ANALYSIS OF NEUROPATHIC PAIN AFTER SPINAL CORD INJURY

Illustrations by Franco Costa

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1 ABSTRACT

Longstanding neuropathic pain is a challenge in spinal cord injury (SCI) rehabilitation. Once established it is difficult to treat successfully. Neuropathic pain has a negative influence on quality of life and on the outcome of rehabilitation. The prevalence of neuropathic pain after SCI varies in different studies. However, pain in adults with spina bifida (SB) seems to be a minor problem.

The aim of this thesis was to study the prevalence of neuropathic pain in patients with traumatic and non-traumatic SCI and in adults with SB and to relate neuropathic pain to completeness and level of injury, gender, age at time of lesion and to study the impact of neuropathic pain on daily life. Another aim was to study the neurological and functional outcome as well as prevalence of neuropathic pain in patients with central cord syndrome (CCS). Patients with SCI who had their yearly check-up at the Spinalis outpatient clinic between 1995 and 2000 were included in the study. Data were gathered from the check-up and include ASIA impairment scale, the neurological level, and the impact of neuropathic pain on daily life.

Patients with CCS rehabilitated at the spinal unit of Florence, Italy during the years 1996-2002 were included. A follow-up visit was performed at least 18 months after discharge. Data were gathered from the examination at admission and discharge from hospital and at follow up. Studied data included ASIA impairment scale, neurological level, WISCI (walking ability), FIM (Functional Independence Measure), spasticity and neuropathic pain. The patients were divided in age groups according to age at the time of injury. Longstanding neuropathic pain was present in 40% and in 38% of the patients with traumatic and non-traumatic SCI, respectively, and in 11% of adults with SB. In the traumatic group neuropathic pain was more common in adults injured late in life. Females in the non-traumatic group had more often below level pain than males. In both traumatic and non-traumatic SCI neurological level and completeness of injury had no relation to the development of neuropathic pain. When pain was present it influenced daily life in the majority of cases.

Patients with CCS over 65 years of age at the time of injury had impaired neurological and functional recovery and more often experienced neuropathic pain (60%) than individuals injured earlier in life (20%). Spasticity was equally common in individuals injured late and early in life.

It is concluded that neuropathic pain is common in traumatic and non-traumatic SCI, and in patients with CCS but is less frequent in adults with SB. Patients with traumatic CCS injured at a young age had better neurological and functional outcome than patients injured later in life.

Keywords: Spinal cord injury, spina bifida, central cord syndrome, neuropathic pain, neuralgia

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2 LIST OF PUBLICATIONS

The thesis is based on the following papers, which are referred to in the text by the corresponding Roman numerals.

I  Werhagen L, Budh CN, Hultling C, Molander C.
Neuropathic pain after traumatic spinal cord injury-relations to gender, spinal level, completeness, and age at the time of injury.

II Werhagen L, Hultling C, Molander C.
The prevalence of neuropathic pain after non-traumatic spinal cord lesion.

III Werhagen L.
Neuropathic and nociceptive pain in adults with spina bifida, relations to gender, completeness of injury, the neurological level and hydrocephalus.
Submitted.

IV Aito S, D’Andrea M, Werhagen L, Farsetti L, Cappelli S, Bandini B, Di Donna V.
Neurological and functional outcome in traumatic central cord syndrome.
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# LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASIA</td>
<td>American Spinal Cord Injury Association</td>
</tr>
<tr>
<td>C</td>
<td>Cervical</td>
</tr>
<tr>
<td>CCS</td>
<td>Central Cord Syndrome</td>
</tr>
<tr>
<td>DVT</td>
<td>Deep venous thrombosis</td>
</tr>
<tr>
<td>FIM</td>
<td>Functional independence measurement</td>
</tr>
<tr>
<td>HC</td>
<td>Hydrocephalus</td>
</tr>
<tr>
<td>IASP</td>
<td>the International Association for the Study of Pain</td>
</tr>
<tr>
<td>ISCOS</td>
<td>International Spinal Cord Society</td>
</tr>
<tr>
<td>L</td>
<td>Lumbar</td>
</tr>
<tr>
<td>LOS</td>
<td>Length of Stay in hospital</td>
</tr>
<tr>
<td>MC</td>
<td>Meningocele</td>
</tr>
<tr>
<td>MMC</td>
<td>Myelomeningocele</td>
</tr>
<tr>
<td>NSCI</td>
<td>Non-traumatic Spinal Cord Injury</td>
</tr>
<tr>
<td>NT</td>
<td>Non Testable</td>
</tr>
<tr>
<td>QoL</td>
<td>Quality of Life</td>
</tr>
<tr>
<td>ROM</td>
<td>Range Of Movements</td>
</tr>
<tr>
<td>S</td>
<td>Sacral</td>
</tr>
<tr>
<td>SB</td>
<td>Spina Bifida</td>
</tr>
<tr>
<td>SCI</td>
<td>Spinal Cord Injury</td>
</tr>
<tr>
<td>SCL</td>
<td>Spinal Cord Lesion</td>
</tr>
<tr>
<td>SCIM</td>
<td>Spinal Cord Injury independence measure</td>
</tr>
<tr>
<td>Th</td>
<td>Thoracic</td>
</tr>
<tr>
<td>UTI</td>
<td>Urinary tract infection</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual Analogue Scale</td>
</tr>
<tr>
<td>WISCI</td>
<td>Walking Index for Spinal Cord Injured Individuals</td>
</tr>
<tr>
<td>ZPP</td>
<td>Zone of Partial Perseveration</td>
</tr>
</tbody>
</table>
4 INTRODUCTION

4.1 Spinal cord

The spinal cord is a part of the central nervous system (CNS) and is a continuation of the neuronal tissue of the brain. It occupies the upper two thirds of the spinal canal and ends below the first lumbar vertebra. At that level the cord broadens to form the conus medullaris. Neural tissue identified as nerve roots constitutes the cauda equina and occupies the remainder of the lumbar canal. The average length of the spinal cord is 43-45 cm. The cord, conus and cauda equine are surrounded by the meninges. The spinal cord consists of 8 cervical nerves C (1-8), 12 thoracic nerves Th (1-12), 5 lumbar nerves L (1-5) and five sacral nerves S (1-5). The cervical nerves control signals to the back of the head, the neck and shoulders, the arms and hands, and the diaphragm. The thoracic nerves Th (1-12) control signals to the chest muscles, some muscles of the back, and parts of the abdomen and the lumbar spinal nerves. L (1-5) control signals to the lower parts of the abdomen and the back, the buttocks, some parts of the external genital organs, and parts of the leg. Finally the sacral spinal nerves S(1-5) control signals to the thighs and lower parts of the legs, the feet, most of the external genital organs, and the area around the anus. The vertebral column is composed of 33 vertebrae: 7 cervical, 12 thoracic, 5 lumbar, 5 sacral which are fused and 3 to 5 fused coccygeal vertebrae. The typical vertebra consists of body and arch and the spinal cord lying within the arch (Gerald Fletcher et al 1992).

The blood supply of the spinal cord derives mainly from the anterior spinal artery. The grey matter of the spinal cord is surrounded by white matter consisting of ascending and descending fibres. Fibres carrying similar sensory information or motor functions travel together in tracts. The major spinal pathways are as shown in table 1.
Table 1. Motor and Sensory tracts (according to Martha Freeman Somers et al 1992)

<table>
<thead>
<tr>
<th>NAME</th>
<th>Travels in the cord Ipsilateral or Contra lateral to muscle it innervates</th>
<th>Type of control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MOTOR TRACTS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lateral corticospinal</td>
<td>Ipsilateral</td>
<td>Voluntary motions (limbs)</td>
</tr>
<tr>
<td>Ventral corticospinal</td>
<td>Contra lateral</td>
<td>Voluntary motions (axial)</td>
</tr>
<tr>
<td>Vestibospinal</td>
<td>Both</td>
<td>Postural reflexes</td>
</tr>
<tr>
<td>Rubrospinal</td>
<td>Ipsilateral</td>
<td>Voluntary motions (limbs)</td>
</tr>
<tr>
<td>Pontine reticulospinal</td>
<td>Both</td>
<td>Modulation of spinal reflexes</td>
</tr>
<tr>
<td>Medullar reticulospinal</td>
<td>Both</td>
<td>Modulation of spinal reflexes</td>
</tr>
<tr>
<td><strong>SENSORY TRACTS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lateral spinothalamic</td>
<td>Contra lateral</td>
<td>Sharp pain temperature light touch</td>
</tr>
<tr>
<td>Dorsal columns</td>
<td>Ipsilateral</td>
<td>Proprioception 2-point discrimination, vibration, fine touch.</td>
</tr>
<tr>
<td>Spinoreticular</td>
<td>Ipsilateral</td>
<td>Deep pain</td>
</tr>
</tbody>
</table>

4.2 Classification of SCI

Traumatic SCI is classified into five types by the American Spinal Cord Injury Association (ASIA) and the International Spinal Cord Injury Classification System. The American Spinal Cord Injury Association or ASIA has defined an international classification as shown in table 2 based on neurological levels, touch and pinprick sensations tested in each dermatome (table 3), and strength of ten key muscles on each side of the body (table 4), i.e. shoulder shrug (C4), elbow flexion (C5), wrist extension (C6), elbow extension (C7), hip flexion (L2), knee extension (L3), ankle dorsiflexion (L4), long toe extension (L5), and ankle plantar flexion (S1) (Ditunno et al 1994).
### Table 2. ASIA classification A-E, type of SCI and description

<table>
<thead>
<tr>
<th>ASIA grade</th>
<th>SCI</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Complete</td>
<td>No motor and sensory functions preserved in the sacral segments S 3-4</td>
</tr>
<tr>
<td>B</td>
<td>Incomplete</td>
<td>Sensory but not motor functions preserved below injury</td>
</tr>
<tr>
<td>C</td>
<td>Incomplete</td>
<td>Motor function is preserved below the neurological level and more than half of key muscles below the neurological level have a muscle grade less than 3.</td>
</tr>
<tr>
<td>D</td>
<td>Incomplete</td>
<td>Motor function is preserved below the neurological level and at least half of key muscles below the neurological level have a muscle grade of 3 or more.</td>
</tr>
<tr>
<td>E</td>
<td>Normal</td>
<td></td>
</tr>
</tbody>
</table>

### Table 3. Motor index 0-5*

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Total paralysis</td>
</tr>
<tr>
<td>1</td>
<td>1 palpable or visible contraction</td>
</tr>
<tr>
<td>2</td>
<td>Active movement, full range of motion, gravity eliminated</td>
</tr>
<tr>
<td>3</td>
<td>Active movement, full range of motion, against gravity</td>
</tr>
<tr>
<td>4</td>
<td>Active movement, full range of motion, against gravity and provides some resistance</td>
</tr>
<tr>
<td>5</td>
<td>Active movement, full range of motion, against gravity and provides normal resistance</td>
</tr>
<tr>
<td>5*</td>
<td>Muscle able to exert, in examiner’s judgement, sufficiently, pain on effort or contracture</td>
</tr>
<tr>
<td>NT</td>
<td></td>
</tr>
</tbody>
</table>
Table 4. Sensory functions 0-2

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Absent</td>
</tr>
<tr>
<td>1</td>
<td>Impaired</td>
</tr>
<tr>
<td>2</td>
<td>Normal</td>
</tr>
</tbody>
</table>

The following definitions are important in order to understand SCI.

**Complete SCI**
Absence of sensory and voluntary motor functions in S3/4 segments.

**Incomplete SCI**
Some voluntary motor or sensory functions present in S3/4 segments

**Neurological level**
The lowest segment where motor and sensory function is preserved on both sides.

**Paraplegia**
Refers to damage in thoracic, lumbar and sacral, including conus medullaris and cauda equine, but excluding lumbosacral plexus and peripheral nerve lesions. The result of the injury is an impaired function of the lower extremities and/or pelvic organs, depending on the level of lesion.

**Tetraplegia**
Refers to damage in cervical segments of the spinal cord resulting in impaired function in all four extremities as well as the trunk and the pelvic organs.

**Vertebral (skeletal) level**
The vertebral level is defined as the level of the vertebral / skeletal injury.

**Zone of partial perseveration**
Only in complete SCI and includes dermatomes and myotomes caudal to the neurological level that remains partially innervated.

**Spasticity classification**
For the classification of spasticity the most important and internationally used scale is the modified Ashworth scale (Table 5).
**Table 5. Modified Ashworth Scale**

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No increase in muscle tone</td>
</tr>
<tr>
<td>1</td>
<td>Slight increase in tone- a catch and release at the end of the range of motion.</td>
</tr>
<tr>
<td>1+</td>
<td>Slight increase in tone- catch followed by minimal resistance in remainder of range of motion.</td>
</tr>
<tr>
<td>2</td>
<td>More marked increase in muscle tone through most of range</td>
</tr>
<tr>
<td>3</td>
<td>Considerable increase in tone, passive movement difficult</td>
</tr>
<tr>
<td>4</td>
<td>Affected parts rigid in flexion or extension</td>
</tr>
</tbody>
</table>

**WISCI** (Walking Index for Spinal Cord Injuries)
Walking index for SCIs is an international walking scale that has established reliability and validity. The scale ranges from 0-20. 0 means no walking capability and 20 means that the patient can walk without assistance or devices. With this scale it is possible to evaluate walking capacity and the need for devices or assistance (Ditunno et al 2000, Kim et al 2007, Morganti et al 2005).

**FIM** (Functional Independence Measure)
The Functional Independence Measure (FIM) is an 18-item, 7-level scale developed to uniformly assess the severity of patients’ disability and medical rehabilitation functional outcome. It measures different functional aspects of daily life. The FIM emerged from a thorough developmental process overseen by the National Task force of Rehabilitation Research (Hamilton et al 1994, Ottenbacher et al 1996).

**SCIM** (Spinal Cord Injury Independence Measure)
SCIM is a newly developed disability scale for patients with SCI. Its sensitivity to functional changes in all subgroups of SCI (incomplete and complete injuries, paraplegia and tetraplegia) was found to be better than that of the FIM (Catz et al 2001, Itzikovich et al 2007, Catz et al 2007).

### 4.3 Spinal cord injuries (SCI)

SCI is a serious lesion in the CNS that may cause lifelong disability.

There are mainly three types of SCI

1. Traumatic SCI
2. Non-Traumatic SCI
3. Congenital SCI spina bifida (SB)
4.4 Traumatic SCI

The annual incidence of traumatic SCI, not including those who die at the scene of the accident is estimated to be approximately 40 cases per million population in the U.S. or approximately 11,000 new cases each year (Price et al 1994). In Sweden the incidence is about 16 cases per million and the incidence in Europe is about 17,5/million (ISCOS meeting report Aito 2004). The incidence of traumatic SCI is highest among young persons. Most patients have their injury when they are between 20 and 40 years of age. About 80% of the SCI patients are males (Pagliazzi et al 2003). Complete SCI is most common early in life and after violent accidents. Patients injured after the age of 40 more often have an incomplete spinal cord injury. These days few patients die during their in-hospital treatment (O’Connor 2005). Traffic accidents are the most common cause of SCIs. Both drivers and passengers are at risk of SCIs from car, motorcycle and bicycle accidents (table 1) (Acton et al 1994, Zargar 2007). The second most common cause is falling accidents which can be both from high heights and minor falls at home. Spinal stenosis (a narrowing of the spinal canal) is common in older patients with SCI after falls at home. Sports accidents are the cause of about 7% of the traumatic SCIs (De Vivo 1997). Diving accidents are the most common sporting accidents and usually give rise to a complete motor tetraplegia. Gun shot injuries are uncommon in Europe but occur more frequently in the United States and in South America (Carroll 1997). The traumatic SCI patient has often suffered from multitrauma. The most common associated injury is light head trauma (Davidoff et al 1992). Other common associated injuries are fractures, pneumothorax, wounds, severe head injuries and injuries to the lungs and abdomen (Table 6). In traumatic SCI patients with remaining SCI about 40% are tetraplegics and 60% are paraplegics. Complete SCI occurs in about 40% of the cases and incomplete injuries in 60%.

Table 6. Causes of traumatic SCI, n=1016.

<table>
<thead>
<tr>
<th>Causes</th>
<th>Causes in percent</th>
<th>Associated injuries in percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Road traffic accidents</td>
<td>52</td>
<td>56</td>
</tr>
<tr>
<td>Falling accidents</td>
<td>32</td>
<td>50</td>
</tr>
<tr>
<td>Sports accidents</td>
<td>7</td>
<td>19</td>
</tr>
<tr>
<td>Gun shots</td>
<td>2</td>
<td>50</td>
</tr>
<tr>
<td>Injuries at work</td>
<td>2</td>
<td>50</td>
</tr>
<tr>
<td>Other traumas</td>
<td>5</td>
<td>50</td>
</tr>
</tbody>
</table>
4.5 Central cord syndrome (CCS)

CCS is an incomplete syndrome that involves a greater motor weakness in the upper extremities than in the lower extremities. The pattern of motor weakness shows greater distal involvement in the affected extremity than proximal muscle weakness. Sensory loss is variable, and the patient is more likely to lose pain and/or temperature sensation than proprioception and/or vibration. Dysesthesias, in the upper extremities (e.g., sensation of burning in the hands or arms), is common as well as sacral sensory sparing. Patients with traumatic CCS are older at the time of injury than other traumatic SCI patients. This is probably due to the fact that many patients with CCS have cervical spinal stenosis and get their SCI after a minor fall at home. Pickett et al 2003 and McKinley et al 2007 stated that CCS is the most common incomplete spinal cord syndrome representing 44% of all cases, followed by cauda equine representing 26% of the incomplete spinal cord syndromes. The prognosis after CCS is usually good (Harrop et al 2006, Pollard and Apple 2003).

4.6 Non-traumatic SCI

Non-traumatic SCI is a growing problem as we currently live longer. The non-traumatic SCI patients are in most cases older at the time of injury than patients with traumatic SCI. Most patients are over 40 years of age at the onset of the disorder (Pagliacci et al 2003). About 40% of the patients are females (Nair et al 2005). Patients with non-traumatic SCI more often have an incomplete SCI than the traumatic SCI patients. The patients with non-traumatic SCI frequently have other medical problems like hypertension, cardiac diseases, degenerative disorders, arthritis and diabetes mellitus (McKinley et al 1999). Their rehabilitation is therefore complicated and they have more medical needs than the traumatic SCI patients (Yokoyama et al 2006).

The major causes of non-traumatic SCI are infections, vascular myelopathies (Frisbie 2002) and spinal stenosis both at lumbar and cervical level. In the last group the patients in many cases get their SCI during or after surgical treatment. Tumours within the nervous system, both benign e.g. meningeomas, lipomas and malignant e.g. astrocytomas, ependymomas and glioblastomas are a cause of non-traumatic SCI. Myelitis can be the first sign of multiple sclerosis (Fadil et al 2007).

Metastasis can giver rise to SCI but cancer patients are not included in the non-traumatic SCI population due to the fact that they have a progressive malignant disease and therefore have other medical needs. Furthermore they are not treated in a spinal cord unit.
4.7 Congenital SCI spina bifida (SB)

SB is a developmental defect which occurs within the first six weeks of pregnancy, possibly caused by a combination of genetic and environmental factors (Padmanabhan 2006, Northrup and Volcik 2000).

The rate of SB among newborns in Sweden gradually diminished from 0.55 per 1000 to 0.29 per 1000 between 1973 and 1993 (Nikkilä et al 2006).

SB is an incomplete closure of the vertebral column which usually is associated with a similar anomaly of the spinal cord. In early embryo the nervous system is represented by the neural groove, the lateral folds which unite dorsally to form the neural tube. An arrest in this process of development leads to defective closure of the bony vertebral canal. In severe cases a sac protrudes through the vertebral opening which may contain meninges only or also the flattered open spinal cord meningomyelocele (MMC). In the least severe cases there is no protrusion but a defect in the laminar arches may be palpable as a depression sometimes is covered by a dimple or a tuft of hair (spina bifida occulta).

The causes of SB are largely unknown. Some evidence suggests that genes may be involved, though in most cases there is no familial connection. Women with diabetes mellitus are more likely to give birth to a child with SB. Apparently folic acid can decrease the occurrence of neural tube defects, especially MMC even when it is given once a week.

The lumbosacral region is the most common site of SB, although it is sometimes also found in the neck. SB may also be associated with other congenital abnormalities such as hydrocephalus (HC). Approximately 90% of newborns with MMC also have HC, an accumulation of fluid in and around the brain caused by the Arnold Chiari malformation. This must be managed early with a shunt, or brain damage will occur when the baby’s head may no longer enlarge, after the skull bones have fused. In Sweden about 80% of children with SB develop HC.

In a study on young adults with SB in Holland 67% suffered from HC (Barf el al 2007).

Children who have MMC have a varying degree of paresis in the lower extremities and higher than usual occurrence of learning disabilities and attention deficits. Children with SB also tend to be less adaptable, are more easily distracted, less attentive and persistent, and less predictable. Neurogenic bladder is a major problem for children with SB and they also have problems with bowel function (Verhoef et al 2005). Most children with MMC, and a small number with meningocele (MC) or spina bifida occulta, have a tethered spinal cord.
4.8 Prognosis after SCI

Neurological recovery and functional improvement occur after traumatic and non-traumatic SCI during standard treatment and rehabilitation, as a part of the natural recovery process. The degree of recovery depends on the type, level and the severity of injury (Celani et al 2001). Studies show that ASIA classification on admission to hospital after the injury is of utmost importance for the prognosis (Burns and Ditunno 2001). If the SCI is complete the prognosis is poor and a majority of the patients will remain complete on discharge from hospital (Alander et al 1994, Coleman et al 2004, Fisher et al 2006, Kirshblum et al 2004, Schönherr et al 1999). However, if the injury is incomplete the prognosis is much better (Catz 2002, Citterio et al 2004). About half of the patients who are ASIA B (motor complete) on admission will improve at least one ASIA grade on discharge. For patients that are ASIA C and D the prognosis is even better as shown in table 7 (Scivoletto et al 2004).

In summary, predicting the final neurological and functional outcome is of great importance in planning the treatment, rehabilitation and discharge of patients with SCI.

<table>
<thead>
<tr>
<th>DISCHARGE</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>92</td>
<td>4</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>B</td>
<td>2</td>
<td>48</td>
<td>49</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>C</td>
<td>0</td>
<td>2</td>
<td>30</td>
<td>60</td>
<td>8</td>
</tr>
<tr>
<td>D</td>
<td>0</td>
<td>2</td>
<td>68</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>0</td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

Table 7. ASIA on Admission and discharge for traumatic SCI, percent, n=816
4.9 Pain after SCI

Longstanding pain is a common problem after spinal cord injury in both traumatic and non-traumatic SCI (Ragnarsson 1997, Turner et al 1999, Finnerup et al 2001, Norrbrink Budh et al 2003). The pain may be nociceptive or neuropathic (for definition see table 8). The incidence of chronic pain was found in earlier studies to vary between 18% and 94%. A study carried out in 1962 which attempted to classify chronic pain in SCI subjects found that 37% of 52 suffered from chronic pain (Kaplan et al 1962). Some years later another study reported an incidence of suffering in 77% (Richards et al 1980). More recent studies have found that nearly all patients with SCI during the in-hospital rehabilitation experience pain and that neuropathic pain is one of the most common types of pain (New et al 1997). Furthermore that 61% of patients with SCI suffered from pain with severe to moderate intensity (Demirel et al 1998).

Nevertheless neuropathic pain is one of the most challenging problems after SCI and neuropathic pain affects quality of life.

A taxonomy of pain was developed and proposed by the SCI pain task force of the International Association for the Study of Pain (IASP). In this classification which is mechanism based, the pain is classified in three tiers (Siddall et al 2000 and 2001) (Table 9). The pain types are firstly divided into nociceptive and neuropathic pain and secondly into musculoskeletal and visceral, and thirdly into above-, at- or below- level neuropathic pain types. The third tier aims to identify pain based on specific structures and pathology when it is possible.

In this thesis the IASP classification of pain was used

Several studies show that neuropathic pain currently affects quality of life and has a negative impact on several domains of life (Nepomuceno et al 1979, Widerstrom-Noga 2001). In Wollaar’s (2007) study chronic SCI pain and quality of life were both largely associated with several psychological factors of which pain catastrophizing and SCI helplessness were the most important (Wollaars 2007).

Usually neuropathic pain starts soon after the SCI. However in the acute phase after injury patients, and especially those with traumatic SCI, may have other pain due to associated injuries like fractures. Nowadays a high percentage of patients with traumatic SCI undergo surgical treatment in order to stabilize the vertebrae and thus avoid further damage to the spinal cord (Aito et al 2005).

One of the most important tasks in the rehabilitation after SCI is to treat neuropathic pain.

Neuropathic pain is difficult to treat successfully and there is currently no existing curative therapy.

Treatment options may include pharmacotherapy, physiotherapy and psychological intervention.

### Table 8. Definition neuropathic and nociceptive pain

<table>
<thead>
<tr>
<th>Neuropathic pain</th>
<th>Nociceptive pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>A pain is diagnosed neuropathic when burning or shooting in an area with sensory disturbances to pinprick and touch and without relation to movements or signs of inflammation.</td>
<td>A pain is diagnosed nociceptive when aching in an area with signs of inflammation or / and with painful joint movements.</td>
</tr>
</tbody>
</table>
Table 9. Proposed classification of pain related to an SCI (Siddall et al 2000 and 2001)

<table>
<thead>
<tr>
<th>Broad type</th>
<th>Broad system</th>
<th>Bone joint, muscle trauma or inflammation</th>
<th>Specific structures and pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>tier 1</td>
<td>tier 2</td>
<td>tier 3</td>
<td></td>
</tr>
<tr>
<td>Nocicpetive</td>
<td>Musculoskeletal</td>
<td>Bone joint, muscle trauma or inflammation</td>
<td></td>
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<td></td>
<td></td>
<td>Mechanical instability</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Muscle spasm</td>
<td></td>
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<tr>
<td>Visceral</td>
<td></td>
<td>Secondary overuse syndrome</td>
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<tr>
<td></td>
<td></td>
<td>Renal calcanus, bowel and/or sphincter</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Dysfunction etc</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dysreflexic headache</td>
<td></td>
</tr>
<tr>
<td>Neuropathic pain</td>
<td>Above–level</td>
<td>Compressive mononeuropathies</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Complex regional pain syndrome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>At level</td>
<td>Nerve root compression (incl. cauda syndrome)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Syringomyelgia</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Spinal cord trauma/ischemia (transitional zone etc)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Dual-level cord and root trauma (double lesion syndrome)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Below level</td>
<td>Spinal cord trauma ischemia (central dysesthesia syndrome)</td>
<td></td>
</tr>
</tbody>
</table>
4.10 Other medical complications after SCI

4.10.1 AUTONOMIC DYSREFLEXIA

SCI and especially cervical SCI imply serious disturbances in autonomic nervous system function (Weaver et al 2006). The symptoms are episodes of high blood pressure, headache, sweating and bradycardia. The rise in blood pressure can cause sudden death due to brain haemorrhage. Common causes of autonomic dysreflexia are an over extended bladder, severe constipation, sexual activity or urinary tract infections (UTI) (Chua et al 1996, Karlsson 2006, Bravo et al 1998).

4.10.2 BOWEL DYSFUNCTION

Bowel dysfunction constitutes a problem in both the acute and chronic phase. Neurogenic bowel dysfunction can cause both faecal incontinence and constipation. Bowel dysfunction has a marked impact on quality of life (Lynch et al 2000). Hemorrhoids are common in the SCI population. SCI patients more often than normal persons are on laxatives. Tetraplegic patients had the highest prevalence of constipation, while patients with low paraplegia were less prone to constipation (de Looze et al 1998, Han et al 1998).

4.10.3 DECUBITE/PRESSURE ULCERS

Pressure sores are more common in complete SCI patients (McKinley et al 1999) and occur over bony prominences. Decubiti can lead to osteomyelitis, sepsis and even death. Several factors make SCI patients vulnerable to the formation of decubiti:
1. SCI patients lack the sensation that stimulates protective weight shifts.
2. Skin collagen degradation
3. Compromised peripheral blood flow resulting in decreased blood flow and nutrient supply to the tissue,
4. The skin and subcutaneous tissue are more vulnerable to normal trauma. Wherever external pressure on soft tissue is greater than capillary pressure the result will be ischemia.

When pressure ulcers occur, healing takes long time, and treatment is costly and may include hospitalization and surgery (Walter et al 2002).

4.10.4 DEEP VEIN THROMBOSIS (DVT)

DVT occurs frequently following SCI, particularly in the acute phase. Peripheral vasodilatation, absent or reduced lower extremity muscular function and immobility leads to venous stasis and are important factors for the DVT development. Thrombi in the deep veins are potentially life threatening and can lead to pulmonary embolism (Jones et al 2005).

4.10.5 DEPRESSION

SCI both traumatic and non-traumatic causes lifelong disability and may lead to depression both in the acute and in the chronic phase. Depression is a significant problem associated with poorer outcome of rehabilitation and lower quality of life (Anderson et al 2007). The suicide rate among individuals with SCI is higher than in the general population especially in females (de Vivo et al 1991). Hence, there is a need for increased awareness among rehabilitation staff and general practitioners regarding depression and psychological adjustment difficulties after SCI (Hartkopp et al 1998).
4.10.6 HETEROTROPHIC OSSIFICATION

Ectopic bone formation is the formation of new bone within muscular and other connective tissue below the level of lesion. It normally appears from 1 month to 4 months after injury and leads to impaired functional status and contractures (Banovac et al 2004).

4.10.7 OEDEMAS, SWELLING OF LEGS AND FEET

Blood and lymph are not evacuated normally after a spinal cord injury and this will cause swelling of legs and feet especially soon after the injury.

4.10.8 OSTEOPOROSIS

Following spinal cord injury both calcium and collagen are lost from the bones. The resulting osteoporosis increases the likelihood of fractures. Osteoporosis progresses gradually for five years after injury, at which time it reaches a plateau. Osteoporosis can cause fractures after light traumas (Jiang et al 2006, Giangregorio et al 2006).

4.10.9 PNEUMONIA/ RESPIRATORY INSUFFICIENCY

Respiratory complications are the most common cause of death following spinal cord injury (Frankel et al 1998). These complications occur as a result of a reduction in inspiratory and expiratory ability. Inadequate inspiration results in reduced ventilation of the lungs leading to atelectasis. Ineffective coughing allows secretions to build up in the lungs with subsequent atelectasis, pneumonia, and respiratory insufficiency resulting (Soden et al 2000).

4.10.10 SPASTICITY

Spasticity is a disorder of the motor system that occurs after injury to the CNS, which may increase the disability of individuals with SCI. In SCI patients symptoms of spasticity are often present after a period of spinal shock and in many cases, the quality of life (QoL) is negatively affected. Spasticity is more prevalent in higher lesions and in incomplete lesions and the presence of problematic spasticity has been significantly correlated with cervical incomplete (ASIA B-D) injury (Sköld et al 1999). There is a significant association between spasticity and contractures (reduced ROM). Quick stretching of muscles excite exaggerated reflex responses, cutaneous stimuli also evoke abnormal reflex responses. The Ashworth scale is used to measure spasticity. There was a poor correlation between clinically rated (Ashworth Scale) spasticity and self-rated general spasticity and a modest correlation between Ashworth Scale and self-rated present spasticity (Lechner 2006).

Treatment includes rehabilitation techniques and modalities, physiotherapy pharmacological options, injection techniques, intrathecal baclofen, and surgery (Adams et al 2005, Sköld 2000). A SCI patient can benefit from spasticity in daily living, when dressing, walking and transfers. To measure spasticity a combination of electrophysiological and biomechanical techniques gives hope of a full characterization of the spastic syndrome (Biering-Sörensen et al 2006).
4.10.11 SEXUAL PROBLEMS

Sexual function and its impact on QoL is a major issue to a majority of people living with SCI. Most SCI women remain fertile and can conceive and bear children. Depending on the level of injury, men may have problems with erection and ejaculation, and most will have compromised fertility due to decreased motility of their sperm (Linsenmeyer and Pekash 1991, Slot et al 1989). Treatments for men include vibratory or electrical stimulation and drugs such as sildenafil. Many couples may also need assisted fertility treatments to aid spinal cord injured men to father children. As SCI victims often are young at the time of injury, sexuality and fertility are of utmost importance for living a full-worthy life (Westgren et al 1997, Monga et al 1999).

4.10.12 UROLOGICAL PROBLEMS

Most spinal cord injuries affect bladder functions because the nerves that control the functions of those organs originate in the segments near the lower termination of the spinal cord and are cut off from brain input. Without coordination from the brain, the muscles of the bladder and urethra cannot work together effectively, and urination becomes impaired. The bladder can empty suddenly without warning, or become over-full without releasing. In some cases the bladder releases, but urine backs up into the kidneys because it is not able to get past the urethral sphincter. The great risk that urologic dysfunction poses is possible damage to the kidney function. It is therefore essential that the bladder is emptied completely to avoid urinary tract infections (UTI), which is a common complication after SCI. (Stover et al 1989 Biering Sörensen et al 1999 Esclarin de Ruz et al 2000).
Most people with spinal cord injuries use intermittent catheterization to empty their bladders (Cardenas et al 1995 Moore et al 2006).

4.11 Incomplete spinal cord syndromes

1. **Anterior cord syndrome** involves loss of motor function/movement and sensation of pain and temperature, but with preserved deep sensation and vibration.

2. **Brown-Séquard syndrome** involves a relatively greater ipsilateral loss of proprioception and motor function, with contralateral loss of pain and temperature sensation.

3. **Central cord syndrome** is described above.

4. **Conus medullaris syndrome** is a sacral cord injury with or without involvement of the lumbar nerve roots. This syndrome is characterized by areflexia in the bladder, bowel, and to a lesser degree, lower limbs. Motor and sensory loss in the lower limbs is variable.

5. **Cauda equina syndrome** involves injury to the lumbosacral nerve roots and is characterized by an areflexic bowel and/or bladder, with variable motor and sensory loss in the lower limbs. Because this syndrome is a nerve root injury rather than a true SCI, the affected limbs are areflexic. This injury is often caused by a central lumbar disk herniation.
4.12 Rehabilitation after SCI

The rehabilitation after SCI starts immediately after the accident. The rehabilitation of SCI can be divided in three parts.

1. The first part is acute rehabilitation which takes place during the first months after the SCI. This period can also be called in-hospital rehabilitation period. The immediate course of action may be a neurosurgical intervention to stabilize the spinal canal in order to avoid further damage to the spinal cord. Following that the patient begins learning to live with the SCI, learning to empty the bladder and bowel and learning to use adequate aids. When this period is over the patient is usually discharged from hospital and the second part starts. Usually the in-hospital period is three months for a paraplegic patient and 6 months for a tetraplegic patient. The in hospital period can be much longer due to medical and social complications.

2. During the second part the patient learns to live in his normal environment, to get in contact with his work, in order to gain optimal quality of life.

3. During the third phase of the rehabilitation the patient is back to “normal” but has to do physiotherapy and yearly check-ups to avoid complications. The rehabilitation after SCI is a life long process.

Spinalis SCI unit

The Spinalis unit is an outpatient clinic for patients with traumatic and non-traumatic SCI and for adults, over the age of 18 with SB in the greater Stockholm area. The greater Stockholm area comprises a population of about 2,0 million. The Spinalis SCI unit provides a life-time care for these patients. The primary activity is a yearly check-up which started in 1991 as a project; Solberga projektet. In 1995 the unit became a part of the Local Muncipal Health. Today the Spinalis SCI unit is a part of the Karolinska University hospital.

Spinal Unit of Florence

The initial activity started in 1978 under the leadership of Professor Massimo Missau. During the years the activity has increased and the spinal unit currently has 50 beds. The director is Dr Sergio Aito. The spinal unit is a part of the Careggi hospital which is the university hospital of Florence. The unit has a urological department and an outpatient clinic for follow-up and visits. The professional staff of the unit includes specialists in neurology, anaesthesiology, rehabilitation medicine, orthopaedic surgery and urology.
5 AIMS OF THE THESIS

The general aim of this thesis was to analyse the prevalence of neuropathic pain in different types of SCI and its relation to different neurological and functional parameters. Furthermore, the neurological and functional outcome after traumatic CCS was analyzed.

The specific aims of the four papers included in the thesis were as follows:

I and II. To analyse the prevalence of neuropathic pain in (I) traumatic and (II) non-traumatic SCI and to asses the predictive values of age at time of injury, gender, level of injury, and completeness of injury for the development of at level and below level neuropathic pain. Furthermore, the impact of neuropathic pain on daily life was evaluated.

III. To analyse the prevalence of neuropathic and nociceptive pain in adults with SB and relate the pain to the level of injury, completeness of injury and to the presence of hydrocephalus.

IV. To analyse the functional and neurological outcome, the prevalence of neuropathic pain and spasticity in patients with traumatic CCS and relate these factors to age at the time of injury.
6 MATERIAL AND METHODS

6.1 Paper I-III

All patients consulting the Spinalis SCI unit, outpatient clinic during the period 1995-2000 with SCI were included in the retrospective register study. The Spinalis post-acute unit provides yearly check-ups for patients with traumatic and non-traumatic SCI and for adults (over the age of 18) with SB living in the greater Stockholm County. Data were gathered at the patients’ first examination at the unit. For the traumatic injured patients the median time point from injury to examination was 6 years (range 0-48 years). A classification according to ASIA (A-E) was performed. Patients with incomplete SCI were due to small numbers of patients with ASIA B and C analysed together. Patients classified as ASIA E were re-classified according to their initial classification usually ASIA E to ASIA D.

Neurological level of injury was defined and the level of injury was classified as tetraplegia or paraplegia. Included in the studies were 402 patients with traumatic SCI, 95 with non-traumatic SCI and 110 adults with SB.

The traumatic (n=402) and non-traumatic SCI (n=95) patients were divided into five age groups according to age at the time of injury/disorder (0-19, 20-29, 30-39, 40-40 and over 50 years of age) Furthermore, the patients with non-traumatic SCI were divided in 5 groups according to the diagnosis of the spinal cord disorder (vascular myelopathy, spinal stenosis both lumbar and cervical, infections, benign tumours, malignant tumours).

Adults with SB (n=110) were divided in two groups; patients with and without HC.

The pain was diagnosed by the experienced examining neurologist as neuropathic when it met the criteria presented by the IASP task force.

When neuropathic pain was diagnosed it was classified as above level pain, at level pain and below level pain. Injuries at level of L3 and below were considered by the examining neurologist as difficult to divide in at level and below level pain. In our study only one included patient with neuropathic pain had a neurological level below L3. This patient’s pain was classified as at-level neuropathic pain. In the SB group, pain was not divided in above-, at- or below neuropathic pain due to the fact that most patients with SB have a lumbar level and therefore it is difficult to divide the pain according to the neurological level.
6.2 Paper IV

All patients with traumatic CCS undergoing acute rehabilitation at the Spinal Unit of Florence, Italy during January 1996 to June 2002 underwent a follow up visit at the outpatient clinic 2004. The follow up was performed at least 18 months after the injury.

In total 87 patients with CCS were admitted to acute rehabilitation at the Spinal unit of Florence during this period. Subjects were excluded if they 1) had died before the follow-up visit; 2) if data were missing 3) they were unable to be assessed by FIM/WISCI due to mental illness or orthopaedic extremity impairment. In total five patients were excluded and thus 82 patients were included in the study.

The collected data were; year of injury, gender, age at time of injury, cause of injury, vertebral lesion (level and type) treatment of vertebral lesion (conservative or surgical) length of inpatient rehabilitation, and complications during the acute rehabilitation, ASIA A-E on admission, discharge and at follow-up, FIM and WISCI on discharge and at follow-up and the presence of spasticity and neuropathic pain at follow-up.

The causes of injury were divided into three groups 1) falls 2) road traffic incidents 3) sport injuries.

The types of vertebral lesions were divided into four groups 1) SCIWORET (SCI without evidence of trauma) 2) fracture 3) fracture/dislocation and 4) pure dislocation.

The treatment of the vertebral lesions was classified as conservative or surgical. Neurological evaluation was performed according to ASIA including motor and sensory scores. The activity of daily living was evaluated by means of the FIM scale (0-126), and the ability to walk was measured by the WISCI scale 0-20. The patients were divided in three groups, group 1 (score range) 0-2: almost impossible to walk, group 2 (score range 3-17) ability to walk with different degrees of help and group 3 (score range 18-20) ability to walk independently.

The pain was classified as neuropathic according to the IASP (Siddall et al 2001) when experienced as burning or shooting in an area with sensory disturbances to pin prick and touch and with no relationship to movements and inflammatory signs. The pain could be spontaneous or provoked by touch or cold, continuous and /or with paroxysmal components. Spasticity was measured by the modified Ashworth scale (0-5)

Finally the patients were divided into four age groups according to the age at the time of injury 1) 0-30 years 2) 31-50 years 3) 51-65 years 4) over 65 years of age.
7  STATISTICAL ANALYSIS

7.1  Paper I-III

Groups and subgroups are presented as absolute numbers and percentages. Fisher’s exact test was used to compare groups when the numbers were too small to allow for chi2 test. Logistic regression was used to quantify the association between some possible risk factors. P<0.05 was considered significant. Categorical variables were compared using chi2 test.

7.2  Paper IV

Groups and subgroups are presented as absolute numbers and percentages. The differences in FIM and WISCI scores across the clinical demographic explanatory variables were assessed using the one way analysis of variance and the corresponding F statistic.
8 RESULTS

8.1 Traumatic SCI (I)

Overall presence of neuropathic pain
40% of the patients included in the study met the criteria of neuropathic pain. 34 % of the patients with neuropathic pain described at level neuropathic pain and 66 % described below level neuropathic pain.

Age
The prevalence of neuropathic pain increased with age up to 30-39 years of age. There was a slight relative decrease in the group aged 40-49 years. The patients above 50 years of age at the time of injury showed the highest prevalence. The prevalence of either an at level pain and below level pain or both in different age groups were significantly different (chi2= 12.37 df=4) and the contribution of the increasing trend with age groups was significantly different (chi2=12.37, df=4).

ASIA impairment scale
42% of the patients with complete SCI (ASIA A) and 39% of the patients with incomplete SCI reported neuropathic pain. Neuropathic pain at the neurological level was present in 9% of the patients with complete SCI and in 15 % of the patients with incomplete injury. Below level pain was present in 33% of the patients with complete SCI and in 24% of the patients with incomplete injury.

Gender
There was a predominance of males in all age-groups. However, in total 46% of the females and 38% of all males described neuropathic pain.

Tetraplegia/paraplegia
In total, 41% of the patients with tetraplegia and 40% of the patients with paraplegia experienced neuropathic pain. Of the patients with tetraplegia 16% had at level neuropathic pain and of the paraplegic patients 11% had at level pain. 29% of the patients with paraplegia and 26% of the patients with tetraplegia described below level neuropathic pain. Furthermore patients with low complete paraplegia (Th10-S4) more often experienced neuropathic pain than patients with high complete paraplegia (Th1-9) This difference reached statistical significance (chi2= 44.57 df=1).

Patient rating of the pain as a problem in daily life
In total 72% of the patients with neuropathic pain reported that their pain was a problem in their daily life. The remaining 28% reported that pain was not a problem in their daily life.
8.2 Non-traumatic SCI. (II)

Prevalence of neuropathic pain
In total 38% of the patients experienced neuropathic pain. 39% reported at level neuropathic pain 61% reported below level neuropathic pain.

Age
No statistically significant difference was found in the prevalence of neuropathic pain between those diagnosed at ages up to 39 years of age and those aged 40 years of age or more (chi 2 =1.30, df=1).

ASIA impairment scale
The frequency of neuropathic pain was similar in patients with complete lesion (ASIA A) and those with incomplete lesion (ASIA B-D).

Gender
Half of the women reported neuropathic pain compared with 30% of the males. However the difference was not statistically significant (chi2=1.88, df=1). Females had more often below level pain than males and this difference was statistically significant (chi2=5, 27, df=1).

Paraplegia/tetraplegia
44% of the patients with tetraplegia and 35% of the patients with paraplegia reported neuropathic pain.

Patient rating of the pain as a problem in daily life
67% of the patients with neuropathic pain rated their pain as a severe problem or a problem to some extent in their daily life. Patients diagnosed with neuropathic pain in older age reported pain as a problem in daily life more often than younger patients. The difference reached significance statistically (p= 0.01). Women reported that pain was a problem in daily life more than males. Also this difference reached significance statistically ( p=0,05).
8.3 Spina bifida (SB) (III)

Prevalence of neuropathic pain
In total 11% experienced neuropathic pain. Eight of 67 patients with lumbar level and 3 of 29 patients with thoracic level experienced neuropathic pain. Five of 54 patients with complete SCI and 6 of 43 patients with incomplete SCI suffered from neuropathic pain. In patients with HC 3 of 57 and 10 out of 53 of the patients without HC experienced neuropathic pain.

Prevalence of nociceptive pain
Nociceptive pain was present in 24% of the patients included in the study. Back pain was the most common type of pain which affected 14 patients. 11 of these patients were walking with or without aids and/or devices. Shoulder pain was present in five patients and four patients were not able to localize their pain.

Age
Most of the patients included in the study were young; 59% were between 18 and 29 years of age and only 19% were over the age of 40. The mean age at the time of examination was 28.7 years (range 18-55 years of age).

Gender
In the material there was a slight female predominance. There was no statistical difference between males and females regarding the prevalence of neuropathic pain.

ASIA impairment scale
49% were classified as ASIA A, 38% patients had an incomplete SCI (ASIA B-D), 9% were ASIA E and 4% were not testable due to cognitive or other intellectual dysfunctions.

Neurological level
In total 26% had a thoracic level and 61% had a lumbar level. L3 was the most common neurological level followed by L1.

HC
HC was present in 52% and was most common in younger patients. In the age group 18-29 years, 63% had HC and 19% had HC in the age groups over of 40 years. This difference reached statistical significance (p=0.011).
In the study 63% of the males and 43% of the females had HC. This difference was statistically significant (p=0.0186). HC was most common in individuals with complete SCI and in patients with a thoracic level of injury. 43% of the individuals with a lumbar level had HC. This difference is statistically significant (p=0.0036). 83% of patients with a complete SCI and 17% with an incomplete SCI (ASIA B-D) had HC. This difference was also statistically significant (p=0.001).
8.4 Traumatic central cord syndrome (CCS) IV

Prevalence of neuropathic pain
Neuropathic pain was present in 47% of patients at follow-up and was more common in older patients.

Age
Patients aged over 65 years of age at the time of injury had poorer neurological and functional outcome and more often experienced neuropathic pain than patients injured before 65 years of age.

ASIA impairment scale and the neurological level
On admission, two patients were classified as ASIA A, 12 as ASIA B, 37 as ASIA C and 31 as ASIA D. On discharge no patient was classified as ASIA A or B, while eleven scored ASIA C, 70 ASIA D, and one was ASIA E. At follow-up eight patients, who were discharged as ASIA D, became ASIA E. The C6 level was found to be the most common neurological level on admission, discharge and at follow-up.

Gender
12% of the included patients were females and 88% were males.

Causes of injury
Road traffic accidents (57%) were the most common cause of injury followed by falls (36%). Diving was the most common sport accident. The mean age for falls was 58 years of age, for road traffic accidents 50 years of age and for sport related injuries 23 years of age.

Vertebral lesion
58% sustained hyperextension injury without evidence of fracture/dislocation (SCIWORET) by imaging/X-ray, but showed evidence of spinal canal stenosis. Fractures in the spine were found in 26% of patients, fracture/dislocation in 13% and pure dislocation in 3%. Patients without radiological evidence of fracture/dislocation were older than patients with fracture dislocation.

Surgical treatment
45% of the patients underwent surgical treatment with anterior decompression and fusion and 55% of the patients were treated conservatively.

Associated injuries
More than half of the patients had associated injuries. Light brain injury was the most common associated injury and was present in 34% followed by fractures in 14% of the patients.

Complications during the acute rehabilitation
Complications occurred in 28% of the cases. The most common complications were respiratory problems (in 30%) and DVT (in 26%). Other complications were cardiac arrhythmia in 13% and pyelonephritis, gastric ulcer and pressure sores in 22%
Length of stay (LOS) in hospital
The mean LOS was 120 days (range 24-390) and was longer for patients who underwent surgical treatment. The explanation was that patients who underwent surgery had a more severe vertebral injury (see discussion). Patients aged between 31 and 50 at the time of injury had the longest hospitalisation while patients aged 66 years or more at the time of injury had a shorter stay in hospital. The older patients were often referred to other hospitals for rehabilitation.

Spasticity
Spasticity at follow-up was present in 66% of the patients. 72% of patients with spasticity claimed that their spasticity was a serious problem in their everyday living. Regarding spasticity, there was no statistically significant difference found between patients aged less than 50 years of age and those aged over 50 years of age at the time of injury.
9 DISCUSSION

9.1 Methodological issues

In all four studies neuropathic pain was studied regardless of its intensity. This method is likely to give a higher frequency of pain reports than studies which include only patients spontaneously complaining of pain, as described in earlier studies. However, in many studies chronic pain and not only neuropathic pain has been included (Richards et al 1980, Turner et al 2001). The standard criteria presented by the IASP task force (Siddall et al 1997, Siddall et al 2000) were used to identify neuropathic pain. In general the reliability is high but the response might be influenced by environmental and psychological factors. Especially in adults with SB the pain diagnosis might be influenced by the cognitive dysfunction that may be present in many adults with SB (Fletcher et al 2002, Dennis et al 2007, Barf et al 2003).

Data were gathered at different times after the onset of the SCI. For patients with traumatic SCI data were gathered in several cases many years after the injury. For the non-traumatic group the data were in most cases gathered within a year after the SCI diagnosis. Adults with SB were in all cases examined after the age of eighteen. The CCS data were gathered at minimum 18 months after trauma and maximum eight years after trauma. Patients with traumatic CCS injured between 1996 and 2002 were examined at follow-up in the year 2004. The pain at various ages was studied rather than pain related to age regardless of the age when the accident happened. Some patients had their injury many years ago and at that time the quality of care was not as it is today. This might be an explanation as to why they had a higher risk of developing neuropathic pain. For example treatments of UTI and pressure sores were not as advanced 20 years ago as they are today. Insufficiently treated pain may give rise to central sensitisation that may induce neuropathic pain or increase the magnitude of a present neuropathic pain. For instance intense and insufficiently treated nociceptive pain may give rise to central sensitisation processes that increase the magnitude of already present neuropathic pain.

All patients in study I-III were examined at their first visit and were classified according to ASIA and the neurological level. In all four studies the ASIA impairment scale was used. This scale was initially created for traumatic SCI and is therefore an excellent measure for the patients with traumatic SCI and for those with traumatic CCS. For patients in study II and III we used the ASIA classification although it is not created for these types of injuries and thus not validated. The ASIA classification was used as there is currently no better existing scale. However, in future methodological studies, a validation of ASIA scales needs to be carried out in these patient groups.

9.2 Neuropathic pain aetiology and age

In the traumatic group the cause of the SCI was not analysed. This means that the patients were not divided in groups according to the cause of the traumatic SCI. Dividing the patients into different groups on the basis of the cause of the SCI may give additional information. Patients with non-traumatic SCI were divided into five diagnostic groups. 95 patients in total were included which means that in, for example, the group diagnosed with malignant tumours only 11 patients were included. As astrocytoma mostly affects children, the mean age in this group was 16, 3 years at the time when the spinal cord symptoms appeared (Yule 2001).
The patients in the subgroup vascular myelopathies had the highest mean age which was expected since the diagnoses in this subgroup (aortaaneyrysm, infarction and other vascular myelopathies) mainly affect persons above the age of 50 (Ohsawa et al 2007).

In CCS, neuropathic pain was analysed at follow-up, performed at least 18 months after injury. Neuropathic pain was most common in the oldest group of patients. Like in the traumatic SCI group neuropathic pain increased with age at the time of injury. Patients with traumatic CCS are usually older at the time of injury than other traumatic SCI. In the present study on patients with traumatic CCS the mean age was 56 years which is more than 10 years older at the time of injury than other traumatic SCI. The result shows that the prevalence of below level neuropathic pain had its peak in patients aged up to 40 years at the time of injury whereas the prevalence of at level neuropathic pain was predominant in those injured after 40 years of age. On the other hand in adults with SB neuropathic pain was found to be rare and was not considered to be a major problem in daily life as was the case among the other studied groups of patients.

9.3 Neuropathic pain and gender

In traumatic SCI there was a strong male predominance (79, 5%). The same predominance was not found in the non-traumatic group but in the group of traumatic CCS patients.
In adult SB patients there was in contrast to the other patient groups a slight female predominance.
A male dominance in the traumatic SCI is likely due to a higher exposure to violent accidents. In the traumatic group it is well-known that the most common cause of accidents is road traffic accidents (Connor 2002). The cause of injury was studied in traumatic CCS and 57 % of the cases in this study were due to traffic accidents.
The analysis of pain showed that a statistically significant difference was found between men and women regarding below level neuropathic pain in non-traumatic SCI. This was however not unexpected. A number of clinical studies have shown that men and women experience pain differently (for a review see Berkley 1997). Females have lower thresholds, greater ability to discriminate, higher pain rating and less tolerance of stimuli. This is valid for all types of pain except Horton’s headache. SCI women also had a higher use of analgesics than males (Norrbrink Budh et al 2003).

9.4 Neuropathic pain, completeness of injury and level of SCI

There were no differences in neuropathic pain between paraplegia/tetraplegia and incomplete /complete SCI. When the patients with complete paraplegia were analysed in detail, those with low paraplegia (Th10-S4) more often had neuropathic pain than those with a higher neurological level (Th1-9). This difference however, is not an effect of age as they had almost the same mean age. Thus, this might be due to the level of injury.
In the non-traumatic SCI group 38% of the patients suffer from neuropathic pain. As in the traumatic group no relation was found between level of lesion and completeness of lesion. It must be emphasized that in the non-traumatic group only 12% had a complete SCI.
In adults with SB no differences in the prevalence of neuropathic pain were found between patients with complete/incomplete lesion or with paraplegia/ tetraplegia.
9.5 Effect of pain on daily life

Pain is one of the factors that influences daily life (Felix 2007). Patients with traumatic and non-traumatic SCI were interviewed about the impact of pain on daily life. 70% of both traumatic and non-traumatic SCI patients experienced a great impact from pain on their daily life. One third of the patients with pain reported that pain was a big problem in their daily life. This is in accordance with a study done by Anke et al 1995 showing that pain caused a significant psychosocial stress in half of the patients. In the studies on patients with traumatic CCS and adults with SB the patients were not interviewed if the pain influenced their daily life. It is reasonable to believe that patients with traumatic CCS also are highly affected by pain on their daily life. Adults with SB seldom complain about pain. This might be due to the fact that SB is an early developmental disease and that they have experienced their pain for many years. Another explanation might be that their cognitive dysfunction makes it difficult for them to express their pain when interviewed. The latter seen to be the most plausible explanation.

9.6 SB and compared with the other diagnostic groups

SB is an early developmental defect. One of the major problems in this diagnostic group is HC, present in about half of the patients included in the study. The prevalence of HC in the study is low compared to other studies. This may be explained by the fact that some patients with HC die during childhood due to shunt-complications (Alatise et al 2006). Another main problem for patients with SB is a cognitive dysfunction causing severities with learning, attention, memory and in social life (Fletcher et al 2002, Iddon et al 2003, Barf et al 2003) thus, it can be difficult to rehabilitate adults with SB.

In study III nociceptive pain was also studied in adults with SB and not only neuropathic pain. The prevalence of nociceptive pain was 26% and it was concluded that it was due to overuse of muscle. Patients with walking capability had back pain. This implies that it is essential to teach the adults with SB to use adequate aids/devices when walking.

9.7 Complications during in hospital rehabilitation/associated injuries

In study IV (traumatic CCS) studied data included different types of vertebral injury, treatment of vertebral lesion, associated injuries complications during the in-hospital rehabilitation. Furthermore, walking capability, FIM, bowel and bladder function, spasticity and LOS were studied. The data give a good understanding of the functional and neurological outcome after traumatic CCS. They showed that half of the patients had associated injuries and that complications occurred in 28% of the cases. Interestingly 58% of the patients with traumatic CCS sustained hyperextension injury without fracture or luxation (Pickett et al 1996). 45% underwent surgical treatment, a low figure when compared with other types of SCI. Nowadays the majority of patients with traumatic SCI are surgically treated (Aito et al 2005). In summary the prognosis is usually good after traumatic CCS but older patients have poorer outcome than younger patients. The length of stay in hospital is long for CCS patients as it is for most of the traumatic SCI patients.
10 GENERAL CONCLUSIONS

-Neuropathic pain is a major problem in patients after traumatic and non-traumatic SCI. It affects the quality of life.

-In traumatic SCI the prevalence of neuropathic pain increases with age at the time of injury.

-No correlation was found between the development of neuropathic pain and level of injury and completeness of injury in both traumatic and non traumatic SCI.

-Age at the time of injury had no impact on spasticity in patients with traumatic CCS.

-No subgroup of SCI with a greater risk of developing neuropathic pain could be identified.

-Patients with CCS are mostly older at time of injury than other traumatic SCI syndromes.

-Adults with SB rarely experience neuropathic and nociceptive pain. Nociceptive pain in patients with SB was mostly back pain in patients with walking capability.

-The most common cause of traumatic CCS was traffic accidents followed by falls.

-The prognosis for patients with CCS is normally good but individuals injured at an older age have a poorer outcome than individuals injured early in life.

-About half of the patients with traumatic CCS underwent surgery after their SCI. This figure is low compared to other traumatic SCI.
11 FUTURE STUDIES

There are several areas in SCI research that need to be further high-lighted.

1) There is a need for a standardized international classification for the taxonomy of pain. In a recently published paper (Treede et al 2007) a definition and a grading system was presented developed by a group of experts from the neurological and pain community. This has to be further evaluated in order to be included in the clinical routine.

2) Concerning pharmacological treatment the important questions are a) when to start pharmacological treatment and which substances to use. Age at the time of injury and pain intensity are factors that play a major role in the choice of pharmacological treatment and have to be further analyzed.

3) Factors associated with neuropathic pain must be identified. Is there a difference between patients stating that their pain has no impact on daily life and patients who classify their pain to be a big problem that affects their quality of life (Hanley et al 2006)? Is neuropathic pain more common in patients with psychiatric diseases or in those who got their SCI after a suicide attempt?

4) Aging with SCI is a very important topic as patients with SCI today can have a normal lifespan. What will happen with pain over time? Will it be more intense due to aging or to other medical complications such as for example arthrosis?

5) In the SB group cognitive impairments and socioeconomic factors need more attention. How can we help young individuals with SB to live a full-worthy life? To find an adequate occupation for these patients is an important task. Today many SB patients live a life apart from the society in general.

Patienter med traumatisk (n=402) och icke-traumatisk ryggmärgsskada (n=95) samt vuxna med ryggmärgsbråck (n=110) som kontrollerades på Spinalismottagningen under åren 1995-2000 ingick. Data insamlades från årskontrollen då patienterna undersöktes och klassificerades enligt ASIA (A-E), neurologisk skadenivå samt intervjuades avseende förekomst av smärta och hur mycket smärten påverkade livskvaliteten. Smärta klassificerades som neuropatisk om kriterier uppsatta av IASP (Internationell Association for the Study of Pain) uppfylldes. Traumatiska och icke-traumatiska ryggmärgsskador indelades i 5 åldersgrupper avseende ålder vid skadetillfället. Icke-traumatiska ryggmärgsskador indelades i fem diagnosgrupper. Vuxna med ryggmärgsbråck indelades efter huruvida hydrocephalus förelåg eller ej.


13 ANALISI DEL DOLORE NEUROPATICO IN PAZIENTI AFFETTI DA LESIONE MIDOLLARE

Lavori inclusi nella ricerca
1. Il dolore neuropatico dovuto ad una lesione midollare traumatica è in relazione al sesso, all’entità della lesione ed all’età del paziente nel momento in cui è insorta la lesione.
2. La prevalenza del dolore neuropatico in seguito a lesione midollare non traumatica.
3. Il dolore neuropatico e muscolosceletrico in adulti con spina bifida in rapporto all’entità della lesione, al livello neurologico, al sesso e alla presenza di idrocefalo.
4. L’outcome neurologico e funzionale nei pazienti affetti da sindrome centromidollare post-traumatica.

Introduzione
Secondo studi fatti in precedenza, la prevalenza del dolore neuropatico, dovuto a lesioni midollari traumatiche e non traumatiche, è variabile.
Il dolore neuropatico in pazienti con diagnosi di spina bifida è meno frequente ed a questo proposito mancano dati.
La sindrome centromidollare è una lesione incompleta che si differenzia dalle altre lesioni midollari e si manifesta soprattutto negli arti superiori.

Obiettivo della tesi
Analizzare la prevalenza del dolore neuropatico in pazienti con lesioni midollari traumatiche e non traumatiche.
Individuare gruppi di pazienti affetti da lesione midollare che corrono un rischio maggiore di sviluppare il dolore neuropatico.
Analizzare in che misura il dolore neuropatico influenzi la loro vita quotidiana.
Definire gli outcome neurologici e funzionali nei pazienti affetti da sindrome centromidollare post-traumatica, diagnosticata clinicamente alla dimissione dall’Unità Spinale di Firenze.

Materiali e metodo

Studi I-III
L’attività principale dello Spinalis è il controllo annuale, durante il quale i pazienti sono esaminati e classificati secondo la scala ASIA, American spinal cord injury association* (vedi nota).
Durante il controllo annuale il paziente deve riferire circa l’eventuale presenza di dolore. Ogni qualvolta ci si trovi di fronte ad un dolore di ordine generale, questo viene classificato come dolore neuropatico, secondo i criteri dettati dal IASP (International Association for the Study of Pain).
In presenza dell’accertamento di un dolore neuropatico, questo viene classificato secondo il livello neurologico. Infine viene chiesto ai pazienti di definire l’intensità del dolore e la misura in cui questo influenza la loro vita quotidiana.
Nella nostra ricerca abbiamo suddiviso i pazienti con lesione midollare traumatica in cinque gruppi, secondo l’età in cui è insorta la lesione.

I pazienti con lesioni midollari non traumatiche sono stati suddivisi a loro volta in cinque gruppi diagnostici ed ulteriormente in altri cinque gruppi a seconda dell’età in cui è insorta la lesione. Gli adulti di età superiore ai 18 anni affetti da spina bifida sono stati suddivisi in due gruppi: a seconda della presenza o meno di idrocefalo.

**Studio IV**

In questa ricerca abbiamo incluso tutti i pazienti che, ricoverati dal 1996 al 2002 con diagnosi di sindrome centromidollare, avevano ricevuto una cura omni-comprensiva presso l’Unità Spinalis di Firenze. I pazienti venivano successivamente chiamati ad una visita di controllo almeno 18 mesi dopo la dimissione.

I dati raccolti all’ammissione erano, oltre a sesso, causa della lesione, lesioni associate, tipo e livello della lesione vertebrale, trattamento conservativo o chirurgico, anche il livello neurologico e l’esame neurologico secondo sia la scala ASIA (A-E) che quella FIM (functional independence measurement).

I dati raccolti al momento della dimissione erano: le eventuali complicazioni durante il ricovero, la gestione vescicale ed intestinale, la scala WISCI (walking index for spinal cord injured individuals) ed il livello neurologico secondo sia la scala FIM che quella ASIA.

Infine i dati raccolti al follow-up erano il livello neurologico, l’esame neurologico, la scala ASIA, WISCI e quella FIM, la gestione vescicale ed intestinale ed inoltre la presenza o meno di dolore e spasticità.

**Risultati**

Il dolore neuropatico era presente nel 40% dei pazienti con lesioni midollari traumatiche. Il 28% accusava dolore inferiormente rispetto al livello neurologico. Il dolore neuropatico era più frequente nei pazienti al di sopra dei quarant’anni al momento della lesione. Durante la ricerca non è stata rilevata nessuna differenza statistica fra uomini e donne e neppure nel dolore neuropatico tra pazienti tetraplegici e paraplegici. Risultati non statisticamente significativi sono stati riscontrati anche quando venivano analizzati pazienti portatori di lesioni complete od incomplete. Circa il 70% di coloro che accusavano dolore dichiaravano che quest’ultimo influenzasse la loro vita quotidiana in modo accentuato.

Il dolore neuropatico era presente nel 38% dei pazienti con una lesione midollare non traumatica ed il 15% accusava dolore neuropatico nel punto della lesione. Le donne accusavano con maggiore frequenza il dolore neuropatico inferiormente rispetto al livello neurologico. L’età non influenzava la prevalenza del dolore neuropatico. Rispetto agli altri gruppi diagnostici, i pazienti con un tumore maligno accusavano più spesso dolore neuropatico. Nel 70% dei pazienti con dolore neuropatico questo veniva considerato un problema più o meno grave nella loro vita quotidiana.

Soltanto l’11% dei pazienti con spina bifida accusava dolore neuropatico. L’idrocefalo era presente nel 52% dei pazienti ed era più frequente in quelli con un livello neurologico toracale e in quelli che avevano una lesione completa (ASIA A).

Per quanto riguarda il dolore, nessuna differenza è stata rilevata tra pazienti con e senza idrocefalo. Lo stesso dicasi per quanto concerne il sesso e l’entità della lesione. Il dolore muscoloschelettrico compariva nel 25% dei pazienti con spina bifida ed era maggiore in quelli che potevano camminare con o senza assistenza, infine il dolore era localizzato soprattutto nella schiena.
L’outcome neurologico nei pazienti con sindrome centromidollare era peggiore nei pazienti che avevano già un’età avanzata al momento dell’incidente, rispetto a quelli più giovani. Il dolore neuropatico era più frequente nei pazienti più anziani. La spasticità era uguale nei due gruppi. La causa più comune della lesione era l’incidente stradale seguito dalle cadute. La lesione associata più frequente era un leggero trauma cranico.

Conclusioni
Questa ricerca vuole dimostrare come il dolore neuropatico sia un sintomo rilevante nei pazienti con lesioni midollari traumatiche e non traumatiche. La maggior parte di loro infatti accusa dolore neuropatico sotto il livello neurologico. In presenza di dolore neuropatico il 70% di essi dichiara che questo influenza in modo determinante la loro vita quotidiana. Nei pazienti con lesioni midollari non traumatiche il dolore neuropatico, sotto il livello neurologico, è più frequente nelle donne che negli uomini. Non è stato rilevato nessun tipo di lesione che comporti un maggior rischio di sviluppare dolore neuropatico. La presenza del dolore neuropatico è significativamente più bassa nei pazienti con diagnosi di spina bifida. Non è stata rilevata nessuna differenza per quello che riguarda il dolore neuropatico tra i pazienti con o senza idrocefalo. Il dolore muscoloscheletrico compare nel 24% dei casi ed è più frequente nei pazienti che possono camminare con o senza assistenza ed è localizzato nella schiena.

Gli anziani con diagnosi di sindrome centromidollare hanno un outcome neurologico e funzionale peggiore ed accusano più spesso dolore a carattere neuropatico rispetto a quelli lesionati in età giovanile. La spasticità compare con la stessa frequenza nei pazienti lesionati in età giovanile che in quelli lesionati in età avanzata. Un’attenta analisi del dolore neuropatico è la premessa per curare i pazienti in modo adeguato e può migliorare notevolmente il risultato della loro riabilitazione in seguito ad una lesione midollare.

*La scala d’ASIA (American Spinal Cord Injury Association) A-E
ASIA A: lesione midollare completa. Questo termine viene utilizzato per descrivere una lesione totale del midollo spinale. In questa situazione si ha una perdita totale della capacità di inviare impulsi nervosi sensoriali e motori.
ASIA B-D: lesione midollare incompleta. Questo termine si riferisce invece ad un danno parziale del midollo spinale. In questa situazione alcune funzioni motorie e sensoriali continuano ad essere attive
ASIA E: funzioni motorie e sensoriali normali
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