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Epidemiology of traumatic spinal cord injury in Estonia. Brain activation in the acute phase of traumatic spinal cord injury

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Paper IV: participation in the study design, identifying and recruiting patients and controls, data collection, examination of patients, participation in data analysis, and writing the manuscript.

ABBREVIATIONS

AIS	American Spinal Injury Association Impairment Scale
ASIA	American Spinal Injury Association
BA	Brodmann area
CI	Confidence intervals
COG	Centre of Gravity
EU-15	Member countries in the European Union prior to the accession of ten candidate countries on 1 May 2004
EU-27	Member countries in the European Union from 1 May 2004: EU-15 + Poland, Czech Republic, Cyprus, Latvia, Lithuania, Slovenia, Estonia, Slovakia, Hungary, Malta, Bulgaria, Romania
FLASH	Fast low-angle shot
fMRI	Functional magnetic resonance imaging
FWE	Family-wise error
ICD-10	International Classification of Disease 10th version
IRR	Incidence rate ratio
ISCoS	International Spinal Cord Society
MNI	Montreal Neurological Institute
MPSS	Methylprednisolone
MR	Magnetic resonance
MRI	Magnetic resonance imaging
MVA	Motor vehicle accidents
NSCISC	National Spinal Cord Injury Statistical Centre
ROI	Region of interest
SCI	Spinal cord injury
SMR	Standardised mortality ratio
SPM	Statistical Parametric Mapping
TBI	Traumatic brain injury
TSCI	Traumatic spinal cord injury
VOA	Volume of activation
wLI	Weighted laterality index

1. INTRODUCTION

Traumatic spinal cord injury (TSCI) is a devastating and costly condition. TSCI typically leads to permanent loss of sensory and motor function. The severity of the condition is largely dependent on the neurological level as well as on the completeness of injury.

About 12,000 to 20,000 people are suffering from TSCI in the United States each year (National Spinal Cord Injury Statistical Centre, 2010). This allows us to infer that every year more than 100,000 people acquire TSCI around the world. An estimated 2–3 million people worldwide are living with spinal cord injury (SCI) related disability (Wyndaele and Wyndaele, 2006). Moreover, a remarkable amount of patients (2.3–37.7%) die at the scene of the accident (Dryden *et al*., 2003; Griffin *et al*., 1985; Martins et al., 1998; Surkin *et al*., 2000; Thurman *et al*., 1994)

Although the incidence of TSCI is relatively rare in comparison to traumatic brain injury, for example, it is an important problem for public health (Pérez *et al*., 2012; Tagliaferri *et al*., 2006; Wyndaele and Wyndaele, 2006). We must bear in mind that traumatic injuries are not inevitable. In order to facilitate injury prevention, standardised and comparable epidemiological data from every region of the world is necessary.

The data about SCI in Eastern Europe is scarce. Considering that mortality due to injuries is several times higher in Estonia than in most European countries, the incidence of TSCI should also be high (Lai *et al*., 2009). The present study was designed to investigate the epidemiological situation of TSCI in Estonia, which would provide valuable data for healthcare planning.

Depending on the type of nervous system lesion and its completeness and recovery, there may occur different patterns of cortical reorganisation. Functional magnetic resonance imaging (fMRI) is a potential surrogate marker of functional outcome (Freund *et al*., 2011; Freund *et al*., 2013). Cortical activation of patients with TSCI in the acute and subacute phases of TSCI was investigated in our study to observe temporal changes in the reorganisation of the sensorimotor cortex.

2. LITERATURE REVIEW

Traumatic spinal cord injury (TSCI) may cause long-term disability which has a significant impact on quality of life and survival.

2.1. Definition and diagnosis of TSCI

TSCI is defined as an acute damage to the spinal cord caused by an external force with loss of motor and/or sensory function attributable to the level of spinal cord injury (SCI) (Kraus *et al*., 1975; American Spinal Injury Association (ASIA), 2011). The injury includes *cauda equina* and *conus medullaris* injuries, but not plexus lesions or injury to peripheral nerves outside the neural canal (Maynard *et al*.,1997). In addition to the motor and sensory deficit, autonomic nervous system impairment is also common (Claydon and Krassioukov, 2006).

The clinical history of the patient is significant because it can provide information about the mechanism and severity of injury and predict outcome. The forces that damage the spinal cord are often great enough to cause injury to other organs, too. The most commonly associated injuries occur to the chest, the abdominal cavity and the brain (Benour *et al*., 2013).

The areas of the spinal cord most susceptible to injury are the cervical segments and the thoracolumbar junction (Burt, 2004). The incidence of cervical level TSCI has been reported to be 41.6–76.0%, the incidence of thoracic spine injuries, 19–34.6% and the incidence of lumbar spine injuries, 13.3–59.4% (Levi *et al*., 1995a; O'Connor, 2002; Pickett *et al*., 2006).

Patients with TSCI may have concomitant vertebral column injuries. SCI without radiological abnormality (SCIWORA) is often encountered and introduces the need for MRI to evaluate and detect any soft tissue or spinal cord injury (Yulesoy and Yuksel, 2008). Due to non-contiguous spinal fractures, the neurological level of injury does not match the vertebral level in 10–15% of TSCI cases. In addition to fractures at several levels of the spine, this may also be a sequel of cord stretching injuries (Silberstein and McLean, 1994).

The minimal information necessary to document the neurologic status is the sensory and motor level on each side of the body and the ASIA Impairment Scale (Appendices A, B).

In order to standardise the terms used all over the world, ASIA has proposed the following definitions of some fundamental terms (ASIA, 2011):

A dermatome is the area of the skin innervated by the sensory axons within a segmental nerve (root).

A myotome is defined as the collection of muscle fibres innervated by the motor axons within a segmental nerve (root).

Sensory scores refer to the summary score of sensory function. The maximum is 56 points per side of the body for light touch and pin prick. Appreciation of sensation is scored on a three-point scale (0, 1 or 2).

Motor score is a numerical summary score of motor function. The maximum score is 50 per side of the body. The strength of each muscle examined is graded on a six-point scale (0 to 5).

The neurological level of injury indicates the most caudal segment of the spinal cord whose sensory and motor functions are normal bilaterally. By convention, provided that sensory and motor functions are normal rostrally, the muscle function has to be at least a grade 3 for the neurological level of injury.

The skeletal level is the most rostral level of the spinal column at which, on radiographic examination, the greatest vertebral damage is found.

2.2. Classification of spinal cord injury

A variety of SCI classification systems has been created. Today, the ASIA classification system is the most widely used among them (Teufack *et al*., 2013).

The simplest method to classify a SCI is into complete and incomplete SCI (Teufack *et al*., 2013). The function of the lowest sacral segment (light touch or pin prick sensation at the S4-5 dermatome, deep anal pressure or voluntary anal sphincter contraction) determines the completeness of SCI. If partial sensory or motor function has preserved below the neurological level and involves the lowest sacral segment (S4-5), the lesion is defined as incomplete. Complete SCI is the term for the absence of sensory and motor functions in the lowest sacral segment (ASIA, 2011).

The outcome for SCI patients correlates with the extent of neurological injury. Thus a reliable and reproducible method of classification of SCI is important.

Over the years several grading systems have been used. The first classification system was published in 1969 by Frankel and colleagues. The main limitation of the Frankel grade was the fact that it did not clearly discriminate patients with different levels of motor function. This scale was not sensitive enough to reflect motor function improvement. The first system has been followed by many others (Teufack *et al*., 2013). The International Standards for Neurological Classification of Spinal Cord Injury was initially developed in 1982 as the ASIA Standards for the Neurological Classification of Spinal Cord Injuries. Revisions were made in 1990, 1992, 1996, 2000 and 2011 (Kirshblum *et al*., 2011b). The ASIA Impairment Scale (AIS) designation is used in grading the degree of impairment and it is based on the Frankel scale but differs from it in several aspects. Sacral sensory spearing or voluntary anal sphincter contraction is added in order to differentiate between complete and incomplete injury. The ASIA scales C and D can be differentiated more clearly.

The 2011 Revised American Spinal Injury Association Impairment Scale (Appendices A and B):

A=Complete. No sensory or motor function preserved in the sacral segments S4-5.

B=Sensory incomplete. Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-5, and no motor function is preserved more than three levels below the motor level on either side of the body.

C=Motor incomplete. Motor function is preserved below the neurological level, and more than half of the key muscles below the neurological level have a muscle grade 0 to 2.

D=Motor incomplete. Motor function is preserved below the neurological level, and at least half of the key muscles below the neurological level have a muscle grade equal to or greater than 3.

E=Normal. Sensory and motor functions are normal in all segments, and the patient had prior deficit. A person without a SCI is not assigned a AIS grade.

2.3. Pathophysiology

The spinal cord consists of longitudinally oriented spinal tracts surrounding central areas. The spinal cord can be divided into segments comprising sensory and motor neurons.

The understanding of the nature and process of pathophysiological events will lead to identification of therapeutic targets and recovery after SCI. In a laboratory animal the force of the trauma impact can be measured. On the other hand, in humans the secondary changes after TSCI cannot be directly observed or calculated (El Masri(y), 2006). Although an animal model of SCI cannot be directly extrapolated to humans with SCI, we can still learn the basic mechanisms of the pathophysiology of SCI from it (Drazin *et al*., 2013).

SCI is a biphasic event with the primary and secondary phases of injury. The primary event evolves the immediate changes caused by the initial mechanical force. The characteristics of the following secondary injury is dictated by the severity and location of the primary event. After TSCI the organism also attempts to elicit molecules that can aid in recovery following the injury. Stem cells, that may proliferate extensively following SCI, have been found in the adult mammalian spinal cord (Austin *et al*., 2013).

Several new notions about the mechanisms of secondary injury have been described (McDonald and Sadowsky, 2002). Secondary changes that take place around the area of the spinal cord have been more widely studied. The pathophysiology involves multiple mechanisms which occur concomitantly and are strongly interrelated (do Amaral, 2010). The changes are caused by vascular mechanisms, by ionic changes that lead to cellular dysfunction, formation of free radicals and by alteration of the cellular DNA. Biochemical mechanisms can be characterised by the release of glutamate and aspartate and provoke cellular death by an excitotoxity mechanism. Inflammation is produced by the release of arachidonic acid from cellular membrane. Vasoconstriction, production of free radicals, apoptosis and cellular death are caused by inflammation and by cellular mechanisms (do Amaral, 2010).

The pathophysiology is complex, however in order to allow new therapeutic approaches and facilitate treatment, physicians should be familiar with the mechanisms of the pathogenesis of SCI. The genesis of the primary lesion is important for the understanding of possible injury and prognosis. The secondary lesion is frequently potentially reversible and the understanding of its pathophysiology may facilitate the treatment of SCI (do Amaral, 2010).

2.4. Incidence of TSCI

The incidence rates differ markedly between countries and it has also been found that the causes are dissimilar (Chiu *et al*., 2010; Hagen *et al*., 2012; Wyndaele and Wyndaele, 2006). Countries with similar economies tend to have similar incidences and features of SCI (Ackery *et al*., 2004).

High incidence of TSCI in younger men results in enormous financial, emotional and physical costs for individuals, their families and society (Ackery *et al*., 2004). Depending on the employed methodology, the incidence rates of TSCI are different ranging from 2.3 per million in a Canadian and an Italian study to 83 per million in Alaska (Ahoniemi *et al*., 2008; Albert *et al*., 2005; Berg *et al*., 2011; Biering-Sørensen *et al*., 1990; Celani *et al*., 2001; Dincer *et al*., 1992; Divangolou and Levi, 2009; Dryden *et al*., 2003; Espagnaq *et al*., 2011; Exner and Meinecke, 2010; Hagen *et al*., 2010a; Jackson *et al*., 2004; Karacan *et al*., 2010; Kondakov *et al*., 2002; Knútsdóttir *et al*., 2012; Lidal *et al*., 2007; Martins *et al*., 1998; O'Connor, 2002; O'Connor and Murray, 2006; Pagliacci *et al*., 2003; Pickett *et al*., 2006; Surkin *et al*., 2000; Tator *et al*., 1993; van Asbeck *et al*., 2000; van den Berg *et al*., 2010b; Warren *et al*., 1995). The incidence in the United States is much higher than in the rest of the world. In North America the incidence rate of 39 per million is more than twice of the Australian 15 per million and the European 16 per million (Cripps *et al*., 2010; NSCISC, 2010; O'Connor, 2002). But even within Europe the numbers are quite varying. The highest incidence has been reported from Portugal (57.8 per million population) (Martins *et al*., 1998) and Russia (44 per million) (Kondakov *et al*., 2002), while it has been the lowest in Italy (2.3 per million) (Celani *et al*., 2001).

Many studies underestimate the magnitude of the problem by excluding the patients who die at the scene of the accident, on arrival at the hospital, or during the first days (Ackery *et al*., 2004; Chiu *et al*., 2011; van den Berg *et al*., 2010b). A number of studies have focused on patients in the rehabilitative phase, excluding deaths occurring in the acute or sub-acute phase of injury (van den Berg *et al*., 2010; Soden *et al*., 2000).

2.5. Risk factors for TSCI

The incidence of TSCI is the lowest in the paediatric group and the highest for persons from 16 to 30 years of age (Teufack *et al*., 2013). The mean age at the time of injury is from 26.8 years in Turkey (Dincer *et al*., 1992) to 55.5 years in Oklahoma (Price *et al*., 1994). Several studies have reported that the average age at the time of injury is increasing, reflecting the increasing median age of the general population in many regions (DeVivo, 2012). Less developed countries display lower mean ages than more developed countries (Wyndeale and Wyndaele, 2006). For example, in the United States the mean age at the time of injury was 28.3 years during the 1970s and 37.1 years between 2005 and 2008 (DeVivo *et al*., 2011). The proportion of new SCIs among persons older than 59 years of age increased from 4.6% in the 1970s to 13.2% between 2005 and 2008 (DeVivo *et al*., 2011).

Being a man is a potential risk factor for sustaining a SCI. All studies have found male preponderance. The male to female ratio ranges from 1:3 to 4.3:1 among developed countries and 1.73:1 to 7.5:1 in developing countries (Cheng *et al*., 2008; Hoque *et al*., 1999; Masood *et al*., 2008; Pickett *et al*., 2006; Shingu *et al*., 1994;).

The incidence rates are higher for the blacks than for the whites. The incidence rate ratio of the whites to the blacks is 1.4:2.0 overall (Teufack *et al*., 2013).

SCI occurs most frequently on weekends and during the warm weather months, which is attributable to certain sport activities, for example, diving and surfing (Teufack *et al*., 2013).

Alcohol is an important risk factor not to be forgotten. Twenty-two to fifty per cent of new SCI cases involve alcohol use or their blood alcohol test is positive after the injury (Teufack *et al*., 2013). People face a substantially elevated risk for SCI on the days when they drink alcohol (Levy *et al*., 2004). A large percentage of fatal injuries are connected to alcohol drinking. The alcohol-attributable mortality rate in the EU-10 (new countries in Central and Eastern Europe, including Estonia) is more than twice as high as in the EU-15 for men and 40% higher for women. In the Baltic countries, the overall alcohol-attributable mortality is more than 4 times higher for men and 3 times higher for women than in the EU-15 (Rehm *et al*., 2011). The drinking pattern in this region is binge-drinking, which is the most hazardous pattern (McKee and Britton, 1998; Popova *et al*., 2007). Alcohol has also been found to be the strongest risk factor for TBI followed by completeness of TSCI (Hagen *et al*., 2010a).

2.6. Causes of TSCI

The aetiology of injury varies. The causes are often grouped into 5 categories: motor vehicle accidents, violence, sports/recreational activities, falls and all other causes. In most countries traffic accident is the leading cause of injury (Ackery *et al*., 2004; Chiu *et al*., 2010; Cripps *et al*., 2011; Hagen *et al*., 2012).

Falls is typically the second cause of TSCI, and has shown a clear increase over the years (Kennedy *et al*., 2012).

According to the National Spinal Cord Injury Statistical Centre (NSCISC) database for 2005 to 2010, 40.4% of injuries were caused by traffic accidents, 27.9% by falls, 15.0% by violence, 8.4% by other causes, 8.0% by sport accidents and in 0.1% of cases the cause of injury was unknown (NSCISC, 2010).

Falls-related SCI rates are high in Western Europe, especially in the Northern countries (Ahoniemi *et al*., 2008; Hagen *et al*., 2010a; Hartkopp *et al*., 1997). However, these countries are known for one of the highest proportions of persons older than 60 years in Europe, too. Elderly people are more prone to falls. Not all falls will result in injury, but 20% require medical attention, 5% result in a fracture, and 5–10% result in other serious injuries (Kannus *et al*., 2007). As falls are common events in the elderly, there has been reported a bimodal distribution of TSCI incidence rates. The first peak occurs among the young, the second peak after the age of 60 years (Berg *et al*., 2011; Dryden *et al*., 2003). Kennedy and colleagues demonstrated that in their study the patients who sustained TSCI due falling were 8.2 years older than those within the non-falls group. Also they showed that the individuals in the falls group had significantly poorer rehabilitation outcomes in bladder management, mobility and discharge compared to those in the non-falls group (Kennedy *et al*., 2013). In the NSCISC database TSCI recorded as a result of falls accounted for 16.5% from 1973 to 1979, for 20% from 1990 to 1994, and finally for 27.9% from 2005 to 2010 (NSCISC, 2010).

Violence has been documented as a frequent cause of TSCI in South-Africa and the United States (US). On the other hand, in Europe violence is the cause of TSCI in less than 5% of cases (Hagen *et al*., 2012). Acts of violence are usually reported as the fourth leading aetiology of TSCI. In the state of Oklahoma in the US, the incidence of violence is as common as the incidence of motor vehicle accidents among the black population (Price *et al*., 1994). Fortunately, the incidence of violence has declined dramatically since the 1990s (DeVivo, 2012).

Sports accidents are common among young individuals. The most frequent fields are diving, gymnastics and rugby (Chiu *et al*., 2010; Cripps *et al*., 2011; van den Berg *et al*., 2010). Sports-related injuries have also declined from 14.2% in the 1970s to 10% since 2000 (DeVivo, 2012).

Like in the incidence, there are also large variations in the aetiology of injury in different countries. An explanation may be geographic and cultural differences, but the methods and study designs used in these areas are not the same, which may also account for the variance (Hagen *et al*., 2012).

2.7. Severity of injury

In addition to the lesion level, TSCI is classified as complete and incomplete (Maynard *et al*., 1997). The severity of TSCI has been measured by combining the neurological level and extent of injury into complete tetraplegia, incomplete tetraplegia, complete paraplegia and incomplete paraplegia (Ahoniemi *et al*., 2008; Hagen *et al*., 2010a; Ning *et al*., 2010). Recently, the Executive Committee for the International Spinal Cord Injury Data Sets Committee has recommended to report the severity of injury under five categories: injury level at segments C1-4 and AIS A, B or C; C5-8 AIS A, B or C; T1-S5 AIS A, B or C; AIS D at any injury level; and ventilator dependent at any injury level (ASIA, 2011; DeVivo *et al*., 2011; Appendix A, B).

Similarly to the aetiological factors (the rising number of TSCI due to falls), there are also possible trends in the severity of injury. The proportion of tetraplegia is rising as well as incomplete injuries (Ahoniemi *et al*., 2008; DeVivo *et al*., 2011; DeVivo 2012; O'Connor 2005). One explanation for that trend may be the fact that older persons are more likely to be injured through falls, which will result in incomplete SCI. Moreover, as the patients have more chances to reach hospital alive, the percentages of C1-C4 injuries are increasing, as well as is ventilator dependency (DeVivo, 2012).

Causes of TSCI also have an important role in determining preserved neurological function. For example, up to 88% of recreational sports-related SCIs result in tetraplegia (Jackson *et al*., 2004). At the same time, violence-related SCIs mostly result in paraplegia (Jackson *et al*., 2004).

2.8. Associated injuries

The International SCI Standards and Data Sets Committee has recommended to document the following associated injuries in SCI (De Vivo *et al*., 2006):

- Moderate to severe traumatic brain injury (TBI)
- Extraspinal fractures requiring surgery
- Severe facial injuries affecting sense organs
- Major chest injury requiring chest tube or mechanical ventilation
- Traumatic amputation of an arm or a leg
- Severe haemorrhages
- Damage to any internal organs requiring surgery

When a person sustains both a TSCI and a concomitant brain injury, morbidity is increased and quality of life is reduced, which has also major influence on the outcome of rehabilitation (Hagen *et al*., 2010a; Macciocchi *et al*., 2004). A combination of TSCI and TBI found in different studies has been 16% to 74% (Macciocchi *et al*., 2007; Tolonen *et al*., 2007). TBI is more frequent in patients who sustain a traffic accident or a fall. The cervical level of SCI is also associated with higher TBI rates (Macciocchi *et al*., 2008; Hagen *et al*., 2012).

Failing to diagnose a TBI will negatively impact TSCI rehabilitation outcomes or even lead to death.

2.9. Survival and mortality of TSCI

Life expectancy of individuals with TSCI has improved significantly during the last decades. Nevertheless, patients with TSCI die earlier than their contemporaries in general population.

The median life expectancy is 33 years after injury (DeVivo *et al*., 1999). A systematic review conducted by van den Berg and colleagues (van den Berg *et al*, 2010) showed that median survival ranges from 35.4 days in a study including pre-hospital death (Martins *et al*., 1998) to 35.6 years (Lhéritier *et al*., 2001).

Typically, as most individuals with TSCI are young men in their twenties, the mortality risk is also higher for men (Strauss *et al*., 2000; DeVivo *et al*., 1999; O'Connor 2005; Espagnacq *et al*., 2011; Krause *et al*., 2008). A Norwegian study reported an increased risk of dying among patients with TSCI, with a standardised mortality ratio (SMR) of 2.88 for women and 1.72 for men (Hagen *et al*., 2010b). Reduced life expectancy has also been found in Finland (Ahoniemi *et al*., 2011) and Denmark (Hartkopp *et al*., 1997).

Crude SMR among the patients with TSCI is 3 times higher than in general population. The period shortly after TSCI poses an especially high risk of death. The mortality risk is extremely increased during the first two years after the injury (van den Berg *et al*., 2010). DeVivo and colleagues have shown that the survival rates in the first year after SCI are improving. However, unlike in general population, no such reduction has been found in long-term annual mortality rates (DeVivo *et al*., 1999, DeVivo *et al*., 2007, Strauss *et al*., 2006).

Survival is considered to be strongly related to neurological level, extent of lesion, age at injury and year of injury (van den Berg *et al*., 2010). Also, patients with more comorbid conditions have showed a significantly elevated risk of dying (Selassie *et al*., 2012).

The causes of death are the diseases or injuries that directly or indirectly cause deaths. Until the mid-1970s, urinary tract complications were reported to be the most frequent causes of death among TSCI patients. Today deaths are most often caused by respiratory complications. Other risk factors for death are suicides, cardiovascular diseases and septicaemia (van den Berg *et al*., 2010; Garshick *et al*., 2005; Hagen *et al*., 2010b; Hartkopp *et al*., 1997; Lidal *et al*., 2007).

2.10. Management of TSCI

Treatment of SCI has evolved over the past decades. It is based on the foundation laid by Sir Ludwig Gutmann, who started to treat "hopeless" cases of spinal injuries during World War II (Kakulas, 2004).

Adequate perfusion and oxygenation of the injured nervous tissue are important to lessen the secondary injury and to optimise recovery. Specialised neurocritical care units provide the needed environment for treating patients with TSCI.

As the direct compression of neural elements by bone fractures and disc material is a significant mechanism of the initial injury, removal of these fragments is an option to decompress the spinal cord. Still, early surgery remains controversial, unless canal integrity is severely compromised (McDonald and Sadowsky, 2002). Prior to the 1970s, the only operative treatment was laminectomy, that was avoided because of the abnormally high incidence of neurological complications. Today, it has been found that surgery accelerates the rehabilitation process, shortens immobilisation, and decreases mortality and medical costs (Niazi *et al*., 2013). Early operative intervention can also decrease the amount of secondary complications (McKinley *et al*., 2004). A recent multicentre international prospective cohort study (Surgical Timing in Acute Spinal Cord Injury Study: STASCIS) in adults with cervical SCI concluded that decompression before 24 hours after SCI can be performed safely and is associated with better neurological outcome (Fehlings *et al*., 2012).

The arguments against surgery are increased risk of infections, bleeding, hypoxia, hypotension. Yet increasingly more specialists conclude that early decompression – within 24 hours after injury – is an option for medically stable patients (Niazi *et al*., 2013).

Among the possible non-surgical treatments is traction that can be used alone or as a preoperative treatment. The halo and Gardner-Wells tongs can be used for the setting of cervical fractures, subluxations or dislocations (Lerman *et al*., 1994).

The first proven pharmacological treatment for TSCI was high-dose methylprednisolone (MPSS). It was reported to reduce swelling, inflammation and accumulation of free radicals when given within 8 hours of trauma (Bracken *et al*., 1984; Bracken *et al*., 1990; Bracken *et al*., 1997; McDonald and Sadowsky, 2002). The MPSS inhibits lipid peroxydation and hence preserves neurons, axons, myelin and glial cells (Marchan *et al*., 2013). On the other hand, it has been shown that MPSS inhibits axonal sprouting and synaptogenesis. High-dose MPSS administration may have serious negative effects by increasing the incidence of gastrointestinal bleeding, wound infection, pulmonary embolism, pneumonia and death (Hulbert, 2000). Given the risks and benefits, the published evidence does not support using high-dose MPSS as a standard treatment in acute SCI (Marchan *et al*., 2013).

Some studies have shown chondroitinase ABC to promote regeneration of corticospinal tract axons. Nogo-A antibodies enhance axon collateral and regenerative sprouting. Different neurotrophins (nerve growth factor (NGF), brain-derived neurotrophic factors (BDNF), neurotrophin 3 (NT-3)) are capable of supporting survival of injured neurons (Onifer *et al*., 2011). Cellular replacement has been widely investigated. These cell types include Schwann cells, olfactory ensheathing glial cells, embryonic and adult stem/progenitor cells,

fate-restricted neural/glial precursor cells, and bone-marrow stromal cells (Tetzlaff *et al*. 2011). The actual mechanisms of how transplanted cells exert their beneficial effect are poorly understood, which may pose several ethical, logistic and safety problems (Tetzlaff *et al*. 2011). Neuroplasticity may also have negative consequences when the re-wiring leads to pain, autonomic dysreflexia or other negative sequellae of SCI (Brown and Weaver, 2012).

2.11. Complications after TSCI

Owing to the improved life expectancy of patients with TSCI, a variety of distressing health conditions and complications can occur in the acute phase or long time after TSCI. Such conditions can cause substantial medical and financial problems, but also psychosocial difficulties. These complications lead to increased health care utilisation and costs (Burns *et al*., 2013), and the start of rehabilitation may be delayed or interfered by different complications (Haisma *et al*., 2007).

In addition to motor and sensor deficits, spinal cord injury implies serious disturbances in autonomic nervous system function. The severity of these dysfunctions depends on the level and completeness of injury of the spinal cord. Individuals with cervical or upper thoracic (≤Th6) spinal cord injury experience episodes of hypertension (autonomic dysreflexia) or falls in blood pressure during a positional change (orthostatic hypotension). Acute SCI can provoke altered cardiac electrophysiology and increase susceptibility to cardiac arrhyth–mias (especially bradycardia). Subjects with tetraplegia also demonstrate elevated vagal activity with reduction in baseline airway calibre, and findings attributed to loss of symphathetic innervation to the lungs. In addition, patients with major injury have thermoregulation disturbances caused by loss of symphathetic control of more than half of the body (Sabre *et al*., 2011).

Respiratory complications are a leading cause of mortality and morbidity after TSCI. Cervical TSCI provide paralysis of respiratory muscles: these patients are at a higher risk for developing pneumonia, atelectasis and respiratory failure. Long-term preventive care is mandatory, which includes chest physiotherapy, assisted coughing, and influenza and pneumococcal vaccinations (Burns *et al*., 2013; Jackson *et al*., 1994).

After TSCI the risk factors for coronary artery disease increase, occur earlier and more often than in able-bodied persons (Bauman and Spungen, 2008). Inactivity also predisposes to metabolic abnormalities, insulin resistance and may lead to hyperinsulinaemia (Bauman and Spungen, 1994). Higher pre–valence of coronary artery calcifications has been demonstrated in persons with TSCI (Bauman and Spungen, 2008).

Deep vein thrombosis is an important complication in the acute phase of TSCI. The incidence of deep vein thrombosis in the acute phase has been reported to be 10 to 100% among the patients without prophylaxis and 0 to 7%

among those with prophylaxis (Agarwal and Mathur, 2009; Casas *et al*., 1977; Green *et al*., 1998; Saraf *et al*., 2007; Todd *et al*., 1976).

Important secondary health conditions are the neurogenic bladder and bowel dysfunction. The clinical manifestations of bladder dysfunction in the lower motor neuron syndrome are urinary retention and/or incomplete bladder emptying (Potter *et al*., 2006). Detrusor-sphincter dyssynergia and involuntary, reflective voiding are caused by a loss of cortical inhibition over reflective voiding in the upper motor neuron syndrome (Potter *et al*., 2006).

Recurrent urinary tract complications, as well as renal and bladder calculi are common after SCI. The detrusor-sphincter dyssynergia increases the intra-vesical pressure that in turn leads to vesicouretral reflux, hydronephrosis, recurrent pyelonephritis and progressive deterioration in renal function (Burns *et al*., 2013). In the past, renal failure was the leading cause of death following SCI. But with the improved management of the neuropathic bladder and urinary tract infections, the incidence of renal failure has decreased significantly (Burns *et al*., 2013; Potter, 2006). Gastric dilatation and ileus are common in the acute phase of SCI. Colonic diverticulae and haemorrhoids are caused by constipation (Chung and Emmanuel, 2006).

Heterotopic ossification is a well-known secondary complication of SCI characterised by the formation of new ectopic bone in soft tissue (van Kuijk *et al*., 2002). SCI patients report more of different pains, and more fatigue, anxiety and insomnia (Levi *et al*., 1995b). Aside from causing pain, spasticity may diminish patient's quality of life by preventing to perform personal hygiene procedures, by interfering with sleep, and by impending rehabilitation efforts and function (Burns *et al*., 2013; Rekand *et al*., 2012; Sköld *et al*., 1999).

Lack of mechanical stress gives rise to loss of bony mass (Werhagen *et al*., 2012). The lack of sensation causes pressure ulcers, which in turn may be complicated by cellulitis, osteomyelitis, sepsis and deconditioning (Burns *et al*., 2013).

2.12. Recovery, prognosis and reorganisation of the brain after TSCI

Not long ago a patient with TSCI was treated as someone with no prognosis and was labelled with the expression "not to be treated" (Kakulas, 2004). For a revolutionary change in the treatment of SCI, we are indebted to Sir Ludwig Guttmann from the United Kingdom and Sir George Bedbrook from Australia. According to the severity and mechanism of the lesion, motor, sensory and autonomic functions can spontaneously return or be recovered to a varying extent (Onifer *et al*., 2011). Even patients without initial motor or sensory function below the injury may still achieve excellent recovery. The key factors for recovery are:

- completeness or incompleteness of injury
- level of injury

- initial strength of muscles in the first caudal level below the injury
- presence of sensation in the sacral segments (Fawcett *et al*., 2013)

The most important predictor of improved outcome is sacral sensation 72 hours to 1 week after injury (McDonald and Sadowsky, 2002; Marino *et al*., 1999). Incomplete injuries will recover with a wider range. The greatest gains in motor skills occur in the first 3 months, with the most of recovery by 9 months. However, additional recovery can occur up to 12 to 18 months post-SCI (Fawcett *et al*., 2013).

The changes that will take place are summarised under the term plasticity. This phenomenon can be found elsewhere in the neuraxis. It is now possible to conclude that adult central as well as peripheral nervous systems respond to TSCI with plasticity (Onifer *et al*., 2011).

Depending on the type of nervous system lesion, completeness and recovery, different patterns of cortical reorganisation may occur (Kokotilo *et al*., 2009a). Earlier, body cortical representations were believed to be stable. Within the last 20 years recent advances in neuroimaging and brain mapping have shown that the cortex may adapt to the environment (Bareyre, 2008; Kokotilo *et al*., 2009a; Pascual-Leone *et al*., 2005). There are different endogenous recovery strategies and spontaneous functional recovery may take place in 40% of SCI patients (Bareyre, 2008; Tsung and Fassett, 2011).

Although spinal cord injury does not affect the brain, changes in the brain function of TSCI patients have been identified in different studies. Several analysts have expressed doubts about the exact pattern of changes after TSCI because of varying and even conflicting results (Kokotilo *et al*., 2009a).

It is worth recognising that reorganisation will not be similar in individuals with paraplegia compared to those with tetraplegia. A growing body of brain reorganisation studies has been performed on paraplegics. Only a few studies have investigated cortical reorganisation after cervical TSCI (Curt *et al*., 2002; Jurkiewicz *et al*., 2007; Jurkiewicz *et al*., 2010; Mikulis *et al*., 2002). Two studies have been performed to report the temporal evolution of cortical sensorimotor activity after TSCI (Jurkiewicz *et al*., 2007; Jurkiewicz *et al*., 2010). The first study, within which TSCI patients with motor recovery were studied, detected progressive enlargement in the primary motor cortex and decreased activation in the associated cortical areas was detected (Jurkiewicz *et al*., 2007). When these authors studied 4 tetraplegic individuals whose paralysis persisted, activation was extensive in the associated areas in the early post-injury period but progressed toward no activation by the end of the first year (Jurkiewicz *et al*., 2010).

Different findings have been reported concerning brain activation. Still, it is difficult to determine the influence of SCI on brain reorganisation because subjects have variable lesion locations and completeness of injury, as well as the length of time after injury. Increase in activation magnitude have been found in several researches (Alkadhi *et al*., 2005; Bruehlmeier *et al*., 1998; Curt *et al*., 2002; Hotz-Boendermaker *et al*., 2008). The cortical areas with increased activation were the bilateral primary motor cortex, supplementary motor area,

premotor area, cingulate motor area, parietal cortex, contralateral primary somatosensory cortex (Figure 1). In contrast, some studies have not found differences in brain activation between patients with SCI and controls (Castro *et al*., 2007; Halder *et al*., 2006; Mattia *et al*., 2006). Two studies have reported reduced activation in individuals with SCI (Cramer *et al*., 2005; Sabbah *et al*., 2002).

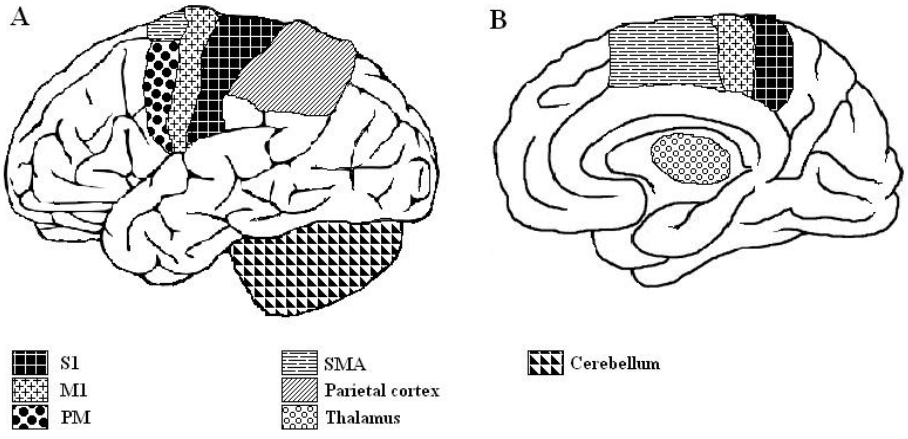


Figure 1. The brain areas with increased activation during motor tasks in spinal cord injury compared to controls. Increased activation has been found in bilateral primary motor cortex (M1), primary somatosensory cortex (S1), supplementary motor area (SMA), premotor area (PM), cingulated motor area (CMA), parietal cortex, cerebellum, thalamus, and basal ganglia. (A) Medial view (B) Lateral view (Kokotilo *et al*., 2009a) (with permission from Mary Ann Liebert, Inc.).

Two types of spatial shift have been observed: medial and posterior (Kokotilo *et al*., 2009a) (Figure 2). The explanation for the posterior shift was the direction of the deafferented limb representation (Green *et al*., 1999). Turner et al. have postulated that it could be possible that a posterior shift relates to increased activation in the somatosensory cortex due to neuropathic pain experienced by some people with SCI. The shift in the direction of the deafferented limb representation in M1 was found by 3 groups (Bruehlmeier *et al*., 1998; Lotze *et al*., 1999; Mikulis *et al*., 2002) and it can be explained by chronicity of SCI. For example, Mikulis *et al*. studied tetraplegic TSCI patients in the chronic phase and showed that when these patients moved their tongue, the primary motor cortex activation was shifted medially and posteriorly into the upper limb representation region (Mikulis *et al*., 2002). Several investigators have suggested that a similar shift takes place among paralyzed patients when they move their hand (Kokotilo *et al*., 2009a; Curt *et al*., 2002; Lotze *et al*., 1999). The possible causes of the changes are destructed sensorimotor tracts, disruption of

the lateral inhibitory network in the cortex, and modification of neuronal activity (Mikulis *et al*., 2002; Streletz, 1995).

Patients with TSCI and stroke share several aspects of brain reorganisation following injury (Kokotilo *et al*., 2009b). The more severe is the hand motor deficit, the greater is the shift of primary motor cortex activation towards the contralateral hemisphere balance.

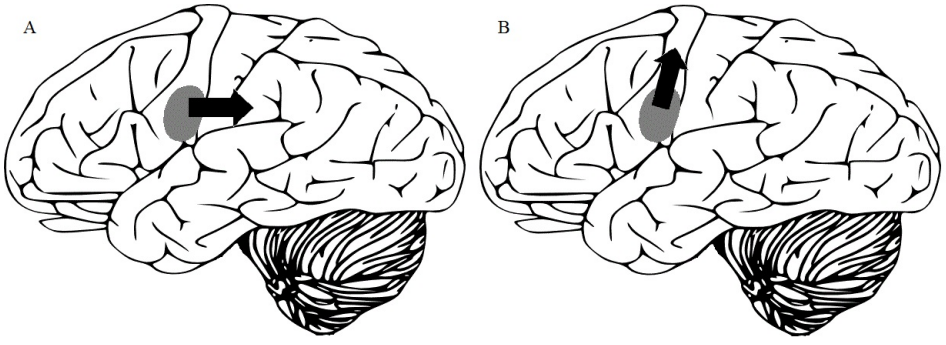


Figure 2. Two types of spatial shift described in activation during a motor task in patients with spinal cord injury (A) Posterior shift of activation towards primary somatosensory cortex during an upper limb motor task (activation represented by shading). (B) Activation of upper limb movement is shifted in the direction of the deafferented upper/lower limb representation in para/tetraplegic SCI subjects (Kokotilo *et al*., 2009a) (with permission from Mary Ann Liebert, Inc.).

3. AIMS OF THE STUDY

1. To evaluate the incidence and temporal trends of TSCI in Estonia from 1997 to 2007 (Paper I)
2. To analyse the demographic and clinical characteristics of an a population based cohort of Estonia from 1997 to 2007 (Paper I)
3. To compare the incidence and survival rates of TSCI in Estonia with those in Western-Norway (Paper II)
4. To study the mortality and causes of acute and long-term death among TSCI victims (Paper III)
5. To establish cortical activation patterns after cervical TSCI within the first year after TSCI (Paper IV)

4. SUBJECTS AND METHODS

4.1. Study design

Papers I and III
The study design was retrospective cohort study including TSCI cases in Estonia between January 1, 1997 and December 31, 2007.

Paper II
Retrospective population based study in two Norwegian counties (Hordaland and Sogn og Fjordane) and in the whole Estonia from 1997 to 2001.

Paper IV
Case series study. Functional magnetic resonance imaging (fMRI) was used to study 6 TSCI patients during the first year after the injury and 12 healthy subjects at Tartu University Hospital.

4.2. Collection of data and case ascertainment

Organisation of TSCI care in Estonia
There are no spinal cord units established in Estonia. As a rule, most patients with TSCI in Estonia are acutely admitted to the Departments of Neurosurgery of the North Estonia Medical Centre or Tartu University Hospital where the patients are evaluated and treated neurosurgically, if needed. Children are usually treated in Tallinn Children's Hospital or Tartu University Hospital.

Patients who are medically stable and for whom neurosurgical management is not indicated are treated at central or general hospitals.

Papers I and III
Case definition
Several overlapping methods of case ascertainment were used to minimize possible missing cases. We selected the cases under the International Classification of Disease-10 (ICD-10) diagnosis codes suggesting TSCI (Table 1). Medical records with the diagnosis codes suggesting spinal fractures were also reviewed in order not to lose any relevant cases. Patients from all age-groups, including children, were recorded.

The inclusion criteria were: 1) traumatic spinal cord or *cauda equina* injury with neurological deficit found at discharge 2) permanent resident of Estonia at the time of injury. Patients with only transient neurological symptoms (varying degrees of motor or sensory deficit) that had lasted less than seven days, and/or pain, or non-traumatic injury, were excluded. Fatal cases before hospitalization were not included.

Table 1. ICD-10 codes used to identify traumatic spinal cord injuries in Estonia, 1997–2007.

ICD-10	
G82	Paraplegia and tetraplegia
S12.0	Fracture of first cervical vertebra
S12.1	Fracture of second cervical vertebra
S12.2	Fracture of other specified cervical vertebra
S12.7	Multiple fractures of cervical spine
S13.0	Traumatic rupture of cervical intervertebral disk
S13.2	Dislocation of other and unspecified parts of neck
S13.4	Sprain and strain of cervical spine
S14.0	Concussion and edema of cervical spinal cord
S14.1	Other and unspecified injuries of cervical spinal cord
S22.0	Fracture of thoracic vertebra
S23.0	Traumatic rupture of thoracic intervertebral disc
S23.1	Dislocation of thoracic vertebra
S24.0	Concussion and edema of thoracic spinal cord
S24.1	Other and unspecified injuries of thoracic spinal cord
S32.0	Fracture of lumbar vertebra
S33.0	Traumatic rupture of lumbar intervertebral disc
S33.1	Dislocation of lumbar vertebra
S34.0	Concussion and edema of lumbar spinal cord
S34.1	Other injury of lumbar spinal cord
S34.3	Injury of cauda equina
T06.0	Injuries of brain and cranial nerves with injuries of nerves and spinal cord at neck level
T06.1	Injuries of nerves and spinal cord involving other multiple body regions
T09.3	Injury of spinal cord, level unspecified
T91.1	Sequelae of injuries, of poisoning and of other consequences of external causes – Sequelae of injuries of neck and trunk – Sequelae of fracture of spine
T91.3	Sequelae of injuries, of poisoning and of other consequences of external causes – Sequelae of injuries of neck and trunk – Sequelae of injury of spinal cord

Abbreviation: ICD-10, International Classification of Diseases, Tenth revision.

Data collection

For the purpose of this study, all medical records of the patients with the diagnosis of TSCI or suspected TSCI in Departments of Neurosurgery of the North Estonia Medical Centre or Tartu University Hospital and in all Estonian rehabilitation hospitals, in central and general hospitals were also looked through.

About 3000 medical records of the patients with possible TSCI diagnosis were retrospectively reviewed. Altogether, medical records from 22 Estonian hospitals (3 regional, 3 rehabilitation, 4 central and 12 general hospitals) were reviewed and data on all cases of TSCI were abstracted.

Information about whether the person was alive or dead by December 31, 2011 was obtained from Statistics Estonia (Statistics Estonia, www.stat.ee). The

cases were linked with the data from the Cause of Death Registry. The cases were matched by the identity codes.

The coding system used was the 10th version of the International Classification of Diseases (ICD). The following 14 categories of the European ICD-10 Causes of Death short list (European Communities, 2009) were used for this study: (1) sepsis, (2) neoplasm, (3) endocrine, nutritional and metabolic diseases, (4) mental and behavioural disorders, (5) diseases of the nervous system, (6) diseases of the circulatory system, (7) diseases of the respiratory tract, (8) diseases of the digestive system, (9) diseases of the skin and subcutaneous tissue, (10) diseases of the musculoskeletal system, (11) diseases of the genitourinary system, (12) external causes of injury and poisoning, (13) suicide, (14) other disorders. Information concerning the date of death and the immediate and underlying cause of death was registered. Information about the cause-specific mortality rates for the general population was obtained from Statistics Estonia (Statistics Estonia, www.stat.ee).

The patients in the Paper I and II were divided into eight age-groups according to the age at the time of injury (0–19, 20–29, 30–39, 40–49, 50–59, 60–69, 70–79, 80+ years). By the time of publishing Paper III, authors were requested to use 15 year increments when grouping the patients: 0–15, 16–30, 31–45, 46–60, 61–75, 76+ (DeVivo *et al*., 2011; Wyndaele, 2012).

As it has been found that the mortality risk is increased during the first two years after the injury (Middleton *et al*., 2012; O'Connor, 2005; Strauss *et al*., 2000), the dead patients in the study III were divided into two groups: those who died during the first two years and those who died thereafter.

Paper II

The scientific collaboration between the Department of Neurology at the Universities of Tartu (Estonia) and Bergen (Norway), uniform data collection, and stable population in both Estonia and Norway gave an excellent opportunity to compare the incidence, characteristics and mortality of TSCI in Western Norway and Estonia.

The data collection system in Estonia and Norway was uniform. Medical records from all hospitals in these areas (8 Norwegian and 22 Estonian hospitals) between 1997 and 2001 were scrutinized. We used the same procedures of patient identification by reviewing the records of all patients with a diagnostic code of the International Classification of Diseases 10th version (ICD-10) suggesting a traumatic spinal cord injury or a fracture of the spinal column at discharge.

The causes of injury were classified into 4 groups: motor vehicle accidents (MVA), falls, sport injuries and other injuries (DeVivo *et al*., 2006). The extent of injury was classified according to the American Spinal Injury Association Impairment Scale (AIS) (Marino *et al*., 1999). The patients were stratified retrospectively according to the level of injury and also depending on complete or incomplete injury. The patients were grouped according to concomitant traumatic brain injury and use of alcohol prior to the injury. When examining the

standardised mortality ratio the patients were also grouped into three age-groups according to age at time of injury; 0–29 years, 30–59 years and older than 60 years.

Records of TSCI related deaths before hospitalisation were not available for either of the countries.

All the patients were followed until death or 14th October, 2011. The date of death was obtained from the National Population Registers of Norway and Estonia.

Paper IV

The patients consecutively admitted to Tartu University Hospital from May 2010 to August 2010 with acute TSCI were studied repeatedly by functional magnetic resonance imaging (fMRI) at 20.8 ± 6.7, 111.3 ± 21.9 and 376 ± 26.3 days after the injury. Six right-handed tetraplegic male patients (mean age 27.3 ± 10.9 years, range 18–41 years) were included to the study.

Twelve age- and gender matched healthy controls (mean age 27.1 ± 10.1 years, range 18–42 years) were studied at a single point of time and 7 controls were studied on 2 occasions (353.7 ± 50.5 days between the studies).

The inclusion criteria were tetraplegia due to cervical TSCI. The TSCI patients had to be medically stable and able to give informed consent before the study. We excluded patients with traumatic brain injury, patients with a previous history of seizures and those who had contra-indications to MRI. Only patients with a neurological deficit lasting more than one week were included.

4.3. Clinical data

Papers I, II and III

Demographic data, length of admission, level of injury, extent of injury according to the American Spinal Injury Association Impairment Scale (AIS), cause of injury and alcohol consumption associated with trauma, and the presence of diagnosis of spinal fracture were recorded from medical records (Maynard *et al*., 1997). In Papers I and III the causes of TSCI were divided into 6 groups (sports and leisure activities, assaults, transport activities, falls, other traumatic causes, unknown) as suggested by the Executive Committee for the International Spinal Cord Injury Data Sets Committees (DeVivo *et al*., 2006). Paper II comprised 4 groups (motor vehicle accidents, falls, sport injuries and other injuries).

Severity of injury was reported by 4 categories according to the recent recommendations by the Executive Committee for the Development of the International Spinal Cord Injury Data Sets: C1-4 AIS A, B or C; C5-8 AIS A, B or C; T1-S5 AIS A, B or C and AIS D at any injury level. Due to the small number of ventilator dependent patients, they were analysed together with the C1-4 AIS A, B, C patients (Appendix A, B; DeVivo *et al*., 2011).

Alcohol consumption prior to a TSCI was registered when on admission to the hospital signs of alcohol were detected in the blood or when alcohol consumption before the trauma was recorded in medical documents.

Paper IV

The extent of injury was estimated according to the American Spinal Injury Association (ASIA) Impairment Scale (AIS) (Appendix A, B; DeVivo *et al*., 2011). The patients were classified according to their motor level of injury (C5, C6 and C7). Recovery of motor function occurred in 3 patients (Table 12).

Patient No 1 was hospitalised with severe tetraplegia after TCSI. The first imaging was performed 19 days after the trauma, when significant recovery had occurred. Patient No 5 was moved from the complete injury group to the incomplete injury group because sensation in the sacral segments improved over the course of the first year. However, he remained in the motor complete group of injury in this study.

4.4. Imaging procedures and data processing

All subjects in the fMRI study were informed about the study, their tasks and the length of the imaging before the procedure. Each activation experiment consisted of a 40 s period of rest, followed by a 40 s period of movement, both repeated three times. The individuals were trained to perform the movements at a frequency of 1 Hz.

During the fMRI study the individuals performed active simple test-retest cycles of 1) flexion/extension of the right hand fingers; 2) flexion/extension of the right ankle. Motor tasks were continuously visually monitored and counted by an observer. The number of movements in each block was summed, and divided by the total number (3) of movement blocks.

All patients were able to perform some hand movement but in patients with complete injury the observed movement was wrist movement. Ankle movement was not feasible for half of the patients and their lower limb motor score remained 0 (Table 12). However, all patients attempted to move ankle.

Images were obtained on a 1.5 T clinical whole body MR scanner (Magnetom Symphony; Siemens Medical Systems, Erlangen, Germany). Prior to functional scans, a high resolution T1 weighted anatomical image was obtained with the gradient echo, fast low-angle shot (FLASH) sequence (repetition time (TR)=12 ms, echo time (TE)=5.68 ms, flip angle 15˚, resolution 224×256, voxel size 1×1×1 mm^3, 176 sagittal planes). Functional T2* weighted images were obtained using the gradient echo planar imaging (EPI) sequence (TR=4 s, TE=50 ms, flip angle 90˚, resolution 64×64, voxel size 3×3×3 mm^3, slice gap 0.75 mm, 36 axial planes, interleaved scan). Altogether 60 whole brain functional images were obtained for each patient and control subject while the subjects were performing the described tasks.

Image processing was performed using the Statistical Parametric Mapping (SPM8, update rev. no. 4290, Wellcome Trust Centre for Neuroimaging, London, UK) software, which is a suite of MATLAB (The MathWorks, Inc., Natick, MA, USA) functions to process and analyse functional neuroimaging data (Ashburner *et al*., 2011).

The first step of spatial pre-processing was the realignment of functional images, where movement effects were discounted. Thereafter high resolution anatomical images were co-registered with functional images, to maximize the mutual information. Pre-processing continued with segmentation of high resolution anatomical images, where the Montreal Neurological Institute (MNI) 452 white matter, grey matter and cerebrospinal fluid probability maps (Brett *et al*., 2002) were used to yield a parametric description for normalisation. During normalisation the images were also bias-corrected. Image pre-processing was completed with smoothing by the 8×8×8 mm^3 FWHM (full-width at half maximum) isotropic Gaussian kernel.

4.5. Statistical analysis

Paper I

Descriptive data were presented as percentage, mean, median and standard deviation. For categorical data, frequencies and percentages were expressed in contingency tables and differences were assessed by the Chi-square test. Incidence rates with the 95% confidence intervals were calculated using the Poisson distribution. The crude incidence rates were calculated using the mid-year population census for each year and were age- and gender-adjusted to Estonian population by direct standardisation (census 2000).

Trends in incidence were calculated using the Poisson regression model. A quasi-Poisson model was used when overdispersion was present. Age (8 categories) and sex (2 categories) specific incidence rates were calculated over time (11 categories).

The analysis of temporal trends was based on chi-square test for categorical data and one-way analysis of variance for continuous data.

A statistical level of significance of 5% was used ($P<0.05$), all confidence intervals were expressed at 95% (95% CI).

Paper II

Descriptive data was presented as number, percentage, mean, median and standard deviation. Differences in categorical data were assessed by the Chi-square test. The T-test and analysis of variance were used for continuous variables. The incidence rates with 95% confidence intervals were calculated using the Poisson distribution. Crude incidence rates of TSCI were calculated for both countries using the mid-year population census for each year. Age- and gender-adjusted incidences were calculated by the method of direct standardisation, using the standard European population structure. We compared mortality by age-groups

using the two-sided Fisher exact test and the Kaplan-Meier curves. Cox proportional hazards analysis was used to determine the probability of survival in the presence of specific risk factors.

Standardised mortality ratios were calculated as the ratios of the actual number of observed deaths to the number of deaths expected in Estonia and Norway. However, comparison of indirectly standardised rates is problematic, because the reference populations of Norway and Estonia are not the same. In order to compare the rates, we calculated SMRs according to EU-15 life tables for 2003. Although Estonia belongs to the European Union and Norway does not, it is recommended to compare the mortality of each European country to the EU-15 average because the EU-27 average would yield a less balanced picture (European Communities, 2009).

A statistical level of significance of 5% was used ($P<0.05$), all confidence intervals (CI) were expressed at 95%.

Paper III

Standardised mortality ratios (SMRs), survival rates and life expectancy were calculated. The SMR is expressed as the ratio of observed deaths of persons with TSCI to expected deaths in the general Estonian population. The Kaplan-Meier curves were used to visualise survival by age at death or to censor the SCI population compared to the general population. The cause specific mortality rates were based on the underlying cause of death. A Cox proportional hazards regression model was used to identify the probability of death in the presence of specific risk factors. We used the log-log plot to test the proportional hazard assumption that the hazard ratio is constant over time. The risk factors were estimated for the patients who lived less than 2 years and for those who outlasted the cut-off point of 2 years. This distribution was chosen since it has been reported that the risk of death is disproportionately higher among patients with high cervical TSCI during the first two years after injury (Middleton *et al*., 2012; Strauss *et al*., 2000; Strauss *et al*., 2006).

The independent variables (age, sex, year of the injury, cause of trauma, pre-injury alcohol consumption, concomitant injury, head injury, extent of injury, vertebral fracture, need for mechanical ventilation, operation in 6 weeks, methylprednisolone in acute phase, complications in acute phase), that were included in the Cox proportional hazards regression model, were obtained from the medical records earlier. Pre-existing conditions or co-morbidities were not included into the model because the information gained from the medical records was too scarce.

Paper IV

Image processing was followed by a general linear model-based statistical analysis of the functional images. Modelling was done with box car functions convolved with canonical hemodynamic response function (HRF). Low frequency noise was eliminated by using a 160 s high-pass filter. Estimation of the model parameters was done by using SPM8, after which task vs. rest

activation was assessed by applying a t-test to the parameter estimates, resulting statistical parametric t-maps for each subject. Multiple comparisons' problems were corrected by masking images with the Brodmann area (BA) masks BA 1-2-3-5 (BA 1, 2, 3 and 5 were analysed as one area), BA 4 and BA 6 from MRIcro (Rorden and Brett, 2000) using SPM8 and by applying FWE (family-wise error) correction with $p<0.05$ and by discounting all clusters smaller than 3 voxels.

From the resulting masked t-maps, the maximum t-test results and the Talairach coordinates of the maximum activation were recorded. The total volume of all activated cluster(s) in each region of interest (ROI) (defined by the masked areas) was calculated and the Talairach coordinates of the geometric centre of gravity (COG) of the cluster with a maximum t-test result in each ROI were found using MarsBaR release 0.43 (Brett *et al*., 2002).

Finally, weighted laterality index (wLI) was calculated using the combined bootstrap/histogram analysis approach (Wilke and Schmithorst, 2006). Bootstrap algorithm helps to evaluate sampling distribution of a sample by repeatedly resampling, with replacement, the original sample, which would yield approximately the "real" distribution of the original sample. By using the bootstrap algorithm, 10 000 indices were iteratively calculated with equation (1) at different thresholds, where Q_{LH} is the sum of all the t-map values in the masked area of the left hemisphere and Q_{RH} is the corresponding sum for the right hemisphere:

$$LI = \frac{Q_{LH} - Q_{RH}}{Q_{LH} + Q_{RH}} \quad (1)$$

For each threshold, trimmed mean laterality index was calculated by finding the mean value of laterality indices from which 25% of the upper and lower values were excluded. Weighted laterality index (wLI) was calculated by equation (2), where $LI_{25,i}$ is the trimmed mean laterality index and W_i is the weighting factor or threshold where the trimmed mean was calculated as:

$$wLI = \frac{\sum_{i=1}^{n} W_i \times LI_{25,i}}{\sum_{i=1}^{n} W_i} \quad (2)$$

To avoid statistically unimportant results, limits for a minimum cluster size of 5 "activated" voxels and a minimal number of 10 "activated" voxels per hemisphere were established.

Additional statistical analysis was performed using the StatsDirect statistical software Version 2.7.8. The t test was used for between-group comparisons when the variables followed a normal distribution. When variables did not follow a normal distribution, the Mann-Whitney U test was used. Repeated measures ANOVA was performed for TSCI between-group comparisons. The associations between the volume of activation (VOA) and ASIA motor score or time post-injury were estimated using a Pearson correlation. All p-values were two-sided. Statistical significance was defined as $p<0.05$.

4.6. Ethics

All the studies were approved by the Research Ethics Committee of the University of Tartu, Estonia.

The second study was also approved by the Regional Committee for Medical Research Ethics in Norway, the Norwegian Data Inspectorate and the Norwegian Directorate for Health and Social Affairs.

The study in Paper III received additional approval from the Data Protection Inspectorate of Estonia.

5. RESULTS

5.1. Incidence of TSCI

The medical records of more than 3000 patients from 22 Estonian hospitals were retrospectively reviewed, of them 595 met the inclusion criteria of TSCI.

The annual crude incidence rate was 39.7 per million population (95% CI 36.6–43.0) for all. After standardization to the Estonian population by age and gender the annual incidence rate was 39.4 (95% CI 36.2–42.6) for all, 72.0 (95% CI 65.7–78.3) for men and 11.5 (95% CI 9.2–13.9) for women.

There was no statistically significant change in the number of TSCI cases during the study period. The crude rate increased but this was not statistically significant (incidence rate ratio (IRR) 1.03, 95% CI 1.00–1.05, p=0.051). After adjustment by age and gender the trend remained statistically nonsignificant (IRR 1.02, 95% CI 1.00–1.05, p=0.09). However, there was a statistically significantly (IRR 1.06, 95% CI 1.02–1.10, p=0.003) increasing trend from 1999 to 2007 (Figure 3).

The incidence was significantly higher among men compared to that of women in all age-groups (IRR 6.4, 95% CI 5.1–8.1, p<0.001) (Table 2).

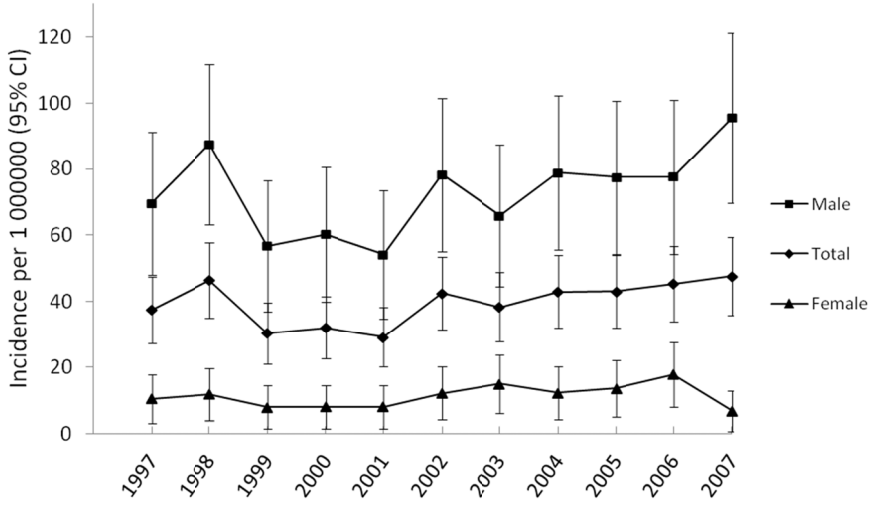


Figure 3. Age-adjusted incidence rates of traumatic spinal cord injury (per 1 000 000 annually) with 95% confidence intervals in Estonia from 1997 to 2007.

Table 2. Traumatic spinal cord injury incident cases, age- and gender-specific incidence rates (per 1 000 000 annually) with 95% confidence intervals for men, women and total population in Estonia from 1997 to 2007.

Age-group	Men			Women			Total			p-value*
	No	Incidence rate	95% CI	No	Incidence rate	95% CI	No	Incidence rate	95% CI	
0–19	47	24.8	18.3–32.0	20	11.1	6.8–17.2	67	18.1	14.1–23.0	<0.01
20–29	144	133.9	113.0–157.7	11	10.5	5.2–18.7	155	72.9	61.9–85.3	<0.001
30–39	95	95.0	76.8–116.1	19	18.3	11.0–28.5	114	55.9	46.1–67.1	<0.001
40–49	77	76.8	60.6–96.0	16	14.3	8.2–23.2	93	43.8	35.4–53.7	<0.001
50–59	68	83.4	64.7–105.7	9	9.0	4.1–17.0	77	42.3	33.4–52.9	<0.001
60–69	49	74.7	55.3–98.8	7	7.3	2.9–15.0	56	34.6	26.1–44.9	<0.001
70–79	15	41.0	23.0–67.7	9	11.8	5.4–22.4	24	21.3	13.6–31.7	<0.01
≥80	8	79.9	34.5–157.5	1	3.0	0.1–16.5	9	20.6	9.4–39.0	<0.001
Total	503	72.8	66.6–79.5	92	11.4	9.2–14.0	595	39.7	36.6–43.0	<0.001

* Statistical significance between the incidence rates of men and women

5.2. Risk factors of TSCI

The majority of the patients were men (84.5%) (Table 3). The male to female ratio was 5.5:1.

The mean age at injury was 39.0. The proportion of patients older than 60 years at injury was 15.0%. The youngest TSCI victim was 1 year old and the oldest 93 years old.

Table 3. Characteristics of traumatic spinal cord injury incident cases in Estonia from 1997 to 2007.

Characteristics		
Number of cases	595	
Gender		
Male (%)	503	(84.5%)
Female (%)	92	(15.5%)
Age		
Mean (s.d.)	39.0	(17.2)
Median (range)	36.0	(1.0–92.0)
Neurological category		
C1-C4 AIS A, B, C (%)	59	(9.9%)
C5-C8 AIS A, B, C (%)	172	(28.9%)
T1-S5 AIS A, B, C (%)	159	(26.7%)
All AIS D (%)	142	(23.9%)
Unknown (%)	63	(10.6%)
Length of stay in hospital (days)		
Mean (s.d.)	20.3	(25.1)
Median (range)	15	(0–368)

Abbreviation: AIS, American Spinal Injury Association Impairment Scale.

Alcohol consumption preceded TSCI in 257 of the cases (43.2%), whereas in 34.2% of the cases alcohol consumption was unknown or not recorded in the medical documents. Significantly more men than women (46.0% vs. 34.7%) had signs of alcohol consumption on admission to the hospital (p=0.002). Almost half of the patients injured at diving had consumed alcohol (52.7%). There was no change in alcohol consumption preceding the trauma from 1997 to 2007 (p=0.1).

5.3. Causes of TSCI

The most common cause of TSCI was falls (41.0%), followed by traffic accidents (29.4%) (Figure 3). Falls was significantly more common reason for TSCI

in patients aged ≥30 years accounting for 51.5% of the TSCI cases compared to 24.4% in those aged <30 years ($p<0.001$). The highest proportion of falls as a cause of TSCI was among patients aged ≥60 years (72.4%). Traffic accidents were the most common cause among patients aged <30 years ($p<0.001$). There was no gender difference in the cause.

Diving was the leading cause of sports injuries (91.4%). Among other injuries 31.0% occurred as a result of traumatic blows on tree felling.

The trauma was work-related in 15.2% of the cases. The main external cause was falls (39.1%), followed by accidental tree felling (31.0%).

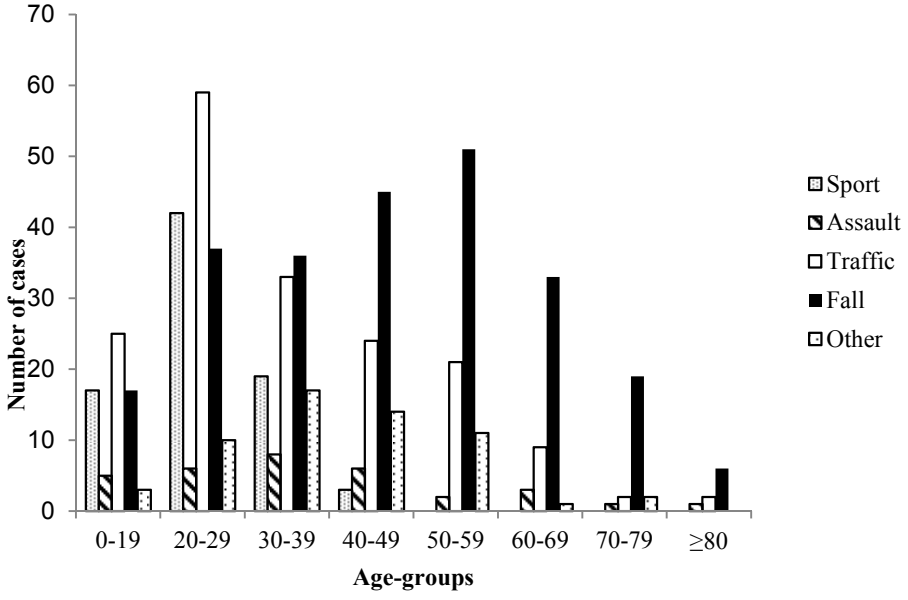


Figure 4. Number of traumatic spinal cord injury cases by cause in Estonia, 1997–2007.

5.4. Severity of TSCI

The cervical part of the spinal cord was the most common site of injury. The injury was sustained at the cervical level in 59.4%, at the thoracic level in 18.3% and at the lumbar or sacral level in 22.3% of the cases. Patients aged ≥60 years had cervical SCI in 80% of cases. Table 3 presents the distribution of cases according to recently recommended guidelines (DeVivo *et al*., 2011). In 53% of the cases the injury was motor complete (AIS: A and B) and 47% of the cases it was motor incomplete (AIS: C and D).

5.5. Associated injuries, management and complications TSCI

Spinal column fractures occurred in 76.3% of the cases. Spinal column fractures were significantly associated with the severity of injury ($p<0.001$). The most common spine injury occurred at the C5 (17.0%), at the C6 (13.0%) level and at the L1 (13.4%) level. In 31.6 % of the cases there occurred an associated injury, the most frequent being brain injury (30.6%).

Complications were present in 48.3% of the cases. The most common complications detected in the acute phase of TSCI were urinary (46.9%) and respiratory tract infections (44.4%) and pressure sores (22.9%). Complications were not different between younger patients (<60 years) and the elderly (≥ 60 years) ($p=0.6$). The presence of complications was strongly influenced by the completeness of injury (more frequent in AIS A, $p<0.0001$) (Sabre *et al*., 2012).

Sixty-five per cent of the patients needed surgical management. Surgical treatment and positive dynamics (AIS grade improvement) were statistically significantly related ($p=0.005$) (data not published). Forty-three per cent of the patients received MPSS during the first day after TSCI. Until 2002, 64% of the patients were treated with high-dose MPSS, thereafter this figure declined to 20%.

5.6. Mortality and causes of death after TSCI

The analysis was based on 595 patients with TSCI, 162 of whom (139 men and 24 women) were dead by December 31, 2011. The mean age at the time of injury in dead was 50.8 ± 17.7 (range 5–93), 51.0 ± 17.5 years (range 16−93) for men and 49.9 ± 19.3 years (range 5−87) for women. Among the patients who survived, the mean age at injury was 34.8 ± 14.6 years (range 1−76). During the first year after TSCI, there were 46.9% (n=76) deaths. Table 4 presents the distribution of deaths in different impairment groups.

Table 4. Distribution of deaths in patients with traumatic spinal cord injury in Estonia from 1997 to 2011.

Impairment (neurol. group and AIS grade)	Injured 1997–2007 N	Death in 12 months N	%	Death in 2. year N	%	Death after 2 years N	%
C1-C4 ABC	59	19	32.2	1	1.7	6	10.2
C5-C8 ABC	172	35	20.3	4	2.3	23	13.4
C1-C8 D	96	5	5.2	4	4.2	12	12.5
Th1-S5 ABC	159	12	7.5	2	1.3	26	16.4
Th1-S5 D	46	0	0	1	2.2	3	6.5
Unknown	63	1	1.6	4	6.3	4	6.3

Abbreviation: AIS, American Spinal Injury Impairment Scale.

The predominant cause of injury of people who died was falls (41.0%), followed by traffic accidents (29.4%).

During the first year, the leading underlying causes of death were external causes of injury (52.6%) and cardiovascular diseases (21.1%). Later, the cardiovascular diseases became predominant (35.6%), followed by suicides (13.8%). All the patients who committed suicide were male, and all but one attempt happened after the first year of TSCI. The survival of the patients whose cause of death was suicide was 1951 ± 1342 days. Seven of the patients had tetraplegia, 6 had paraplegia.

The overall SMR was 2.81 (95% CI 2.40−3.28). The SMRs were higher for women (Tables 5 and 6). Men with TSCI younger than 76 years and women younger than 61 showed increased mortality compared to the general population. Figures 5 and 6 illustrate the survival in the study population among men and women.

Table 5. Standardised mortality ratios (SMRs) for age-groups among males with traumatic spinal cord injury in Estonia from 1997 to 2011.

Age-group	Observed	Expected	SMR	95% CI
0–15	0	0.01	0	0–435.2
16–30	16	2.7	5.9	3.4–9.7
31–45	32	6.3	5.1	3.5–7.2
46–60	43	14.4	3.0	2.2–4.0
61–75	36	18.7	1.9	1.3–2.7
>75	12	9.4	1.3	0.7–2.2
Total	139	51.5	2.7	2.3–3.2

Table 6. Standardised mortality ratios (SMRs) for age-groups among females with traumatic spinal cord injury in Estonia from 1997 to 2011.

Age-group	Observed	Expected	SMR	95% CI
0–15	1	0.004	214.2	5.4–1193.6
16–30	2	0.1	17.4	2.1–63.0
31–45	8	0.3	23.4	10.1–46.2
46–60	6	0.6	10.3	3.8–22.3
61–75	4	1.4	2.8	0.8–7.2
>75	2	3.6	0.6	0.1–2.0
Total	23	6.1	3.8	2.4–5.7

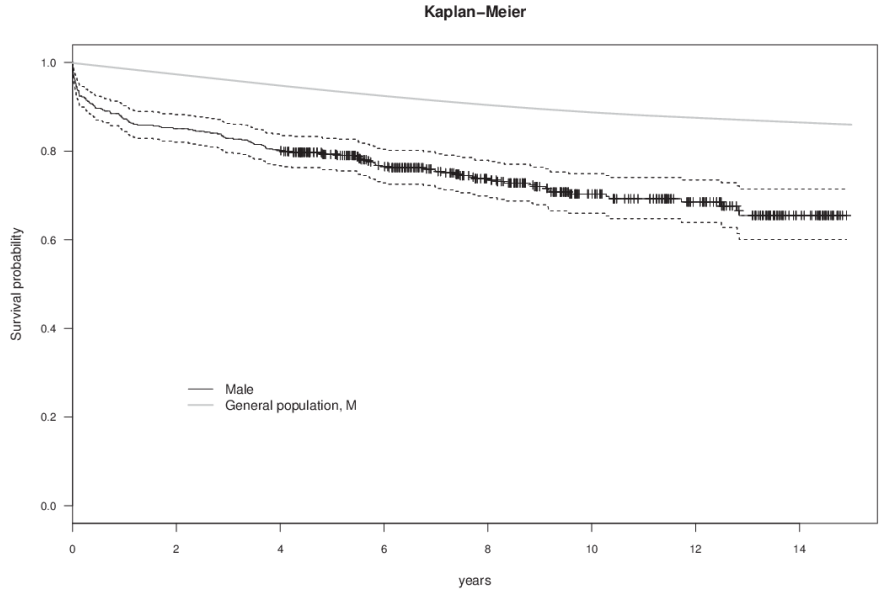


Figure 5. Survival probability of male with traumatic spinal cord injury (with 95% confidence interval), injured from 1997 to 2007, compared with the Estonian population.

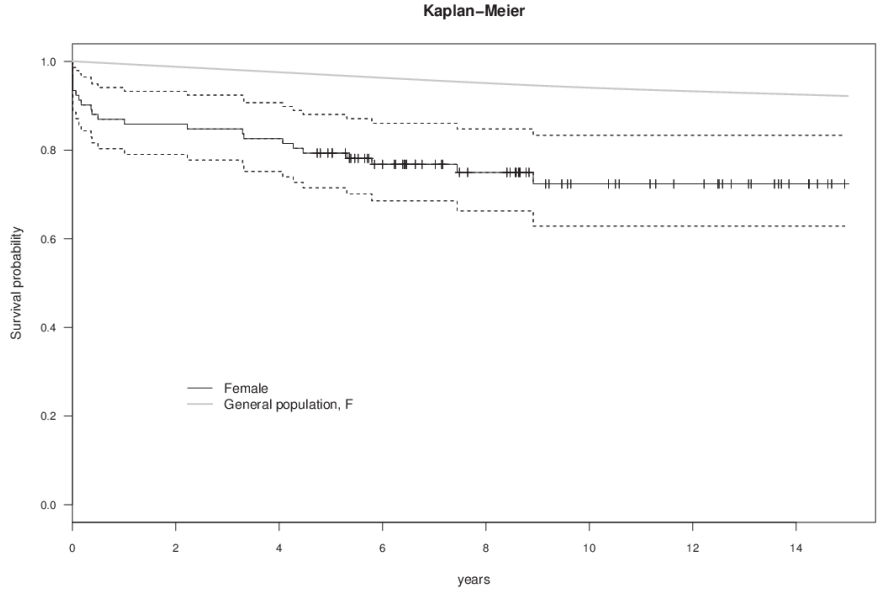


Figure 6. Survival probability of female with traumatic spinal cord injury (with 95% confidence interval), injured from 1997 to 2007, compared with the Estonian population.

Table 7. Causes of death of deceased TSCI patients in Estonia from 1997 to 2011.

	No of deaths			
Causes of death	Observed	Expected	SMR	(95% CI)
Sepsis				
Total	12	0.04	339.5	175.5–593.1
Male	9	0.03	296.3	135.5–562.4
Female	3	0.01	604.3	124.6–1765.9
Cancer				
Total	7	13.9	0.5	0.2–1.0
Male	5	12.3	0.4	0.1–1.0
Female	2	1.6	1.2	0.2–1.0
Cardiovascular disease				
Total	46	30.9	1.5	1.1–2.0
Male	41	25.7	1.6	1.1–2.2
Female	5	5.2	1	0.3–2.3
Respiratory disease				
Total	13	2.4	5.5	2.9–9.4
Male	11	2.2	2.5	2.5–8.9
Female	2	0.2	13.1	1.6–47.2
Digestive system disease				
Total	5	2.6	1.9	0.6–4.4
Male	5	2.4	2.1	0.7–4.9
Female	0	0.3	0	0–13.1
Skin disease				
Total	5	0.05	105.4	34.2–246.0
Male	5	0.04	128.4	41.6–298.9
Female	0	0.01	0	0–439.0
Musculoskeletal disease				
Total	2	0.13	14.6	1.8–52.6
Male	2	0.1	19.9	2.4–71.8
Female	0	0.03	0	0–100.8
Genitourinary disease				
Total	9	0.5	18	8.2 – 34.2
Male	8	0.42	18.9	8.2 –37.2
Female	1	0.08	13.2	0.3 – 73.7
External causes of injury				
Total	48	8.4	5.7	4.2–7.6
Male	38	8	4.7	3.3–6.5
Female	10	0.4	28.3	13.6–52.1
Suicide				
Total	13	1.6	8.3	4.4–14.3
Male	13	1.5	8.7	4.6–14.8
Female	0	0.05	0	0–65.8

Abbreviations: TSCI, traumatic spinal cord injury; SMR, standardised mortality ratio; CI, confidence interval.

During the study period, SMR decreased 11% per year from 7.99 to 2.13 ($p<0.001$). The mortality rate in the first year of injury did not show any change ($p=0.29$).

Cause-specific SMR was the highest for sepsis (Table 7). Cause-specific SMR for suicide was 8.7 among the men, none of the women committed suicide during the study period in Estonia. The sole cause of death with decreased SMR compared to the general population was cancer (Table 7).

Cox proportional hazards modelling revealed several predictors of mortality (Table 8). During the first two years, the significant risk factors of death were higher age at injury, cervical spinal cord injury, completeness of injury and concomitant trauma, including head injury. During the first post-injury year, the patients with C1-4 (AIS A-C) neurological impairment had 6.25 times higher risk of dying compared with the patients with injury below the cervical level. They had also 7 times higher risk of dying than those with C1-8 AIS D impairment (Table 4). After the first year, the risks levelled off. Figure 7 illustrates survival probability in the study population for different levels of neurological impairment. Two years after the injury only age and completeness of lesion remained significant risk factors for death, the cause of injury also became significant.

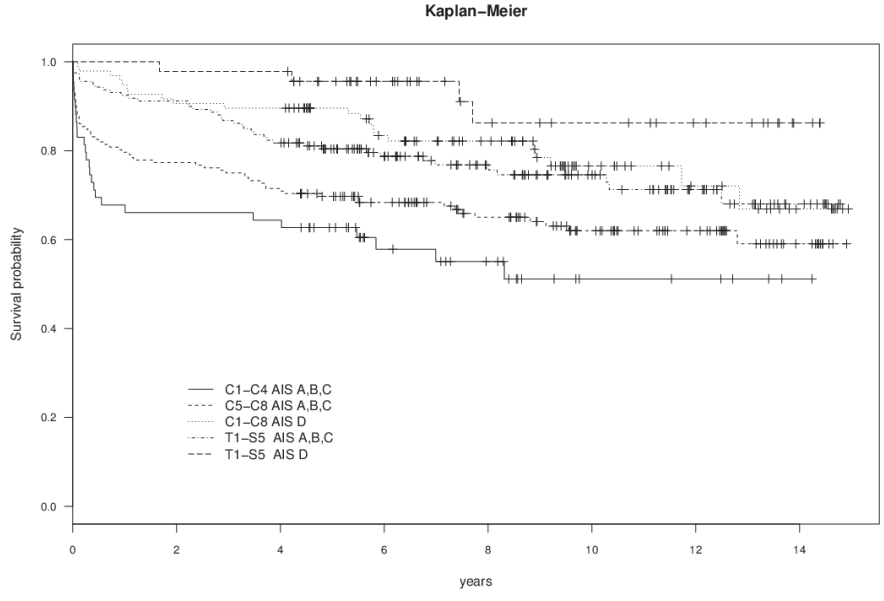


Figure 7. Survival probability of patients with traumatic spinal cord injury with different level and extent of neurological impairment, injured from 1997 to 2007 in Estonia.

Table 8. Risk factors for death of patients with TSCI in Estonia from 1997 to 2011.

Factors	<2 years after TSCI			>2 years after TSCI		
	RR	95% CI	p-value	RR	95% CI	p-value
Age at injury	1.05	1.04–1.06	<0.001	1.04	1.03–1.05	<0.001
Gender						
Male	1.00	–	–	1.00	–	–
Female	0.96	0.54–1.74	0.91	0.84	0.44–1.67	0.65
Year	0.97	0.91–1.03	0.29	0.92	0.85–1.00	0.06
Cause of trauma						
Sport (ref.)	1.00	–	–	1.00	–	–
Assault	1.35	0.45–4.04	0.59	1.04	0.20–5.36	0.96
Traffic accident	1.02	0.46–2.23	0.97	1.52	0.56–4.15	0.41
Falls	1.70	0.83–3.48	0.14	3.90	1.56–9.83	0.004
Other	1.24	0.48–3.21	0.66	0.79	0.19–3.32	0.75
Preinjury alcohol consumption						
No (ref.)	1.00	–	–	1.00	–	–
Yes	1.29	0.75–2.24	0.40	1.39	0.76–2.54	0.29
Concomitant injury						
No (ref.)	1.00	–	–	1.00	–	–
Yes	1.34	0.87–2.06	0.18	0.93	0.55–1.58	0.80
Head injury						
No (ref.)	1.00	–	–	1.00	–	–
Yes	1.84	1.20–2.83	0.005	0.96	0.57–1.61	0.87
Neurological level						
C1–4	5.00	2.64–9.48	<0.001	1.19	0.54–2.59	0.67
C5–8	2.88	1.64–5.06	<0.001	0.98	0.60–1.60	0.93
T1–S5	1.00	–	–	1.00	–	–
Completeness of injury						
Complete (ref.)	1.00	–	–	1.00	–	–
Incomplete	0.29	0.19–0.45	<0.001	0.80	0.50–1.30	0.37
Vertebral fracture						
No (ref.)	1.00	–	–	1.00	–	–
Yes	0.75	0.48–1.87	0.23	0.67	0.42–1.09	0.12
Mechanical ventilation[a]						
No (ref.)	1.00*	–	–	1.00	–	–
Yes	*	*	0	0.89	0.39–2.06	0.78
Operation in 6 weeks						
No (ref.)	1.00	–	–	1.00	–	–
Yes	0.30	0.19–0.47	<0.001	0.80	0.51–1.25	0.33
Methylprednisolone in acute phase[b]						
No (ref.)	1.00	–	–	1.00	–	–
Yes	1.26	0.80–1.98	0.32	0.97	0.60–1.59	0.92
Complication in acute phase[b]						
No (ref.)	1.00	–	–	1.00	–	–
Yes	2.00	1.25–3.16	0.004	1.48	0.93–2.35	0.1

Abbreviations: TSCI, traumatic spinal cord injury; RR, relative risk; CI, confidence interval.

* Assumptions for the proportional hazards analysis were not fulfilled

a – use of ventilation assistance during hospital stay in the acute phase of injury

b – acute phase is defined as the first hospitalisation after the injury

5.7. Comparison of TSCI between Estonia and Western Norway

A total of 71 patients were identified in Western Norway and 244 patients in Estonia during the study period from 1997 to 2001. The male to female ratio was higher in Estonia 6.0:1 than in Western Norway 3.4:1. The mean age at the time of injury was 10 years higher in Norway ($p<0.001$) (Table 9).

The annual crude incidence rate was 26.3 (95% CI 20.5−33.1) in Norway and 35.4 (95% CI 31.1−40.1) in Estonia. After standardisation to the standard European population the annual age- and gender adjusted incidence rates were 24.9 (95% CI 19.4−31.7) in Norway and 37.4 (95% CI 32.8−42.5) in Estonia. Figure 8 shows the age- and gender-specific incidence rates in the two countries.

The leading cause of TSCI was falls in both countries, followed by MVA (Table 9).

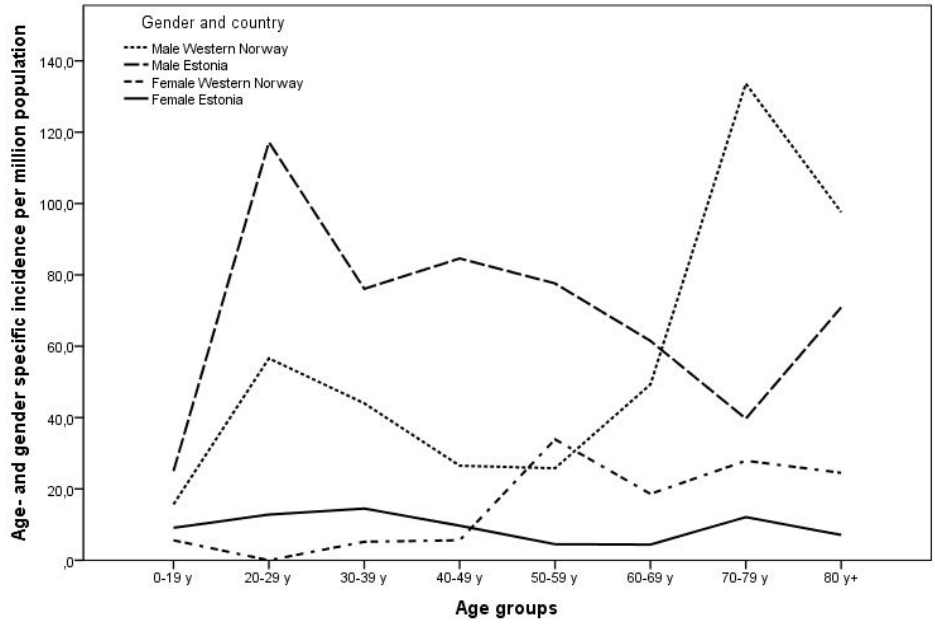


Figure 8. Age- and gender-specific incidences in Western Norway and Estonia in the period 1997 to 2001.

Table 9. Characteristics of traumatic spinal cord injury in Western Norway and Estonia from 1997 to 2001.

	Overall cases		Deceased cases	
Characteristics	Western Norway	Estonia	Western Norway	Estonia
Number of cases	71	244	26	86
Gender				
Male (%)	55 (77.5)	209 (85.7)	20 (76.9)	74 (86.1)
Age				
Mean (s.d.)	48.9 (23.0)	38.9 (17.3)	65.0 (19.2)	47.4 (17.8)
Median (range)	51.0 (8−90)	36.0 (5−93)	72.5 (22−90)	47.5 (5−93)
Cause of injury (%)				
Fall	32 (45.1)	89 (36.5)	14 (53.9)	39 (45.4)
Motor vehicle accident	29 (40.8)	74 (30.3)	9 (34.6)	26 (30.2)
Sport	7 (9.9)	34 (13.9)	2 (7.7)	10 (11.6)
Other	3 (4.2)	47 (19.3)	1 (3.9)	11 (12.8)
Level of injury (%)				
Cervical	41 (57.8)	141 (57.8)	21 (80.8)	59 (68.6)
Thoracic	15 (21.1)	44 (18.0)	3 (11.5)	15 (17.4)
Lumbar	15 (21.1)	48 (19.7)	2 (7.7)	10 (11.6)
Unknown	0 (0.0)	11 (4.5)	0 (0.0)	2 (2.3)
Severity of injury (%)				
Complete	22 (31.0)	99 (42.3)	8 (30.8)	44 (51.2)
Incomplete	49 (69.0)	135 (57.7)	18 (69.2)	40 (46.5)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.3)
Neurological level				
Tetraplegia	30 (42.3)	115 (47.1)	21 (80.8)	51 (59.3)
Paraplegia	41(57.7)	116 (47.5)	5 (19.2)	33 (38.4)
Unknown	0 (0.0)	13 (5.3)	0 (0.0)	2 (2.3)
Traumatic brain injury				
Mild	23 (32.4)	60 (24.6)	8 (30.8)	25 (29.1)
Moderate/ hard	12 (16.9)	26 (10.7)	5 (19.2)	13 (15.1)
No	36 (50.7)	141 (57.8)	13 (50.0)	43 (50.0)
Unknown	0 (0.0)	17 (7.0)	0 (0.0)	5 (5.8)
Alcohol				
Yes	15 (21.1)	86 (35.2)	5 (19.2)	35 (40.7)
No	18 (25.4)	61 (25.0)	4 (15.4)	17 (19.8)
Unknown	38 (53.5)	97 (39.8)	17 (65.4)	34 (39.5)

Abbreviation: s.d.: standard deviation.

Examining the causes of trauma in different age-groups, it appeared that falls was the main cause among the elderly patients in both countries. The mean age for patients having to sustain a TSCI due to falls was much higher in Norway ($p<0.001$). There were more MVA among people aged <60 years in Norway ($p=0.005$), but the mean age at MVA was rather similar in both countries.

There was a statistically significantly higher proportion of cervical injuries among the patients aged ≥60 years than among the younger patients (p=0.03) in Western Norway, while cervical injuries was predominating in both age groups in Estonia. The majority of the elderly presented with tetraplegia in both countries (68% in Estonia, 89% in Norway).

Analysis showed that a higher percentage of the patients had consumed alcohol prior to the accident in Estonia (35% in Estonia and 21% in Western Norway, p=0.03). However, as in more than half of the cases in both countries alcohol consumption remained unknown, the percentages may be underestimated.

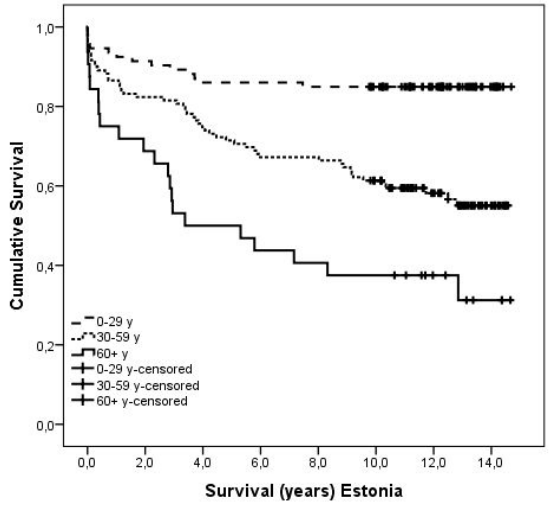
By the end of the follow-up, 35.3% of the patients in Estonia and 36.6% in Western Norway were dead. Mortality was high among the TSCI patients in both countries (Table 10).

Table 10. Standardised mortality ratios (SMRs) for age-groups in Western Norway and Estonia from 1997 to 2011 (EU-15 as the reference population).

	Western Norway				Estonia			
Age-group	Observed	Expected	SMR	95% CI	Observed	Expected	SMR	95% CI
0–29	1	0.09	10.53	0.27–58.67	13	0.37	35.45	18.88−60.62
30−59	4	0.82	4.88	1.33–12.48	48	3.94	12.18	8.98−16.15
60+	21	10.34	2.03	1.26–3.10	25	16.01	1.56	1.01−2.30
Total	26	13.77	1.89	1.23–2.77	86	17.21	5.00	4.00−6.17

Abbreviation: CI: confidence interval.

The median survival time among the deceased was 4.0 (95% CI 1.50−6.50) years in Norway and 2.79 (95% CI 1.54−4.04) in Estonia. Although the overall mortality was similar in the two countries, the Kaplan-Meier curves confirmed the large discrepancies (Figure 9). Higher percentage of young victims died during the follow-up period in Estonia. The survival of people older than 60 years was similar in two countries.



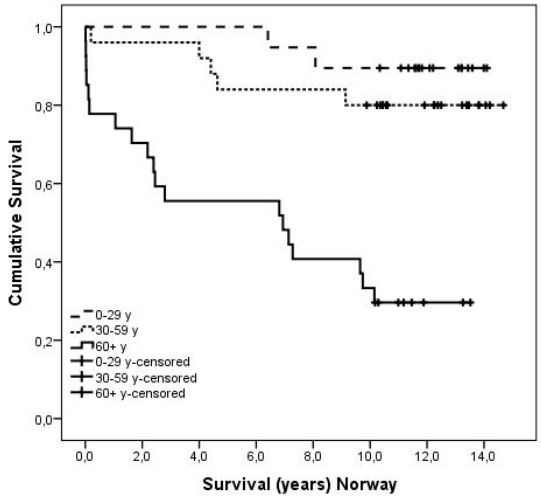


Figure 9. Survival of persons with traumatic spinal cord injury in three age-groups in Western Norway and Estonia from 1997 to 2011.

The SMR was significantly higher among the women compared to the men in Estonia (3.55 vs. 2.85), with an overall SMR of 4.00. In Norway the numbers were more similar: SMR 2.35 (1.98 for women, 2.14 for men). As reported in Methods, in order to compare the SMRs we used EU-15 as the reference population. The SMR values were 2.65 times higher in Estonia (Table 10). Analysis of SMR in different age-groups revealed that the ratio for the two countries was 3.4 times higher in Estonia among the patients aged 0−29 years, 2.5 times higher among the 30–59-year-old victims and slightly lower (RR= 0.77) among the patients 60 years or older compared to Norway.

When using Cox regression analysis, age and neurological and anatomical levels of injury were significant risk factors for mortality in Western Norway. In Estonia age, severity and neurological and anatomical levels of injury, as well as concomitant brain injury and alcohol consumption were significant risk factors for mortality within 15 years of TSCI (Table 11).

Table 11. Cox regression model for risk indicators for death in Western Norway and Estonia.

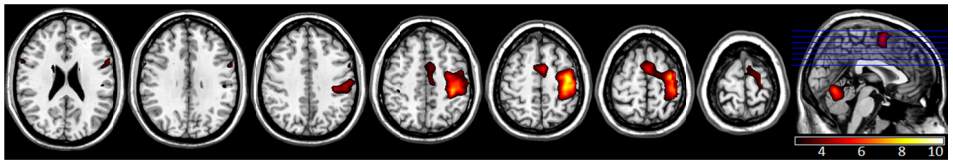
	Western Norway			Estonia		
Potential risk factors	Hazard ratio	95 % CI	*p*-value	Hazard ratio	95 % CI	*p*-value
Age at injury, years	1.05	1.03−1.07	<0.001	1.03	1.02−1.05	<0.001
Gender						
Male	0.94	0.38−2.34	0.89	1.00	0.55−1.85	0.99
Female	1.00	ref		1.00	ref	
Aetiology of injury			0.81			0.71
Fall	1.20	0.16−9.15		2.11	1.08−4.13	
MVA	0.73	0.09−5.75		1.62	0.80−3.29	
Sport	0.71	0.06−7.82		1.35	0.57−3.17	
Other	1.00	ref		1.00	ref	
Neurological level						
Tetraplegia	3.72	1.40−9.87	0.003	1.84	1.17−2.89	0.008
Paraplegia	1.00	ref		1.00	ref	
Completeness						
Completeness	0.97	0.42−2.22	0.94	1.83	1.18−2.84	0.007
Incomplete	1.00	ref		1.00	ref	
Anatomical level						
Cervical injury	3.72	1.40−9.87	0.003	1.74	1.07−2.82	0.02
Thoracic/lumbosacral injury	1.00	ref		1.00	ref	
Traumatic brain injury						
Yes	1.03	0.48−2.22	0.94	1.70	1.10−2.63	0.02
No/ unknown	1.00	ref		1.00	ref	
Alcohol consumption						
Yes	0.84	0.32−2.23	0.72	1.27	0.81−1.98	0.30
No/ unknown	1.00	ref		1.00	ref	

Abbreviation: CI: confidence interval.

5.8. Brain activation in the acute phase of TSCI

Figure 10 shows brain activation during hand movement in the TSCI patients and the control subjects. Figure 11 shows the activated brain areas at the time when the subjects moved or attempted to move their right ankle.

A



B

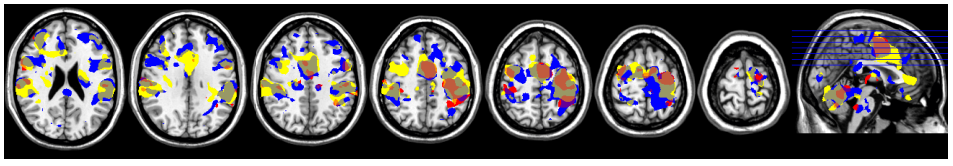
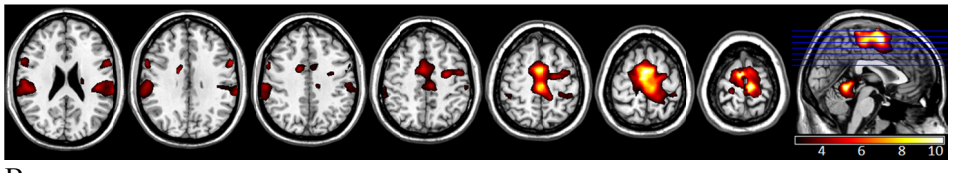


Figure 10. Group activation maps
(A) Serial activation maps of right hand movements for control-group (B) Serial activation maps of right hand movements for patients at 1 month (red), 3 months (blue) and 12 months (yellow) post-injury. Uncorrected, $p<0.01$.

A



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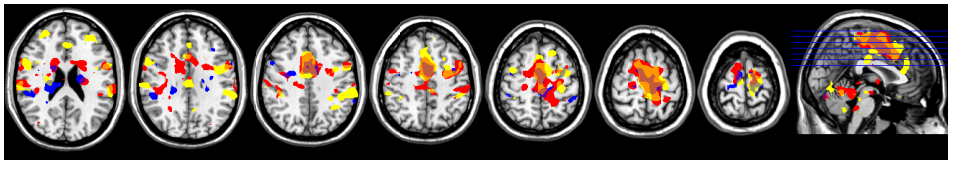

Figure 11. Group activation maps
(A) Serial activation maps of right ankle movements for control-group (B) Serial activation maps of right ankle movements for patients at 1 month (red), 3 months (blue) and 12 months (yellow) post-injury. Uncorrected, $p<0.01$.

Table 12. Clinical data of functional magnetic resonance imaging patients with traumatic spinal cord injury.

Patient		1			2			3			4			5			6		
Age		41			18			21			18			23			40		
Time post-TSCI (months)		0.5	4.3	10.9	0.4	3.9	13.5	0.8	3.4	12.9	0.8	2.4	12.4	1.0	4.2	13.0	0.6	4.1	12.5
Level of injury	R	C5	IN	IN	C5	C5	C5	C5	C7	C7	C7	C7	C7	C6	C6	C6	C5	C5	C5
	L	C5	IN	IN	C5	C6	C7	C7	Th12	Th12	C7	C7	C7	C6	C6	C6	C5	C5	C5
ASIA grade		D	E	E	C	D	D	C	D	D	A	A	A	A	A	B	A	A	A
AIS total motor score	R	39	50	50	18	28	34	27	39	39	18	16	18	14	14	14	13	14	14
	L	39	50	50	22	45	48	46	50	50	18	16	18	14	14	14	13	14	14
Upper limb motor score	R	19	25	25	7	13	15	17	19	19	18	16	18	14	14	14	13	14	14
	L	19	25	25	7	22	23	21	25	25	18	16	18	14	14	14	13	14	14
Lower limb motor score	R	20	25	25	11	15	19	10	20	20	0	0	0	0	0	0	0	0	0
	L	20	25	25	15	23	25	25	25	25	0	0	0	0	0	0	0	0	0
AIS total sensory score	R	32	55	56	36	36	56	46	46	56	15	18	15	12	13	21	10	10	10
	L	32	55	56	35	35	38	46	46	46	15	18	15	12	13	21	10	10	10

Abbreviations: TSCI, traumatic spinal cord injury; ASIA, American Spinal Injury Association; AIS, ASIA Impairment Scale; R, right; L, left; IN, intact

Activation patterns of the control subjects

The mean movement rate of the control subjects was 0.58 ± 0.17 Hz during hand movement and 0.46 ± 0.13 Hz during ankle movement (in patients with complete TSCI, the rate was 0). There was no significant correlation between movement rate and volume of BA 4 activation in the control group. In the control subjects studied twice (7 individuals), no significant change of VOA in BA 4 (hand p=0.56, ankle p=0.18), BA 1-2-3-5 (hand p=0.45, ankle p=0.42) or BA 6 area (hand p=0.48, ankle p=0.99) was found. The location of BA 4 activation was in the left anatomical hand region for all but one subject, who had no activation in this region at the chosen threshold. The COG coordinates did not change significantly during one year (Table 13).

Table 13. Volumes of activation, maximum t-values, centres of gravity and weighted laterality indexes of the right hand and ankle movement representation in the controls during 1 year in fMRI study.

	Hand Study 1	Study 2	Ankle Study 1	Study 2
FWE corrected	0.05	0.05	0.05	0.05
BA 1-2-3-5				
No. of subjects with activation	6	6	3	3
VOA ± s.d. (mm^3)	3748 ± 4657	1536 ± 909	172 ± 33	169 ± 34
Maximum t-value	8.7 ± 1.7	8.5 ± 1.0	6.6 ± 0.6	6.6 ± 1.2
COG x	–42.9 ± 3.4	–41.6 ± 5.8	–10.3 ± 7.7	–5.7 ± 0.6
COG y	–26.9 ± 3.6	–25.9 ± 4.8	–37.9 ± 0.8	–39.2 ± 1.2
COG z	54.6 ± 4.1	52.8 ± 4.5	66.1 ± 3.4	64.0 ± 1.6
wLI	0.79 ± 0.15	0.68 ± 0.16	0.17 ± 0.52	0.12 ± 0.36
BA 4				
No. of subjects with activation	6	6	6	5
VOA ± s.d. (mm^3)	2579 ± 974	2142 ± 610	1823 ± 1131	2073 ± 1174
Maximum t-value	9.8 ± 1.2	9.8 ± 1.2	8.5 ± 1.2	8.4 ± 2.3
COG x	–39.0 ± 1.7	–39.3 ± 2.7	–5.5 ± 1.6	–6.1 ± 1.4
COG y	–21.3 ± 1.8	–20.9 ± 2.4	–27.2 ± 2.1	–26.0 ± 1.4
COG z	57.3 ± 2.0	57.1 ± 2.3	66.2 ± 1.5	67.3 ± 1.5
wLI	0.94 ± 0.04	0.88 ± 0.18	0.65 ± 0.17	0.73 ± 0.14
BA 6				
No. of subjects with activation	6	6	6	5
VOA ± s.d. (mm^3)	4728 ± 3148	2743 ± 1195	1869 ± 1300	1794 ± 707
Maximum t-value	11.2 ± 1.4	9.4 ± 1.1	7.6 ± 1.4	8.4 ± 2.3
COG x	–32.7 ± 4.1	–34.5 ± 4.1	–3.4 ± 3.0	–7.8 ± 6.9
COG y	–13.6 ± 1.8	–14.8 ± 11.7	–9.6 ± 4.2	–12.2 ± 2.9
COG z	62.4 ± 3.2	62.3 ± 3.4	69.1 ± 2.9	69.2 ± 2.4
wLI	0.79 ± 0.14	0.69 ± 0.15	0.27 ± 0.13	0.46 ± 0.22

Abbreviations: FWE, corrected for family-wise error; BA, Brodmann area; VOA, volume of activation; s.d., standard deviation; COG, centre of gravity; wLI, weighted laterality index.

Activation patterns of the TSCI patients

The mean hand movement rate was lower in the TSCI patients' group compared to the controls (0.36 ± 0.19 Hz, p=0.02). A significant relationship was found between movement rate and the ASIA motor score (r=0.53, p=0.001). There were also significant correlations between the VOA in BA4 and ASIA motor score. The correlation was the highest immediately after injury (r=0.82, p=0.002), veering towards no correlation by 3 months later (r=0.63, p=0.03) and 12 months later (r=0.23, p=0.52).

Among the patients who recovered, the VOA in BA 4, BA 6 and BA 1-2-3-5 was increased compared to those whose neurological state did not change during the year. This phenomenon was found in hand as well as in ankle movement.

The overall VOA in the primary motor cortex of the patients who recovered was higher compared with that of other patients (hand p=0.06, ankle p=0.02). Due to the huge variability of VOA in BA 1-2-3-5 and BA 6 the difference did not reach a statistically significant level (BA 1-2-3-5: hand p=0.08, ankle p=0.1; BA 6: hand p=0.05, ankle p=0.04).

At the first, second and third study sessions, a specific pattern of activation was found. The activation area was enlarged at the beginning of the study (first three months) and reached the level of the controls and the patients who did not recover by the end of the first year.

The overall location of COG in BA 1-2-3-5, BA 4 and BA 6 was similar among the patients who did not recover and the controls. There was no shift in COGs during the first year post-TSCI. During the hand task from the first to the third study session there was an expansion of COG laterally, anteriorly and inferiorly among the patients who recovered (BA 4: x –35.5 to –46.9, p=0.13; y –22.5 to –14.0, p=0.15, z 57.4 to 48.8, p=0.21; BA 1-2-3-5: x –38.2 to –47.2, p=0.14; y –28.9 to –27.1, p=0.14; z 54.5 to 47.8, p=0.23). Among the TSCI patients who recovered, the shift of COG during ankle movement was medial, anterior and superior in BA 4 (x: –6.3 to –1.8, p=0.02; y: –25.7 to –23.2, p= 0.16; z 63.8 to 66.0, p=0.25).

Brain activation was more bilateral in the TSCI patients than in the controls (Table 14). In BA 4 the mean wLI was 0.72 ± 0.19 during right hand movement among the patients compared to 0.90 ± 0.11 among the controls (p<0.001). Similarly, in BA 6 and BA 1-2-3-5 wLI was less lateralised during hand movement among the patients (0.59 ± 0.29 vs 0.74 ± 0.16, p=0.005; 0.50 ± 0.29 vs 0.73 ± 0.14, p=0.02). During leg movement the differences in wLI between the patients and the controls did not become statistically significant (BA 4 p=0.22; BA 1-2-3-5 p=0.95; BA 6 p=0.37).

6. DISCUSSION

TSCI constitutes a major source of the socio-economic burden to society (Ackery *et al*., 2004). As the costs of acute care, inpatient rehabilitation and postdischarge community therapeutic interventions are rising, there is a strong need to determine the situation in a concrete country (Ackery *et al*., 2004; Chiu *et al*., 2010; Wyndaele and Wyndaele, 2006).

6.1. Incidence of TSCI in Estonia

The reason why the current study was undertaken is that there is a paucity of studies of TSCI in Eastern Europe and Estonia (Figure 15). Relevant data reflect the level of controlling SCI and point to the need for improving preventable strategies. Neither reduction in the number or severity of TSCI or mortality after TSCI, nor improvements in the care of SCI will be possible if there is no reliable information about the epidemiological scale of SCI.

Paper I shows the high incidence of spinal cord injuries in Estonia. Previous international studies have been mostly hospital based (van Asbeck *et al*., 2000; Berg *et al*., 2011) or limited to adult population (Ahoniemi *et al*., 2008). To our knowledge, the present study is the first population-based research that included all age groups from all hospitals across the whole country.

The incidence of TSCI differs greatly between countries. The crude incidence of TSCI was 39.7 per million in Estonia from 1997 to 2007, which is one of the highest in Europe. Only a Portugal study, which included prehospital mortalities reported higher incidence rate (Martins *et al*., 1998).

On the other hand, lack of standardised global reporting of aetiology data on TSCI reduces the ability of the data to contribute to specific injury prevention strategies or hypotheses worldwide (Cripps *et al*., 2011). Until now, only one study group has conducted a comparative research on TSCI in two different countries at the same time (Divanoglou and Levi, 2009). In the second paper we compared the incidence, characteristics and mortality of TSCI in Western Norway and Estonia. Previous population studies have revealed several differences in the lifestyle in the Baltic countries compared to Western Europe, differences that may negatively influence the health status and the risk of trauma (Rekand *et al*., 2004).

The standardised annual age- and gender adjusted incidence rates were 24.9 and 37.4 in Norway and Estonia, respectively, i.e. 1.5 times higher in Estonia than in Western Norway.

Table 14. Volumes, maximum t-values, centres of gravity and weighted laterality indexes of the right hand and ankle movement representation in the TSCI patients during the first year after injury.

Group	Hand	Study 1	Study 2	Study 3	Ankle	Study 1	Study 2	Study 3
FWE corrected		0.05	0.05	0.05		0.05	0.05	0.05
BA 1-2-3-5								
No. of patients with activation		6	6	6		3	2	3
VOA ± s.d. (mm^3)		6960 ± 7136	8212 ± 11183	3702 ± 2029		1985 ± 2938	6208 ± 5419	2117 ± 1178
Maximum t-value		9.9 ± 3.0	10.6± 3.5	7.9 ±1.3		7.8 ± 1.7	11.6 ± 2.5	7.8 ± 0.6
COG x		–40 ± 2	–41 ± 5	–46 ± 8		–37 ± 27	–31 ± 28	18 ± 38
COG y		–30 ± 3	–29 ± 3	–24 ± 9		–31 ± 9	–31 ± 18	–39 ± 15
COG z		54 ± 3	53 ± 2	49 ± 7		47 ± 17	53 ± 15	56 ± 11
wLI		0.71 ± 0.12	0.46 ± 0.26	0.34 ± 0.32		0.38 ± 0.38	0.17 ± 0.59	0.09 ±0.51
BA 4								
No. of patients with activation		6	6	6		5	4	4
VOA ± s.d. (mm^3)		4229 ±3126	4897 ± 5495	2849 ± 2184		3516 ± 2828	4068 ± 5020	2868 ± 692
Maximum t-value		11.2 ± 3.9	12.3 ± 4.5	9.9 ± 3.0		10.3 ± 3.7	10.3 ± 4.4	9.6 ± 2.4
COG x		–37 ± 5	–38 ± 5	–42 ± 8		–5 ± 2	–6 ± 2	–2 ± 3
COG y		–22 ± 3	–21 ± 3	–18 ± 8		–23 ± 2	–26 ± 3	–24 ± 1
COG z		57 ± 4	56 ± 4	53 ± 8		64 ± 4	65 ±4	63 ± 4
wLI		0.76 ± 0.13	0.72 ± 0.15	0.66 ± 0.25		0.70 ±0.11	0.63 ± 0.24	0.42 ± 0.33
BA 6								
No. of patients with activation		6	6	6		6	5	5
VOA ± s.d. (mm^3)		16121 ± 12075	17583 ± 24548	9931 ± 9799		9865 ± 10668	8259 ± 13229	5873 ± 3685
Maximum t-value		13.1 ± 3.0	13.1 ± 4.9	9.9 ± 2.7		9.6 ± 2.1	8.7 ± 3.3	9.0 ± 2.0
COG x		–25 ± 8	–24 ± 12	–33 ± 16		–8 ± 7	–7 ± 3	0 ± 5
COG y		–10 ± 4	–14 ± 8	–10 ± 11		–7 ± 3	–8 ± 3	–6 ± 4
COG z		63 ± 2	63 ± 4	57 ± 16		64 ± 5	69 ± 5	67 ± 5
wLI		0.70 ± 0.13	0.61 ± 0.19	0.46 ± 0.24		0.29 ± 0.20	0.32 ± 0.20	0.04 ± 0.34

Abbreviations: FWE, corrected for familywise error; BA, Brodmann area; VOA, volume of activation; s.d., standard deviation; COG, centre of gravity; wLI, weighted laterality index.

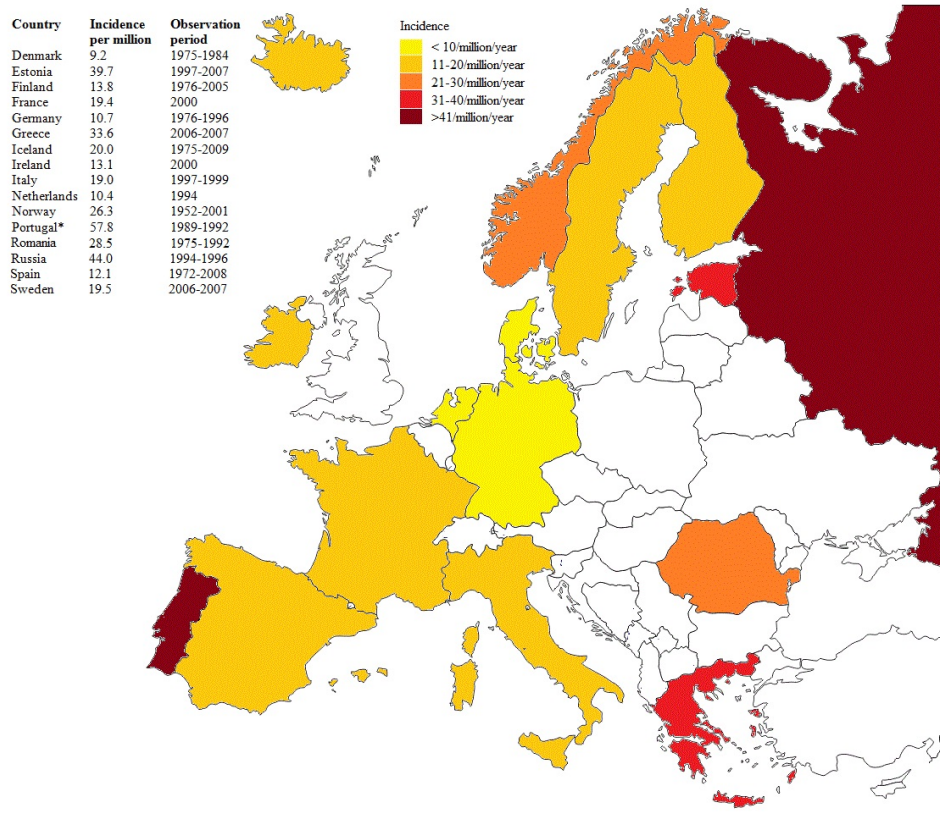

Figure 15. Incidence of TSCI in Europe, per million population.
(Ahoniemi *et al*., 2008; Albert *et al*., 2009; Biering-Sorensen *et al*., 1990; Divanoglou *et al*., 2009; Exner *et al*., 1997; Hagen *et al*., 2010a; Kondakov *et al*., 2002; Knútsdóttir *et al*., 2012; Martins *et al*., 1998; O'Connor *et al*., 2006; Pagliacci *et al*., 2003; 1998; Soopramanien, 1994; van Asbeck *et al*., 2000; van den Berg *et al*., 2010b)

The first reason for the difference is due to socioeconomic circumstances. Poorly managed societal transition to market economy, higher unemployment, inequalities in wealth, poor regulatory and enforcement mechanisms predispose Eastern Europe and Eurasian countries to high personal burden of injuries (Hyder and Aggarwal, 2009). It has been found that people in low-to-middle outcome countries are 3.6 times more likely to die from injuries (Sethi *et al*., 2006).

The second explanation is closely related to preventive measures. There has been an extensive focus on prevention of traumas in Norway while less effort has been directed to prevention in Estonia. Campaigns targeting young drivers have reduced the number of injuries among younger people (Lai *et al*., 2005)

The third explanation is geographical differences. The risk of traumatic spinal cord injury was 2.5 times higher in rural than in urban areas of Canada

(Dryden *et al*., 2003). Western Norway is dominated by mountains and fjords, which reduces speeding options. On the other hand, falling from height could be more frequent in these regions. The landscape of Estonia is flatter, allowing motor vehicles to drive at a high speed.

In the first study we found an increasing trend in the incidence from 1999 to 2007 in Estonia. The possible explanation is that the prevention of TSCI was ineffective. Another explanation may be that we missed some cases in the first study years. However, the incidence rates were fluctuating at the beginning of that period (Figure 4). In this connection it should be noted that Hagen and colleagues have reported an increasing trend in the TSCI incidence rates when the study period was longer (Hagen *et al*., 2010a). Still, no clear explanation has been given yet for this phenomenon.

The strength of the studies in Papers 1 and 2 was the inclusion of the whole Estonian population in the study. Also, several overlapping sources of information were reviewed to minimize errors and missing cases. Medical records were reviewed even in the smallest local hospitals where patients with TSCI are usually not treated. Thus, we probably missed no cases.

The studies had some limitations. Firstly, we did not include the patients who died before the arrival to hospital. Only three studies by other authors have included fatal cases before hospitalisation so far and have presented higher incidence rates than other studies (Wyndaele and Wyndaele, 2006). A study of prehospital mortality is currently in progress in Estonia. Secondly, we identified the TSCI patients by the diagnostic codes only. However, the list of the ICD-10 codes suggesting a TSCI was expanded to cover spinal fractures at every level in order to obtain more cases. Thirdly, as the study was performed with a retrospective design available information was probably limited. In order to show trends in TSCI, a prospective register providing full coverage of the population would be needed.

6.2. Risk factors of TSCI

Consistent with previous studies (Ackery *et al*., 2004; Ahoniemi *et al*., 2008; Albert *et al*., 2005; Berg *et al*., 2011; Biering-Sørensen *et al*., 1990; Celani *et al*., 2001; Chiu *et al*., 2010; Dincer *et al*., 1992; Divangolou and Levi, 2009; Dryden *et al*., 2003; Espagnaq *et al*., 2011; Exner and Meinecke, 2010; Hagen *et al*., 2010a; Jackson *et al*., 2004; Karacan *et al*., 2010; Kondakov *et al*., 2002; Knútsdóttir *et al*., 2012; Martins *et al*., 1998; O'Connor, 2002; O'Connor and Murray, 2006; Pagliacci *et al*., 2003; Pickett *et al*., 2006; Soopramanien, 1994; Surkin *et al*., 2000; van Asbeck *et al*., 2000; van den Berg *et al*., 2010b; Wyndaele and Wyndaele, 2006), men were more prone to TSCI in all age-groups in Estonia. There is no clear explanation why men are at greater risk for TSCI. It has been suggested that women perform risky activities more cautiously than men and therefore may be exposed to lower risk of injury. An international comparative study from 19 European countries found that women drive safer

than men (Golias *et al*., 2002). This study also showed that men below the age of 55 have the most dangerous driving behavior.

Many developed countries have reported the bimodal distribution of TSCI incidence rates with the second peak after the age of 60 (Berg *et al*., 2011; Dryden *et al*., 2003). This has been explained by the fact that the mean age at the time of injury is increasing because population is aging. The percentage of people older than 65 years is even higher in Estonia than the European region average (European Union, 2010). However, our data did not reveal this bimodal distribution. The incidence was very high in the age-group of 20-29 years in Estonia and declined substantially with increasing age becoming similar to that in other European countries.

In comparing Estonia and Western Norway in the Paper 2, the general population aged 60 years or more is high in both regions. Still, the proportions of TSCI patients in Estonia and in Western Norway are poles apart – young men in Estonia and elderly men in Norway. There is no convincing explanation for that. We may postulate that the elderly in Estonia might be less healthy, functionally less capable and do not take part in potentially dangerous activities. The latter hypothesis is based on the finding that physical activity is associated with increased longevity (Gulavik *et al*., 2012). Studies have found people in the Baltic countries to be physically inactive (Pomerleau *et al*., 2000). For example a study on the lifestyle and sequels of poliomyelitis found that physical activity is lower in Estonia compared with Norway (Rekand *et al*., 2004). However, intrinsic and also extrinsic risk factors should be taken into consideration.

Alcohol consumption is high in Estonia and alcohol abuse before TSCI was recorded in almost half of the cases in Estonia. Higher percentage of patients had consumed alcohol prior to accident in Estonia compared with Western Norway. Since 2005 the government alcohol policy has become more strict in Estonia and alcohol consumption has decreased since 2008 (Lai and Habicht, 2011). Our study included the cases until 31 December, 2007 and it found no statistically significant decrease in alcohol consumption preceding trauma. Alcohol abuse is a clear risk factor for TSCI. There is a need for more effective preventive measures concerning alcohol.

6.3. Causes of TSCI

In Europe traffic accidents cause 23 to 72% of all TSCI, with the highest percentage in Central Europe (Cripps *et al*., 2011; Divangolou and Levi, 2009; Soopramanien, 1994). The percentages of TSCI due to falls vary between 17 to 49% (Catz *et al*., 2002; Cripps *et al*., 2011; van Asbeck *et al*., 2000). In line with previous studies (Ahoniemi *et al*., 2008; Hagen *et al*., 2005; Silberstein and Rabinovich, 1995), falls is the most frequent cause of TSCI in Estonia as well as in Western Norway.

Persons between 20 and 29 years of age are most often injured in traffic accidents and diving. We also found that most of the sport injuries in Estonia

were caused by diving. Consistent with a previous report (European Union, 2010), young healthy men in their early twenties are usually the victims of diving accidents. In Estonia falls became the most prevalent cause of TSCI among persons older than 29 years.

U-shaped association has been found between physical activity and the risk of falling (Chan *et al*, 2007; Gregg *et al*., 1998). Although a less active lifestyle is a risk factor for falling, the highly active lifestyle in patients with balance problems as well as coexisting medical problems may predispose the Norwegian elderly to falls.

Falls was also the most prevalent external cause of TSCI occurring in the workplace, followed by blows to the vertebral spine. It shows that Estonian workers as well as employers should be better educated regarding safety.

Taking into consideration that TSCI incapacitates a higher proportion of inhabitants in Estonia than in other European countries, preventive measures should be more efficacious in general. The measures should be specifically targeted to the younger age-groups, particularly men.

6.4. Mortality and causes of death after TSCI

Our study is the first research to examine mortality after TSCI in Eastern Europe. As expected, the life expectancy of patients with TSCI was found to be significantly reduced in comparison to the general population. Almost half of the patients died during the first year after TSCI. The risk of death was higher in the group with C1-4 AIS A-C lesions. The rate of SMRs is higher among women and the cause-specific SMRs in Estonia were noted to be extremely high for sepsis and skin-related causes, as well as also significantly increased for other causes including genitourinary disease and suicide. In fact, there is a large discrepancy in life expectancy rates between different survival studies, which can be attributed to some methodological differences. Most of them have excluded patients who die at the scene of the accident, on arrival at the hospital, or during the first days. Many studies have focused on patients in the rehabilitative phase and have excluded deaths occurring in the acute or sub-acute phase of injury (van den Berg *et al*., 2010; Soden *et al*., 2000). Therefore, the mortality rates are considerably variable.

Our results have a number of similarities with the findings of Hagen *et al*.'s, showing that women and patients younger than 40 years of age at the time of injury have particularly decreased life expectancy (Hagen *et al*., 2010b). It is noteworthy that so far only Scandinavian countries have reported higher female mortality (Ahoniemi *et al*., 2011; Hagen *et al*., 2010b; Hartkopp *et al*., 1997; Lidal *et al*., 2007). However, in our study, gender was not statistically significant in the Cox proportional hazard modelling. This could be explained by the fact that mortality among men in the general population in Estonia is high, which diminishes differences between the sexes (European Communities, 2009).

Physical changes after TSCI affect the patient emotionally, socially and psychologically. Krause et al. have pointed out that important predictors of mortality are social support, income, psychology and behavioural factors (Krause *et al*., 2009; Krause *et al*., 2011). It is worthwhile noting the results from Pentland *et al*. claiming that women with TSCI feel themselves in isolation and have the perception of being forgotten (Pentland *et al*., 2002). Factors such as these may have an impact on the observed high risk of death in women.

Consistent with earlier studies, the incidence of death in patients with TSCI from septicaemia, respiratory diseases, diseases of urinary system and suicide is significantly higher than in general population (Hagen *et al*., 2010b; Soden *et al*., 2000). Soden *et al*. suggest that TSCI places patients at a considerable risk of suicide (Soden *et al*., 2000). Suicide generally is also a major issue in Estonia (Värnik, 2012). After the first year, the incidence of suicides increased to 13.8% among patients with TSCI in Estonia. In contrast to a Finnish study (Ahoniemi *et al*., 2011), the patients who committed suicide in Estonia were men, and half of them had tetraplegia.

Survival is considered to be strongly related to neurological level and degree of impairment (DeVivo *et al*., 1999; Middleton *et al*., 2012; van den Berg *et al*., 2010). Although in recent years there has been a trend towards improvement in acute phase survival rates, longer term mortality has remained constant (DeVivo, 2007). As might have been expected, we also found a strong relationship between neurological level and completeness of injury. During the first year, the mortality risk was significantly higher among the patients with C1-4 injury level, AIS A, B, C, which stabilised thereafter. No significant reduction in the first-year mortality was detected during the follow-up period from 1997 to 2011 in Estonia. This is hard to explain, because progressive economical development and improvements in medical care were taking place in Estonia during the period predicting decline in mortality.

Surprisingly, alcohol consumption before the trauma did not have an effect on early or late mortality in our research. It is plausible that data about regular alcohol drinking, not available in our study, could have influenced the obtained results. Alcohol-attributable mortality is more than 4 times higher for men and more than 3 times higher for women in the Baltic countries (Rehm *et al*., 2011). Krause et al. showed that alcohol drinking, especially binge-drinking, is a type of behaviour related to early mortality (Krause *et al*., 2009). According to this risk factor, and the findings that Estonians engage in binge drinking (McKee and Britton, 1998), we would suggest that alcohol drinking be considered as an important risk factor in Estonia for mortality after TSCI.

Limitations of the mortality study include insufficient information on the patients' death certificates regarding the causes of death. This has also been a noted problem in other studies (Middleton *et al*., 2012). Some SMRs have been calculated on the basis of few deaths and should therefore be interpreted with caution. The risk factors were collected during the first hospitalisation and were not assessed later. Chronic diseases as a potential risk factor for death were not included in the analysis because the data were too scarce. Our study was

retrospective and identification of patients took place according to the diagnostic codes. Patients who died before arrival at the hospital were excluded, which may have induced underestimation of the mortality rates.

Despite the above-mentioned limitations, it is a unique study focused on all age-groups in the Estonian population. Patients with TSCI were sought retrospectively from every Estonian hospital, and the list of ICD-10 codes suggesting a TSCI was expanded to include spinal fractures at every level in order to gain more cases (Table 1). The overall SMR confirm that mortality is high among patients with TSCI in Estonia. In the current study we identified that age at the time of injury, C1-C4 neurological level and completeness of injury, as well as concomitant injuries, are the risk factors for death during the first two years after the injury. Later, only age, completeness of trauma and cause of TCSI are significant risk factors for mortality.

In conclusion, the main causes of death among patients with TSCI are cardiovascular diseases, pneumonias, genitourinary tract infections and infections related to pressure areas, and suicide. The overall life expectancy of the patients is significantly decreased compared with general population. The assertion by Hitzig *et al*. that TSCI represents a model of premature aging (Hitzig *et al*., 2011) affecting multiple body structures and functions, should lead us to a holistic focus on multi-system management addressing all modifiable risk factors and their potential interactions.

6.5. Prediction of recovery after TSCI

Our study provides considerable insight into the changes of brain activation after TSCI. We found that the brain activation patterns for patients who have recovered and for those who have not recovered are significantly different during the first three months after the injury. Activation is increased among the patients who recover. To our knowledge, our study is the first to identify a shift in activation during the acute phase of cervical TSCI. We suggest that the results offer unique evidence for the usefulness of fMRI as a surrogate marker for outcome after TSCI.

One of the main goals of the study was to find brain activation pattern changes in patients with cervical TSCI. Until now, only two studies have been performed to report the temporal evolution of cortical sensorimotor activity after TSCI (Jurkiewicz *et al*., 2007; Jurkiewicz *et al*., 2010). In their first study, where TSCI patients with motor recovery were studied, a progressive enlargement in the primary motor cortex and decreased activation in associated cortical areas was detected (Jurkiewicz *et al*., 2007). When they studied 4 tetraplegic individuals whose paralysis persisted, the activation was extensive in associated areas in the early post-injury period but progressed toward no activation by the end of the first year (Jurkiewicz *et al*., 2010). Our results differ slightly from the earlier findings. Soon after the injury the activation was enlarged only among those TSCI patients who recovered and the enlargement

was detected in every ROI we investigated. However, the activation decreased by the end of the first year and became similar among the patients and the controls.

Despite the fact that 2 types of spatial shift have been observed, medial and posterior, we detected a shift of COG in BA 4 and BA 1-2-3-5 laterally, anteriorly and inferiorly during right hand movement. Earlier studies that have demonstrated these spatial shifts tested patients in the chronic phase. For example, Mikulis *et al*. studied tetraplegic TSCI patients in the chronic phase and showed that when these patients moved their tongue, primary motor cortex activation was shifted medially and posteriorly into the upper limb representation region (Mikulis *et al*., 2002). Several investigators have proposed that a similar shift takes place among paralyzed patients when they move their hand (Curt *et al*., 2002; Kokotilo *et al*., 2009a; Lotze *et al*., 1999). It has been argued that representation migrates superiorly and medially, since it borders on the adjacent disconnected upper or lower extremity cortex (Kokotilo *et al*., 2009a). The possible causes of the changes are destroyed sensorimotor tracts, disruption of lateral inhibitory network in the cortex, modification of neuronal activity (Mikulis *et al*., 2002; Streletz *et al*., 1995).

Methodically, the hand motor task that we have used was more complex than those used in many other studies. The patients with TSCI were able to perform the hand task but there was a significant reduction in force and speed of movements. Patients with a complete injury performed movements only by the wrist. Hence, we speculated that by supporting the proximal arm muscles there would be a medial shift of activation as well as a decreased volume of activation. Surprisingly, there occurred an opposite shift among the patients who recovered and their VOA was larger compared with that of the control subjects.

Our results demonstrate a shift towards intact face representation during hand movement, while the shift is opposite to hand movement during ankle movement. As a result, the COG shifts towards cortical representation of the toes. We are not aware whether there occurs invasion of the cortical representation of the affected body part exactly into the zone of the face or the toes but, contrary to other studies, shifts in different directions were noticed during the first year. Our acute phase findings appear to be well supported by a previous report suggesting that the cortical representation of body parts is continuously changing depending on activity, the location of lesion in the nervous system, or the new skills learned (Chen *et al*., 2002).

Patients with TSCI and stroke share several aspects of brain reorganisation following injury (Kokotilo *et al*., 2009b). The more severe the hand motor deficit, the greater is the shift of primary motor cortex activation towards the contralateral hemisphere (i.e. ipsilateral to the deficit) balance (Kokotilo *et al*., 2009b). According to wLI, cortical activation during hand movement was less lateralised among the patients than among controls in our study. Lower limb cortical representation occupies a smaller and medial spatial extent in the primary cortex, which may have been the main cause of non-significant wLI differences during ankle movement among the patients and the controls. As the

sample was small, we did not find any statistically significant difference in laterality regarding recovery.

Contrary to earlier studies (Freund *et al*., 2011), we can conclude that cortical functional reorganisation is larger among the patients who recover.

There were some limitations to the study. As we did not image the spinal cord, it was not possible to correlate the size of the damaged area with cortical reorganisation.

The number of patients was quite small in our study and the results would have been more conclusive when there have been more patients with cervical TSCI. What we know about the cortical reorganisation is largely based on a small number of cases because of the strict inclusion and exclusion criteria (Kokotilo *et al*., 2009a). The patients had to be medically stable during imaging and were not allowed to have concomitant traumatic brain injury. We were able to study every patient regularly at given time points. However, there was also more activation in the associated cortical sensorimotor areas of the controls in our study compared with other studies.

In conclusion, our results show that compensatory changes of brain function take place during the first post-TSCI year. The increase of VOA is more extensive among the patients who recover.

7. CONCLUSIONS

The epidemiological state of TSCI is "bittersweet". Although the incidence of TSCI is relatively low and the numbers are presented as per million population per year, most victims are young men in their highly productive period of life. When TSCI has occurred, it represents one of the most devastating injuries of the human body, usually with lifelong disability.

Paper I
Compared to recent studies from Europe where the incidence of TSCI is between 15 and 30 per million population the incidence of TSCI in Estonia (39.7 per million) is among the highest. The rates are significantly higher for men compared with women and especially among the youngest men (age-group 16 to 30 years). The leading cause of TSCI is falls. A significant proportion of injuries are related to alcohol consumption before trauma in Estonia.

Paper II
Although the two cohorts, Estonia and Western Norway, have similar demographic, injury and clinical characteristics, the age profile of the victims is different. The incidence rate is 1.5 times higher and SMR is 2.7 times higher in Estonia. Probable explanations for the different outcomes of the two European countries are socioeconomic differences, lower physical activity level, lower life expectancy and insufficient injury prevention programs in Estonia.

Paper III
Life expectancy is significantly decreased in TSCI patients compared with the general population in Estonia. Deaths during the first year after the injury have an important impact on survival. Treatment of cardiovascular diseases, infections and prevention of suicides are useful for reducing mortality among TSCI patients.

Paper IV
The study found broadening of cortical activation and a shift of COG during the first year after TSCI depending on the recovery. To our knowledge this is the first study to show the dynamic changes of activation in the acute phase of TSCI.

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9. SUMMARY IN ESTONIAN

Seljaajutraumade epidemioloogia Eestis. Peaaju aktivatsioonimuster seljaajutrauma ägedas faasis

Seljaajutrauma (SAT) tõttu invaliidistub maailmas igal aastal üle saja tuhande inimese. Lisaks märkimisväärsele eluaegsele puudele on SAT-l mõju ka inimese elukvaliteedile ning elulemusele. Epidemioloogilised SAT-uurimused said alguse umbes 40 aastat tagasi (Wyndaele ja Wyndaele, 2006).

SAT haigestumuskordajad erinevad riigiti. Arenenud riikide haigestumuskordajad on arenguriikidest suuremad ning seda seletatakse andmete erineva kättesaadavuse, meditsiinilise abi taseme ning üldise erineva elukvaliteediga (Chiu jt, 2010). SAT-haigestumus on avaldatud andmete kohaselt Euroopas 10,4 (van Asbeck jt, 2000) kuni 57,8 (Martins jt, 1998); Põhja-Ameerikas 27,1 (Burke jt, 2001) kuni 83 (Warren jt, 1995); Aasias 18 (Chen jt, 1997) kuni 40,2 (Shingu jt, 1995) ning Austraalias 14,5 (O'Connor, 2002) juhtu miljoni inimaasta kohta.

Varasemate uuringutega on näidatud, et SAT haigestumuskordajad on suurimad nooremates vanuserühmades (Wyndaele ja Wyndaele, 2006; van den Berg, 2010). Hiljutiste uuringute tulemusel on leitud ka, et haigestumises on tekkinud 2 haripunkti: esimene suurem haigestumine leiab aset vanuserühmas 15–29 aastat, teine aga ≥ 65-aastaste seas (Wyndaele ja Wyndaele, 2006). SAT põhjused erinevad vanuserühmiti ning ka riigiti (Chiu jt, 2010). Kuigi endiselt on põhjustest esimene liiklustrauma, on sagenema hakanud kukkumine ja seda just eakate hulgas (Ahoniemi jt, 2008; Couris jt, 2010; Hagen jt, 2010; Ning jt, 2011).

SAT-patsientide elulemus on viimaste aastakümnete jooksul suurenenud, sest varasemast tõhusam taastusravi võimaldab ennetada tüsistusi, nii et paljud patsiendid kohanevad puudega ja naasevad tavaellu. Ometi on SAT-patsientidel suremus tavarahvastikuga võrreldes oluliselt suurem (DeVivo jt, 1999).

Eestis epidemioloogilised andmed SAT kohta puuduvad. Haigestumus aga peegeldab SAT-ennetustööd ja näitab, kas see vajab tõhustamist. Haigestumus koos elulemuse, tüsistuste, sotsiaalse toimetuleku ning elukvaliteeti peegeldavate näitajatega on väärtuslikuks allikaks tervishoiu planeerimisel ja sotsiaalabi korraldamisel.

Erinevalt aastaid valitsenud arusaamast, et täiskasvanud imetajate kesknärvisüsteemi närvirakud pole uuenemisvõimelised, on viimasel ajal leitud, et ka inimese närvirakud taastuvad (Bareyre, 2008). On olemas endogeenne regeneratsioonivõime: isegi ilma sekkumiseta toimub 40% SAT-patsientidel kahjustusest allpool osaline motoorse või sensoorse funktsiooni paranemine (Tsung ja Fassett, 2011). Lisaks muutustele trauma piirkonnas ehk seljaajus leiavad aset ümberkorraldused ka peaajus. Närvisüsteemi plastilisust on uuritud insuldi ja ajutraumaga patsientidel, kuid vähem seljaajutraumaga patsientidel. Neuroradioloogiliste uuringutega (funktsionaalne magnetresonantstomograafia (fMRT), positronemissioontomograafia (PET), elektroentsefalograafia (EEG), trans-

kraniaalne magnetstimulatsioon (TMS), magnetentsefalograafia (MEG)) on täheldatud muutusi peaaju aktivatsioonis ka SAT järel neil patsientidel, kellel kaasuvat peaajukahjustust ei ole. Peaaju funktsioonide reorganisatsioon kesknärvisüsteemi kahjustuse järel on üks põhilisi sensomotoorse funktsiooni taastumise mehhanisme (Kokotilo jt, 2009a).

Varasemate uuringutega ei ole motoorse ajukoore aktivatsioonimustri kujunemist ja muutusi SAT järel täielikult välja selgitatud. Erinevate uuringute metoodika kui ka uuritavate rühmad pole sageli omavahel võrreldavad. On leitud nii seda, et motoorse ajukoore aktivatsioon SAT-patsientidel suureneb, kui ka seda, et muutust ei toimu või et aktivatsioon hoopis väheneb. Ka jäsemete liigutused, mida patsientidel on palutud motoorse ajukoore aktivatisooni hindamiseks uuringu ajal teha, on väga erinevad ning mõnedes uuringutes pole olnud võrdluseks kontrollrühma (Kokotilo jt, 2009a).

Seni tehtud uuringud on enamasti läbilõikeuuringud, kus on hinnatud aju aktivatsioonimustrit ühel ajahetkel ja enamasti juba kroonilises staadiumis patsientidel (Curt jt, 2002; Mikulis jt, 2002; Cramer jt, 2005; Lotze jt, 1999). Jurkiewicz jt hindasid patsiente esimese traumajärgse aasta vältel ja leidsid, et SAT ägedas perioodis, kui jäseme liigutus pole täielik, väheneb aktivatsioon primaarses motoorses ajukoores (PMK) ning suureneb sensomotoorsetel lisaaladel (motoorne lisaala, tsingulaarne motoorne ala, premotoorne koor, parietaalne ajukoor), motoorika paranedes aga suureneb PMK aktivatsioon uuesti, seevastu sensomotoorsetel lisaaladel väheneb (Jurkiewicz jt, 2007).

Samad autorid uurisid püsiva neuroloogilise leiuga SAT-patsiente esimese traumajärgse aasta jooksul ka korduvalt. Võrreldes tervete kontrollisikutega ei olnud PMK aktivatsioonis muutusi, lisaalade aktivatsioon aga laienes sarnaselt eespool mainitud uuringuga. Tetrapleegia püsimisel vähenes aasta jooksul ka lisaalade aktivatsioon (Jurkiewicz jt, 2010).

Uurimuse eesmärgid

- Leida SAT haigestumuskordaja ja hinnata selle muutust (I publikatsioon).
- Analüüsida kogu Eesti rahvastikust leitud SAT-patsientide isikuandmeid ja kliinilisi omadusi aastatel 1997 kuni 2007 (I publikatsioon).
- Võrrelda SAT-patsientide haigestumust ja elulemust Eestis ning Lääne-Norras aastatel 1997 kuni 2007 (II publikatsioon).
- Uurida SAT-patsientide suremust ja surmapõhjusi (III publikatsioon).
- Leida ajukoore aktivatsioonimustri muutused seljaaju kaelaosa kahjustusega patsientidel esimese traumajärgse aasta jooksul (IV publikatsioon).

Patsiendid ja meetodid

Retrospektiivselt vaadati läbi aastatel 1997–2007 kõikides Eesti regionaalhaiglates, keskhaiglates, üldhaiglates, maakonnahaiglates ja taastusravi keskus-

tes (kokku 22 haiglat) RHK-10 diagnoosikoodidega S12.0, S12.1, S12.2, S12.7, S13.0, S13.2, S13.4, S14.0, S14.1, S22.0, S23.0, S23.1, S24.0, S24.1, S32.0, S33.01, S34.0, S34.1, S34.3, T06.0, T06.1, T09.3, T91.1, T91.3 ravil olnud kõikides vanustes patsientide haiguslood. Iga patsiendi kohta täideti protokoll, mis sisaldas isikuandmeid, andmeid trauma põhjuste ja sellega seotud asjaolude kohta, radioloogilist diagnoosi, neuroloogilisi sümptomeid ning muid meditsiinilisi andmeid.

31. detsembri 2011. aasta seisuga saadi haiglajärgse surma fakti ja kuupäeva andmed rahvastikuregistrist. Surnud patsientide andmed on lingitud surmapõhjuste registrist saadud surmapõhjustega.

IV publikatsioonis kajastatud uuringusse kaasati Tartu Ülikooli Kliinikumis 2010. aasta maikuust kuni augustini seljaaju kaelaosa traumaga ravil viibinud patsiendid, kelle neuroloogiline defitsiit püsis üle 1 nädala. Patsiendid pidid uuringu ajaks olema stabiilses üldseisundis. Kõik uuritud andsid ka osalemiseks nõusoleku. Uuringust jäid välja kaasuva peatraumaga patsiendid; patsiendid, kellel oli varem diagnoositud epilepsia; ning need, kellele oli MRT-uuring vastunäidustatud.

fMRT tehti 1,5 T aparaadiga Tartu Ülikooli Kliinikumi radioloogiakliinik. Peaajukoore aktivatsioonimustrit hinnati patsientidel ägedas perioodis 1 kuu pärast traumat, seejärel 3 kuu ja 1 aasta möödudes. fMRT-uuring tehti ka 12 tervele vabatahtlikule, kelle vanus ja sugu vastas SAT-patsientidele (± 2 aastat) ning kes olid paremakäelised. Neist 7 kontrollisikul korrati uuringut aasta möödudes.

Uuritavatel tuli uuringu ajal sooritada (või üritada sooritada) parema labakäega ja sõrmedega pigistusliigutus ning parema labajala fleksioon ja ekstensioon. Liigutused tehti soovitavalt 1 Hz kiirusega 40-sekundiliste tsüklitena, millele järgnesid pausid.

Uuringute andmed töödeldi statistiliselt tarkvaraga SPM (versioon 8), aktivatsioonialad kujutati nn normeeritud templaatkujutistel. Lisaks arvutati patsientidele lateralisatsioonikõverad erinevate olulisusenivoo väärtustega.

Statistiliseks analüüsiks kasutati vabavaraprogrammi R ja programmi StatsDirect. Olulisuse nivooks oli kõikides arvutustes 5%.

Peamised tulemused

Läbi vaadati üle 3000 haigusloo 22 Eesti haiglas. Kokku registreeriti aastatel 1997 kuni 2007 595 seljaajutrauma juhtu. Aastane standardimata esmashaigestumuskordaja oli 39,7 juhtu miljoni inimaasta kohta (95% usaldusvahemik (uv) 36,6–43,0), mis on üks kõrgemaid Euroopas. Standardides andmed vanuse järgi Eesti rahvastikule, oli haigestumuskordaja 39,4 ning seda 72,0 miljoni inimaasta kohta meeste hulgas ja 11,5 miljoni inimaasta kohta naiste hulgas. Haigestumus oli oluliselt suurem meeste hulgas (haigestumusmäärade suhe (IRR) 6,4; 95% uv 5,1–8,1; $p = 0,003$). Vaadeldud ajaperioodi vältel ei esinenud

statistiliselt olulist muutust haigestumuskordajates (IRR 1,02; 95% uv 1,00–1,05; p = 0,09).

Keskmine vanus SAT-patsientidel oli 39,0 aastat. Alkoholi oli enne traumat tarvitanud 43,2% patsientidest. Peamine traumapõhjus oli kukkumine (41,0%), millele järgnesid liiklustrauma (29,4%) ning sporditraumad (14,0%).

31. detsembriks 2011 oli 595 traumapatsiendist surnud 162. Surnute vanus SAT ajal oli kõrgem võrreldes ellujäänutega (50,1 ± 18,0 *vs*. 34,8 ± 14,6). Peaaegu pooled surmadest toimusid esimesel traumajärgsel aastal. Esimesel aastal oli põhiliseks surmapõhjuseks traumast tingitud väline põhjus (52,6%), hiljem olid ülekaalus kardiovaskulaarsed haigused (35,6%) ning suitsiidid (13,8%).

Üldine standarditud suremusmäär (SMR) oli 2,81 (2,40–3,28) ning erinevalt paljudest teistest riikidest oli SMR Eestis naistel suurem kui meestel. Surma põhjusespetsiifiline SMR oli suurim sepsise korral. Ainus surma põhjus, mida esines SAT-patsientidel harvem võrreldes tavarahvastikuga, oli kasvajaline haigus.

Hulgitunnusanalüüsil Coxi regressioonimudeli järgi olid kahe esimese SAT-le järgneva aasta vältel olulisteks surma riskiteguriteks vanus, tservikaalne SAT, täielik seljaajukahjustus ning kaasuv trauma. Esimesel traumajärgsel aastal oli suurem risk surra kaelaosakahjustusega patsientidel, kelle kahjustus oli 1.–4. kaelalüli kõrgusel ning kellel oli Ameerika spinaaltrauma ühingu (AIS) kahjustuse skaala järgi A, B või C astme kahjustus (ASIA, 2011).

IV publikatsioonis tutvustatud uuringust selgus, et esimesel traumajärgsel aastal leiavad ajukoore aktivatsioonimustris aset olulised muutused. Funktsionaalsest paranemisest lähtudes muutub ka aktivatsioonimuster. Paranejate ajukoore aktivatsioonimahud olid oluliselt suuremad esimestel traumajärgsetel kuudel, esimese aasta lõpus olid need aga jõudnud samale tasemele kontrollide ning sügava tetrapareesiga patsientidega. Lisaks leiti, et paranejate aktivatsioonimuster nihkus käe liigutamisel lateraalsele, anterioorsele ning inferioorsele ehk näo primaarsesse korteksisse. Samas nihkus jala liigutamisel tsenter hoopis mediaalsele ehk varvaste motoorsesse korteksisse.

SAT-patsientide kortikaalne aktivatsioon oli võrreldes kontrollidega vähem lateraliseerunud. Erinevalt varasematest uuringutest võib saadud tulemuste põhjal väita, et paranejatel on peaajukoore aktivatsioon laialdasem ja intensiivsem. Seetõttu võib arvata, et fMRT on SAT-patsientide funktsionaalse tulemuse potentsiaalne prognoosija.

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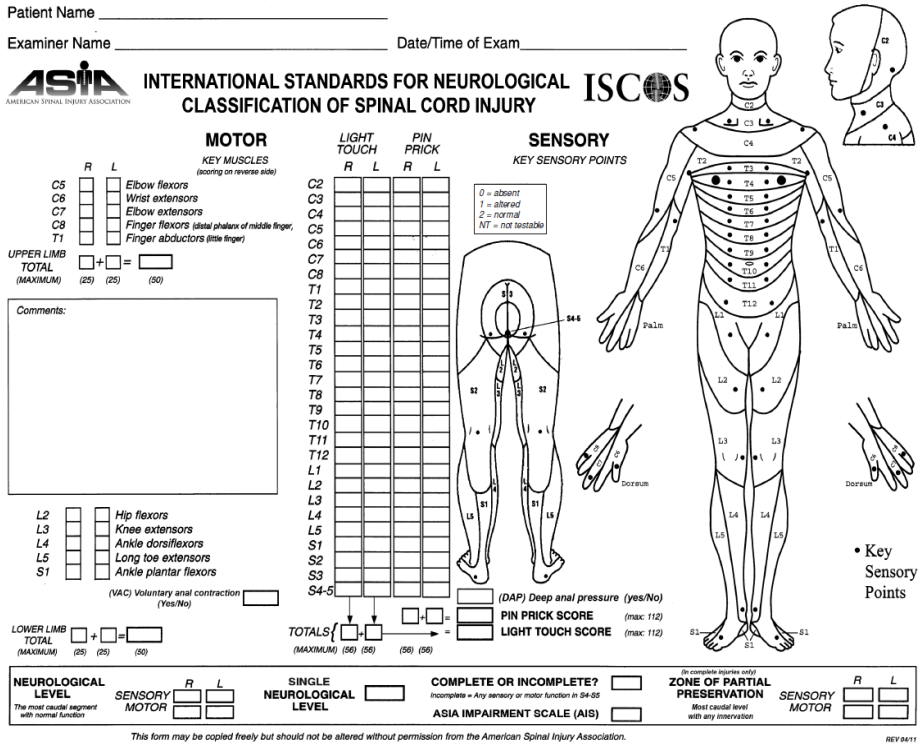
11. APPENDICES

Appendix A. American Spinal Injury Association Impairment Scale (permission to publish the chart has been obtained from ASIA).



Appendix B. American Spinal Injury Association Impairment Scale (permission to publish the chart has been obtained from ASIA).

Muscle Function Grading

0 = total paralysis

1 = palpable or visible contraction

2 = active movement, full range of motion (ROM) with gravity eliminated

3 = active movement, full ROM against gravity

4 = active movement, full ROM against gravity and moderate resistance in a muscle specific position.

5 = (normal) active movement, full ROM against gravity and full resistance in a muscle specific position expected from an otherwise unimpaired peson.

5* = (normal) active movement, full ROM against gravity and sufficient resistance to be considered normal if identified inhibiting factors (i.e. pain, disuse) were not present.

NT = not testable (i.e. due to immobilization, severe pain such that the patient cannot be graded, amputation of limb, or contracture of >50% of the range of motion).

ASIA Impairment (AIS) Scale

☐ **A = Complete.** No sensory or motor function is preserved in the sacral segments S4-S5.

☐ **B = Sensory Incomplete.** Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-S5 (light touch, pin prick at S4-S5: or deep anal pressure (DAP)), AND no motor function is preserved more than three levels below the motor level on either side of the body.

☐ **C = Motor Incomplete.** Motor function is preserved below the neurological level**, and more than half of key muscle functions below the single neurological level of injury (NLI) have a muscle grade less than 3 (Grades 0-2).

☐ **D = Motor Incomplete.** Motor function is preserved below the neurological level**, and at least half (half or more) of key muscle functions below the NLI have a muscle grade ≥ 3.

☐ **E = Normal.** If sensation and motor function as tested with the ISNCSCI are graded as normal in all segments, and the patient had prior deficits, then the AIS grade is E. Someone without an initial SCI does not receive an AIS grade.

**For an individual to receive a grade of C or D, i.e. motor incomplete status, they must have either (1) voluntary anal sphincter contraction or (2) sacral sensory sparing with sparing of motor function more than three levels below the motor level for that side of the body. The Standards at this time allows even non-key muscle function more than 3 levels below the motor level to be used in determining motor incomplete status (AIS B versus C).

NOTE: When assessing the extent of motor sparing below the level for distinguishing between AIS B and C, the ***motor level*** on each side is used; whereas to differentiate between AIS C and D (based on proportion of key muscle functions with strength grade 3 or greater) the ***single neurological level*** is used.

Steps in Classification

The following order is recommended in determining the classification of individuals with SCI.

1. Determine sensory levels for right and left sides.
2. Determine motor levels for right and left sides.
   Note: in regions where there is no myotome to test, the motor level is presumed to be the same as the sensory level, if testable motor function above that level is also normal.
3. Determine the single neurological level.
   This is the lowest segment where motor and sensory function is normal on both sides, and is the most cephalad of the sensory and motor levels determined in steps 1 and 2.
4. Determine whether the injury is Complete or Incomplete.
   (i.e. absence or presence of sacral sparing)
   If voluntary anal contraction = **No** *AND all S4-5 sensory scores* = **0** *AND deep anal pressure* = **No**, *then injury is COMPLETE. Otherwise, injury is incomplete.*
5. Determine ASIA Impairment Scale (AIS) Grade:

Is injury Complete? If **YES**, AIS=A and can record ZPP (lowest dermatome or myotome on each side with some preservation)

NO ↓

Is injury motor Incomplete? If **NO**, AIS=B (Yes=voluntary anal contraction OR motor function more than three levels below the motor level on a given side, if the patient has sensory incomplete classification)

YES ↓

Are at least half of the key muscles below the single neurological level graded 3 or better?

NO ↓ AIS=C

YES ↓ AIS=D

If sensation and motor function is normal in all segments, AIS=E
Note: AIS E is used in follow-up testing when an individual with a documented SCI has recovered normal function. If at initial testing no deficits are found, the individual is neurologically intact; the ASIA Impairment Scale does not apply.

12. PUBLICATIONS

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Valdkonnad:	Peavalu ja valu, neurodegeneratiivsed haigused, traumad
Publikatsioonid:	4 rahvusvahelistes, 6 kohalikes meditsiiniajakirjades
Liikmelisus:	*International Spinal Cord Society* – liige
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