Cerebral Palsy

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February 7, 2008

What is Cerebral Palsy?

Any neurological disorder appearing in childhood that permanently affects movement and coordination but doesn't worsen over time

History of Cerebral Palsy

- 1860s Little's disease

  Thought to be due to oxygen deprivation during birth

- 1897 Sigmund Freud disagreed

  "Difficult birth, in certain cases, is merely a symptom of deeper effects that influence the development of the fetus."

- 1980s NINDS retrospective analysis

  <10% of cerebral palsy cases associated with difficult birth

Epidemiology

- 10% of surviving low-birth weight (<1500g) babies will develop cerebral palsy
- Incidence: 2 per 1000 live births
- Prevalence: 2.3 per 1000 children
- Male to Female Ratio 1.33 to 1
- 10,000 diagnosed each year in U.S.
- Average lifetime cost: $921,000 [$2003]

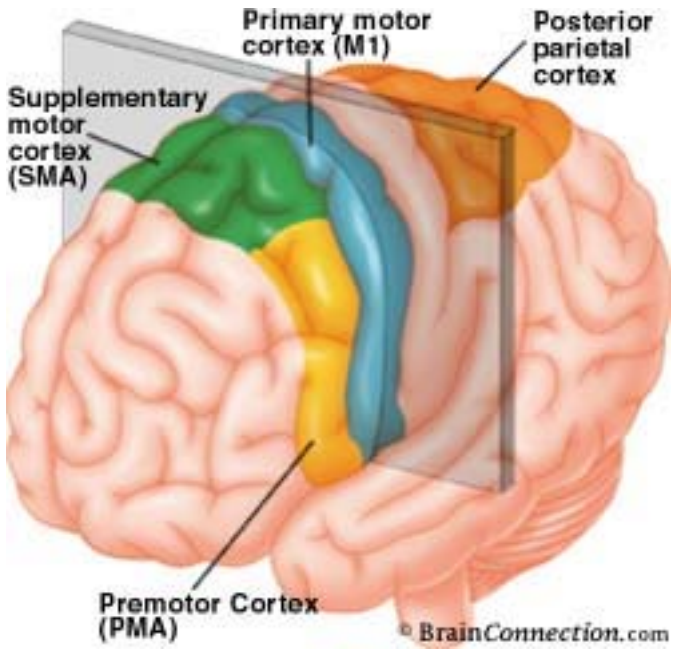
Symptoms of Cerebral Palsy

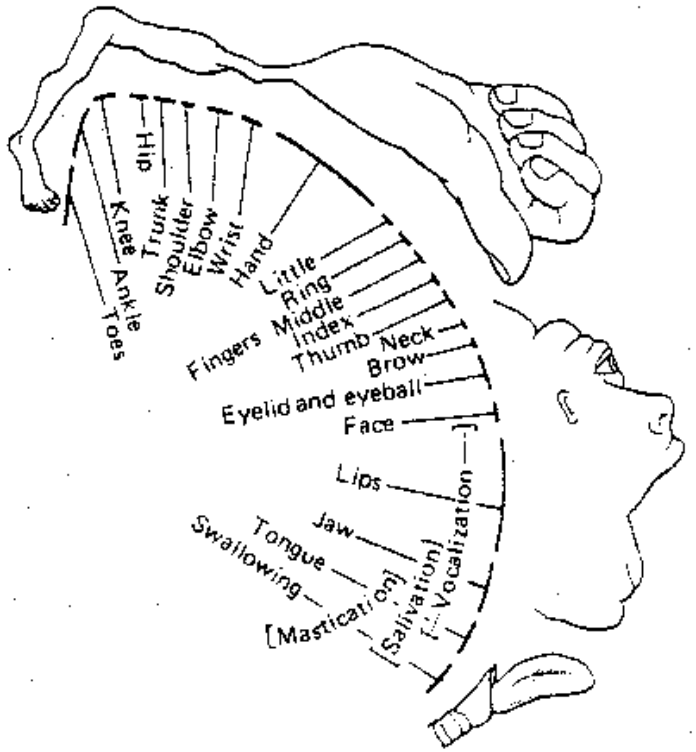
- Primary symptoms
  - ***Ataxia*** (lack of muscle coordination during voluntary motion)
  - ***Spacticity*** (stiff muscles, exaggerated reflexes)
  - ***Hypotonia*** (floppy baby) or ***hypertonia*** (stiff baby)
  - ***Dyskinesia*** (random involuntary movements)
  - ***Tremor*** (shaking)
  - Leg dragging, walking with one foot
  - Crouched gait, “scissored” gait, walking on toes
  - Drooling, difficulty swallowing or speaking
  - Difficulty with precise motions
- Non-progressive
- Onset prior to 3 years of age

Developmental Delay

Classification of Cerebral Palsy

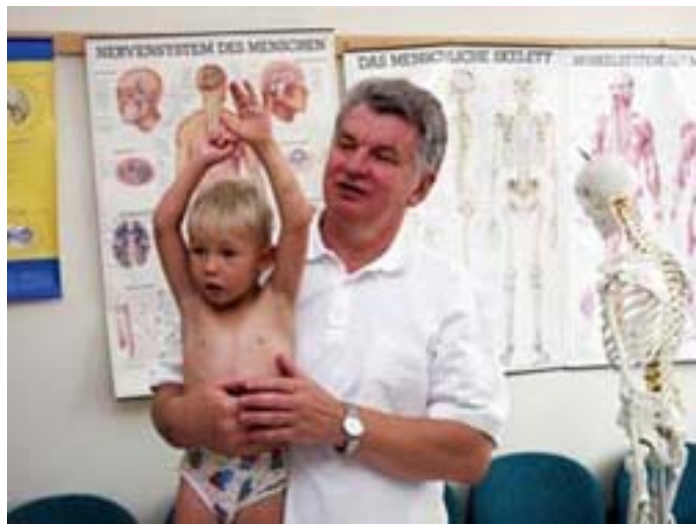
Determined by extent, type, and location of child's abnormalities





Classification of Cerebral Palsy

- **Spastic hemiplegia/hemiparesis**
  - Affects contralateral arm and hand, sometimes leg
  - Scoliosis and seizures may be present
  - Delayed and garbled speech, but intelligence usually normal



Classification of Cerebral Palsy

- **Spastic diplegia/diparesis**
  - Affects contralateral leg
  - Hyperactive tendon reflexes, toes point up, scissor-gait
  - Intelligence and language usually normal

Classification of Cerebral Palsy

- **Spastic quadriplegia/quadriparesis**
  - Widespread damage to brain or significant brain malformation
  - Moderate to severe mental retardation common
  - Severe stiffness in limbs but floppy neck, rarely able to walk
  - Frequent seizures

Classification of Cerebral Palsy

- **Dyskinetic**
  - Also includes *athetoid*, *choreoathetoid*, and *dystonic* CP
  - Uncontrollable writhing movements make walking difficult
  - Intelligence usually normal, although speech may be affected
- **Ataxic**
  - Poor coordination
  - Wide-based gait (walk with legs unusually far apart)
  - Difficulty with precise movements
  - May have *intention tremor*
- **Mixed Types**

Associated Symptoms

- **Mental Retardation**

  - Present in 30-60% of cerebral palsy patients

  - More common in spastic quadriplegia

  - Usually have abnormal EEG and/or MRI

- **Seizure Disorder**

  - Present in up to 50% of cerebral palsy patients

  - May be tonic-clonic seizures or partial seizures (only symptoms may be muscle twitches and weakness)

  - Usually have abnormal EEG and/or MRI

- **Delayed Growth and Development**

Associated Symptoms

- **Impaired vision, hearing, speech**

  - Strabismus (difference in muscle tone in L & R eye muscles causes misalignment)

  - Hemianopia (defective vision or blindness in one eye)

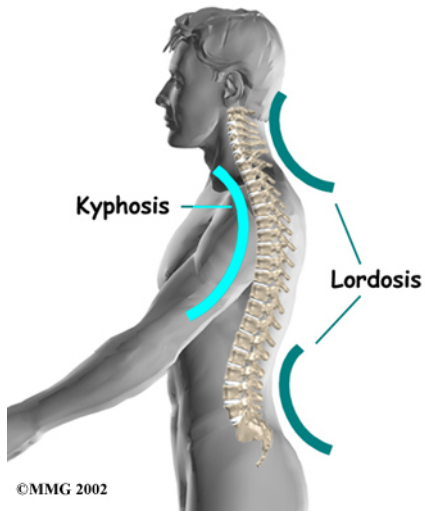
  - Homonymous hemianopia (blindness in same part of visual field in both eyes)

- **Spinal Deformities**

  - Scoliosis (curvature)

  - Kyphosis (humpback)

  - Lordosis (saddle back)



Associated Symptoms

- **Drooling**

  - Poor control of muscles of throat, mouth, and tongue

- **Incontinence**

  - Poor control of bladder muscles

- **Abnormal sensations and perceptions**

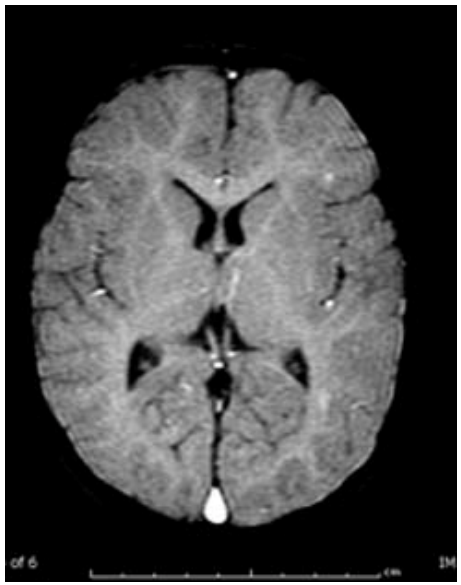
  - Sterognosia (difficult to perceive objects using only touch)

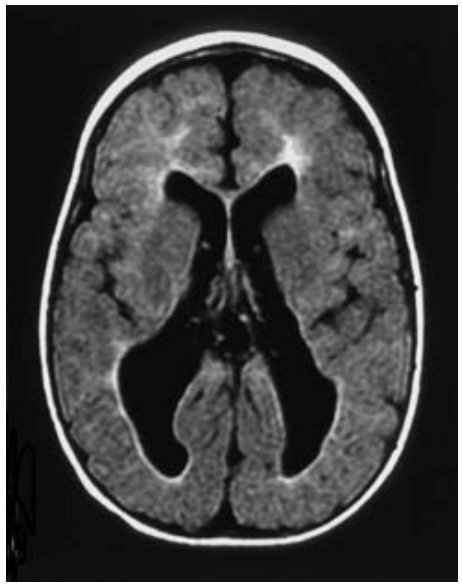
What causes cerebral palsy?

Types of Brain Damage Resulting in Cerebral Palsy

- ***Periventricular Leukomalacia***
  Damage to the white matter of the brain
- ***Cerebral Dysgenesis***
  Abnormal development of the brain
- ***Intracranial Hemorrhage***
  Bleeding in the brain
- ***Hypoxic-Ischemic Encephalopathy***
  Lack of oxygen in the brain

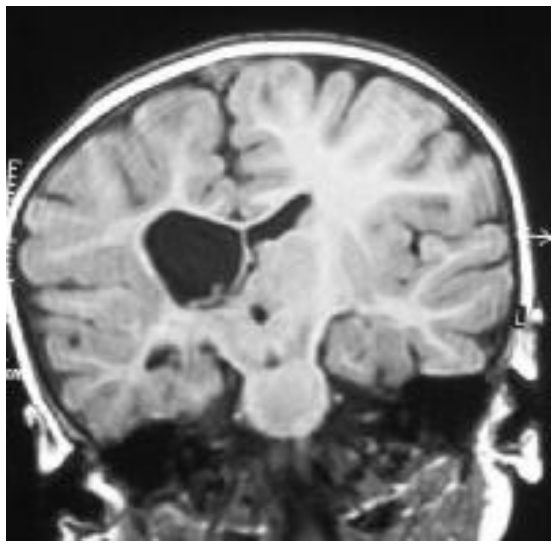
Periventricular Leukomalacia





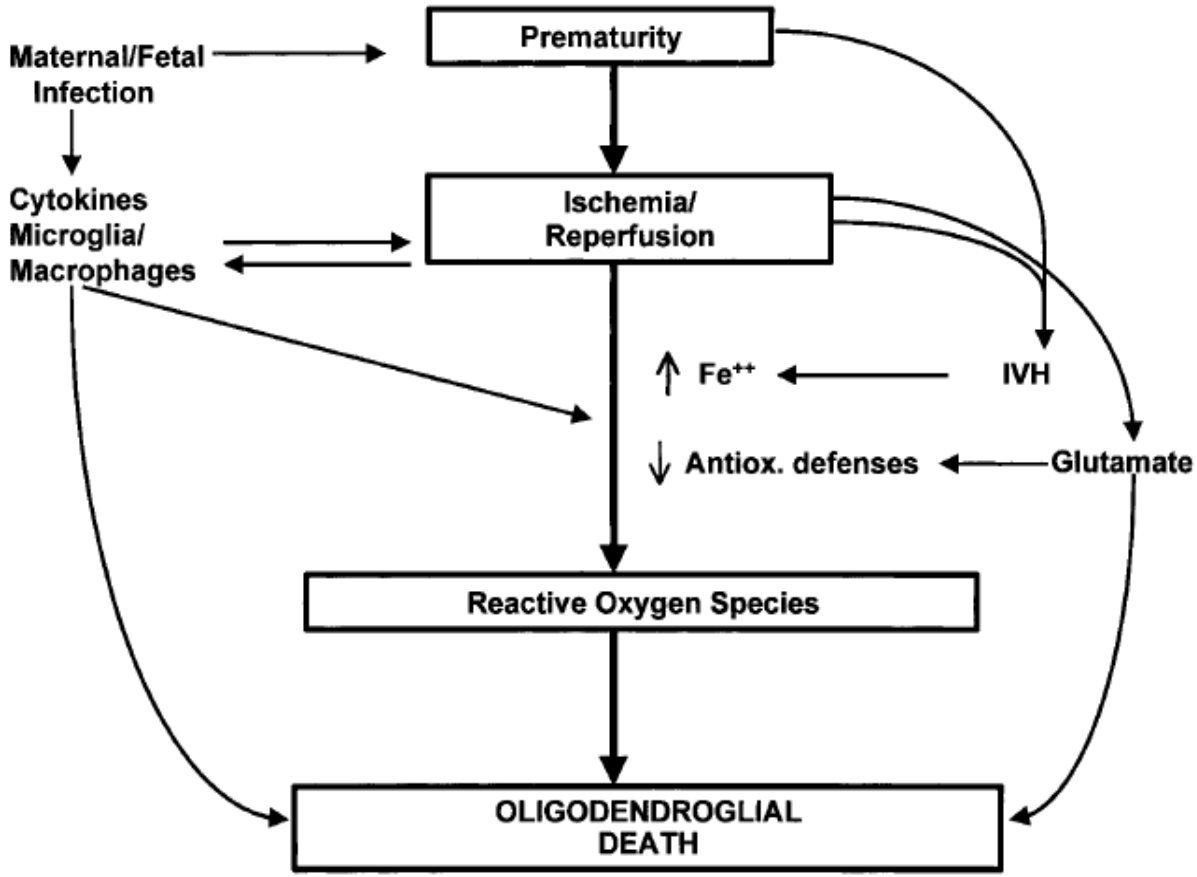
Oligodendrocyte precursor death due to moderate ischemia

Vulnerability period: 24-36 weeks



Diffuse PVL tends to occur in the border zones between long penetrating arteries and the end zones of short penetrating arteries

Periventricular Leukomalacia



Cerebral dysgenesis

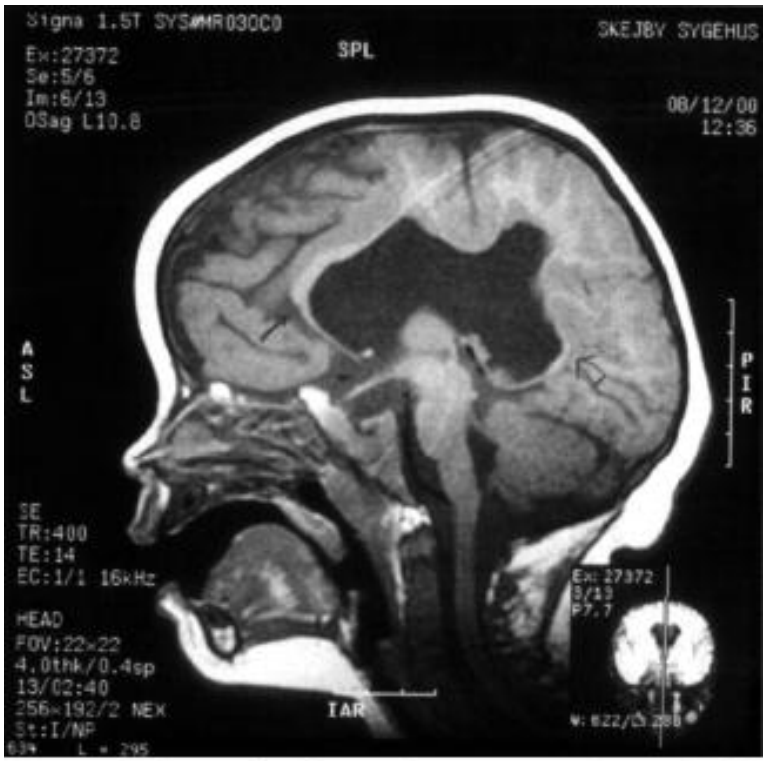


Fig. 1. *Sagittal T1 weigted image shows an apparently normal callosal splenium (open curved arrow) and genu (closed curved arrow), but an absent callosal body.*

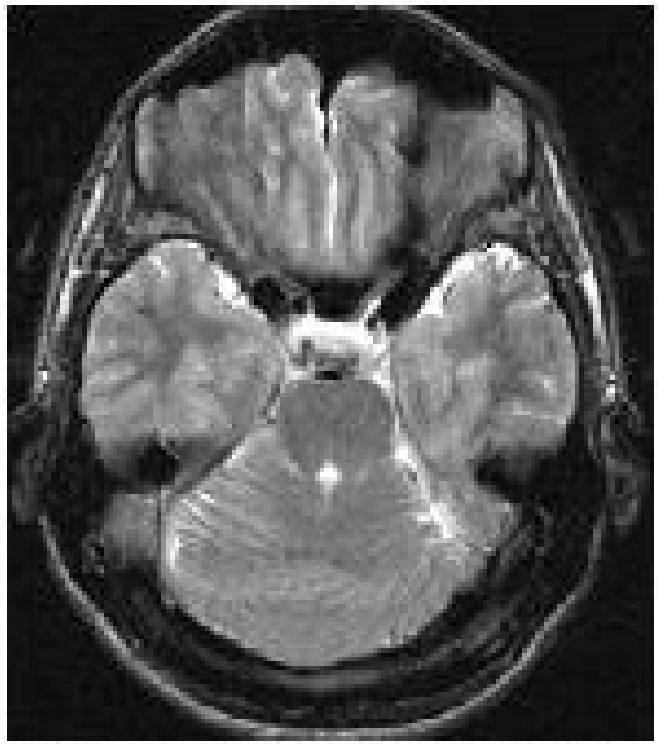
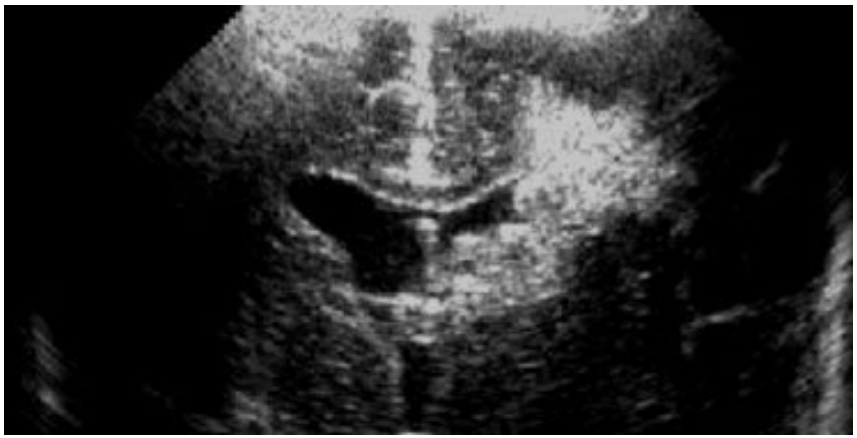


Fig. 2. *Rhombencephalosynapsis*

Intracranial Hemorrhage



Intracranial hemorrhage

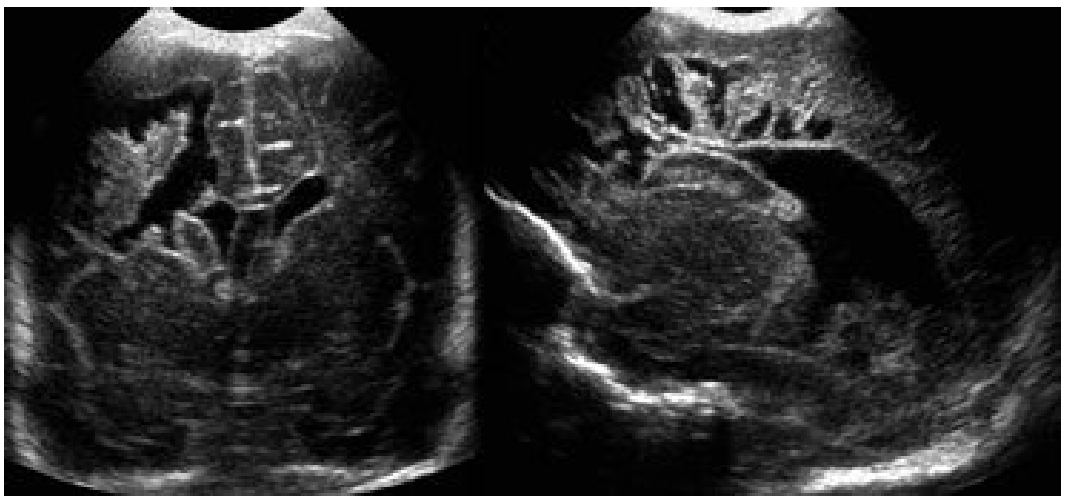
Classification according to Papile

Grade 1. Hemorrhage limited to subependymal matrix

Grade 2. Hemorrhage extending into ventricular system, < 50%, without acute ventriculomegaly

Grade 3. Hemorrhage extending into ventricular system, with acute dilatation because of flooding of 50% or more of one or both lateral ventricles

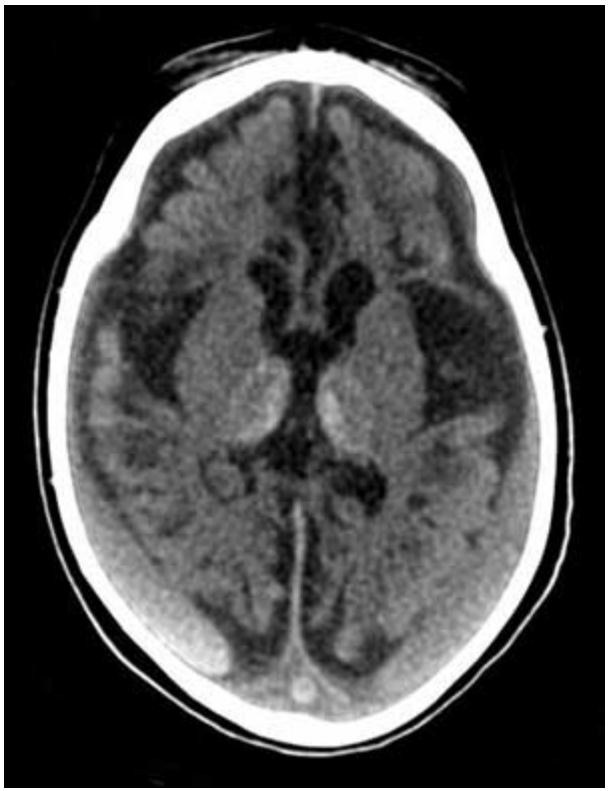
Grade 4. Hemorrhage grade 1, 2 or 3 with extension into brain tissue

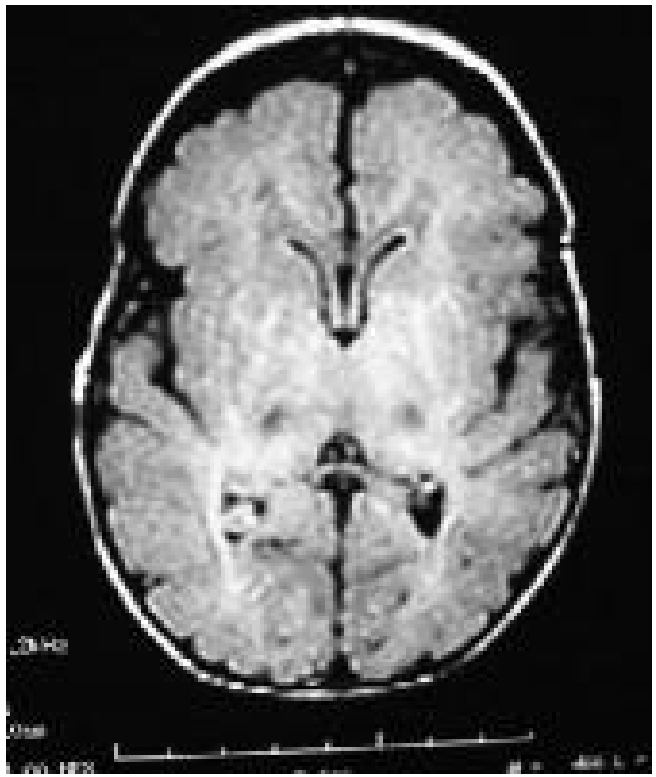


Infants <32 weeks

Infants <1500g

Hypoxic-Ischemic Encephalopathy





Risk Factors for Cerebral Palsy

- **Low birthweight and premature birth.**
  - Higher risk for babies who weigh less than 5 ½ pounds at birth or are born less than 37 weeks into pregnancy

- **Multiple births**
  - Increased risk even for those born at term
  - Death of a baby's twin or triplet further increases the risk.

- **Infections during pregnancy** **TORCH Syndrome**
  - Toxoplasmosis, *rubella*, cytomegalovirus, and herpes
  - O = other agents
  - Maternal infection leads to elevated levels of cytokines, triggering inflammation which may to cause central nervous system damage in an unborn baby.

- **Blood type incompatibility.**
  - *Rh incompatibility* is routinely tested for and treated in the United States ,but conditions in other countries continue to keep blood type incompatibility a risk factor for cerebral palsy.

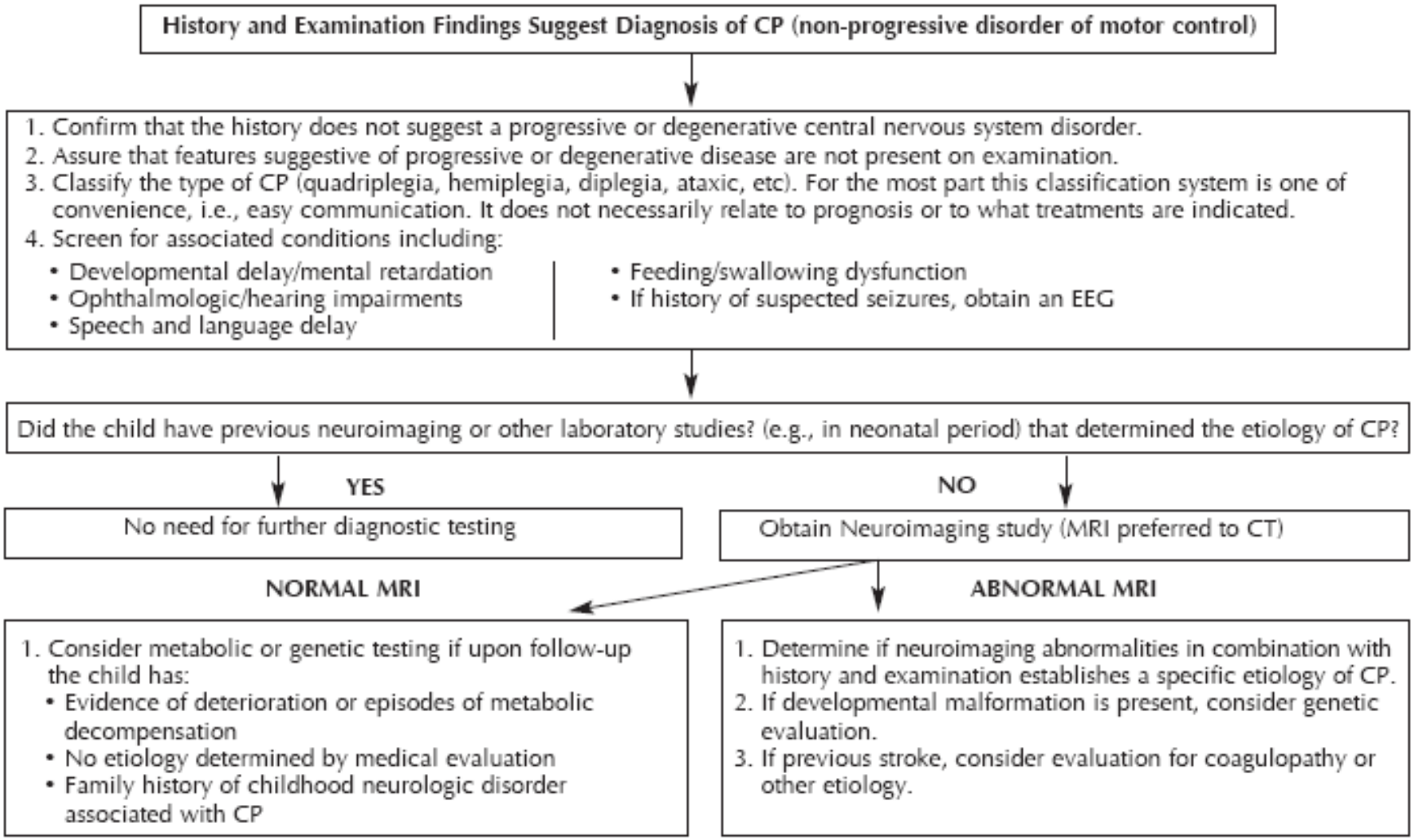
Risk Factors for Cerebral Palsy

- **Exposure to toxic substances**
- **Mothers with thyroid abnormalities, mental retardation, or seizures.**
- **Increased risk during labor and delivery**
  - Breech presentation
  - Complicated labor and delivery
  - Small for gestational age
  - Low *Apgar score*. A low score at 10-20 minutes after delivery is often considered an important sign of potential problems such as cerebral palsy.
- **Jaundice**
  - 50% of newborns develop jaundice after birth due to bilirubin build-up
  - Severe, untreated jaundice can cause a neurological condition known as *kernicterus,* which kills brain cells and can cause deafness and cerebral palsy.
- **Seizures**

Clinical Management of Cerebral Palsy

Diagnosis of CP

AMERICAN ACADEMY OF NEUROLOGY
1080 Montreal Avenue • St. Paul, MN 55116
www.aan.com • www.thebrainmatters.org
(651) 695-1940



Physical and Occupational Therapy

- Physical Therapy

  - Prevent disuse atrophy

  - Prevent contracture (often in combination with braces to stretch spastic muscles)

  - Strength training, other exercise programs

- Occupational Therapy

  - Activities of daily living: eating, dressing, using bathroom

  - Boosts self-reliance, self-esteem

Speech and Language Therapy

- 20% of children with cerebral palsy unable to produce intelligible speech
- Exercises to master difficult sounds
- Social skills of communication
- Computer with voice synthesizer for children with severe disabilities

Treatment for eating and swallowing difficulties

- Children with cerebral palsy at risk for:
  - Gastroesophageal reflux disease,
  - Recurrent lung infections due to inhalation of food or liquid
  - Malnutrition
- Modified barium swallow study to evaluate swallowing ability
- Diet modifications, intra-oral devices
- Gastrostomy in severe cases of malnutrition

Pharmaceutical Treatments

- Relaxation of spastic muscles
  - Baclofen
  - Diazepam
  - Dantrolene sodium
  - Tizanidine
  - *Botulinum* toxin (BT-A) injections
- Intrathecal baclofen

Surgical Treatments

- Orthopedic surgery

  - Gait analysis: cameras to record motion, force plates that detect when and where feet touch the ground, *electromyography* to measure muscle activity

  - Surgical lengthening of problem muscles and tendons

- Selective dorsal rhizotomy

  - Severe cases when other therapies fail to reduce spasticity or chronic pain

  - Selectively severs over-activated nerves

  - Side effects: numbness, sensory loss, phantom sensations

Social Impact of Cerebral Palsy

CP patient challenges

- Workplace activities
- Depression
- Pain & post-impairment syndrome
- Incontinence
- Drooling
- Medical complications
  - Osteoarthritis, degenerative arthritis
  - Premature aging
  - Hypertension
  - Peridontal disease

CP Parent Challenges

- Denial, anger
- Guilt
- Lack of time
- Fatigue
- Depression
- Financial distress

Basic Science Research

Approaches

Any neurological disorder appearing in childhood that permanently affects movement and coordination but doesn't worsen over time.

Low Birth Weight	**Premature Birth**	**Maternal Infection**
Multiple Pregnancies	**Toxicity**	**Complicated Birth**
Hypoxia	**Ischemia**	**Asphyxia**

All converging on damage to motor cortex…

How does one approach a disorder with such heterogeneous phenotypes and causations?

Approaches

Pick which aspect of the disease to study…

Hypoxia? **Ischemia?** **Inflammation?**

Periventricular Leukomalacia? **Perinatal Stroke?**

White matter damage? **Gray matter damage?**

Then choose a method…

1. postmortem studies (34 hits)
   - gross pathology
   - histology/morphometry
2. *in vivo*
   - animal models (99 hits)
   - neuroimaging studies (87 hits)
3. *in vitro* (57 hits, 1/4 actually tissue culture)

Animal Models

There are no perfect animal models.

Does the model manifest the same pathological features?

Are long-term clinical manifestations present?

Can the model produce possible clinical interventions?

The first animal model of CP - asphyxia in fetal monkey in late 1950s.

Current (common) animal models include:
- hypoxia and/or ischemia
- asphyxia
- lipopolysaccharide exposure in utero to induce inflammation
- premature birth plus “neonatal intensive care” for 2-3 weeks in baboons

Current animals include rodents, rabbits, pigs, sheep, and primates. In general, the larger the animal, the greater the validity.

In vitro studies

Answers mechanistic questions

1. culture tissue of interest (i.e. developing white matter)
2. add experimental factor - over/under-expression of a protein, hypoxia and/or ischemia, hyperoxia, lipopolysaccharides
3. measure response - necrosis/apoptosis, increase/decrease in protein expression

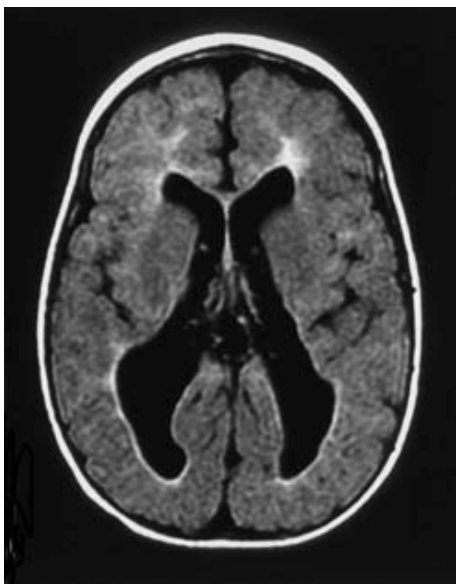
Example cool new studies:

- Hyperoxia causes maturation-depedent cell death in developing white matter (2008).
- Estradiol attentuates hyperoxia-induced cell death in developing white matter (2007).
- Acute lipopolysaccharide-mediated injury in neonatal white matter (2005).

Narrowing the topic

Periventricular leukomalacia (PVL) is a common lesion of the periventricular cerebral white matter and underlies the subsequent development of CP and cognitive impairment.

- Results in chronic perturbation of myelination.

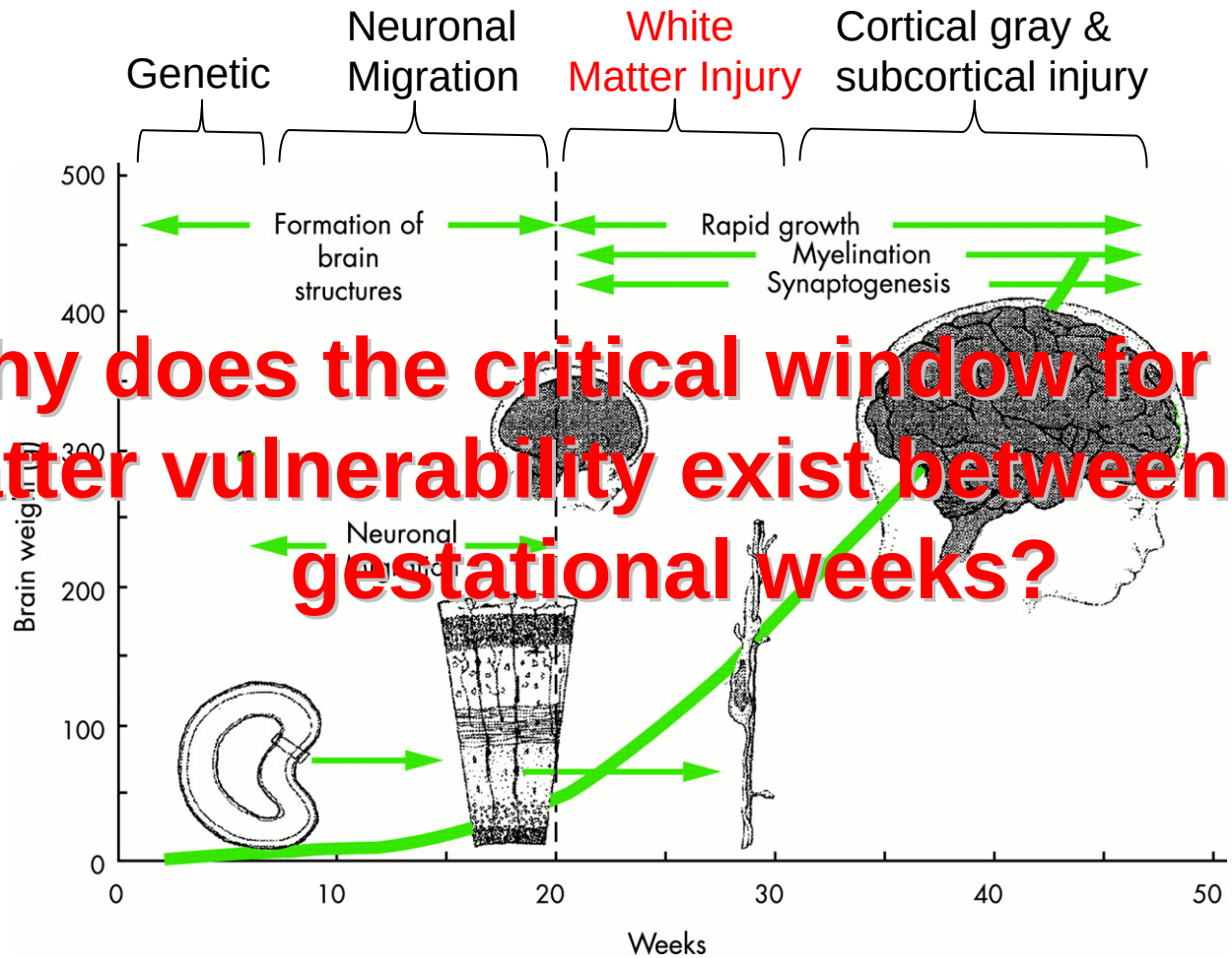


Causes:

- Maternal/fetal infection
- Inflammation
- Prematurity
- Ischemia/reperfusion
- Reactive oxygen species
- Excitotoxicity

White matter injury in CP

Feature Topic



Why does the critical window for white matter vulnerability exist between 23-32 gestational weeks?

Feature Basic Science Paper

Basic Research

Feature Paper

Late Oligodendrocyte Progenitors Coincide with the Developmental Window of Vulnerability for Human Perinatal White Matter Injury

Stephen A. Back,[1,3] Ning Ling Luo,[1] Natalya S. Borenstein,[3] Joel M. Levine,[2] Joseph J. Volpe,[3] and Hannah C. Kinney[3,4]

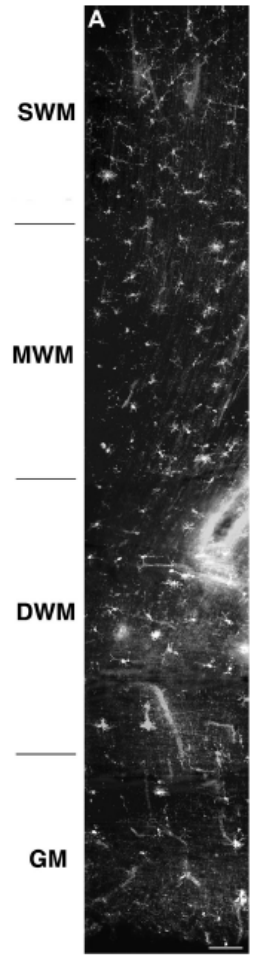
- Descriptive study of OL lineage in 26 human postmortem brains ranging in age from 18-41 postconceptional weeks
- Background: The chronic disturbance of myelination suggests that OL progenitors are the targeted in PVL injury. Which OL lineages are at risk for the developmental window of vulnerability for PVL?
- Methods: Immunofluorescence histochemistry
  - Progenitor OLs (Pre-OLs): label with O4 and NG2
  - Immature OLs: label with O4 and O1
  - Mature OLs: label with myelin basic protein (MBP)

Basic Research

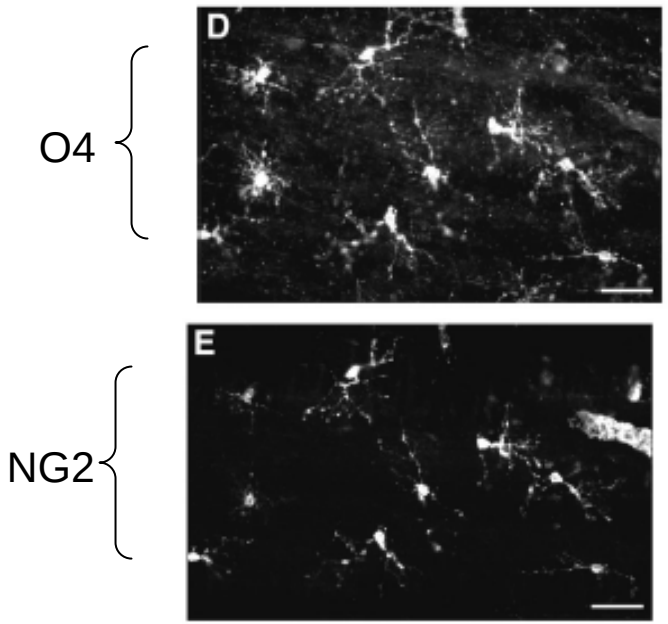
Feature Paper

Results

- O4-labeled cells were present in cerebral white matter at 18 weeks with more appearing in the superficial and mid cerebral white matter and fewer in the deep white matter, germinal matrix, and cortical mantle.



- At 18 weeks NG-2 labeled cells were distributed similarly to O4 cells. All NG-2+ cells coexpressed O4.



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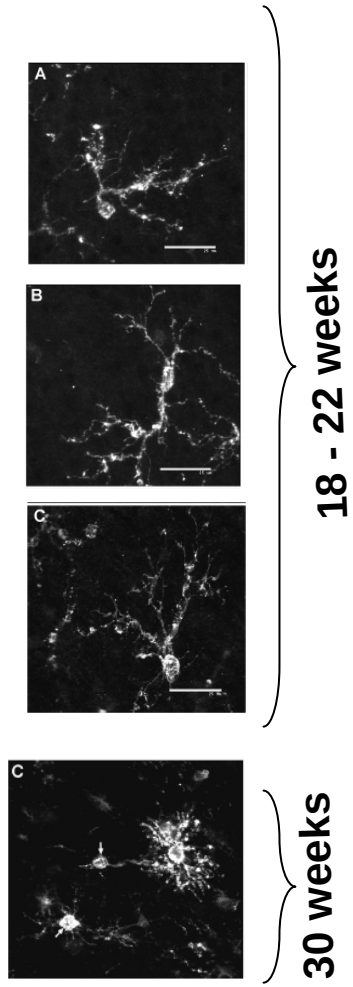
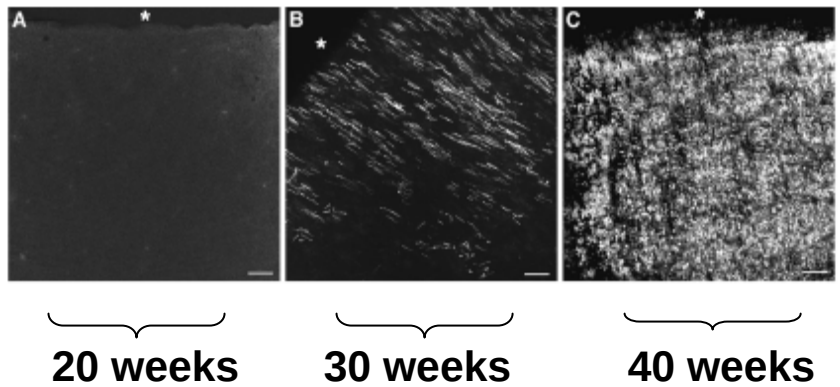
- O4+NG2+ cells were morphologically diverse and distinct from neurons, astrocytes, and microglia.
- O4+NG2+ cells persisted throughout development.



• In most cases, temporal migration of mature OL began at ~30 weeks with full localization by 40 weeks.



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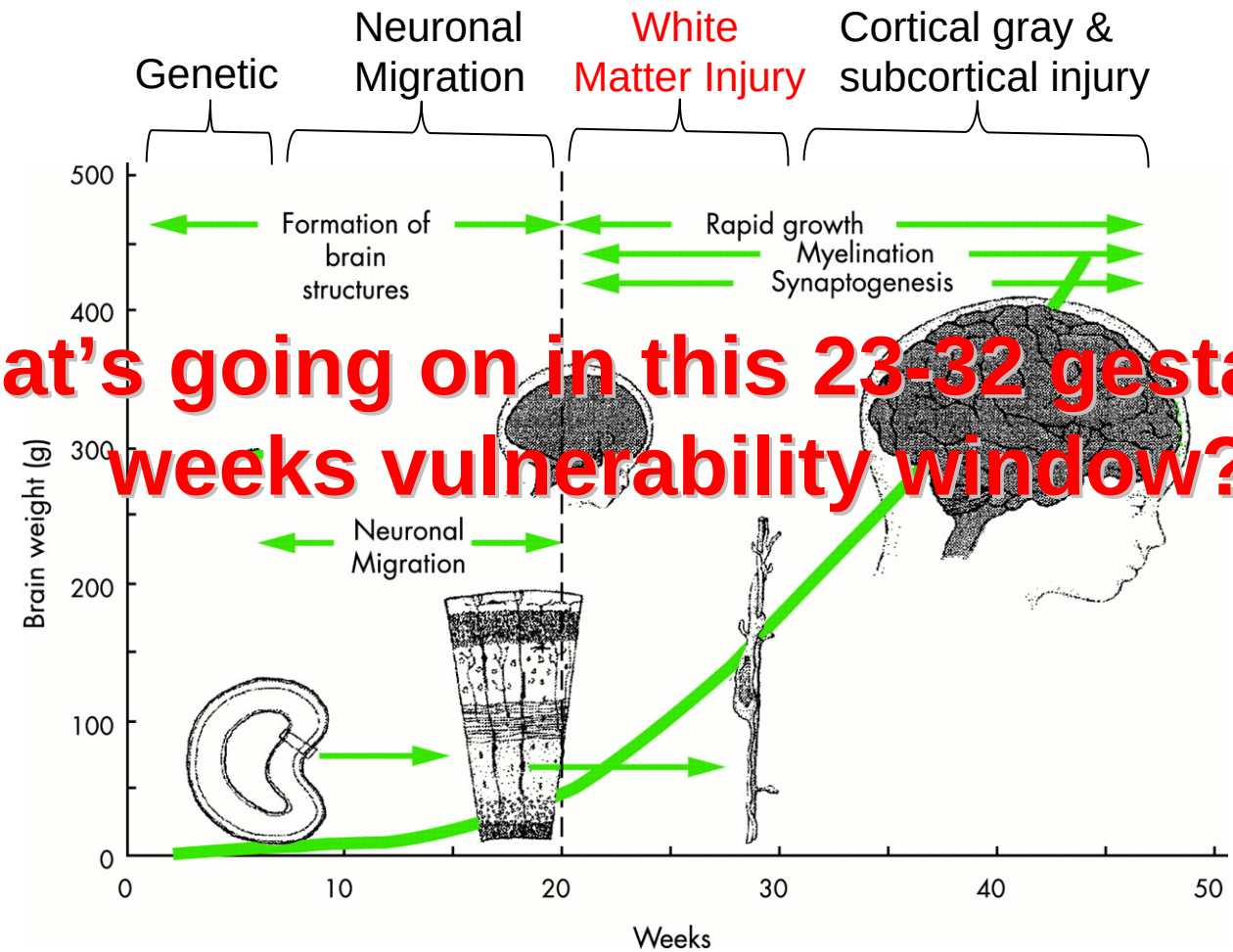

What's going on in this 23-32 gestational weeks vulnerability window?

Basic Research

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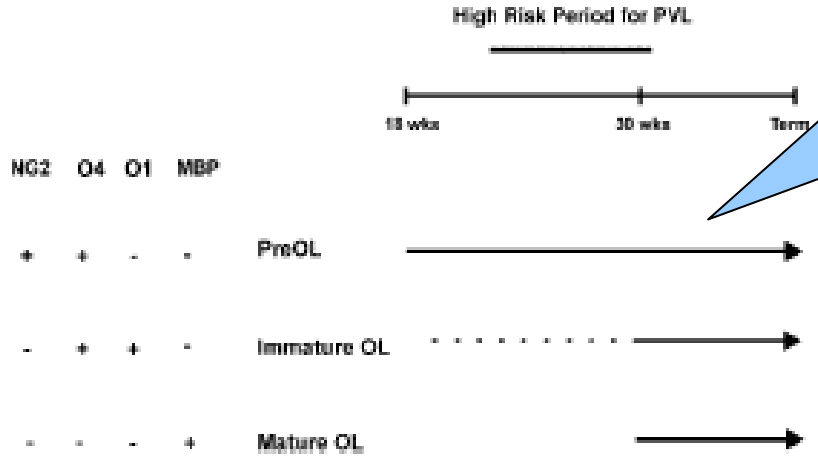


Causes:

- Maternal/fetal infection
- Inflammation
- Prematurity
- Ischemia/reperfusion
- Reactive oxygen species
- Excitotoxicity

Conclusions

- Vulnerability of PVL is highest at 23-32 weeks when pre-OLs comprise ~90% of the total cells derived from the OL lineage.
- The decline of PVL coincides with differentiation of OLs and maturation of periventricular white matter at ~30 weeks.
- This study also found substantial temporal differences in myelination between rodents and humans → implications for animal studies.

Clinical Research

Clinical Research

Where the Field Stands

Any neurological disorder appearing in childhood that permanently affects movement and coordination but doesn't worsen over time.

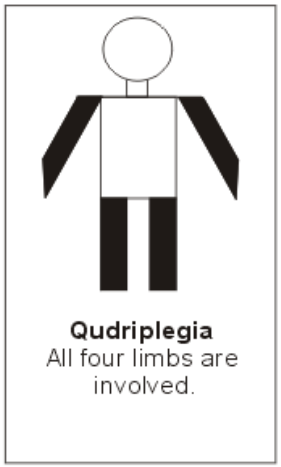
- want to rule out other possible diagnoses first
- no genetics (correlation b/w cytokine polymorphisms and CP?)
- possible correlation b/w blood cytokine levels at birth and degree of CP

"No antenatal, perinatal, or postnatal test can predict CP with a degree of certainty high enough to help providers or parents plan for an infant's future or make the best of early intervention resources."

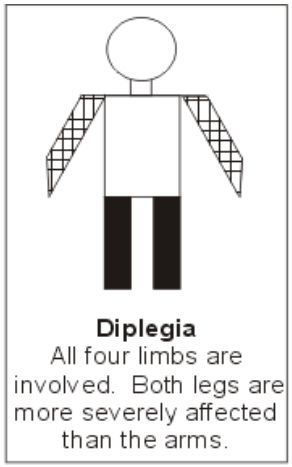
- Donohue & Graham (2007)

Clinical Research

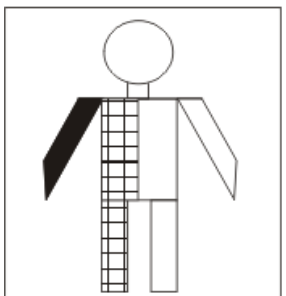
Current Options



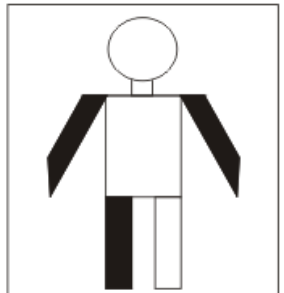
Qudriplegia
All four limbs are involved.



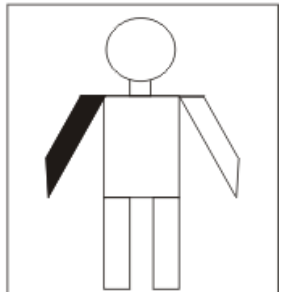
Diplegia
All four limbs are involved. Both legs are more severely affected than the arms.



Hemiplegia
One side of the body is affected. The arm is usually more involved than the leg.



Triplegia
Three limbs are involved, usually both arms and a leg.



Monoplegia
Only one limb is affected, usually an arm.

Typical Clinical Care Team:

- pediatrician
  - general well-being, medication
- neurologist
  - diagnosis, extent of damage
- physical therapist
  - exercise of unused/spastic muscles
- occupational therapist
  - speech, feeding, dressing
- orthopedic surgeon
  - lengthens muscles and tendons, adjust muscle imbalances
- neurosurgeon
  - intrathecal baclofen pump, selective dorsal rhizotomy

Illustration from http://www.ofcp.on.ca/guide.html

Clinical Research

What is SDR?

A main goal of many CP patients: **walking as normal as possible.**

Last resort treatment option - surgery, specifically selective dorsal rhizotomy (SDR).

- usually reserved for cases of severe spasicity

<u>Cause of spasticity</u> - simple if we remember the knee reflex.

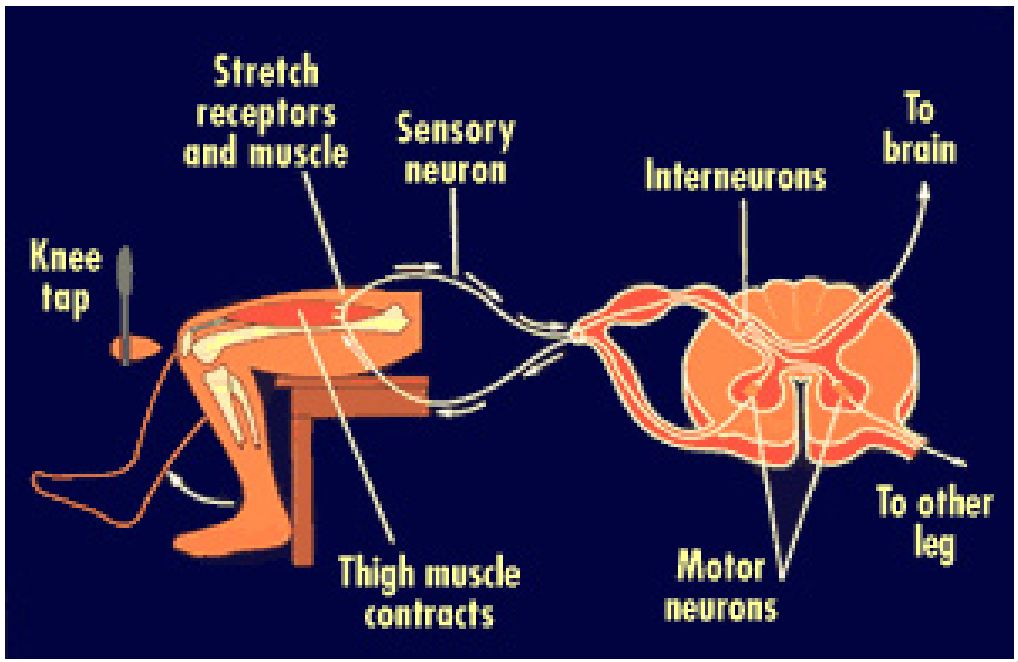


Illustration from http://www.stlouischildrens.org/tabid/89/itemid/1539/Cerebral-Palsy-Spasticity--Selective-Dorsal-Rhiz.aspx

Clinical Research

Selective Dorsal Rhizotomy

SDR seeks to selectively sever the dorsal roots lacking descending inhibition and causing spasticity.

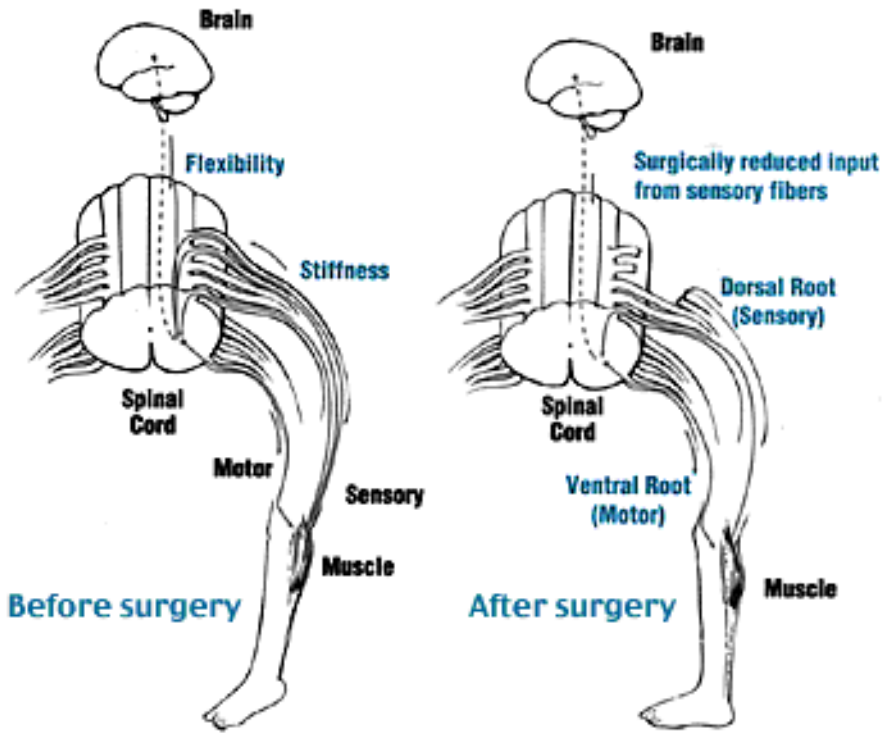
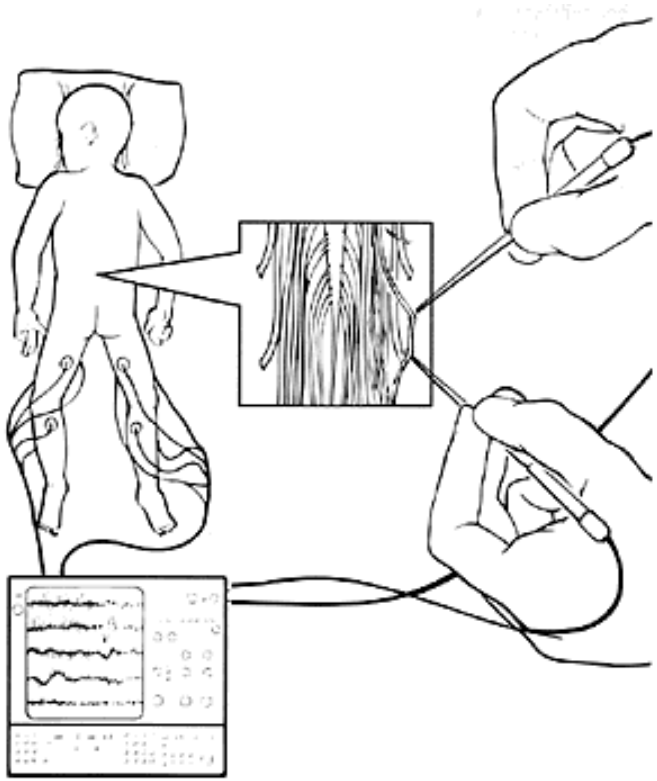


Illustration from http://www.stlouischildrens.org/tabid/96/itemid/1540/About-Selective-Dorsal-Rhizotomy.aspx

Clinical Research

Selective Dorsal Rhizotomy



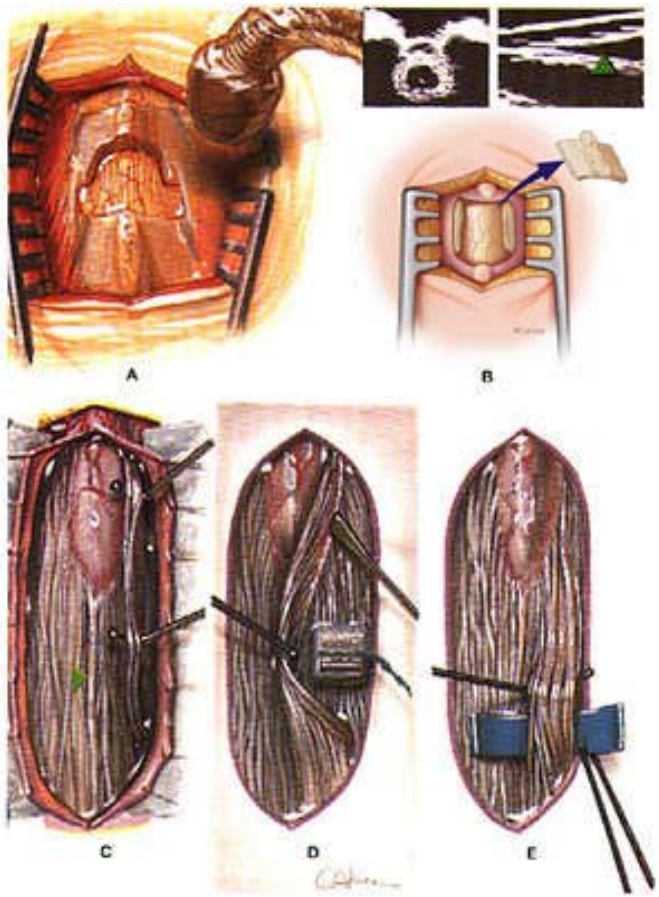
Procedure

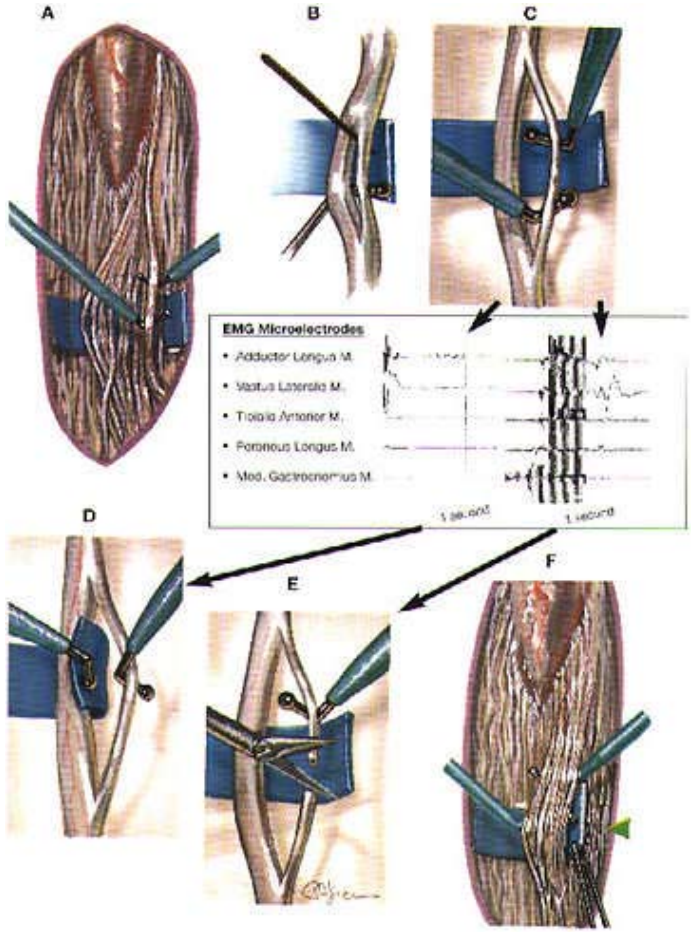
- Dorsal roots are exposed through a one to two inch L1-S2 laminotomy flap.
- Each root is then divided into 3-5 rootlets and electrically stimulated.
- Abnormal EMG responses are recorded from rootlets and ranked from 1 (mild) to 4 (severe). Grade 4 rootlets are severed.
- Electrical stimulation also accurately identifies sacral nerves controlling bowel and bladder control

Illustration from http://www.stlouischildrens.org/tabid/96/itemid/1540/About-Selective-Dorsal-Rhizotomy.aspx

Clinical Research

Selective Dorsal Rhizotomy





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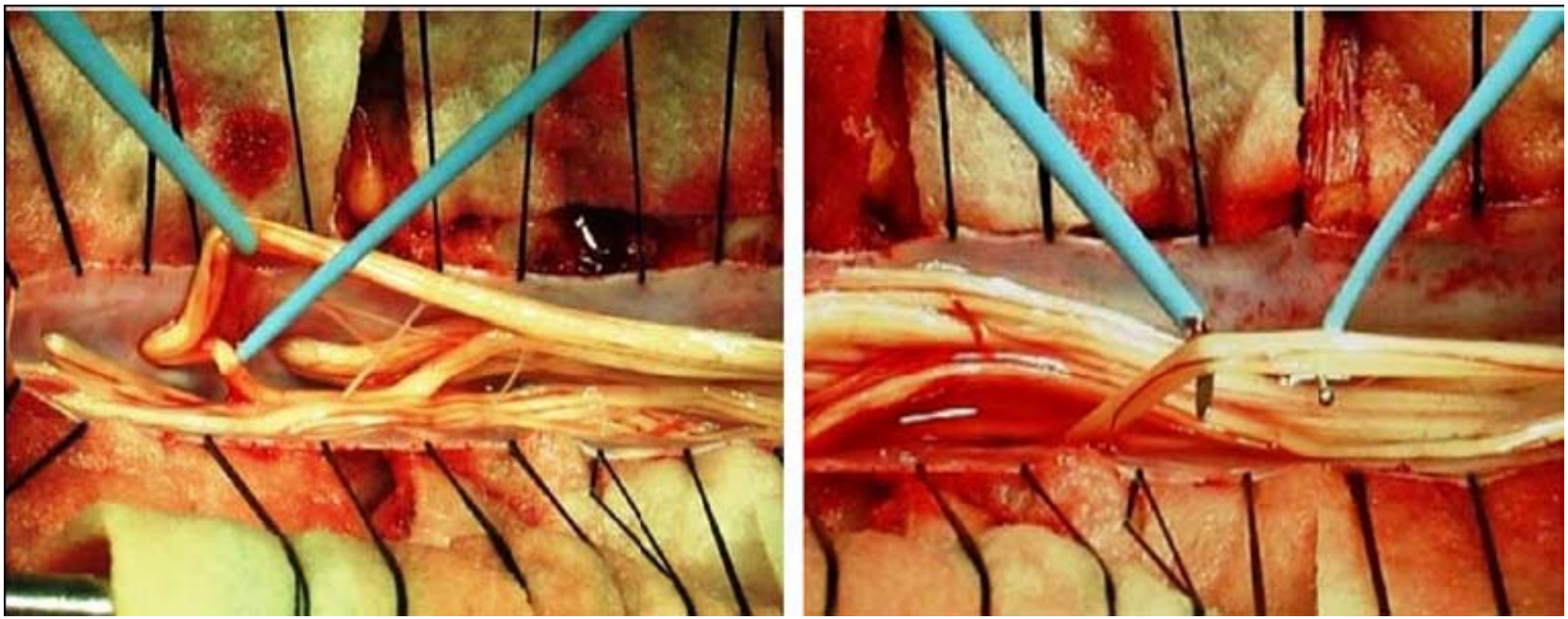
Clinical Research

Selective Dorsal Rhizotomy



from Farmer, J.P and Sabbaugh, A.J. (2007). Selective dorsal rhizotomies in the treatment of spasticity related to cerebral palsy. *Childs Nerv Syst 23,* 9, 991-1002.

Feature Clinical Research Paper

Clinical Research

Feature Paper

QuickTime™ and a
TIFF (LZW) decompressor
are needed to see this picture.

Study design: 71 patients with mild to moderately severe spastic CP underwent SDR and were clinically evaluated preoperatively and at 1, 3, and 5 years post-operatively.

Goal: Measure long-term functional benefits from SDR

Demographic factors in 71 patients in the study population

Factor	Value
sex	
male	43
female	28
extent of disability	
diplegic	57
triplegic	4
quadriplegic	10
prerhizotomy locomotive abilities	
Group I	22
Group II	27
Group III	18
Group IV	3
Group V	1
age at surgery (yrs)	
minimum	3
maximum	10.7
mean	5.2

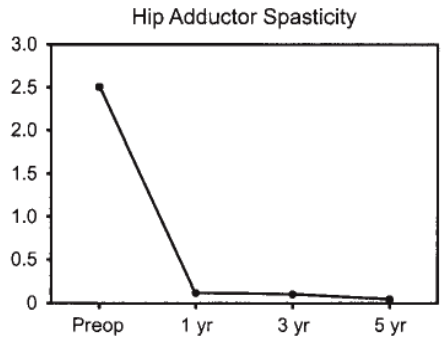
Clinical Research

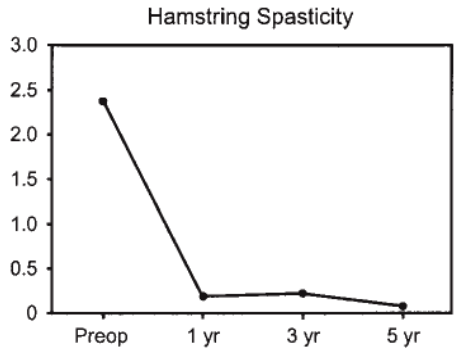
Feature Paper

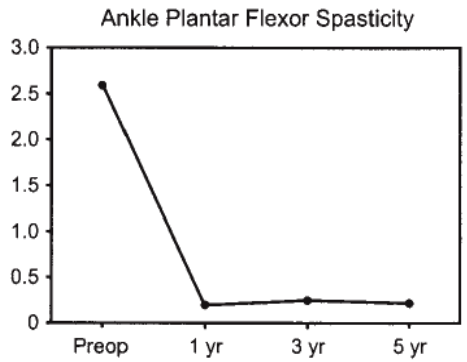
Evaluations

NYU tone scale – measures spasticity of hip adductors, hamstrings, and ankle plantar flexors on a 5-point scale

- 1: floppy
  0: normal
  1: mild
  2: moderate
  3: severe





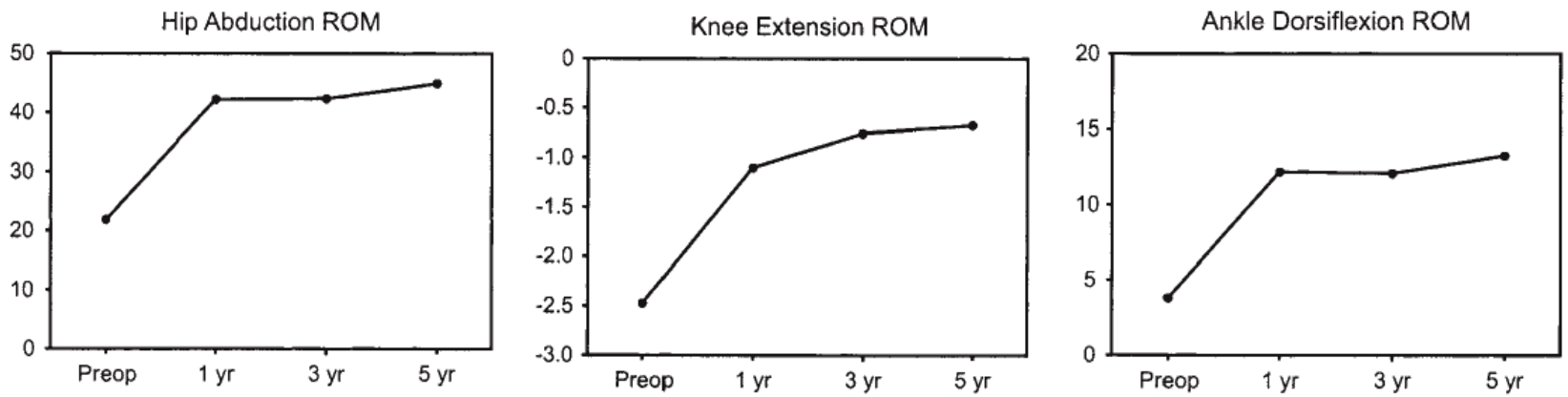


Clinical Research

Feature Paper

Range of motion (ROM)

1. angle of hip abduction from midline with hip and knee extended (normal 45˚)
2. knee extension when lying on back (normal 0˚)
3. ankle dorsiflexion with knee extended (normal 20˚)



Clinical Research

Feature Paper

Rusk/NYU rhizotomy evaluation form: measures performance of holding development positions (long sitting, bench sitting, side sitting, half kneeling, standing) as well as the transitional movements between positions.

Scores

1: Unable to hold position / complete transition
2: Full external support / complete therapist-assisted movement
3: Bilateral upper extremity support / limited therapist assistance for movement
4: Unilateral upper extremity support / limited therapist assistance for support (not movement)
5: Independent - no support

Clinical Research

Feature Paper

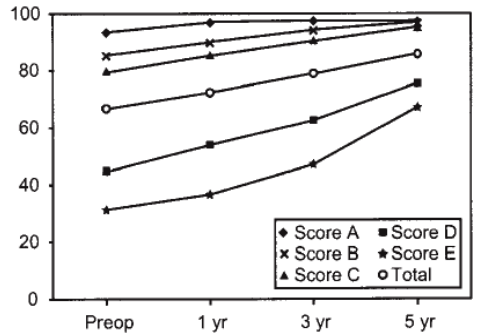
Gross motor function measure (GMFM)

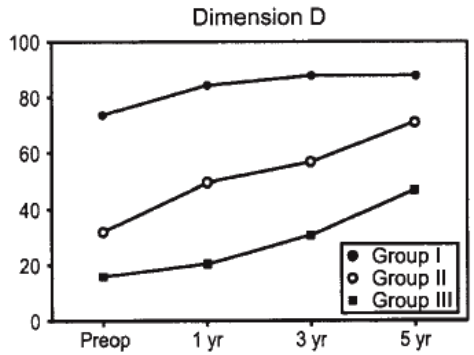
Dimensions

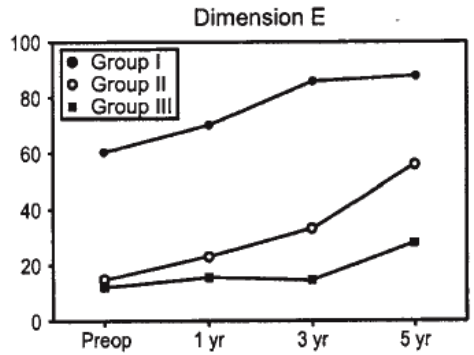
A: lying and rolling
B: sitting
C: crawling and kneeling
D: standing
E: running, walking, and jumping

Patient Categorization

I. Independent Ambulators
II. Assistive motility devices
III. Quadruped crawlers
IV/V. Non-ambulators







Clinical Research

Feature Paper

Conclusions:

- SDR is an invasion neurosurgery that can produce profound long-term effects in patients with CP.
- Conjunctive therapy may still be needed post-operatively.
- Significant improvements were observed in all forms of evaluation. The most functionally important improvements were the ability to stand, walk, run, and jump.
- CP patients with mild to moderate degree of ambulatory function are more likely to benefit from SDR than non-ambulatory patients.