Overview

- Epidemiology
- Pathophysiology
- Classification of SCI’s & descriptive terms
- Natural History & functional prognosis
- Treatment Strategies
Spinal Cord Injury

epidemiology

• Incidence: 10-12,000/ yr
• 80-85% males (usually 16-30 y/o), 15-20% female
• 50% of SCI’s are complete
• 50-60% of SCI’s are cervical
• Immediate mortality for complete cervical SCI ~ 50%
Spinal Cord Injury

epidemiology

− Cause
  • MVC 42%
  • Fall 20%
  • GSW 16%

− Gender
  • Male 81%
  • Female 19%

− Level of Education
  • To 8th Grade: 10%
  • 9th to 11th: 26%
  • High School: 48%
  • College: 16%
Etiology of SCI by Age

Employment Status

Percent Employed

Spinal Cord Injury

*pathophysiology*

**Primary injury**
- Initial insult to cord
- Local deformation
- Energy transformation
Spinal Cord Injury

pathophysiology

Secondary injury

- Biochemical cascade
- Cellular processes

*Most acute therapies aim to limit secondary injury cascade*
Secondary Injury

theories

• 1970’s: free radicals

• 1980’s: Ca, opiate receptors
  lipid peroxidation

• 1990/2000’s: apoptosis
  intracellular protein synthesis
  glutaminergic mechanisms
Secondary Injury Cascade

current understanding

INJURY → GLUTAMATE RELEASE

Ca++ INFLUX

NMDA receptors

Thrombin

PETECHIAL HEMORRHAGE

Phospholipase activation

Arachidonic acid

PROSTAGLANDIN SYNTHETASE ACTIVITY → O2•−

PGF_{2α} → TXA₂ → PGI₂

Gray matter ischemia

Hypoxic free radical generation (O_{2•−}, OH)

Lactic acidosis

Fe^{+++} release

Hemoglobin

LIPID PEROXIDATION

MICROVASCULAR DAMAGE

Spread to white matter

Ischemia

MYELIN/AXONAL DAMAGE

PERMANENT NEUROLOGICAL DEFICIT
Definitions

Spinal shock:
• transient flaccid paralysis
• areflexia (including bulbocavernosus reflex)
• while present (usually <48 h), unable to predict potential for neurological recovery.

Neurogenic Shock:
• Loss of sympathetic tone, vasomotor and cardiac regulation.
• Hypotension with relative bradycardia.
**Classification**

**Complete**
- absence of sensory & motor function in lowest sacral segment after resolution of spinal shock

**Incomplete**
- presence of sensory & motor function in lowest sacral segment (indicates preserved function below the defined neurological level)
ASIA Examination

Motor level (MLI) = lowest normal level with 3/5 strength (& level above = 5/5)
Each muscle has 2 root innervations, 3/5 strength = full innervation by the more rostral root level.
(4/5 acceptable with pain, de-conditioning)

- Motor Index Score (MIS) = total 100 pts
- **Superiority of Motor level versus Sensory Level
Neurologic Examination

- American Spinal Injury Association (ASIA)
  - A = Complete – No Sacral Motor / Sensory
  - B = Incomplete – Sacral sensory sparing
  - C = Incomplete – Motor Sparing (<3)
  - D = Incomplete – Motor Sparing (>3)
  - E = Normal Motor & Sensory
ASIA Sensory Exam

- 28 sensory “points” (within dermatomes)
- Test light touch & pin-prick pain

**Importance of sacral pin testing**

- 3 point scale (0,1,2)
- “optional”: proprioception & deep pressure to index and great toe (“present vs absent”)
- deep anal sensation recorded “present vs absent”
Motor Examination

- 10 “key” muscles (5 upper & 5 lower extremity)

  C5-elbow flexion  L2-hip flexion
  C6-wrist extension  L3-knee extension
  C7-elbow extension  L4-ankle dorsiflexion
  C8-finger flexion  L5-toe extension
  T1-finger abduction  S1-ankle PF

  Sacral exam: voluntary anal contraction (present/absent)
Motor Grading Scale

- 6 point scale (0-5) ..... (avoid +/-’s)
  - 0 = no active movement
  - 1 = muscle contraction
  - 2 = active movement without gravity
  - 3 = movement thru ROM against gravity
  - 4 = movement against some resistance
  - 5 = movement against full resistance
# STANDARD NEUROLOGICAL CLASSIFICATION OF SPINAL CORD INJURY

## MOTOR

| C2 | C3 | C4 | C5 | C6 | C7 | C8 | T1 | T2 | T3 | T4 | T5 | T6 | T7 | T8 | T9 | T10 | T11 | T12 |
|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
|    |    |    |    |    |    | Elbow flexors | Wrist extensors | Elbow extensors | Finger flexors (distal phalanx of middle finger) | Finger abductors (little finger) |    |    |    |    |    |    |    |

**KEY MUSCLES**

- 0 = total paralysis
- 1 = palpable or visible contraction
- 2 = active movement, gravity eliminated
- 3 = active movement, against gravity
- 4 = active movement, against some resistance
- 5 = active movement, against full resistance

**NT** = not testable

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## SENSORY

| C2 | C3 | C4 | C5 | C6 | C7 | C8 | T1 | T2 | T3 | T4 | T5 | T6 | T7 | T8 | T9 | T10 | T11 | T12 |
|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
|    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |

**KEY SENSORY POINTS**

- **0** = absent
- **1** = impaired
- **2** = normal
- **NT** = not testable

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**TOTALS**

- **MOTOR SCORE** (maximum) 50 (50) (100)
- **LIGHT TOUCH SCORE** (maximum) 56 (56)
- **PIN PRICK SCORE** (maximum) 112

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**NEUROLOGICAL LEVEL**

The most caudal segment with normal function

**COMPLETE OR INCOMPLETE?**

Incomplete = Any sensory or motor function in S4-S5

**ZONE OF PARTIAL PRESERVATION**

Caudal extent of partially innervated segments

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Classification

Incomplete SCI syndromes

Central Cord Syndrome

- Motor loss UE>LE
- Hands affected
- Common in elderly w/ pre-existing spondylosis and cervical stenosis.
- Substantial recovery can be expected.
Classification
Incomplete SCI syndromes

Brown Sequard
- Ipsilateral motor, proprioception loss.
- Contralateral pain, temperature loss.
- Penetrating injuries.
- Good prognosis for ambulation.
Classification

Incomplete SCI syndromes

Anterior Cord Syndrome

- Motor loss
- Vibration/position spared
- Flexion injuries
- Poor prognosis for recovery
Classification

Incomplete SCI syndromes

Posterior Cord Syndrome

• Profound sensory loss.
• Pain/temperature less affected.
• Rare.
Classification

Other SCI syndromes

Conus Medullaris Syndrome

- Loss of bowel or bladder function
- Saddle anaesthesia
- Looks like cauda equina
- Skeletal injuries T11-L2
Expected Neurorecovery
Complete Tetraplegia

- Little chance for functional motor recovery in LE’s
- extent of neurorecovery in UE’s determines functional independence
Expected Neurorecovery

Complete Tetraplegia

• 70-85% chance of gaining at least one additional level

• Motor grade 2/5 for a given level @1 week, all gained functional strength at next level

Ditunno, Arch Phys Med Rehabil, 2000
Expected Neurorecovery

Incomplete Tetraplegia

- >90% gain at least one UE motor level
- If pinprick spared in same dermatome, 92% chance of recovery to ≥ 3/5 motor strength

Ditunno, Arch Phys Med Rehabil, 2000
Poynton, JBJS-Br, 1997
Expected Neurorecovery

Incomplete Tetraplegia

- Majority of improvement in first 6-9 months.

Despite the Medical Advances of the last 50 years, Prediction of Functional Capacity Based on Neurologic Level is still similar to that described in:

Functional Capacity
C1-C4

• C1-C3 need mechanical ventilation (portable vent or phrenic nerve stimulator)

• C4 may need CPAP or Bi-PAP for nocturnal hypoventilation
Functional Capacity
C1-C4

- Dependent for self-care and transfers.
- Motorized wheelchair with special controls
  - mouthsticks (C3-C4)
  - infrared
  - sip-and-puff
Functional Capacity

C5

- Active elbow flexion present

- Capable of some simple ADL’s with appropriate setup:
  - Eat with balanced forearm orthosis.
  - Write and type with opponens splint.

- Still dependent for transfers % bed positioning
Functional Capacity

C6

- Added shoulder stability due to rotator cuff innervation.
- Active wrist extension (extensor carpi radialis).
- Tenodesis grip: passive finger flexion and thumb opposition with wrist extension.
- Tenodesis grip strengthened with flexor-hinge orthosis.
Functional Capacity

C6

- Improved capability for self-feeding.
- Self-catheterization (males), bowel programs required.
- Upper body dressing possible.
- Lower body dressing difficult.
- Assistance for transfers, bed mobility.
Functional Capacity

C7

- Functional strength in triceps.
- Can roll over, move in seated position, transfer.
- Can eat independently (except cutting).
- Long distance manual wheelchair propulsion.
Functional Capacity
C8-T1

- Intrinsic hand function.
- Improved grasp and dexterity.
- Independent bed mobility & transfers.
- Independent for ADL’s.
Functional Capacity
Thoracic Paraplegia

- Abdominal strength beginning at T6.
- Sitting balance improved.
- Bipedal ambulation with KAFO & walker (swing-to gait pattern).
- Energy consuming, difficult for community use.
Ambulation after SCI

Motor Requirements

- Grade $\geq 3/5$ strength in hip flexors on one side
- Grade $\geq 3/5$ strength in quadriceps on other side
Ambulation after SCI

Incomplete Injuries

Community ambulators @ 1 year:
- 46% of incomplete tetraplegics
- 76% of incomplete paraplegics

Waters, Arch Phys Med Rehabil, 1994
Treatment Strategies
*(current & future)*

**Acute Stage Therapies:**

- Optimize critical care management
- Modulate the secondary injury cascade
- Includes steroids, Sygen, hypothermia
Treatment Strategies
(current & future)

Subacute Stage Therapies

- Modify the environment of adult CNS which inhibits neural tissue recovery.
- Includes peripheral nerve grafts, olfactory ensheathing cells, activated macrophages.
Optimize Critical Care Management

- Acute respiratory failure has been observed in patients after external immobilization for displaced odontoid fractures.
- 32 patients with posteriorly displaced fractures, 13 experienced acute respiratory compromise, whereas only one of 21 patients with anteriorly displaced fractures had respiratory difficulties ($p = 0.0032$).
  - All 13 were initially managed using flexion traction for reduction of these fractures.
- Two of these patients died because of failure to emergently secure an airway during closed treatment of the fracture.
- Frequent respiratory deterioration during acute closed reduction of posteriorly displaced Type II odontoid fractures was observed, whereas respiratory failure in patients with anteriorly displaced fractures was rare.
- **Manage the airway!**

Myth of Myelopathy

- No clear case of spinal cord injury after direct laryngoscopy in English language literature
  - McLeod and Calder Criteria
- All airway maneuvers cause some motion at fracture site
  - Lessened with manual in line immobilization
  - Increased with increasing instability
- Fiberoptic intubation minimizes displacements
  - May still require direct laryngoscopy
  - May require surgical airway

Crosby, E. Airway Management in Adults After Cervical Spine Trauma. *Anaesthesiology*. 2006
Incidence and Clinical Predictors For Tracheostomy After Cervical Spinal Cord Injury: A National Trauma Databank Review.

• After CSCI, a fifth of patients will require tracheostomy.
• Intubation on scene or ED, complete CSCI at C1-C4 or C5-C7 levels, ISS ≥16, facial fracture, and thoracic trauma were independently associated with the need for tracheostomy.
• Patients requiring tracheostomy had a higher Injury Severity Score (ISS) and required intubation more frequently on scene and Emergency Department (ED)
• Patients requiring tracheostomy had higher rates of complete CSCI at C1-C4 and C5-C7 levels
• Patients requiring tracheostomy had more ventilation days, longer intensive care unit and hospital lengths of stay, but lower mortality.

Breathing

• Of patients with CSCI above C5, 87.5 per cent required intubation compared with 61 per cent of patients with CSCI at C5-C8 (P = 0.026).

• Similarly, of patients with complete quadriplegia, 90 per cent required intubation compared to 48.5 per cent of patients with incomplete quadriplegia or paraplegia (P < 0.001).

• There were 3 independent risk factors for the need of intubation:
  – Injury Severity Score > 16
  – CSCI higher than C5
  – Complete quadriplegia.

• The combination of the 2 latter risk factors resulted in intubation in 21 of 22 patients (95%).

• The majority of patients with CSCI require intubation.

• In patients with CSCI above C5 and complete quadriplegia, intubation should be offered routinely and early because delays may cause preventable morbidity.

Intubation after cervical spinal cord injury: to be done selectively or routinely?

Circulation

- Early appropriate fluid resuscitation is necessary to maintain tissue perfusion
  - Avoid fluid overload!
- Appropriate resuscitation endpoint and optimal mean arterial blood pressure for maintenance of spinal cord perfusion are not known
  - Uncontrolled studies using vasopressin to maintain a MAP of 85 for 7 days have shown improved outcomes
Steroids

methylprednisolone sodium succinate

- Large body of animal studies
- Various neuroprotective mechanisms postulated
Neuroprotection w/ MPSS

- Preservation of Spinal Cord Blood Flow
- Preservation of Aerobic Metabolism
- Inhibition of Lipid Peroxidation
- Attenuation of delayed Glutamate release
- Preservation of Na, K Homeostasis
- Inhibition of Calpain-mediated Cytoskeletal damage
- Preservation of Calcium Homeostasis
National Acute Spinal Cord Injury Studies

**NASCIS II**
- 10 hospitals, 487 patients
- Compared:
  - MPSS (30 mg/kg bolus + 5.4 mg/kg x 23°)
  - Naloxone (5.4 mg/kg bolus + 4.5mg/kg x 23°)
  - Placebo
- ≤ 8 hours, steroids ⇒ neurologic improvement
- Infections, PE ↑ but not significant

**NASCIS III**
- 16 hospitals, 499 patients
- 3 treatment arms (all got MPSS bolus)
  - MPSS 5.4 mg/kg 24 hrs
  - MPSS 5.4 mg/kg 48 hrs
  - Tirilazad 2.5 mg/kg Q6 hr for 48 hrs
- 48 hr protocol better than 24 hr protocol (*if treated between 3 and 8 hours*)
- 2x incidence of pneumonia, sepsis in 48 hr group (NS)


Bracken, JAMA, 1997
Bracken, J Neurosurg, 1998
Criticism of NASCIS II

- All primary outcomes (-)
  (no diff in neuro improvement between grps)
- (+) findings only in post-hoc analyses
  (arbitrary stratification to before or after 8hrs)
- Only 38% of original enrollment included
- <8 hr control group poor results
- Treatment effect small
- Inappropriate statistics
  60 t-tests
  no correction
  Parametric
- 6 mo results reported in media
- Prior to peer-review publication
- 1 yr results less encouraging
Criticism of NASCIS III

- Primary outcomes negative (no diff in treatment among groups)
- All positive findings in post hoc analyses (when arbitrarily divided into <3hr/ >3 hr)
- Treatment effects small
- Effect NS @ 1yr
- ? Inappropriate statistics
• Monosialotetrahexosylganglioside GM1 sodium salt

• Found in CNS cell membranes
SYGEN®

experimental models

- Acute neuroprotection
- Anti-excitotoxic
- Potentiates neuritic sprouting

Roisen, 1981
Agnati, 1983
Toffano, 1983
Fass, 1984
Schneider, 1998

- Single center trial, 37 pts: promising
- Multicenter trial, 800 pts: disappointing

Geisler, Spine, 2001
Acute Neuroprotective Agents

new areas of interest in household drugs

minocycline

erythropoietin

Recombinant human erythropoietin counteracts secondary injury and markedly enhances neurological recovery from experimental spinal cord trauma

Neuroprotection by minocycline facilitates significant recovery from spinal cord injury in mice

Lipitor

Attenuation of Acute Inflammatory Response by Atorvastatin After Spinal Cord Injury in Rats

Ravinder Pannu, Ernest Barbosa, Avtar K. Singh, and Inderjit Singh
Pharmacologic Neuroprotection in Patients with SCI

- No clinical evidence exists to definitively recommend the use of any neuroprotective pharmacologic agent, including steroids, in the treatment of acute SCI to improve functional recovery. *(Scientific evidence–NA; Grade of recommendation–NA; Strength of panel opinion–5)*

- If it has been started, stop administration of methylprednisolone as soon as possible in neurologically normal patients and in those whose prior neurologic symptoms have resolved to reduce deleterious side effects. *(Scientific evidence–NA; Grade of recommendation–NA; Strength of panel opinion–5)*
Subacute Stage Therapies
modify environment of adult spinal cord

OBSTACLES TO REGENERATION

1. POOR REGENERATIVE RESPONSE at the level of the cell body
   - Failure to sufficiently express regeneration associated genes and trophic factors
   - GAP-43, CAP-23, Tα1-Tubulin
   - BDNF, FGF-2
   - Atrophy/death of neurons

2. ENVIRONMENTAL INHIBITORS at the level of the injured axon
   - Glial Scar
     - chondroitin sulfate proteoglycans
     - semaphorins, ephrins
   - Cyst / Cavitation
     - neuronal and glial death
   - Myelin Inhibitors
     - NOGO, MAG, O9
     - Myelin Inhibition
     - Anti-NOGO antibodies
     - Immunologic disruption
   - Growth Cone Signalling
     - Rho/ROCK inhibition
     - cAMP, cGMP
   - Cellular Bridges
     - Fetal tissue
     - Schwann cells
     - Stem cells
     - Olfactory ensheathing cells

THERAPEUTIC STRATEGIES TO PROMOTE REGENERATION
Augmentation of Regenerative Ability of CNS Neurons

Neurotrophic Factors

- Epidermal growth factor
- Fibroblast growth factor 2
- BDGF: brain derived growth factor
- Cyclic AMP

Kojima, J Neurotrauma, 2002
Inhibitors of Neurite Outgrowth

• ECM molecules in CNS myelin

• Glial scar/ cystic cavity that forms at injury site

Jones, J Neuroscience, 2002
Cellular substrates

- Bridge the gap across cystic cavity glial scar.
- Facilitate axonal regeneration in the face of various inhibitors.
Peripheral Nerves

*Rat Model*

- Multiple intercostal nerve grafts
- Stabilized w/ fibrin glue & FGF
- Redirect white matter proximal to gray matter distal

Cheng, Olsen, Science, 1996
Olfactory-ensheathing glial cells

- Unique ability to regenerate in adults
- “Escort” axons across CNS-PNS boundary
- May support axonal regeneration after SCI
Stem Cell Therapy

- Ongoing studies of adult mesenchymal stem cell therapy
- Animal studies are promising
- Human trials are lacking

3 weeks post-implantation, the adult neural stem cells implanted in the spinal cord.
Activated Macrophages

Macrophages play an important role in the successful regeneration of injured peripheral nerves by clearing cellular debris.

- Injure spinal cord of rats
- Extract macrophages from blood
- "Activate" them by exposing them to peripheral nerve
- Implant into spinal cord.

Activated macrophages result in significant functional recovery.

Proneuron, activated macrophages, now in clinical trials.

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