphasic response of neurotransmitter release to lead with stimulation of the basal rate and inhibition of the depolarization-induced fraction may have special relevance to the immature nervous system. The continuous release of subthreshold amounts of neurotransmitter into the synaptic cleft is thought to have a trophic influence on maintaining the efficiency of a synaptic connection and the survival of the postsynaptic cell. Depolarization-induced release of presynaptic neurotransmitter, on the other hand, is responsible for producing the signal summation that excites (or inhibits) the postsynaptic cell. The trophic and functional events that these two types of activity produce in neural networks are particularly important during development [21].

The number of synaptic connections established during the first few years of life greatly exceeds the number that are present in the adult brain [30]. Pruning of excess synapses begins early in life and appears to be influenced by the experiences of the infant as represented by the amount and pattern of activity in specific neural networks [21]. The

precision of this relationship between experience and neuronal activity would be disrupted if lead increases basal neurotransmitter release and decreases the response of activated circuits in children. Since the pattern of neuronal activity appears to drive a pruning process, exposure to lead early in life may have a lasting adverse effect upon synaptic anatomy and brain function [31]. Such changes may underlie the effects of low level lead-exposure upon the learning skill and behaviour of young children in the absence of overt pathologic damage.

The above-mentioned processes are present mainly in a developing nervous system. The brain is exposed to minima amounts of lead throughout life. There are several other possibilities why neural transmission could appear as a target of the harmful effect of lead.

Several researchers have found changes in different receptor densities and affinities [32] and in concentrations of neurotransmitters in the brain of lead-exposed animals [33]. The data of several studies are difficult to interpret, but in general they suggest enhancement of catecholaminergic functions [34] and deficits in central cholinergic functions [28, 32, 35].

If the alteration of the presynaptic function of neural transmission might be due to the above-mentioned interaction between calcium and lead, no one single mechanism appears to account for the diverse effects of this heavy metal on postsynaptic function. Alteration in the structure of postsynaptic membranes could have different, and possibly coexisting mechanisms.

There are data indicating that lead may induce excessive free radical generation [36] and lipid peroxidation [37]. Inordinate lead induced lipid peroxidation could damage the structure of membrane receptors. It is well-known that heavy metals exhibit a high affinity for sulfhydryl groups. The acetylcholine receptor is known to contain sulfhydryl groups [38], the modification of which leads to an altered affinity of the receptor for cholinergic mediator.

Alterations of neurotransmitter metabolism also take place in the case of undue lead-burden in the organism. The ability of lead to interact with sulfhydryl groups of enzymes and interfere with their action [39, 40] and the lead-induced deficit of copper and zinc in the organism together with the altered function of enzyme-systems containing them [41] are both causes of disturbances in the turnover of neurotransmitters.

Altered synaptic transmission is often cited as a cause of different diseases of the nervous system. Presumably lead, altering steady state levels of neurotransmitters, could facilitate to bring out manifestations of several diseases.

Alteration of cerebral microvasculature

Lead exposure at high doses in humans, especially children, can cause encephalopathy, and in these cases neuropathological findings are mostly vascular changes often accompanied with vasogenic edema [42 for review]. Several laboratories have also obtained evidence suggesting that the capillary may be a vulnerable site in acute lead-exposure and it seems likely that capillary dysfunction underlies the pathogenesis of acute lead encephalopathy [43]. Results obtained in different investigations show that lower doses of lead also affect some of the important capillary functions, but these changes are rapidly reversible [44, 45]. Thomas and co-workers have demonstrated that 62 % of brain lead is associated with brain endothelial cells [46].

The damage of endothelial cells can alter microcirculation. There are data indicating changes of local cerebral blood flow (ICBF) [47] and vascular reactivity [48] in lead-exposed animals. These manifestations can be the consequence of alteration in the regulatory mechanisms of microcirculation. Minimal morphological alteration of endothelial cells may indicate a loss of their normal properties [49]. It is possible to discuss the endothelium alteration in different contexts, e.g. the interaction of the endothelium with platelets or role of endothelium as a source of mediators, controlling vascular tone or above-mentioned changes in neural transmission.

The above-mentioned lead-induced excessive free radical generation and lipid peroxidation can be one of the nodal points of endothelial malfunction. A free radical is cited as a prime candidate for the physiologic mediator of vascular tone regulation [50, 51] and the tone might be controlled by a balance of extremely short-lived radicals [49]. Lead induced excessive lipid peroxidation and free radical production could cause a disturbed balance of radicals and alter the physiological regulation of vascular tone.

Lead-induced excessive free radical generation can disturb vascular tone also in another way. It is well known that vascular tone is regulated by arachidonic acid metabolites. The observation of Deby and Deby-Dupont has shown, that radicals may both stimulate and inhibit prostaglandin production and suggest that opposite biological responses may be produced by radicals, depending on their concentrations and the balance achieved between stimulation and inhibition of prostaglandin synthesis [52]. The disturbed balance between thromboxane and prostacyclin can cause an inadequate vascular tone.

For several years such data have appeared which indicate that minimal endothelial injury is sufficient to initiate platelet aggregation

[53, 54]. Substances released by platelets may not only elicit a further aggregation and changes in microcirculation, but also injure the endothelium [55]. These substances may activate cyclo-oxygenase and disturb the balance of prostacyclin and thromboxane, which might be a cause of inadequate vascular tone.

The endothelial cell is known to be a rich source of chemicals that can be released into the local environment. These include also endothelial dependent relaxing factor(s) (EDRF). Rosenblum and co-workers have shown *in vivo* [56] that EDRF can be eliminated and/or interfered with by minor endothelial damage and in this situation endothelial cells are incapable of mediating endothelial-dependent relaxation by an acetylcholine and other dilating factors.

As has been indicated there exists innervation of cerebral microvessels and it plays a role in ICBF regulation [57 for review]. The above-described lead-induced dysbalance in neural transmission can interfere in the regulation of cerebral microcirculation and disturb adequate ICBF.

It is important to consider the ability of lead to mimic the action of calcium as regulator of cell function [23]. Because the contractile state of the vascular smooth muscle varies in proportion to the concentration of calcium in the cytoplasm, several investigators have tested the hypothesis that increased vascular reactivity is due to the ability of lead to alter cellular calcium metabolism. Chai and Webb proposed [48] that an important action of lead may be to alter the activity of protein kinase C and therefore modify subsequent cellular phosphorylation events leading to contraction. Markovac and Goldstein found that lead was more potent than calcium in increasing the activity of the enzyme. In addition, it was observed that lead may have a synergistic action with calcium in the activation of protein kinase C in cerebral microvessels and thereby can alter cerebral microcirculation [58].

The described heavy metal is considered as one of the pathogenic factors of such diseases as atherosclerosis and arterial hypertension. Data obtained in experimental and epidemiological investigations in recent decades have shown that chronic low-level lead intoxication causes an increase of arterial blood pressure, depending on the individual, up to 40 mmHg (average 15 mmHg) [59]. Several above-mentioned processes can be involved in the development of such changes in arterial blood pressure.

These are main risk factors of cerebrovascular diseases [60]. As has been shown by epidemiological investigation in groups with elevated blood lead levels the incidence of cardiovascular and

cerebrovascular diseases is higher than in groups with lower blood lead levels [61].

Therefore, the harmful effect of lead is multifarious and has become more serious and widespread in the present time. Particularly important is to emphasise the injurious effect of this heavy metal on neural transmission and manifestations which lead to impairment of the microvascular system.

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CHANGES OF LOCAL CEREBRAL BLOOD FLOW AND CEREBROVASCULAR REACTIVITY CAUSED BY LEAD EXPOSURE IN ADULT RABBITS

Ü. Linnamägi, A. Schotter, A.-E. Kaasik.

The ICBF and vascular reactivity to CO₂ (VR) were investigated in hypothalamus and cerebral cortex in rabbits by hydrogen clearance method during and after lead exposure (40 mg/kg 10 days). During lead exposure ICBF and VR were reduced in both investigated regions. Some days after the end of the protocol both investigated parameters had a tendency to increase compared to control group. 10 days after the end of the exposure ICBF and VR stabilized at control group level. The conclusion is that inorganic lead induces cerebral microvascular dysfunction which causes changes in ICBF and VR. These alterations have biphasic character.

Introduction

Neurotoxicity is one of the consequences of an undue lead burden and the mechanisms by which lead produces disturbances in the neural function constitute the basis of many current studies [1, 2 for review]. Endothelial cell alteration and cerebral microvessel dysfunction are often cited as a cause of neurotoxicity and is obviously important in lead induced encephalopathy [3, 4, 5, 6, 7, 8]. Lead may disturb many different processes in the cellular and molecular level and there is a possibility that the altered functional state of the brain microvasculature cannot ensure the adequate level of local cerebral blood flow (ICBF).

The aim of the present research was to assess the effect of different levels of lead exposure on the pattern of changes in ICBF and vascular reactivity (VR).

Material and methods

Animals. All experiments were performed on adult rabbits of either sex, weighing 3.5–4.5 kg. Animals were maintained on a standard laboratory diet and tap water *ad libitum*. Environmental temperature (22° ± 1°C) and humidity were controlled. The animals

were divided into two groups. In the first group they received lead acetate in dosing regime 40 mg/kg per day for 10 days. The second group was a sham-operated group, without lead administration.

Lead exposure regime. Solution of lead acetate in demineralized water ($\text{Pb}(\text{Ac}_2)$, 40 mg Pb/ml) was titrated to pH 5,5 with acetic acid to maintain solubility. Experimental animals were given 40 mg lead acetate per kg body weight per day by oral intubation for 10 days. Blood samples for lead analyses were taken from several lead treated and control animals just after ICBF measurements.

Lead analyses. Lead in the whole blood was measured by flame-method atomic absorption spectrophotometry (Philips PU 9100 X). The blood samples were mineralized with nitric acid and hydrogen peroxide.

Cerebral blood flow measurements. The hydrogen clearance method was chosen for ICBF determination because it enables repeated and long-term measurements in the unanesthetized animals [9, 10, 11]. At least 1 week before the first experiment on each rabbit a platinum glass sheathed microelectrode with a bare conical tip about 1 mm in length and 0.1 mm in diameter was stereotaxically inserted into precentral cortex (CTX) and lateral hypothalamus (HYP) on the left hemisphere and attached to the skull by dental cement. Polarization was at +0.3 V with a reference Ag/AgCl electrode, fixed on the left ear. Hydrogen gas was administered via the face mask so that the hydrogen concentration of the inhaled gases was 5–10% and the oxygen concentration was not altered.

Before the experiments were carried out, each animal had been accustomed to restraint for several times. The animals were restrained in conventional stocks, they were unable to move their heads but had a free range of movement of trunk and limbs. The rabbits did not appear to be distressed by the procedure.

The mean ICBF values in CTX and HYP were obtained before intoxication on three different days and thereafter on the 5th day of the exposure to lead and on the 1st, 5th, 10th day after the end of the protocol. In the control group the ICBF measurements were performed in same localisations of electrodes and in same time points.

Coefficient of reactivity. One measurement of ICBF was performed to determine the reactivity of microvessels each experimental day after the mean value of ICBF was obtained.

Reaction of microvessels was expressed as coefficient of reactivity (CR), calculated by the change of ICBF after the CO_2 content was increased in inspired gases.

$$CR = \frac{ICBF(CO_2)}{ICBF(\text{mean})}$$

where ICBF (CO_2) was the ICBF after CO_2 /air (5–7% CO_2) inhalation and ICBF (mean) was the mean value of 4–6 measurements of ICBF before the CO_2 inhalation.

Carbon dioxide inhalation via the face mask was started after the air/hydrogen mixture inhalation had been finished and before the beginning of desaturation of hydrogen. Normal value of CR is considered to range from 1.3 to 2.0 [12].

At the end of the study the brains were sectioned by freezing microthome to confirm the electrode's position and to observe any tissue alterations.

Data analysis. Statistics. The values of blood flow were calculated by manual analysis from the initial slope, the mono-exponential part of the desaturation curve reported on semilogarithmic paper. The mean values of 4–6 measurements, performed on each experimental day were used. The average value of ICBF mean values in three different days before the intoxication were considered as basal flow and all subsequent mean flow values were expressed as percentage of the basal flow. The mean value of CR (mean value of two different experimental days) before the intoxication was considered as an initial and changes were expressed as percentage of it.

The data are presented throughout as the mean \pm SD. For statistical comparison between groups the unpaired/paired Mann/Whitney tests were used.

Results

Effect of peroral lead-exposure on general appearance, body growth and blood lead-levels. Adult animals, administered a daily dose of 40 mg/kg lead-acetate/kg body weight during 10 days gained weight at the same rate as the control. Their gross behaviour was normal. Changes of blood lead concentration of the control group and lead-exposed groups are shown in Table 1.

Table 1. Lead concentrations in whole blood ($\mu\text{g}/100\text{ml}$) during the experiment (mean \pm SD)

Group	Before exposure	5th day of exposure	Days after exposure	
			1	10
40 g/kg	11.2 \pm 1.9	93.3 \pm 22.5**	138.3 \pm 40.7 **	53.3 \pm 7.6*
Controls	11.3 \pm 3.6	11.5 \pm 1.7	12.8 \pm 5.1	14.2 \pm 5.3

1) 3 animals in each group

2) * $p < 0.05$; ** $p < 0.01$

The values of ICBF in the control group. The values of ICBF in the control group showed a tendency to gradual decrease over 4 weeks, but those changes were statistically not significant when compared to mean values at the beginning of the experiment.

Changes of ICBF during and after lead exposure. Changes of ICBF during the experiment in CTX and HYP are shown in Table 2 and Figures 1 and 2.

Table 2. Changes of ICBF in cortex and hypothalamus during lead exposure, compared ICBF in control group (basal flow value is considered as 100 per cent and changes expressed as percentage of it)

Group	Region	Basal flow ml/100g/min	Changes of ICBF (% of basal flow)		
			5th day of exposure	Days after exposure	
				5	10
40 mg/kg	HYP	54.4 \pm 17.3	-19.9 \pm 4.6**	6.0 \pm 5.7	-21.3 \pm 21.0.
	CTX	35.4 \pm 7.7	-28.6 \pm 8.3 *	1.4 \pm 17.2	-10.0 \pm 16.8
Controls	HYP	47.5 \pm 9.2	0.5 \pm 10.5	-13.0 \pm 12.8	-15.6 \pm 12.0
	CTX	39.3 \pm 8.7	-8.9 \pm 14.1	-5.8 \pm 27.0	-9.9 \pm 19.3

1) 7 animals in each group

2) * $p < 0.05$, ** $p < 0.001$ compared to controls

3) HYP – hypothalamus, CTX – cerebral precentral cortex

4) all values are mean \pm SD

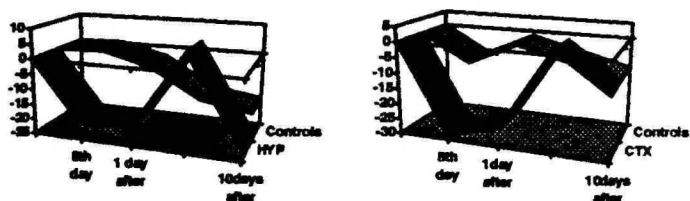


Fig. 1 and 2. Changes of ICBF in hypothalamus (HYP) and cortex (CTX) On the vertical axis changes expressed as % of basal flow, on the horizontal axis days during and after exposure.

Apparent decrease of ICBF on the 5th day of exposure in both investigated regions was observed ($p < 0.05$ for CTX, $p < 0.001$ for HYP when compared to controls).

On the 1st day after the protocol the mean values of ICBF in HYP and in CTX remained on the same reduced level as during the exposure, at the same time the interindividual variability of changes in ICBF was higher and in some experimental animals a tendency to an increase of ICBF was observed.

On the 5th day after the exposure in both regions a tendency to an increase of ICBF was noticed (changes statistically NS when compared to controls, due to high interindividual variability).

10 days after the exposure differences in the changes of ICBF in the control group and lead-exposed animals were not significant.

Coefficient of reactivity. Values of CR before and after the lead exposure are shown in Table 3 and in Figure 3 and 4.

Table 3. Changes of CR in cortex and hypothalamus during lead exposure compared control values (initial value is considered as 100 per cent and changes expressed as percentage of initial)

Group	Region	CR Initial value	Changes of CR (per cent of initial)		
			5th day of exposure	Days after exposure	
				5	10
40 mg/kg	HYP	1.64 ± 0.21	$-24.5 \pm 30.6^*$	$27.2 \pm 32.8^{**}$	-9.8 ± 12.1
	CTX	1.64 ± 0.20	-29.4 ± 37.2	$77.2 \pm 48.4^*$	1.6 ± 42.6
Controls	HYP	1.66 ± 0.27	1.5 ± 10.8	-5.4 ± 13.3	-7.1 ± 21.5
	CTX	1.40 ± 0.26	-17.3 ± 6.7	-11.5 ± 13.5	-12.3 ± 26.6

1) 7 animals in each group

2) * $p < 0.01$, ** $p < 0.001$ compared to controls

3) HYP – hypothalamus, CTX – cerebral precentral cortex

4) all values are means \pm SD

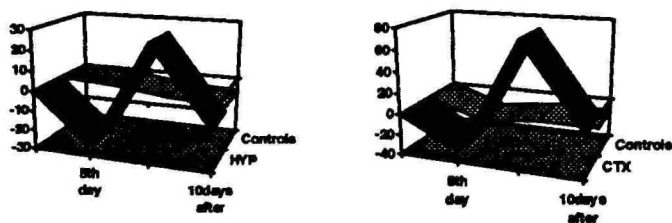


Fig. 3 and 4. Changes of CR during and after exposure in HYP and CTX. On the vertical axis are depicted changes expressed as % of initial, on the horizontal days during and after exposure.

On the 5th day of lead exposure CR decreased in both investigated regions (statistically significant only in HYP, $p < 0.01$). 1 day after the exposure, due to high interindividual variability of reactions (CR 0.91–2.65), mean values of CR remained in both regions approximately on the same level as before the exposure. 5 days after the end of the protocol CR was higher in lead-treated animals than in animals in normal physiological conditions (HYP $p < 0.001$, CTX $p < 0.01$). On the 10th day after the lead exposure had been finished CR remained on same level as in the control group.

Discussion

Choice of model and method. Animals. Most of the works reported so far have utilized infant animals in studying the effects of lead on the brain. The effects of lead on the mature central nervous system is of equal importance, especially in relation to present day environmental pollution. In this model adult animals were used, to exclude the differences in reactions, due to different maturity of tissues.

The lead exposure regime was chosen on the principle that concentration of lead in the blood should not cause gross histological changes as microhaemorrhages or brain swelling [8]. Oral intubation was chosen as a method of exposure, because it enables to estimate relatively accurately and minimise uncertainties of exposure, so that a daily definable dose could be administered [13].

Duration of exposure and days of ICBF measurements were based on the knowledge that on the third day of intoxication the concentration of lead in the blood reaches a stable state and falls rapidly after end of the exposure [14].

Basal flow The relatively low basal flow values obtained in the cortex are probably caused by the fact that the thickness of the rabbit cerebral cortex is approximately 2 mm, but the method used by us

measures the flow in a wider region [15] and desaturation curves can be changed by diffusional effects of hydrogen in the white matter. In such conditions the use of the initial slope of clearance curves has been recommended. However, to minimize errors arising from other sources, as recommended by Pearce & Adams [16], as much of the mono-exponential clearance curve as possible were used. The obtained values can reflect a slow and fast compartment of blood flow without needing multi-exponential analysis [17].

The values of ICBF in the control group The tendency to gradual decrease in flow over the experimental period (4–5 weeks) might be explained by moderate local tissue reactions due to tissue trauma. Such changes have been observed also by other investigators [18].

Possible mechanisms of ICBF disturbances Many different molecular and cellular processes might be involved in lead-induced changes in ICBF: disturbed balance of free radicals and lipid peroxidation [19, 20]; dysbalance in arachidonic acid metabolism [21]; ability of lead to inhibit or mimic the action of calcium and alter calcium mediated cellular processes [1, 22]; alteration of endothelium and activation of platelets [23, 24], altered neural transmission [25, 26, 27, 28].

One of the conclusions, which may be made on the basis of the performed investigation is possible impairment and in some cases abolishment of autoregulatory ability of microvessels due to increased lead burden in the organism. The normal value of CR is cited to range from 1.3 to 2.0, but in the lead treated group the values of CR indicated a tendency to decrease during the exposure and increase in some days after the end of the exposure.

Another conclusion of this study is the manifestation of the biphasic character of changes in ICBF and vascular reactivity during and after the lead treatment. During the exposure to lead ICBF decreased, together with reduced ability to dilate in response to CO₂, the physiological regulator of the vascular tone. After the end of the protocol an increase of ICBF was manifest and there was an excessive reaction to the CO₂ inhalation compared with the control group.

Several processes, as was pointed out earlier, might be responsible for the decrease of ICBF. In point of view of neural transmission, enhancement of catecholaminergic and reduction of cholinergic functions in overload of lead may have influenced such changes [25, 26, 27, 28]. Minimal endothelium alteration shown in lead intoxication [6] can alter functions of cerebral microvessels [3, 4, 6, 8]. Rosenblum & al have shown that a minor endothelial damage can induce incapability of microvessels of mediating endothelial dependent relaxation by acetyl-

choline and other dilators [29, 30, 31]. Activation and aggregation of platelets, due to endothelial damage by lead-induced excessive free radical generation or by disturbed balance of prostacyclin and thromboxane can be a cause a vasoconstriction and reduced cerebral blood flow [21, 23, 24]. High affinity of lead to calcium binding sites might excite protein kinase C and thereby cause vasoconstriction [32, 33, 34].

More disputable is the tendency of increasing ICBF after exposure to lead and excessive reaction after CO₂ inhalation. We are inclined to presume, that at this point the ability of the endothelium to ensure dilatation (to mediate endothelium-dependent relaxation and release relaxing factors) is restored.

An acceptable explanation of the biphasic response of the vascular tone to lead exposure may be based on the assumption reported by Rosenblum that free radicals might be a physiologic mediator of the vascular tone [31]. Lead is known to produce free radicals in the organism and thereby might cause a dysbalance in the physiological regulation. Certain investigators have shown that production of excessive free radicals in the organism can produce biphasic response — constriction in response to higher concentrations of reactants producing free radicals, which is followed by dilation [30, 36]. Some investigators obtained only a dilatory response of microvessels to free radicals production [35].

Deby and Deby-Dupont emphasize that radicals may both stimulate and inhibit prostaglandin production, and they suggest that opposite biological responses may be produced by radicals, depending on their concentration and the balance achieved between stimulation and inhibition of prostaglandin synthesis. This would be an explanation of dilation, if the concentrations of constrictor and dilator prostaglandins were differently affected by radicals [21].

It is possible that lead-induced disturbances in the synthesis of catecholamines [27, 37] are more clearly expressed a few days after the end of the protocol and contractile capability of microvessels is limited partially for this reason.

Many investigators have reported that lead-induced subtle changes in the vascular functional state are rapidly reversible [6, 38, 39]. On the 10th day after the end of the intoxication the blood lead levels decreased approximately to half of their maximal value, obtained during the exposition. The values of ICBF obtained at this point did not differ significantly from those in the control group. Our investigation of ICBF enables us to assert that changes of microvascular functions are reversible.

In conclusion, results of this study prove that moderate-level lead intoxication produces a biphasic reaction of changes in ICBF during and after the exposure and these disturbances are reversible.

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IS LEAD-INDUCED EXCESSIVE LIPID PEROXIDATION IMPLICATED OF ALTERATION IN LOCAL CEREBRAL BLOOD FLOW AND VASCULAR REACTIVITY?

Ü. Linnamägi, K. Zilmer, M. Zilmer

Lead ions are able to accelerate lipid peroxydation (LP) and, hence, induce cellular damage. Reactive oxygen species are implicated in the pathogenesis of various vascular disorders. There is evidence of lead-induced alteration of the steady state of LCBF. The purpose of the present study was to evaluate LP in brain tissue homogenates of the cerebral cortex and hypothalamus after short-time lead-exposure (5 and 10 days, 40 mg/kg). The basal level of thiobarbituric acid reactive substances (TBARS) and the Fe-stimulated part of the TBARS (Fe-TBARS) method were used for the evaluation of LP in the brain tissue. Another aim of the study was to test the possibilities of a correlation between LP changes and LCBF and VR changes detected before in the same exposure-model by the H₂ clearance method. A tendency to the enhancement of TBARS concentration in brain homogenates during and after the lead-exposure was found, this was more expressed on the 5th day after the exposure, especially in CTX ($p < 0.05$). The enhancement of the Fe-stimulated part of TBARS was more expressed 1 day after the exposure in both investigated regions of the brain (CTX $p < 0.05$, HYP $p < 0.001$ compared to controls). In the same exposure-model a biphasic reaction of changes in ICBF and VR was detected. During the exposure and 1 day after the protocol an 18–29% decrease of ICBF and VR was found ($p < 0.05$ to 0.001). At that time point the Fe-stimulated LP is showing significant enhancement. The results recorded on the 5th day after the exposure showed an evident tendency to increase of LCBF and especially VR, i.e. 27.2% ($p < 0.01$) in HYP and 77.2% ($p < 0.001$) in CTX. Considering, that LP at the same time points is significantly accelerated, there is a possibility that excessive LP production of free radicals may be a mediators of the vascular tone, depending on their chemical nature and concentration. It is concluded that lead induces excessive LP in brain which is more expressed on the 5th day after the exposure, especially in CTX. It is possible that changes in ICBF and VR are correlated with the intensification of LP.

Introduction

Undue lead burden in the organism can induce oxydative stress. Lead ions are able to accelerate Fe^{++} -dependent lipid peroxidation (LP) *in vitro* which may have physiological significance in lead poisoning [1]. It has been suggested that lead ions change the membrane structure, restricting phospholipid movement and facilitating the propagation of LP. If lead stimulated LP occurs *in vivo*, the tissue damage observed in lead-poisoning could be due to oxygen free radicals toxicity. The high activity of erythrocyte antioxydant enzymes in lead-exposed workers is consistent with oxygen radical involvement in plumbism [2].

The participation of free radicals in plumbism should be seriously considered. This may occur at three distinct levels. First, the aminolevulinic acid (ALA) overload, induced by lead inhibition of the haem biosynthesis pathway, could be a source of oxygen radicals formation *in vivo*, leading to extensive cellular lesions [3]. Secondly, the binding of Pb ions to biological membranes (to proteins and phospholipids) could facilitate propagation of Fe-stimulated LP. Thirdly, lead could accelerate LP induced by ALA-generated oxygen free radicals. Thus, tissue damage, leading to neurological dysfunction promoted by ALA-generated oxygen free radicals formation could be directly stimulated by lead [4].

Iron-derived reactive oxygen species are implicated in the pathogenesis of various vascular disorders including atherosclerosis and vasculitis [5]. There is evidence of alteration of steady-state of local cerebral blood flow (LCBF) [6, 7] and vascular reactivity (VR) [8].

Considering above mentioned results the aim of the present study was to evaluate LP in brain tissue homogenates in the cerebral cortex (CTX) and hypothalamus (HYP) after short-time lead-intoxication (10 days, 40 mg/kg) at different time points and to test the possibilities of a correlation between the detected changes and changes in LCBF and VR in same exposure model.

Material and methods

Twenty-two healthy adult rabbits were used in this study. They were maintained under standard ambient conditions. Experimental animals were given a daily solution of lead acetate in demineralized water ($\text{Pb}(\text{Ac}_2)$, 40 mg Pb/ml, 40 mg lead per kg body weight) by oral intubation for 5 and 10 days.

The brains of animals were removed for evaluation of LP at different time points. In the first group they were sacrificed on the 5th day of exposure to lead, in the second 1 day and in the third 5 days after a 10 day exposure period. The brains of 7 animals were removed for assessment of the basal level of LP in the brain. The tissue samples of different brain regions (cerebral precentral cortex and hypothalamus of left hemisphere) were separated for LP determination.

A compiled method set [9] was used for the evaluation of LP markers in brain tissue homogenates. The brain was homogenised in cold 1.25% KCl solution containing $3 \times 10^{-5}\%$ BHT (antioxidant). The concentration of BHT was sufficient to prevent any LP during the manipulation, but without effects on Fe-initiated TBARS. By the above mentioned set the values of diene conjugates (DC), the level of thiobarbituric acid reactive substances (TBARS) and Fe-stimulated part of TBARS (Fe-TBARS) were estimated.

The H_2 clearance method was chosen for the measurements of LCBF and VR in the same exposure model and time points (see previous article).

All data are presented as the mean \pm SD. Mann/Whitney unpaired — t-test was used to calculate the significance of differences between the groups.

Results and discussion

Changes of TBARS and Fe-TBARS in brain tissue homogenates in different regions are shown in Table 1.

Table 1. Values TBARS and Fe-TBARS in brain homogenates of HYP and CTX during and after lead-exposure

Region	nmol/g wet tissue	Controls (n=7)	5th day of exposure (n=4)	1 day after exposure (n=5)	5 days after exposure (n=6)
CTX	TBARS	25.0 \pm 5.8	28.3 \pm 4.3	28.2 \pm 12.4	33.0 \pm 3.4 *
HYP	TBARS	27.3 \pm 9.4	31.6 \pm 23.1	27.9 \pm 1.3	32.5 \pm 9.4
CTX	Fe-TBARS	128.5 \pm 33.2	133.9 \pm 22.3	166.3 \pm 20.1*	146.2 \pm 27.8
HYP	Fe-TBARS	135.7 \pm 15.5	150.3 \pm 22.5	170.9 \pm 18.4**	161.2 \pm 34.9

All values are mean \pm SD

* $p < 0.05$, ** $p < 0.001$ compared to controls

There is a clear tendency towards LP acceleration during the protocol. Enhancement of Fe-stimulated LP occurs more significantly 1 day after the lead-exposure ($p < 0.05$ in CTX, $p < 0.001$ in HYP) and has a certain tendency towards normalisation several days after the exposure. The gradual increase of basal LP in brain homogenates, reflected by changes in TBARS concentration, manifests itself significantly on the 5th day after the exposure, especially in the cerebral cortex ($p < 0.05$).

The results of time-course study in respect to DC are depicted in Table 2.

Table 2. Changes of DC ($\mu\text{mol/g}$ wet tissue) in brain tissue during and after lead exposure (40 mg/kg, 10 days) in different brain regions

Region	Concentration of DC ($\mu\text{mol/g}$ wet tissue)			
	Controls (n = 6)	5th day of exposure (n = 2)	1 day after exposure (n = 2)	5 days after exposure
CTX	130.5 \pm 44.5	122.9 \pm 30.6	175.1 \pm 22.6	207.9 \pm 8.3** (n = 4)
HYP	145.3 \pm 60.8	239.8 \pm 20.4*	174.5 \pm 34.6	188.6 \pm 13.0 (n = 3)

All values are mean \pm SD,
* $p = 0.08$, ** $p = 0.02$

As shown in table 2, the values of DC content have a significant tendency to increase during and after the exposure to lead, and changes are expressed more significantly in CTX.

These findings in basal LP coincide with the suggestion of Zhang and co-workers [10] who showed that in comparison with other regions of the brain CTX is more vulnerable to oxidative stress.

In the same exposure-model a biphasic reaction of the changes in LCBF and VR was detected. During the exposure and 1 day after the protocol an 18–29% decrease of LCBF and VR was found ($p < 0.05$ to 0.001). At that time point the Fe-stimulated LP showed significant enhancement.

The results recorded on the 5th day after the exposure showed evident tendency to increase LCBF and especially VR i.e. 27.2% ($p < 0.01$) in HYP and 77.2% ($p < 0.001$) in CTX.

As can be concluded, lead-exposure induced excessive basal LP in the brain and this was expressed more significantly on 5th day after the exposure and, hence, changes of LP coincided with the increase in ICBF and VR.

In several reports the role of oxygen free radicals in the endothelium-dependent regulation of the vascular tone is suggested [11 for review]. It is known that responsible for this action is nitric oxide (NO) [12]. Recently it was suggested that superoxide anions are responsible for endothelium-dependent contractions in several ways [13]. It is probable that this oxygen radical production is associated with prostaglandin synthesis and the vasoactive constrictive effects may be mediated through the generation of thromboxane A_2 [14]. Although superoxide anions may induce direct smooth muscle contraction, it is more likely that inactivation of released NO is responsible for the observed contraction [15].

Conclusions

The first conclusion we can draw from the present study is that short-time lead-exposure has a real accelerating effect on LP in the brain. Due to the increased values of DC (absence of Fe^{++}) we affirm that lead has direct LP stimulating effect.

Secondly, it is possible to conclude that lead-induced changes in LCBF and VR correlated to intensification of LP and free radicals may be mediators of the vascular tone, depending on their chemical nature and concentration.

Thirdly, the cerebral precentral cortex is more vulnerable to oxidative damage than the hypothalamus.

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QUANTITATIVE DETERMINATION OF MUSCLE TONE IN SPINAL CORD LESION

T. Asser, P. Mustafin

The method of determination of viscoelastic properties of the muscles is based on the computerized on-line measuring and data analysis of the muscle oscillations after a dosed mechanical impact using an acceleration probe. The results are reflected in three parameters: 1) frequency, reflecting muscle tone; 2) logarithmic decrement (damping characteristic) of muscle oscillation, 3) stiffness and damping indexes which reflect the ability to contract the muscle under the investigation. Repeated muscle tone measurements on both legs were performed in ten patients with spinal cord lesions (3 patients with spinal tumors, 7 patients with traumatic spinal cord lesions) in cervical or thoracic-lumbar level. The measurements were performed in relaxed and if possible also voluntarily contracted muscles. The control group consisted of 16 healthy volunteers (7 men and 9 women), aged from 23 to 63. Notwithstanding the wide dispersal of the data in the individual patient, the general trends can easily be followed. In the subgroup of patients with spastic paraplegia the decrements of spastic muscles were significantly higher compared to age-matched healthy volunteers.

Comparison of the spasticity grade determined by the Ashworth scale, and decrement values revealed a positive correlation. The positive correlation between the degree of spasticity, determined by the Ashworth scale, and logarithmic decrement (damping characteristic) of muscle oscillation, determined with myotonometer, probably reflect mainly the visco-elastic properties of the muscle fibers and not spasticity itself. Nevertheless, myotometry seems to be a sensitive technique for revealing these changes. The stiffness index in patients with spastic paraparesis was compared to muscle strength graded subjectively — the lower stiffness index value, the weaker muscle strength.

Introduction

Patients with chronic neurological deficits after spinal cord trauma constitute a challenge to the healthcare system because of their increasing number, their marked degree of disability, and their high consumption of healthcare resources. In-patient rehabilitation is therefore becoming a growing economic factor. Spinal cord dysfunction, except in the acute stage of spinal shock, results in muscle hypertonicity. The various forms of hypertonia are important clinically and need to be

assessed quantitatively as well as qualitatively so that response to treatment could be graded accurately.

In recent years numerous mechanical and electronic devices of varying complexity and applicability to clinical muscle testing have been developed. Myometers, accelerometers, goniometers, three-dimensional movement analysis systems, and magnetic measurement devices are being used. These methods potentially offer more sensitivity but their application in clinical practice is still a question.

At Tartu University a hand-held device called myotonometer has been developed to determine the viscoelastic properties of the muscles [1]. This method is based on the computerized on-line measuring and data analysis of the muscle oscillations after a dosed mechanical impact using an acceleration probe.

The myotonometer, originally designed to be used in sports medicine, has been tested at the department of Neurosurgery Tartu University to determine the muscle tone in spinal cord lesion patients.

Myotonometer

The instrument consists of a rocking lever, mounted on a fulcrum in the tool and carrying an acceleration transducer, a contact-end with a wheel and armature set between the poles of an electromagnet [2]. The acceleration transducer presses the wheel at the contact of about 0.3–0.4 N. The electromagnet is supplied with an impulse of 13 ms in duration which produces a short mechanical impulse. The contact end impacts the muscle and muscle responds with a damped vibration. These oscillations are picked up by the acceleration transducer and are registered (Fig. 1). The cycle of measuring and processing data on-line on a personal computer (IBM-AT compatible) takes a few seconds. The results are reflected in three parameters: 1) frequency, reflecting muscle tone; 2) logarithmic decrement (damping characteristic) of the muscle oscillation, 3) stiffness and damping indexes which reflect the ability to contract the muscle under investigation.

Frequency (ν) was calculated according to the formula:

$$\nu = \frac{1}{T},$$

while ν is the frequency (Hz), T – period of the oscillations (sec).

Decrement (Θ) was calculated according to the formula:

$$\Theta = \ln \frac{A_1}{A_3},$$

while Θ is the decrement, \ln – natural logarithm, A_1 – first amplitude, A_3 – third amplitude.

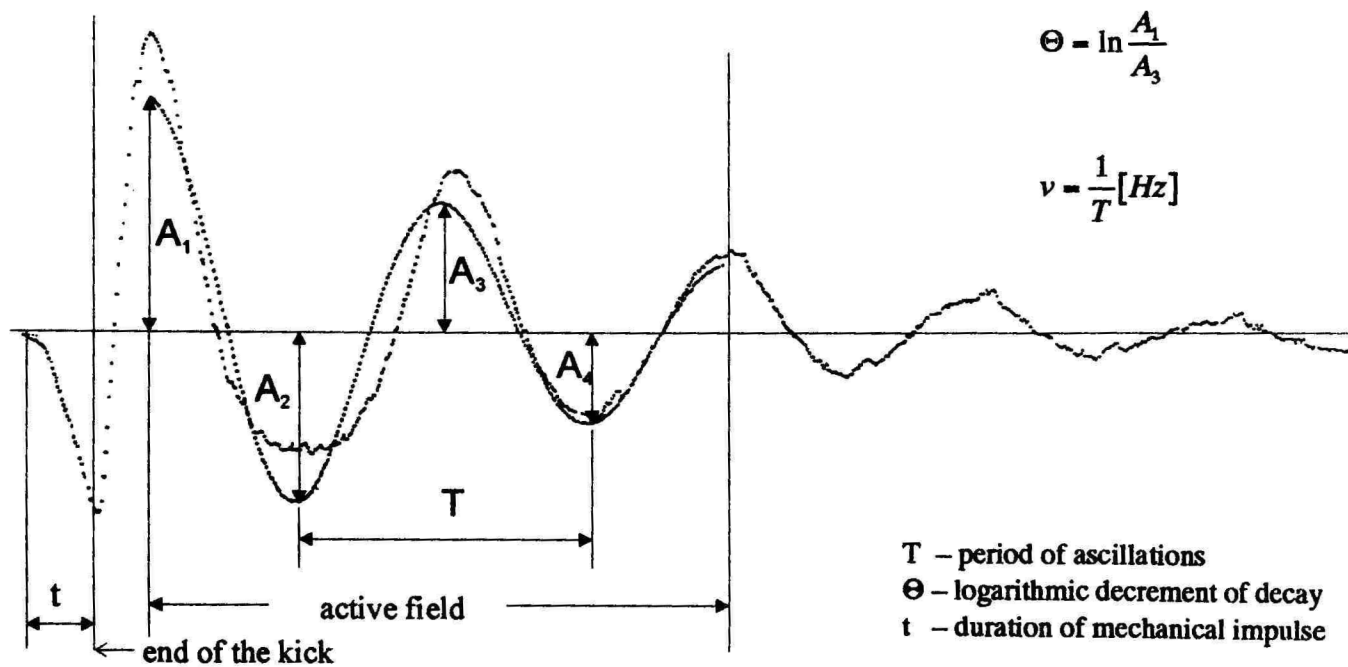


Fig. 1. Myotonogram

Stiffness index was calculated according to the formula:

$$\text{Stiff. index} = \frac{v_{\text{contr.}} - v_{\text{rel.}}}{v_{\text{rel.}}}$$

while $v_{\text{contr.}}$ is the frequency of the contracted muscle, $v_{\text{rel.}}$ — the frequency of the relaxed muscle.

Damping index was calculated according to the formula:

$$\text{Damp. index} = \frac{\Theta_{\text{rel.}} - \Theta_{\text{contr.}}}{(\Theta_{\text{rel.}} + 1) \Theta_{\text{contr.}}}$$

while $\Theta_{\text{rel.}}$ is the decrement of the relaxed muscle, $\Theta_{\text{contr.}}$ — the decrement of the contracted muscle.

Patients

Ten patients with spinal cord lesions were selected for this study. Their ages ranged from 19 to 59. Six of them suffered from spastic paraplegia due to spinal cord trauma. In four cases the spinal cord was affected by primary or secondary tumor. Clinical findings are summarized in table (Table 1).

One patient (case No 10) was followed up during five months after the partial removal of the intraspinal astrocytoma in the cervical region. He had preoperatively moderate tetraparesis — spastic lower paraparesis (right > left) and partial peripheral paralysis of both hands predominantly on the right. The duration of the neurological symptoms before the operation had been three years. Immediately after the surgical intervention his right leg remained plegic, left leg paretic. Both hands were also affected (right > left), in all extremities there was some degree of spasticity and he could not stand. During the stay in hospital the patient showed motor improvement — he regained ability to stand and walk for approximately forty steps supported by an attendant. Spasticity of legs (Ashworth scale) before the treatment was graded as 3 on the right and 2 on the left, after the treatment respectively 2 and 1. The first quantitative determination of the muscle tone in this patient was performed three weeks after the operation.

All patients had also various degrees of sensory deficits in affected limbs. Four patients had pain in the legs; in two of these the pain was associated with spastic contractions, and in the other two it was of a deafferentation type. The bladder function was normal in four patients. Three patients had an automatic reflex bladder and two had an indwelling catheter.

Table 1. Patients under investigation

Case No	Sex, Age (yrs)	Diagnosis	Duration of disease	Motility of legs	Spasticity (Ashworth Scale)	Strength of legs	Spinal automatism
1	M 25	spinal injury (Th)	13 mo.	paraplegic in wheelchair	2	0	+
2	M 26	spinal injury (C)	13 mo.	paraplegic in wheelchair	3	0	+
3	M 48	spinal injury (Th)	14 mo.	paraplegic in wheelchair	4	0	-
4	M 58	lymphosarcoma (Th - L)	30 mo.	paraplegic in wheelchair	4	0	-
5	M 59	hypernephroma (L)	30 mo.	paraplegic in wheelchair	3	0	-
6	M 38	spinal injury (Th)	5 mo.	rt. leg - plegia lt. leg - paresis	rt. 3 lt. 2	rt. 0 lt. 2	-
7	M 19	spinal injury (C)	2 weeks	rt. leg - plegia lt. leg - paresis	0	rt. 0 lt. 2	+
8	M 42	spinal cord tumour (C)	18 mo.	independent walker	0	4	-
9	M 54	spinal injury (C)	5 days	paraplegic in bed	0	2	+
10	M 45	astrocytoma (C)	36 mo.	paraparesis, rt. leg more affected	rt. 3 lt. 2	rt. 2 lt. 4	+

Abbreviations: C - cervica, Th - thoracic, L - lumbar

The control group consisted of 16 healthy volunteers (7 men and 9 women), aged from 23 to 63 (Table 2).

Table 2. Normal values

Muscle	Frequency (Hz) \pm SD relaxed muscle	Decrement \pm SD relaxed muscle	Stiffness index \pm SD
<i>M. tibialis ant.</i>	16.37 \pm 1.49	0.88 \pm 0.26	0.92 \pm 0.26
<i>M. gastrocnemius</i>	12.10 \pm 1.45	1.18 \pm 0.35	0.37 \pm 0.22

Examination of muscle tone

All patients with spinal cord lesions were repeatedly, on average 3 or 4 times, examined. Every examination consisted of manual muscle tone assessment (hyper- or hypotony of muscles), evaluation of muscle strength, passive moving of joints to evaluate spasticity (Ashworth Scale), and myotonometric measurements.

Spasticity was graded according to the Ashworth Scale [3]: 0 – no increase in tone; 1 – slight increase in tone, giving a “catch” when the affected part(s) is moved in flexion or extension; 2 – more marked increase in tone but limb easily flexed; 3 – considerable increase in tone, passive movement difficult; 4 – limb rigid in flexion and in extension.

Muscle strength was graded: 0 – no evidence of movement, 1 – a trace of muscle movement, 2 – complete range with gravity eliminated, 3 – complete range against gravity, 4 – complete range against gravity with some resistance, 5 – normal strength [4].

For myotonometric detection of muscle tone bilaterally *m. gastrocnemius caput mediale* and *m. tibialis anterior* were examined. Muscle tone measurements were performed in relaxed, and if possible voluntarily contracted muscles. The patient layed on the back with legs stretched up.

All patients had been treated in the Department of Neurosurgery of the University Hospital in Tartu.

Results and discussion

There have been several attempts to give a basic definition of spasticity, but they all failed because of the clinical spectrum of spasticity consists of a variety of signs and symptoms. The definition proposed by Lance in 1980 is currently accepted and in use. Spasticity has been defined as "a motor disorder characterised by a velocity-dependent increase in tonic stretch reflexes ("muscle tone") with exaggerated tendon jerks, resulting from hyperexcitability of the stretch reflex, as one component of the upper motoneuron syndrome" [5].

Notwithstanding the wide dispersal of the data in the individual patient, the general trends can easily be followed.

In the subgroup of patients with spastic paraplegia the decrements of spastic muscles was significantly higher compared to age-matched healthy volunteers (Table 3).

Table 3. Myotonometrical characteristics of the *M. tibialis anterior*

	Frequency (Hz) \pm SD relaxed muscle	Decrement \pm SD relaxed muscle	Stiffness index \pm SD
Normal value	16.37 \pm 1.49	0.88 \pm 0.26	0.92 \pm 0.26
Paraplegia	14.64 \pm 3.53	1.74 \pm 0.84	—

Comparison of spasticity grade determined by the Ashworth scale and decrement values revealed a positive correlation (Table 4).

Table 4. Ashworth scale and myotonometric decrement values in spasticity

Ashworth scale	Decrement of the relaxed <i>m. tibialis ant.</i>
0	1.00 \pm 0.18
1	1.37
2	1.54 \pm 0.25
3	1.67 \pm 0.14
4	1.57 \pm 0.93

In vivo muscle tone (or "stiffness") is dependent on both inherent mechanical properties of the muscle fibers and neuronal activity. Moreover, these factors are mutually related. In patients with long lasting spastic paresis, changes in the visco-elastic properties of the extra- and intrafusal muscle fibers may well contribute to increased

reflex and non-reflex stiffness [6]. The strong positive correlation between the degree of spasticity, determined by the Ashworth scale, and logarithmic decrement (damping characteristic) of the muscle oscillation, determined with myotonometer probably reflect mainly the visco-elastic properties of the muscle fibers and not spasticity itself. Nevertheless, myotonometry seems to be a sensitive technique to reveal these changes.

The stiffness index in patients with spastic paraparesis is compared to muscle strength graded subjectively in Table 5 – the lower stiffness index value, the weaker muscle strength.

Table 5. Comparison of stiffness index values and muscle strength scale values

Muscle strength	Stiffness index
0	-
2	0.10 ± 0.2
4	1.00 ± 0.2

A positive correlation was revealed between clinical improvement and both, stiffness index dynamics and decrement changes, when the patient was followed up during 5 months (Fig. 2 and 3).

Manual muscle testing as a systemic approach has been used almost during a century. Although it is possible to detect a wide spectrum of muscle impairments by palpation, the reliability of manual muscle assesment in the clinical use is disputed. The results indicate, that these tests can be highly reliable in spite of variations in the training of physical therapists and the use of different techniques of manual muscle testing. The average difference in grading among the physical therapists in this study was approximately 4 per cent [7]. Traditional testing of muscle strength against the examiner might be insensitive to changes in muscle properties [8].

Numerous attempts have been made to obtain objective measurements of spasticity. Wave analysis of recordings of electromyographic activity, tendon jerks, clonus and the H reflex have been used to evaluate th effectiveness of muscle relaxants, but the results are inconclusive. The tests of spasticity based on the EMG have not been wholly practical [8, 9].

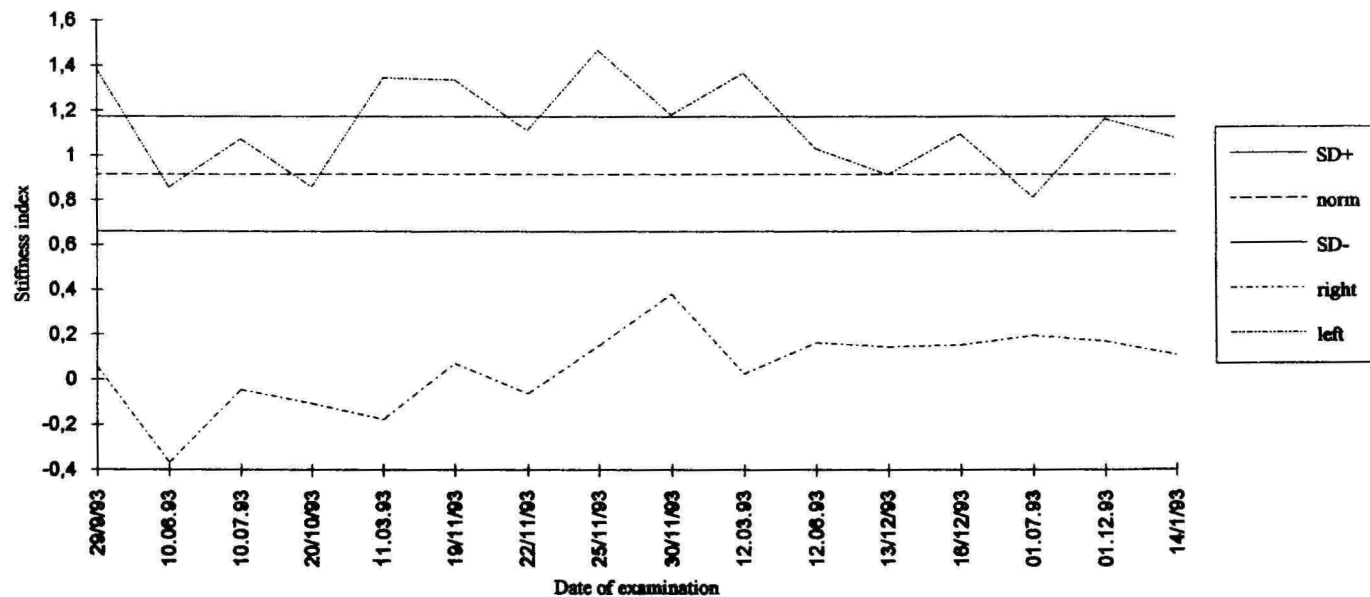


Fig. 2. Stiffness index of the m. tibialis ant. Intramedullary astrocytoma in cervical region

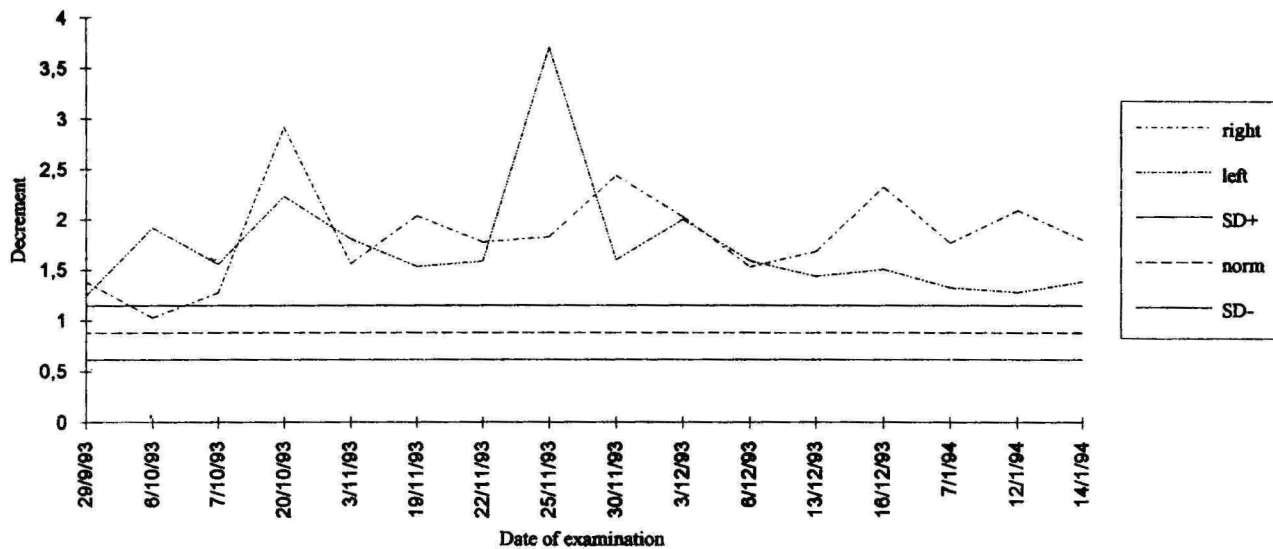


Fig. 3. Decrement of the relaxed m.tibialis ant. Intramedullary astrocytoma in cervical region

Conclusions:

1. Decrement of relaxed muscle oscillations (damping characteristic) determined with myotonometry, corresponds to the degree of spasticity by the Ashworth scale.

2. Stiffness index correlates with the strength of the muscle under investigation.

3. This computerized technique enables dynamic quantitative evaluation of the muscle tone changes and the ability of muscles to contract voluntarily contraction in different stages in spinal cord lesion.

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COMPUTERIZED QUANTITATION OF MUSCLE TONE IN LUMBAR DISC RADICULOPATHY

T. Asser, P. Eelmäe, J. Eelmäe

Myotonometer consists of a rocking lever, mounted on a fulcrum in the tool and carrying an acceleration transducer, a contact-end with a wheel and armature set between the poles of an electromagnet. The acceleration transducer presses the wheel at the contact of about 0.3–0.4 N during 13 ms. The contact end impacts the muscle and muscle responds with a damped vibration. These oscillations are picked up by the acceleration transducer and are registered. The results are reflected in three parameters: 1) frequency, reflecting muscle tone; 2) logarithmic decrement (damping characteristic) of the muscle oscillation, 3) stiffness and damping indexes which reflect the ability to contract the muscle under the investigation. Our examination revealed that the most informative indicator is stiffness index. Preoperatively the stiffness index values of the *m. tibialis ant.* and *m. gastrocnemius* on affected side in unilateral lumbar monoradiculopathy are lower compared to the second and tenth postoperative day. In lumbar disc radiculopathy the contraction ability of affected muscles are worse compared to control group and nonaffected side. The myotonometric changes detected in L₅ radiculopathy are much more pronounced as in S₁ radiculopathy. This new computerized non-invasive technique enables dynamic quantitative measurement of the muscle tone to evaluate the effectiveness of the medical and surgical treatment in patients with lumbar disc radiculopathies.

Introduction

The neurologic evaluation attempts to assess the distribution and severity of motor, sensory, and autonomic deficits. Although this is adequate for some clinical purposes, it may not be so objective, quantitative, or reproducible as desirable. The reasons are that evaluations do not provide quantitative results; normal values for site, age, and sex may not be available and might be different from observer to observer and from time to time; judgments may be influenced by the bias of patient and observer; and adequate test instruments and methodology may not have been developed or used.

At the Tartu University a hand-held device called myotonometer has been developed to determine the viscoelastic properties of the muscles [1]. The method is based on the computerized on-line measuring and data analysis of muscle oscillations after a dosed mechanical impact. The device has been tested at the Department of Neurosurgery, Tartu University to quantify the muscle tone in lumbar disc radiculopathies.

Patients and technique of muscle tone testing

Repeated muscle tone measurements on both legs (*m. tibialis ant.*, *m. gastrocnemius caput lat.*) were performed in 34 patients with unilateral monoradicular L₅ or S₁ nerve root compression before the lumbar discectomy, 2–3 days, and 10 days postoperatively. The description of the device, basic principles of myotonometry and formulas to calculate the basic indices have been described elsewhere [2]. Patients were divided into four groups by sex and level of the intervertebral disc prolapse: 8 men with L₄₋₅ disc prolapse, 12 men with L_{5-S₁} disc prolapse, 9 women with L₄₋₅ disc prolapse, and 5 women with L_{5-S₁} disc prolapse. The control group consisted of 27 healthy volunteers (12 men and 15 women) (Table 1).

Table 1. Normal values

Muscle	Frequency (Hz) ± SD relaxed muscle	Frequency (Hz) ± SD contracted muscle	Stiffness index ± SD
Men			
<i>M. tibialis ant.</i>	17.161 ± 1.92	31.927 ± 2.72	0.881 ± 0.26
<i>M. gastrocnemius lat.</i>	12.048 ± 1.05	18.123 ± 2.9	0.783 ± 0.25
Women			
<i>M. tibialis ant.</i>	16.527 ± 1.69	29.201 ± 3.19	0.783 ± 0.256
<i>M. gastrocnemius lat.</i>	10.547 ± 0.77	14.688 ± 2.27	0.386 ± 0.198

For the measurements of muscle tone the patients were positioned supine or prone. Patients were examined lying on one side only on the second postoperative day. The device, hand-held by the examiner, was placed on a standard point of the muscle, which was determined by Altenberger [1], and labeled in the middle of the muscle during voluntary contraction. Each muscle group was measured two or three times and the average of these measurements was automatically taken

to represent the muscle tone. The measurements were performed in the relaxed and contracted muscle.

For visualization of suspected disc herniation before the operation the spine X-rays were examined, and myelography with water-soluble contrast media was routinely performed. In selected cases, additionally computerized tomography (CT) or magnetic resonance imaging (MRI) was used. All the operations were performed under general anesthesia by microsurgical interlaminectomy.

Results and discussion

The good functional state of the muscle is reflected by high indices of the stiffness index, low level of damping characteristics, and their great positive difference, determined in the relaxed state and during maximal voluntary contraction [1].

There was no principal differences in men and women, although the results in men were clearer. The most informative indicator was the stiffness index. Preoperatively the stiffness index values of the *m. tibialis ant.* and *m. gastrocnemius* on the affected side in unilateral lumbar monoradiculopathy were lower compared to the second and tenth postoperative day (Fig. 1 and 2). The stiffness index values were lower on both sides, but on the affected limb these changes were much more evident (Table 2 and 3). The myotonometric changes on the nonaffected side can be explained by persistent pain before the operation.

Table 2. Stiffness index values for *m. tibialis anterior* in men (average \pm SD)

	Affected side		Nonaffected side	
	L ₅	S ₁	L ₅	S ₁
Before the operation	0.395 \pm 0.32	0.814 \pm 0.32	0.605 \pm 0.42	0.854 \pm 0.25
Two days after the operation	0.683 \pm 0.34	0.771 \pm 0.30	0.965 \pm 0.37	0.849 \pm 0.32
10 days after the operation	0.783 \pm 0.44	0.85 \pm 0.22	1.014 \pm 0.36	0.913 \pm 0.25

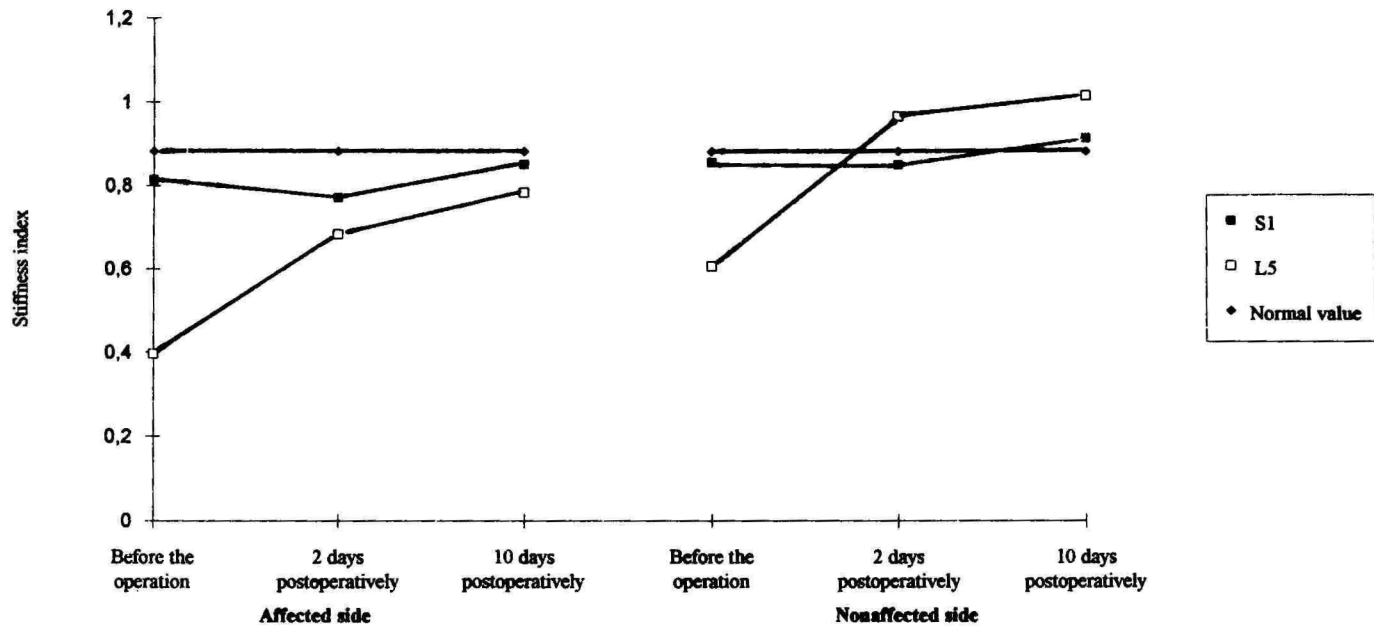


Fig. 1. Stiffness index of the m.tibialis anterior in men

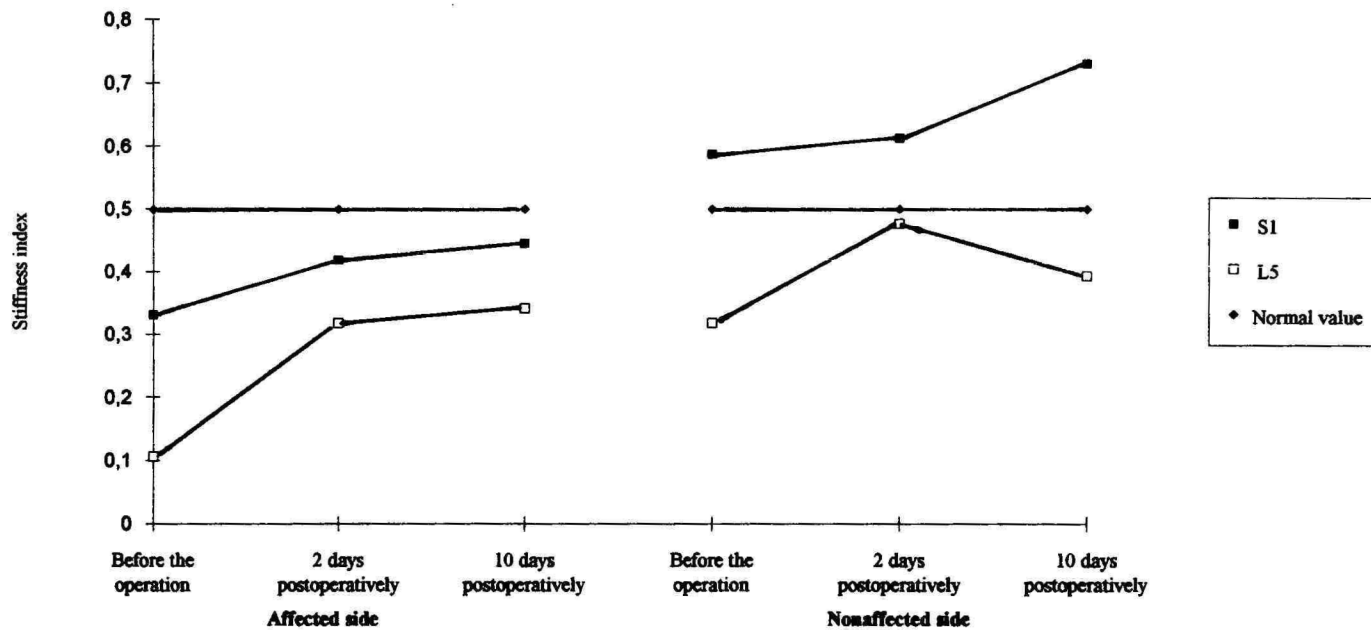


Fig. 2. Stiffness index of m.gastrocnemius lateralis in men

Table 3. Stiffness index values for *m. gastrocnemius lat.* in men (average \pm SD)

	Affected side		Nonaffected side	
	L ₅	S ₁	L ₅	S ₁
Before the operation	0.105 \pm 0.16	0.33 \pm 0.34	0.317 \pm 0.22	0.586 \pm 0.24
Two days after the operation	0.317 \pm 0.30	0.418 \pm 0.42	0.475 \pm 0.44	0.611 \pm 0.17
10 days after the operation	0.34 \pm 0.30	0.444 \pm 0.45	0.392 \pm 0.34	0.728 \pm 0.22

Frequency values (Hz) for the relaxed and contracted muscles were also lower if compared to normal age-matched volunteers, but these changes were much more evident on relaxed muscles (Table 4, Fig. 3 and 4).

Table 4. Frequency values for relaxed and contracted *m. gastrocnemius lat.* in men (average \pm SD)

	Affected side		Nonaffected side	
	L ₅	S ₁	L ₅	S ₁
Relaxed muscle				
Before the operation	10.545 \pm 1.67	11.405 \pm 1.13	11.448 \pm 1.48	11.516 \pm 1.68
Two days after the operation	10.647 \pm 1.98	11.193 \pm 3.7	10.766 \pm 1.22	11.259 \pm 1.64
10 days after the operation	11.442 \pm 1.65	11.73 \pm 2.75	11.629 \pm 1.27	10.865 \pm 1.20
Contracted muscle				
Before the operation	11.588 \pm 2.16	14.94 \pm 3.43	15.288 \pm 4.36	18.167 \pm 3.40
Two days after the operation	13.574 \pm 1.82	14.978 \pm 3.79	15.635 \pm 4.08	18.243 \pm 3.69
10 days after the operation	14.963 \pm 2.81	16.209 \pm 3.85	16.086 \pm 4.84	18.703 \pm 2.69

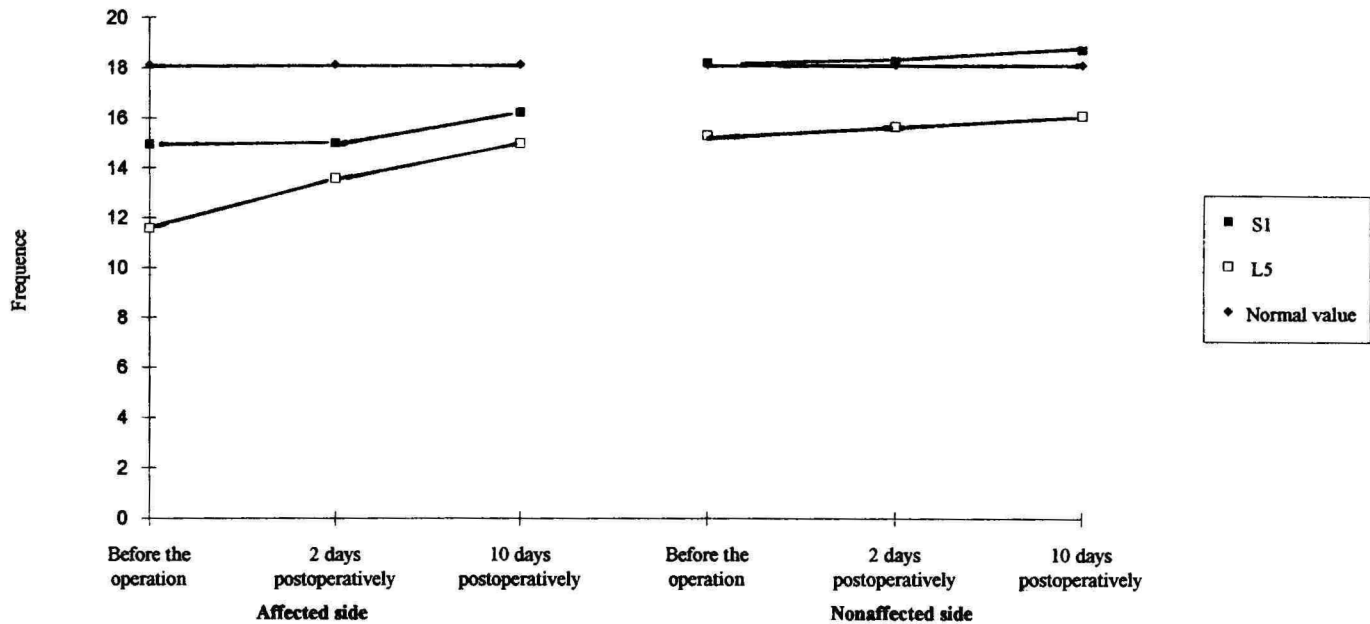


Fig. 3. Frequence of contracted m. gastrocnemius lateralis in men

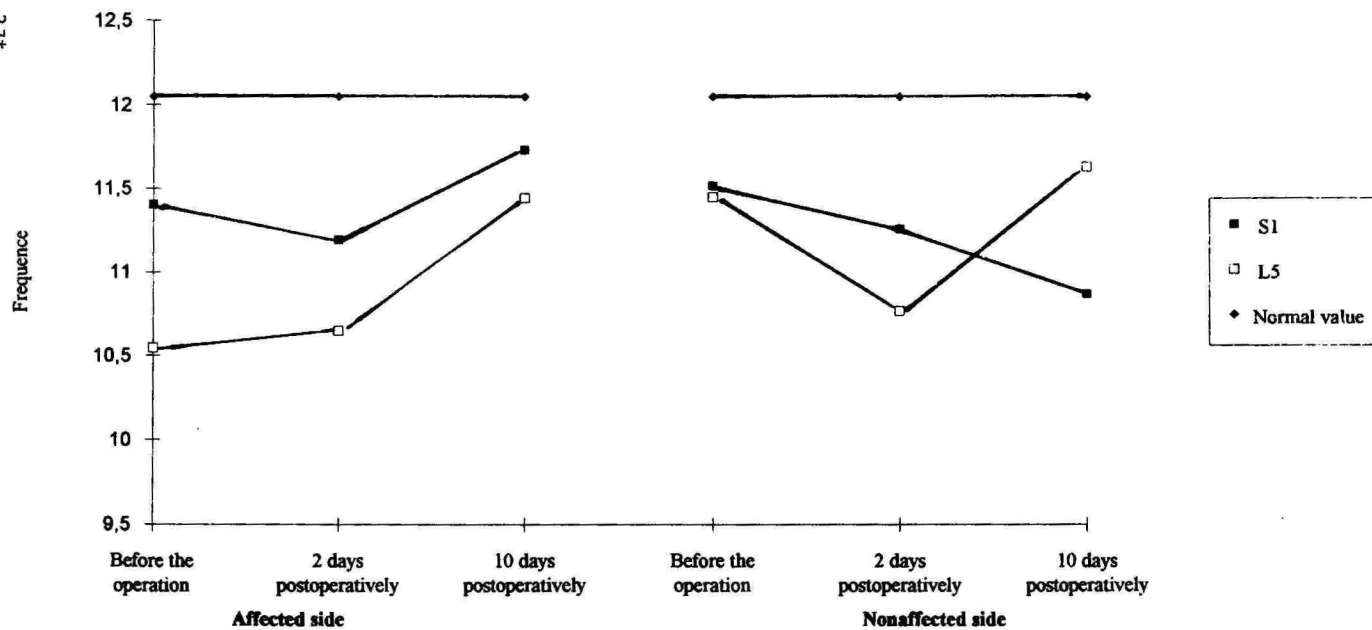


Fig. 4. Frequency of relaxed m.gastrocnemius lateralis in men

The measurement of force is the most direct means of assessing the function of many muscle groups. The most common motor deficit in lumbar disc disease is weakness of extension of the toe or foot, which is the most critical impairment [3]. Symptoms of weakness or fatigue may be increased by a wide variety of factors such as muscle, bone, or joint pain; spasticity; proprioceptive or cutaneous sensory deficits. In lumbar disc radiculopathy pain may inhibit effort and strong contraction, as may deformity of joints or an effusion within a joint. Very often patients complain of weakness or fatigability for which no cause can be found [4].

Several studies have compared the accuracy and sensitivity of electromyography and myelography in the diagnosis of lumbosacral radiculopathy [5]. Although these studies varied in some details, most agreed that these two diagnostic procedures were nearly equal in their ability to detect radiculopathy, each being positive in about 80% of patients. Several studies reported that EMG abnormalities were more prevalent than myelographic ones with L₅-S₁ disc herniation, whereas the converse was true with L₄₋₅ lesions [6, 7]. We found that myotonometric changes detected in L₄₋₅ disc herniation were much more pronounced than in L₅-S₁ disc herniation, which means that myotonometric changes are more in correlation with EMG abnormalities.

Conclusions

1. The most informative indicator is the stiffness index. Preoperatively the stiffness index values of the *m. tibialis ant.* and *m. gastrocnemius* on the affected side in unilateral lumbar monoradiculopathy are lower compared to the second and tenth postoperative day.

2. In lumbar disc radiculopathy the contraction ability of affected muscles is worse compared to the control group and the nonaffected side.

3. The myotonometric changes detected in L₅ radiculopathy are much more pronounced than in S₁ radiculopathy.

4. This new computerized noninvasive technique enables dynamic quantitative measurement of the muscle tone to evaluate the effectiveness of the medical and surgical treatment of patients with lumbar disc radiculopathies.

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CHANGES AFTER LASER DESTRUCTION OF RABBIT INTERVERTEBRAL DISC

A. Kulla, T. Asser, A. Õun, M. Ulst, S. Kruup, K. Pöldvere

Healing processes were observed morphologically after laser and mechanical injuries to rabbit intervertebral discs. 13 animals of the total number of 17 were treated with a laser-scalpel and 4 with a steel-needle. Comparison of histological changes was performed at different stages of the healing process. Although laser-destruction began to heal earlier and showed ossification tendencies also earlier, no differences in the general process of healing were observed. The amount of regenerative tissue masses (fibrous cartilage) was also the same in both cases.

Lumbar disc disease has traditionally been treated surgically by laminectomy or interlaminectomy and manual removal of the offending disc material. Chymopapain was extensively used to decompress the disc pressure in a relatively noninvasive manner, but has been abandoned due to serious complications including anaphylaxis, subarachnoid hemorrhage associated with acute paraplegia or transverse myelitis [10, 4, 1, 16, 3].

Percutaneous nucleotomy was first described in 1975 by Hijikata in Japan. Since 1982 additional intradiscal optical control has been included by means of an adapted arthroscopic kit for more accurate and effective removal of the nucleus pulposus under direct view.

Percutaneous ablation of degenerative disc material by laser has been introduced recently. A number of research works have been performed on evaluating the optical properties of degenerative disc material and on choosing the wavelengths that would generate minimal heat in the surrounding tissues [17, 15, 14]. However, practically no one has dealt with the histologic analysis of healing processes in the laser-destroyed intervertebral disc. Detailed histologic descriptions of regeneration in mechanically destroyed discs of several animals have been published since 1935, when Filippi first introduced with this kind of experiment [8, 12, 2, 9].

The purpose of the present study is to describe histologic changes taking place in healing laser-destroyed intervertebral discs and compare them with changes that take place after a simple mechanical injury to the disc.

Table 1.

Time after destruction (weeks)	Extent of wound canal		Amount of regeberative tissue		Size of osteophutes		Extent of ossification		NP replacement by fibrous cartilage		Extent of metachromatic area	
	M	L	M	L	M	L	M	L	M	L	M	L
4	++++	+	±	++	±	+	-	±	++	++++	-	++++
8	++	+	++	+++	+	+++	-	+	++++	++++	++++	++++
16	+	+	+++	++++	+++	+++	++	+++	++++	++++	++	++
26		±		++++		+++		++++		++++		+

NP- nucleus pulposus

M - mechanical destruction

L - laser destruction

Material and methods

17 rabbits of both sexes weighing 2.5–3.5 kg were used in the investigation. A midline abdominal incision was made on anesthetized (*sol. calypsolii* – 5 mg/kg, *sol. relanii* – 2.5 mg/kg, *sol. droperidoli* – 0.8 mg/kg) animals. The bowel and inferior vena cava were displaced to the left. The retroperitoneum was entered laterally to the ureter, and the lumbar intervertebral discs were exposed by blunt dissection of the psoas muscle. Using a steel needle (1 mm in diameter) or laser beam, a transverse injury was made into the disc through the ventral annulus and nucleus pulposus so that the immediate prolapse of the nucleus was in most cases visible. Injuries to discs were usually made at three or four levels in each animal. A 510 nm CuBr-laser with a fibertip 600 μm in diameter was used to perform the thermal destruction of intervertebral discs. The bowel was replaced and the abdominal wound closed in layers. Animals were killed at desired intervals with overdose of aether and intracardiac air embolism. Four rabbits with mechanical injury were killed 4, 8, 12, and 16 weeks after the operation. Four rabbits (of the total number of 13) with laser-destruction died within 2–6 days after the operation, others were killed 4, 8, 18, and 26 weeks later. After killing the animals the lumbar spine was immediately removed intact by osteotomy of adjacent vertebral bodies and fixed in 10% neutral formalin or in Heidenhein's modification of mercury fixative, decalcified and blocked into celloidin. Staining methods used in histologic sections were as follows: 1) hematoxylin-eosin; 2) van Gieson's staining with picrofuxin; 3) thionine-staining by Schmorl to reveal metachromasia.

The following characteristics were considered subjectively graded from + to ++++ (see the table of results): size of wound canal, extent and size of cartilaginous regenerative masses, size of osteophytes, extent of ossification in regenerative masses, extent of nucleus pulposus replacement by fibrous cartilage, extent of metachromatic areas in regenerative masses (Table 1).

Results

The disc immediately (2–6 days) after laser-destruction. The ventral fibers of the annulus fibrosus were destructed midway between the adjacent vertebrae and the wound canal was protruded through the annulus to the nucleus pulposus, which in most cases had also been destructed. The zone of lateral necrosis was clearly visible in H&E stained sections. In some cases parts of the nucleus pulposus were preserved

and it was possible to detect nests of "notochordal" cells in them. By the 6th day the cells in the inner third of the annulus along the wound were proliferating with metaplasia into chondrocytic cells. Material from mechanically destructed discs was not obtained at this stage.

4 weeks after the operation. After mechanical incision the wound remained still unhealed. In the outermost part of the wound proliferation of granulation tissue was observed. This tissue material then covered but did not enter the opening in the annulus fibrosus. Only a weak proliferation of cartilage cells was seen around the superficial part of the incision. At this stage after laser-destruction of IVD intensive proliferation of cartilage cells surrounding the wound canal had been taken place. Proliferation had caused a semilunar-shaped protuberance to the ventral aspect of the intervertebral disc and had extended to the ventral surfaces of the adjacent vertebrae blending with their epiphyseal cartilage. These parts of confusion showed intensive metachromasia when stained with thionine and also the highest density of chondrocytes was observed just here. In their peripheral part of this regenerate blood vessels had protruded into them and calcium deposits appeared around them (Fig. 2).

8 weeks after operation. Changes in mechanically injured discs were similar to those that took place 4 weeks after laser-destruction. The innermost part of the had stabwound yet remained unhealed. Laser-destructed specimens at this stage showed the beginning of osteophyte formation in adjacent vertebral bodies. Peripheral parts of the regenerate showed focal areas of ossification that also lacked metachromasia. Although the whole nucleus pulposus was replaced by fibrous cartilage, the wound canal in the innermost part of the annulus fibrosus still remained unhealed.

16 weeks after operation. The process of ossification in the regenerate formed by fibrous cartilage was prominent both after mechanical and laser destruction of IVD. Osteophytes of considerable size were formed from adjacent vertebrae in both cases. The size of regenerative cartilaginous masses was almost the same as after laser-destruction and mechanical injury.

Subsequently **26 weeks after laser-injury** the spread of ossification from the original annulet had completely or almost completely replaced the cartilage, a bony ankylosis between the vertebrae adjacent to the damaged disc was established, and a considerable bony prominence was formed on the ventral aspect of the disc (Fig. 3), whereas the part of the destruction-canal that lied between the inner third of annulus fibrosus fragments, was still not fulfilled with fibrous cartilage tissue and remained unhealed.

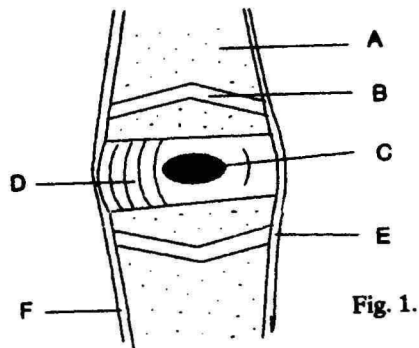


Fig. 1.

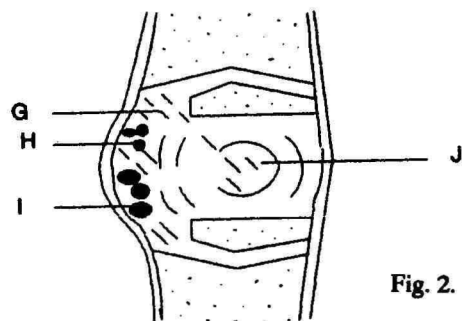


Fig. 2.

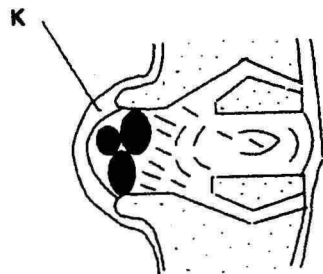


Fig. 3.

- A – vertebral body
- B – cartilaginous growth plate
- C – nucleus pulposus
- D – annulus fibrosus
- E – post. longit. ligament
- F – ant. longit. ligament
- G – regenerative fibrous cartilage tissue
- H – blood vessels
- I – ossification nests
- J – nucleus pulposus replaced by fibrous cartilage
- K – osseous “bridge”

Discussion

Results of this experimental study show differences in time-sequences of healing processes after laser and mechanical destruction of rabbit IVD. Healing after laser-destruction was more extensive already 4 weeks after the operation and regenerative fibrous tissue with chondromatous metaplasia had proliferated to a considerable extent. Although healing after the mechanical injury did not begin until 8 weeks after the injury, manifested by proliferation of fibrous tissue and only 8 weeks after the injury was performed, it reached the same extent as the previously described laser-wound healing. The beginning of ossification was not observed at this stage after the mechanical injury as it had taken place in laser destruction reparation. This certainly contradicts in classic theory of the wound healing process (by which the rapidity of the process depends directly on the amount of necrotic tissue masses).

Laser-destruction, which obviously had a wider zone of lateral necrosis, began to heal earlier and more intensely than mechanical injury. Skobelkin [11] also states that healing processes are induced rapidly after laser injury and Yelisseyenko [7] proposes that this is due to very intensive and prolonged invasion of coagulated tissues by macrophages and this will stimulate strongly the production of collagen in reparative fibrous tissue.

Subsequent events were also more rapid after laser-destruction, the ossification of regenerative cartilage tissue took place almost 4 weeks earlier, likewise osteophyte formation from adjacent vertebral bodies. Changes in metachromatic staining with thionine provided information about the extent of ossification. 2 months after the injury intensive metachromasia was observed in regenerative tissues and it began to decrease stepwise in correlation with the process of ossification and replacement of cartilage by bone tissue. Lipson and Muir [9] observed a decrease of the molecular size of proteoglycan monomers, degree of aggregation of these monomers and also the chondroitin/keratin sulfate ratio in destructed discs of rabbits. Namely the chondroitin sulfate content is responsible for the metachromatic properties of fibrous cartilage tissue [5].

Regardless of differences described above the main direction of healing processes in both cases is principally the same. Both cases showed ossification in regenerative cartilaginous tissue 16 weeks later and the size of these tissue masses also was almost the same. The final outcome in both cases was the formation an ankylosing bridge between the adjacent vertebral bodies. So we can state that our experiment did

not agree with the general standpoint that in laser wounds the proliferation of connective tissue components is less intensive [13].

In this investigation we pruned that the wound canal in the innermost parts of the annulus fibrosus failed to heal and did not close. This has also been observed by other authors [8, 12, 6], this is associated with the recognized avascularity of the deeper annular fibers [12]. But there is correlation between osteogenesis in the peripheral part of regenerative masses and vascular supply of the outermost part of the annulus fibrosus. Ham and Cormack [5] have found that differentiation of osteogenic cells into osteocytes or chondrocytes depends on the adequate blood supply of the corresponding area.

The source of regenerative tissues proliferating in the injured IVD remains an unresolved problem. There is no perichondrium and no germinative layer on the IVD as appears in other types of cartilage or bone formations where perichondrium or periosteum have healing potentials. IVD-s are ventrally and dorsally covered with longitudinal ligaments that may have some cambial potentials, but Lipson and Muir [9] showed that cutting the outer annular fibers and clearing the surface of the disc space do not stimulate healing processes and osteogenesis. That nucleus pulposus itself is unlikely to induce osteogenesis through cartilage metaplasia is shown in several observations. In this study we saw a zone of lateral necrosis of considerable width. One could argue that it also extends to the epiphyseal part of the adjacent vertebral body and thus can stimulate the osteogenic potentials of bone tissue (reticular cells of bone marrow, pericytes of blood vessels), as is the case with injuries to synovial joint cartilage, when these reach the bony tissue below. But there is no support to this argument and thus the source of proliferative connective tissue still remains enigmatic.

In conclusion it should be underlined that the normal mechanism of the intervertebral joint is dependent on an intact annulus fibrosus and nucleus pulposus and any gross interference with these structures will lead to tissue reaction in them which tends to immobilize the joint.

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CERVICOGENIC HEADACHE

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The role of the cervical spine in producing headache is controversial. There is little consensus on the problems how disorders of the cervical spine cause headache, what diseases of the cervical spine produce headache, and how these headaches may be identified.

Barré [2] was the first to describe occipital headache under the term of posterior cervical sympathetic syndrome which comprises headache, vertigo, tinnitus and visual disturbances. He proposed that the cause was arthritis of the cervical spine and that the symptoms were produced by irritation of the vertebral nerve — the sympathetic nerves accompanying the vertebral artery.

Bärtschi-Rochaiz [6] renamed the syndrome "migraine cervicale" and regarded it as a reversible ischemic syndrome of the vertebral artery. He postulated that the artery is compressed either in the region of an apophyseal joint or in the neighbourhood of the odontoid process. However, although vertebrobasilar ischemia might be an acceptable explanation of vertigo and visual disturbances, it is not a satisfactory explanation of headache.

Bogduk [4] studied the effect of stimulation of the vertebral nerve and the cervical sympathetic trunk in the monkey and found only minimal changes in vertebral artery blood flow. He concluded that the irritation of the vertebral nerve is not a pathogenic mechanism of cervical headache.

It appears to be widely accepted nowadays that occipital pain usually results from an affection in the territory of the C_2 nerve root, the nerve or its branches. The C_2 cord segment accepts input from the C_{1-2} lateral articulation, from the periosteum of these vertebrae, and the ligaments, muscles and scalp.

Sjaastad introduced the term cervicogenic headache and later described its diagnostic criteria [16, 17]. Sjaastad's group has the opinion that cervicogenic headache is a pain syndrome, not an entity. Any structure within the innervation zone of the C_2 root and the greater occipital nerve might give rise to this syndrome.

The diagnostic criteria of cervicogenic headache according to Sjaastad [17] are as follows:

- unilaterality of pain;
- pain is usually moderate, it starts in the neck and eventually

spreads to the ocular and frontotemporal areas, where the pain frequently reaches its maximum;

- pain episodes may last from few hours to a couple of weeks, there may also be continuous pain with a fluctuating course;

- various attack-related phenomena may also be present: blurred vision ipsilaterally, difficulties on swallowing, photophobia and nausea; periocular and facial edema and flushing may appear on the symptomatic side;

- signs of neck involvement; frequent pain in the neck and shoulder and a reduced range of motion of the neck;

- pain attacks may be provoked by pressure on the greater occipital nerve, which is usually tender, on the ipsilateral side.

It is suggested that in the diagnosis of cervicogenic headache a considerable emphasis must be placed on the effect of anaesthetic blockade of the greater occipital nerve. A positive blockade effect, which involves more or less complete pain relief from an injection near the greater occipital nerve where it penetrates the nuchal muscles, may be indicative of a pain producing mechanism at or distal to the point of blockade [9].

In the Departments of Neurology and Neurosurgery, Mustamäe Hospital, cervicogenic headache is usually treated with injection of local anaesthetic and corticosteroids into the tender points around the greater occipital nerve. In most cases one to three injections give a more or less prolonged relief of pain. However, there are some refractory cases where the relief of pain lasts only a few hours, which corresponds to the duration of the nerve conduction blockade.

During the years 1986-1987 in four patients with cervicogenic headache refractory to medical treatment neurolysis of the greater occipital nerve was performed. Since pain relief was of short duration, it was decided to carry out neurotomy of the greater occipital nerve. From 1987 to 1990 occipital neurotomy was performed the authors by one of (A. E.) in 28 patients. There were 11 males and 17 females aged 35-76 years. The duration of symptoms ranged from several months to 19 years. The indication for the operation was the intractable pain which only temporarily responded to the occipital nerve blockade. In 1992 a written questionnaire was mailed to each patient and answered by 19 patients. The mean follow-up was 38 months, range 16 to 53 months.

Results. At the discharge from the hospital 16 patients were pain-free, in two the pain was the same and in one it was less than before the operation. During the follow-up the pain returned in 12 patients: during the first two months in 4, 6 to 8 months after surgery in 5 and

12 to 24 months after surgery in three patients. At the end of the follow-up 4 patients reported complete pain relief, in comparison with the preoperative period the pain was less in 8, the same in 4 and worse in three patients. 11 patients used analgesic medications every day, three sometimes and 5 never. 12 patients reported dissatisfaction with the treatment outcome, three partial satisfaction and 4 were pleased that they had undergone surgery.

Discussion. Treatment of cervicogenic headache has included occipital nerve zone blocks with a local anaesthetic, a local anaesthetic plus corticosteroid, greater occipital nerve neurolysis and neurotomy, nerve root decompressive procedures, C₂ rhizotomy [1, 8, 10, 11, 12, 14, 15].

The most commonly used treatment of cervicogenic headache is the tender points injection with local anesthetics. Some clinicians prefer the occipital nerve block which is performed just above the superior nuchal line about 2.5–3 cm lateral to the external occipital protuberance. The needle is advanced until paresthesia along the course of the nerve is obtained, whereupon 2–3 ml of solution is injected. A corticosteroid hormone is usually added. The mechanism whereby corticosteroid hormone produces relief from pain is not clear. It has been suggested that it is capable of causing demyelination of nerve fibers when injecting near the nerve trunks.

Blume [3] treated 600 patients with occipital myalgia-neuralgia by percutaneous radiofrequency electrocoagulation in the greater occipital nerve territory. In the follow-up period of one to ten years, the results of the procedure afforded complete pain relief in 80 percent of patients and good pain relief with occasional mild pain in 5 percent of cases. Only 15 percent had temporary relief of pain for a few months or there was no pain relief at all. The patient became a candidate for the procedure if temporary relief of pain was achieved with a local anesthetic in combination with cortisone. The thermoelectrode was inserted 4 cm below the occipital protuberance and 2 cm lateral to the midline. Altogether 40 radiofrequency lesions were made in several directions bilaterally.

Ehni and Benner [8] described 7 patients with an upper neck and occipital pain due to unilateral arthrosis of the C₁₋₂ lateral articulation. The disease was demonstrated by radiography through the open mouth and by computerized tomography scanning. Temporary relief was obtained by local anaesthetic and steroid injection, and permanent relief achieved by C₂ dorsal rhizotomy.

Horowitz and Yonas [12] treated 9 patients suffering from severe occipital pain with associated C₂ hyperesthesia, unilateral retro-orbital

pain and occipital trigger points by intradurally sectioning the C₁-C₄ dorsal rootlets. 6 patients underwent procedures such as neurolysis, neurectomy, and neuroma excision prior to intradural selective dorsal rhizotomy. During the average 31-month forlow-up 4 patients received complete relief of their pain, two patients were partially relieved and two patients had recurrences after 9 and 12 months of complete relief. The authors presume that most patients with occipital neuralgia should be managed conservatively for at least one year to ascertain whether the entity resolves on its own or responds to nerve blocks or physical therapy or both. Should the patient continue to have pain they recommend intradural dorsal rhizotomy.

Bovim et al [5] performed neurolysis of the greater occipital nerve in 58 patients with cervicogenic headache. They supposed that the patients had the entrapment of the nerve where it penetrates the nuchal muscles. The immediate effect of the operation was good, but the pain returned in most patients during the follow-up which ranged from 3 to 43 months. The authors concluded that this operation should not be performed in patients with cervicogenic headache.

Anthony [1] carried out surgical division of the occipital nerve in 60 patients with "occipital neuralgia". 42 of the 60 patients were rendered headache-free for periods ranging from 21 days to 23 months, mean duration of relief being 244 days or 8.1 months.

Consequently, the neurolysis and neurotomy of the greater occipital nerve do not give a long-lasting relief of pain and these results as well as ours suggests that the cause of the pain might be in the deeper seated cervical structures.

In our opinion there are at least two large groups of occipital headache. A more common type is a more diffuse uni- or bilateral neck and occipital pain with trigger and tender points in the neck muscles which probably is a myofascial pain syndrome. The latter is characterized by trigger points which may cause local and referred pain. Trigger points are usually found in tense and shortened muscles. The quality of pain is deep, aching, and often poorly circumscribed. It may be associated with swelling, numbness and stiffness. The pain is aggravated or perpetuated by factors that affect or stress the muscle containing the trigger point. These include physical stressors as poor posture and psychological factors as depression and mental stress that cause increased muscle tension. Other perpetuating factors include cold damp weather, poor sleep, and fatigue. This type of occipital headache responds usually better to the injection of local anaesthetic and corticosteroid than the unilateral occipital headache with tenderness only over the greater occipital nerve and without muscle spasm and tender-

ness. The source of this type of occipital pain might be the irritation of the greater occipital nerve or the C₂ root in deep cervical structures, e.g. by the arthrosis of the C₁₋₂ articulation. The pain of this origin can be relieved by the injection of the posterolateral border of the joint with local anesthetic and corticosteroid. Other possible causes of occipital headache include the entrapment of the C₂ root or the nerves between the C₁ and C₂ vertebrae in traumatic hyperextension or in atlanto-axial dislocation, compression of upper cervical nerve roots by caudally displaced cerebellar tonsils in the Arnold-Chiari malformation or posterior fossa tumors.

In conclusion, cervicogenic headache is a syndrome with many different causes. Unfortunately, the clinical presentation does not give reliable clues to its etiology. The most effective treatment of the myofascial pain syndrome seems to be the block with local anesthetics and corticosteroids. The surgical methods on the greater occipital nerve (neurolysis and neurotomy) in the cases refractory to medical therapy do not have long-lasting effect. The investigation of the therapeutic effectiveness of other methods, such as C₁-C₂ joint block, C₂ root block or C₂ radicotomy is necessary.

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OPTIMIZATION OF MICROWAVE THERAPY

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The aim of the present study was to investigate the use of a layer of sand instead of air space as a contact medium in microwave therapy. We compared the warming of tissues both by the decimetrewave and centimetrewave therapy with air space and sand medium. Investigations were performed on 20 healthy adult volunteers. Using a layer of sand the temperature on the dorsal hand surface was 1.4 times higher and on volar surface even 2.1 times higher compared with the use of air space. Our results clearly demonstrate increased warming of tissues by distancing the emitter with a layer of sand in centimetrewave and also in decimetrewave therapy.

Microwave therapy is broadly used in contemporary physiotherapy, especially in several peripheral nervous system and musculoskeletal diseases. The focus is radiated by electromagnetic field with ultrahigh frequency in the range from 300 to 3000 MHz, in wavelength range from 1 to 0.1 m. A part of the body is placed closed to the electromagnetic direction emitter. Microwave therapy is divided into two categories according to the wavelengths of ultrahigh frequency oscillation: centimetrewave therapy (CMW-therapy) and decimetrewave therapy (DMW-therapy). Their effect on tissues is somewhat different. In different countries the apparatus for microwave studies is tuned to different frequencies. The equipment used in the former Soviet Union and Estonia operates with frequency of 2375 MHz and on the wavelength 12.6 cm for CMW-therapy and with the frequency of 460 MHz, on the wavelength 65 cm for DMW-therapy. The optimal air space between emitter and skin is 5 to 7 cm for CMW-therapy and 3 to 5 cm for DMW-therapy to acquire a steady effect if we use a stationary microwave therapy equipment with high output power (100–150 W). However, due to the air space the reflection from the skin and loss of energy due to the surrounding environment are extensive, therefore the local effect is insufficient [6].

The portable microwave therapy equipment with small output power (up to 25 W), has an emitter with a special ceramic filler to achieve high dielectric permeability. Its dielectric properties are close to those of the skin and muscles that enable the use of contact application with a good focusing effect. The portable equipment is designed for

procedures in the face region and intravaginally. Since it has small power and small emitters, the possibility of using it for other parts of the body is limited. Due to technical reasons, it is not possible to use a ceramic filler in large emitters.

The distribution of ultrahigh frequency electromagnetic waves in space is dependent on energy transport. Its absorption in tissues changes tissue metabolism causing first of all their endogenous warming. Although both categories of microwave therapies have similar effect on tissues, DMW-therapy has several advantages. They are the following: greater depth, steadier warming of tissues, milder influence on the cardiovascular system. "Fixed waves" are absent and the danger of overheating and heat damage to dermal tissues is excluded [1, 2, 3, 5, 8]. The advantages mentioned above have caused an increase in the popularity of DMW-therapy.

According to the data literature, the substitution of a layer of sand for the air space between emitter and skin remarkably concentrates the local effect of the ultrahigh frequency electromagnetic field due to the increased heat effect if a high output stationary CMW-therapy equipment is applied [4, 7]. According to our knowledge, similar data about DMW-therapy are not recorded in the literature. The aim of the present study was to investigate the possibility of using a layer of sand instead of air space. We also compared the warming of tissues both by DMW- and CMW-therapy using air space and sandlayer.

Methods

Investigations were carried out on 20 healthy adult volunteers. In 10 volunteers we radiated the dorsum of the hand with the stationary CMW-therapy apparatus "LUTCH 58". 10 volunteers were radiated with the stationary DMW-therapy apparatus "VOLNA 2" with doses 50 W during 5 minutes. On the left hand we used a 4 cm air space, on the right hand a 4 cm cloth bag filled with dry sea sand. Before and immediately after the procedure we measured the skin temperature on the dorsal and volar surfaces of the hand. The thickness of the central part of the hands was 3 to 5 cm.

Results and discussion

According to the results of the performed experiments the increase in skin temperature is remarkably higher with a layer of sand both in DMW- and CMW-therapy. In CMW-therapy procedures the mean increase on the dorsal surface of the hand with air space was $4.0 \pm 0.4^\circ$

and on the volar surface $1.2 \pm 0.5^\circ$, but when the sandlayer was applied the measured increases was $5.6 \pm 0.6^\circ$ and $2.5 \pm 0.4^\circ$ respectively. In DMW procedures with air space the increase in temperature on the dorsal and volar hand surfaces was $2.4 \pm 0.5^\circ$ and $1.7 \pm 0.5^\circ$ and through the layer of sand $3.7^\circ \pm 0.7^\circ$ and $2.6^\circ \pm 0.3^\circ$.

Consequently, the temperature on the dorsal hand surface was 1.4 times higher through the layer of sand and on the volar surface even 2.1 times higher, if compared with air space. In DMW procedures the use of the sandlayer caused an increase in temperature 1.5 times both on the dorsal and volar surface. The temperature of sand did not change during the procedure.

Our results demonstrate clearly the increased warming of the tissues by distancing the emitter with a layer of sand in both CMW- and DMW-therapies. We assumed that the skin temperature of the volar surface shows the warming of deep tissues. Therefore we were able to conclude that using a layer of sand in CMW-therapy an increased warming of the deep tissues can be achieved. In DMW-therapy the warming of the tissues is steadier. The warming of deep tissues is more intensive in both methods with a sandlayer. We suppose that thanks to the sandlayer the ultrahigh frequency electromagnetic field is concentrated on the exposed area. In this case, like in the ceramic emitter filler of a portable equipment, the reflection is decreased. Considering the uneven surface of the body, a bag filled with sand is a good contactmedium between emitter and skin. According to the results of the present investigation, distancing with a layer of sand is preferable not only in CMW-, but also in DMW-therapy procedures. We recommend taking the above results into consideration in everyday clinical work.

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