Neurosciences

(Med I, Block 5, NE)
<table>
<thead>
<tr>
<th>Class number</th>
<th>Class name</th>
<th>Type</th>
<th>Department</th>
<th>Instructor</th>
</tr>
</thead>
<tbody>
<tr>
<td>NE002</td>
<td>Brain Development</td>
<td>L</td>
<td>PA</td>
<td>Dr. M Del Bigio</td>
</tr>
<tr>
<td>NE084</td>
<td>Pediatric Neurology I - Seizures and epilepsy in childhood</td>
<td>L</td>
<td>NE</td>
<td>Dr. F Booth</td>
</tr>
<tr>
<td>NE085</td>
<td>Pediatric Neurology II - Hypotonia</td>
<td>L</td>
<td>NE</td>
<td>Dr. M Rafay</td>
</tr>
<tr>
<td>NE091</td>
<td>Pediatric Neurology tutorial</td>
<td>T5</td>
<td>NE</td>
<td></td>
</tr>
</tbody>
</table>
Learning objectives

- To appreciate overlapping contributions of cell proliferation, migration, and differentiation.
- To understand how signaling molecules define dorsal/ventral and rostro/caudal differentiation.
- To always remember that the central nervous system does NOT develop in isolation.
- Rudiments of major brain structures appear by week 8 in utero, the brain reaches 1/3rd full size by term, full size by ~8-10 years, but not all pathways are myelinated until ~25 years.
- Genetic, toxic, infectious, traumatic or ischemic disturbances can cause malformation.
- From a preventative standpoint, remember that prenatal folate can reduce the likelihood of spina bifida.

Structural development of brain & spinal cord

One learns by comparison

12 week human fetus

20 day rat fetus

Notochord and neural tube floor plate induction
Neural tube - 20/21 days (3 weeks)

Neural tube closure - multiple sites

Neural tube - 28 days (4 weeks)

Differential gene expression (homeobox, etc.) determines neural tube induction and subsequent segmentation

Neural tube - 36 days (5 weeks)

Neural tube - 49 days (7 weeks)
8 weeks - end of embryonic period

All major brain structures have appeared

22 week  27 week  40 week

Fetal brains

Embryonic & fetal brain development - gross

~500g @ birth (1/3 adult size)

Cerebral cortex development (neurons all generated by 18 weeks, most glial cells by 32 weeks

20 week fetus

Cerebral cortex development - cell migration continues to birth

38 week fetus
Postnatal cortex development - expansion of synaptic contacts and myelination of axons

Cerebellum development (postnatal)
- 3 weeks (proliferation continues to 9 months)
- 3 years

Interactions with the “outside”

Arterial supply to brain - embryonic period

Vein development
Outgrowth of cranial and spinal nerves in embryo

Cranial and spinal nerve distribution

Spinal cord / vertebral column - differential growth

Eye development - embryo

Cytologic development

Proliferation of cells
Early neuron precursor generation and migration

The major zone of proliferation is not constant over time - it shifts rostrally (i.e. toward the forebrain)
From Kahle 1951

Migration of cells

Pyramidal neuron precursors from VZ migrate radially along radial glia

Non-radial migration of inhibitory neuronal precursors from ganglionic eminence occurs during later fetal development (from ten Donkelaar 2008)

Growth cone guidance by trophic and repellant factor gradients
Cells that fail to make appropriate connections or fail to receive sufficient trophic factors are eliminated by apoptosis (programmed cell death).

Differentiation of cells

Stem cells are pluripotent and respond to certain growth factors

Timing of cell generation, migration, and differentiation

Cortical Development - 1

Cortical Development - 2
Not all brain development is complete in childhood.

New neurons are produced in the normal olfactory bulb and the dentate gyrus of the hippocampal formation.

Myelin deposition in central nervous system.

Highlights of Human Nervous System Development:
- Neural tube closes by 26 days, multiple closure sites.
- By 8 weeks, the end of the embryonic period, the crude precursors of all major brain structures have formed.
- Development proceeds in bottom-up direction (spinal cord/brain stem first).
- Patterning determined by gene expression.

CNS Development Highlights (ctd.):
- Most cerebral neurons with long projections are generated by ~18 weeks in human.
- Gial cells and interneurons generated until birth.
- Cell migration and synapse formation continue well into 1st year.
- Cerebellum development complete ~2 years.
- Myelination corresponds to functional status and is not complete in cerebral association pathways until third decade.

Malformations of the Central Nervous System:
- Variable susceptibility to disturbance.
- Molecular mutations, ischemia, trauma, viruses, toxins, nutrition, etc.
Genetic or exogenous insult

Neural tube - normally closes at 24-26 days
What if that fails?

Myelomeningocele

Occipital encephalocele

CNS Malformations

- Failure of neural tube closure - myelomeningocele (spina bifida), et al.
- IMPORTANT - preconception administration of folic acid (5 mg daily) reduces risk by >90% (Recommended dose updated 2007 Soc Obs Gynec Can)
Prosencephalon normally divides into telencephalic vesicles at ~34 days - what if that fails?

Holoprosencephaly (failure of forebrain separation)

Holoprosencephaly associated with cleft lip, cyclopia, et al.

What if cells are generated but fail to migrate and are not eliminated by apoptosis?

Periventricular heterotopia

What if generation or layering of early neuron precursors fails?
Lissencephaly (smooth brain) due to failure of cell generation and migration with secondary failure of gyration.

What happens if the infant is born too early, prior to maturation of the brain?

Periventricular hemorrhage from immature germinal matrix blood vessels with subsequent cerebral palsy.

End
Childhood Epilepsies

Learning Objectives
• Illustrate some types of childhood epilepsy
• Emphasize the diverse and subtle nature
• Illustrate some of the associated features
• Discuss principles of management
• Emphasize the special aspects of living with childhood epilepsy

Definitions
• Seizure Disorder/Epilepsy: a tendency to have recurrent seizures implying an abnormality within the central nervous system
• Seizure: a clinical event resulting from an abnormal electrical discharge in the central nervous system

How Frequent is Epilepsy?
• 50 million worldwide
• 0.5-1% of children through age 16 years
• 75% of new cases begin in childhood

What is the Impact of Epilepsy on a Child?
• Seizures themselves
• Developmental Delay/Learning Disability
• Behavioural Dysfunction
• Poor Social Interaction

Classification of Seizures
• The events themselves
• An individual can have > one seizure type
Classification of SEIZURES

- Partial (focal, localization-related)
  - Generalized

Partial Seizures

- Simple partial seizures
- Complex partial seizures
- Partial seizures secondarily generalized

Generalized Seizures

- Absence
- Generalized tonic-clonic
- Tonic seizures
- Clonic
- Atonic
- Myoclonic

Classification of EPILEPSIES

- Seizure type
- Age at occurrence
- Etiology
- Prognosis

Classification of the Epilepsies and Epilepsy Syndromes

- Localization-related (partial, focal)
  - Idiopathic (genetic)
  - Symptomatic (known cause)
  - Cryptogenic (cause unknown)
- Generalized
  - Idiopathic
  - Cryptogenic
  - Symptomatic
Patient KP

- Normal term infant
- Well until 5 months
- Developed “colic” with spasms of limbs
- Cried with episodes
- Lost ability to sit
- Less visually responsive

Infantile Spasms (West Syndrome)

- Generalized epilepsy
- Spasms (individual events)
- EEG findings of hypsarrhythmia
- Mental regression or mental retardation

Seizures

- Onset in first 18 mo of life (peak 4-10 mo)
- Sudden usually bilateral tonic contraction of neck, trunk and extremities
- Flexion, extension or both
- May be unilateral, asymmetrical or subtle
- Generally < 10 seconds
- Series of repetitive movements
**Electroencephalogram (EEG)**

- Most common pattern is hypsarrhythmia
- Chaotic high amplitude slow waves
- Multifocal spikes/ sharp waves
- In sleep, pattern may become discontinuous

**Mental Deterioration**

- At onset in 68-85%
- Some infants previously normal
- Some delayed before the onset of spasms

**Etiology**

- Symptomatic
- Cryptogenic
- Idiopathic

**Etiology: Symptomatic**

- Brain dysgenesis
- Tuberous sclerosis 10-20 % of some series
- Central nervous system infections
- Hypoxic-ischemic encephalopathy
Etiology: Cryptogenic
- No identifiable cause
- Development may be normal prior to spasms

Etiology: Idiopathic
- Uncommon, controversial

Prognosis
- Seizures persist in 50%-60%
- Developmental delay in majority

Differential Diagnosis
- Infantile colic
- Benign myoclonus of early infancy
- Myoclonic seizures
Key Points
- Repetitive nature of movements should raise suspicion
- May be subtle (head nodding, shrugging)
- May be mistaken for colic
- History of regression important

Patient NW
- Onset of seizures at age 3.5 years
- Cessation of activity, rhythmic arm jerks
- Multiple seizure types
- Atonic/tonic/myoclonic seizures with falls (drop attacks)
- Poor response to multiple medications

Patient NW
- Developmental delay more apparent over time
- Behavioural dysfunction significant

Patient NW
- EEG: slow spike and wave activity
- MRI: band heterotopia (double cortex syndrome)
Lennox-Gastaut Syndrome

- Severe form of childhood epilepsy
- Onset 1-7 years of age
- Multiple seizure types:
  - Tonic/atonic/myoclonic seizures (drop attacks)
  - Atypical absence seizures
  - Partial, generalized tonic-clonic seizures
  - Non-convulsive status epilepticus

- Mental retardation: may be present at onset
- Mental retardation: 90% by age 5 years
- Etiology: multiple causes
- EEG: slow spike-wave pattern
- Prognosis: poor; 80% continue to seizure
  few become independent

Patient BG

- Febrile seizures 4mo to 2.5 yr
- From age 2.5 years, afebrile seizures
- Myoclonic seizures most frequent type
- Absence seizures/non-convulsive status
- Generalized tonic-clonic seizures
- Developmental and behavioural regression
Severe Myoclonic Epilepsy of Infancy (Dravet Syndrome)
- Frequent prolonged febrile seizures at < 1 yr
- Myoclonic seizures and jerks age 1-4 yr
- Developmental slowing and behavioural dysfunction follow onset of seizures
- All mentally retarded
- SCN1A gene mutation (sodium channel)

Myoclonic Epilepsies of Infancy and Childhood
- May be confused with Lennox-Gastaut syndrome
- Myoclonic seizures predominate
- Seizures may cause loss of tone and falls (drop attacks) impossible to distinguish from atonic seizures

Myoclonic Epilepsies of Infancy and Early Childhood
- Outlook: favourable (seizures controlled; development normal)
- Outlook: poor (intractable seizures, developmental and behavioural dysfunction)

Severe Myoclonic Epilepsy & Lennox-Gastaut Syndrome
- KEY POINTS:
  - Severe childhood epilepsies
  - Prognosis for seizure control guarded
  - Generally significant cognitive/behavioural dysfunction
  - Likelihood of independent living low

Patient AJ
- Referred at age 8 years
- Difficulty attending to task
- Inattentive, hyperactive
- Poor school performance
- Repeated kindergarten and grade 1
- Problems since at least age 6 years
Absence Epilepsy

- Generalized Epilepsy
- Idiopathic (genetic)

Absence Epilepsy: Seizures

- Brief: most 5-15 seconds
- Onset and termination abrupt
- No post-ictal phase
- Staring +/- subtle limb movements
- Eyelid jerking, change in tone
- Many time per day
Absence Epilepsy

- Childhood: onset between 3-8 years
- Juvenile: onset between 9-10 years
- EEG: generalized 3/second spike and wave
- Development/behaviour: usually normal
- Etiology: genetic (primary generalized)
- Prognosis: generally favourable

Absence Epilepsy

- Child generally unaware of events
- Hyperventilation (3 min) may precipitate seizure
- 40-50% will have generalized tonic-clonic seizures

Absence Epilepsy: Key Points

- Unrecognized seizures may cause educational problems
- Hyperventilation may establish the diagnosis
- 40-50% will have generalized tonic-clonic seizures

Patient TP

- 3 generalized seizures starting at age 12 yr
- One outside with flickering sunlight
- Two while watching television
- Jerks of arms in morning especially if tired
- Neurological/developmental status normal
- Seizures controlled on medication

Juvenile Myoclonic Epilepsy (Myoclonic Epilepsy of Adolescence)

- Janz Syndrome
- Onset between ages 12-18 years
- 5-11% of adolescents with epilepsy
- Myoclonic jerks affecting mainly arms and shoulders especially on awakening
- Generalized tonic-clonic seizures in most

Juvenile Myoclonic Epilepsy

- EEG: bursts of high frequency spikes (>3 per second)
- May be photosensitive
- Neurodevelopmental status normal
- Etiology: genetic
- Prognosis: seizures controlled with medication
Patient RW

- Episodes beginning at 9 years
- Right facial twitching especially lower face
- Garbled speech
- 30-100 seconds
- No alteration in awareness
- Development and behaviour normal

Patient RW

- EEG: left midtemporal and central spikes
- Seizures controlled with medication

Benign Epilepsy with Centrotemporal Spikes

- Benign partial epilepsy of childhood with centrotemporal spikes (BECTS)
- Benign rolandic epilepsy
- Most common type of idiopathic partial epilepsy in childhood (15-25%)
- Onset 2-13 years

Benign Epilepsy with Centrotemporal Spikes

- Generalized seizures may occur
- Neurodevelopmental status in most: normal
- EEG: focal centrotemporal discharges
- Etiology: genetic
- Prognosis: excellent; most do not seizure after mid-adolescence (age 16 years)

Benign Epilepsy with Centrotemporal Spikes

- Simple partial seizures common
- Face and oropharyngeal muscles involved
- Salivation and/or speech arrest; “gutteral”
- Hemifacial twitching
- With or without sensory change
- 30-60 seconds
- Often when asleep or awakening
### Epilepsies of Childhood with Partial Seizures
- At least 50% of childhood seizures
- Onset is limited to one part of a cerebral hemisphere
- Clinical manifestations depend on area of brain involved

### Etiology
- Etiology can be idiopathic (genetic) or symptomatic/cryptogenic (secondary to a known or suspected lesion)
- Etiology important in determining prognosis

### Differential Diagnosis of Epilepsy in Infants and Children
#### Neonate (0 to 2 mo):
- Apnea/ jitteriness/ **benign neonatal sleep myoclonus**

#### Infant (2-18 mo):
- Breath-holding spells/ shuddering attacks, infantile masturbation/ paroxysmal torticollis

#### Toddlers/Preschool (18 mo-5 yr):
- Breath-holding spells/ night terrors/ nocturnal enuresis/ agitated delirium with fever/ drug-induced paroxysmal dystonia

#### School-aged and pre-adolescent (5-12 yr):
- Tics & Tourette syndrome/daydreaming/ migraine/somnabulism/syncope/ enuresis

#### Adolescents (>13 years):
- Syncope/ hyperventilation/ narcolepsy & cataplexy/ migraine/ psychogenic pseudoseizures/ rage attacks
Diagnosis

- HISTORY critically important
- Information from witness and child

- PHYSICAL EXAMINATION including evaluation for neurocutaneous lesions and hyperventilation in selected patients

Figure 3.1. Two hypomelanotic macules and a shagreen patch in the lumbar and sacral areas of a young boy with tuberous sclerosis.

Figure 3.4. Fibrous plaque on the forehead and facial area.
Diagnosis

A CLINICAL DIAGNOSIS!

Investigation: EEG

- Provides direct evidence of an epileptiform abnormality
- May be the only abnormal test
- BUT low sensitivity and specificity
- 10-20% with epilepsy have normal EEG's
- 1-2% without epilepsy have abnormal EEG's

Investigation: EEG

- Usefulness depends in part on clinical information

Investigation: Imaging

- CT
- MRI
Investigation: Other

- Routine bloodwork: electrolytes, glucose
- Metabolic investigations, lumbar puncture
- Other electrophysiological studies
- Biopsies
Treatment

• Is treatment indicated?

• Single event – is this epilepsy?
• Infrequent seizures
• Mild seizures

• Mainly medication
• Choice dependent on: seizure type(s)
• Age

• Dietary treatment: ketogenic diet

• Surgical treatment

Medications

• Increasing number of medications available

• Seizure type important

• Generalized versus localization-related

• Infantile spasms: ACTH, vigabatrin
• Localization-related seizures:
  – Carbamazepine
  – Clobazam
  – Lamotrigine
  – Topiramate
• Generalized seizures:
  – Valproic acid
  – Lamotrigine
  – Topiramate
  – Ethosuximide

Medication

• Infantile spasms: ACTH, vigabatrin
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Management

• PSYCHOSOCIAL ISSUES IMPORTANT

• COMPREHENSIVE MANAGEMENT

Management: Safety Issues

• Dependent in part on seizure type and seizure control

• Home/school/community issues
**Safety Issues: Home**
- Showering preferred to bathing
- Appropriate supervision in bath/shower
- Doors should not be locked preventing access
- Care around ovens/stoves/moving machinery

**Safety Issues: Sports**
- Participation encouraged
- Individualize
- Caution for activities where loss/alteration of awareness could be critical

**Safety Issues: Sports**
- Dependent on seizure control in part
- Swimming always supervised
- Bicycle riding with helmet, quiet streets
- Hockey/soccer with appropriate equipment and supervision
- Driving

**Lifestyle Issues**
- **MAY HAVE NB INFLUENCE ON SEIZURE CONTROL**

**Lifestyle Issues: Trigger Factors**
- Sleep deprivation
- Undue stress
- Prolonged fasting
- Irregular eating habits
- Excessive alcohol intake
- Use of street drugs

**Lifestyle Issues: Medication**
- Compliance
- Regular timing
- Missed dosages
- Drug interactions
- Medic alert bracelet
Lifestyle Issues: Protection

- Protective helmet for children with frequent drop seizures resulting in falls and head injuries

Education for Parents/Caregivers/Child

- Teachers/coaches should be involved
- When to call ambulance
- What to do during a seizure
Conclusions

- Childhood Epilepsies: diverse and subtle
- Cognitive +/- behavioural abnormalities NB
- History/physical important
- Differential diagnosis extensive
- Comprehensive management critical
FEBRILE SEIZURES

SIMPLE
- BRIEF BILATERAL CLONIC OR TONIC-CLONIC SEIZURES

COMPLEX
- > 15 MINUTES
- FOCAL FEATURES
- ONE SEIZURE IN 24 HOURS

RECURRENT OF FEBRILE SEIZURES

33% 1 RECURRENT
9% 3 OR MORE SEIZURES

78% OF RECURRENTS WITHIN 1 YEAR
90% OF RECURRENTS WITHIN 2 YEARS

ONSET OF SEIZURES IN 1ST YEAR OF LIFE - 50% RECURRENT
ONSET OF SEIZURES AFTER 4 YEARS - 10 - 15% RECURRENT

ACUTE MANAGEMENT OF FEBRILE SEIZURES

HISTORY AND PHYSICAL EXAMINATION
INVESTIGATIONS
- BLOODWORK
- CULTURES
- LUMBAR PUNCTURE

PROPHYLACTIC TREATMENT

PROPHYLACTIC TREATMENT CAN REDUCE INCIDENCE OF RECURRENT FEBRILE SEIZURES

THERE IS NO EVIDENCE PROPHYLAXIS CAN PREVENT THE LATER OCCURRENCE OF NON FEBRILE SEIZURES

RISK OF EPILEPSY FOLLOWING FEBRILE SEIZURES

INCREASED RISK PRESENT
< 5% IN MOST SERIES

RISK FACTORS FOR NONFEBRILE SEIZURES:
- COMPLEX INITIAL SEIZURE
- PRIOR NEURODEVELOPMENTAL ABNORMALITY
- NONFEBRILE SEIZURES IN PARENT OR SIBLING
- RISK INCREASES WITH INCREASING NUMBER OF RISK FACTORS

PROPHYLACTIC TREATMENT

PREVIOUS NEUROLOGICAL ABNORMALITY
SEIZURE-LASTING > 15 MINUTES
WITH FOCAL FEATURES
WITH TRANSIENT OR PERSISTENT NEUROLOGICAL ABNORMALITIES
FAMILY HISTORY OF NONFEBRILE SEIZURES IN PARENT OR SIBLING
MULTIPLE RECURRENCES
< 12 MONTHS OF AGE

83h CONSENSUS STATEMENT
Treatment of a Child with a First Unprovoked Seizure

- Recurrence by 2 years: 37-54%
- Seizure Type: CPS > GTC
- Prior neurological abnormality
- Epileptiform features in EEG
- Specific epilepsy syndrome of childhood

Majority with have few or no recurrences
- 10% > 10 seizures regardless of therapy
- Tx appears not to improve chance of long-term remission
- Tx generally not indicated after first sz
- To consider tx, benefits must outweigh risks of psychosocial and drug side effects

Patient NP

- Born prematurely
- First seizure at age 2 years
- Generalized seizure with fever > 15 min
- Intractable partial seizures after age 15 yr
- Confused, pick at clothing, no memory of events
- Required surgical therapy

Patient NP

- EEG: left temporal slowing and sharp waves
- MRI: mesial temporal sclerosis
Objectives

- What are pediatric seizure disorders?
- How common are they?
- How do we classify them?
- What do they look like?
- How do we manage them?
- What is new in management?
- What is the evidence for what we do?
Approach to a Floppy Infant

Mubeen Rafay
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Learning Objectives

- Understand the clinical examination of a floppy infant
- Differentiate between central and peripheral hypotonia
- Describe the various causes of floppy infant
- Outline the appropriate investigations required to diagnose this condition
- Understand the multidisciplinary management of infants with severe hypotonia

Definition of Muscle Tone

- Resistance of muscle to stretch
- Two kinds of tone: Postural vs. Phasic
  - Postural tone: Prolonged contraction of antigravity muscles in response to low intensity stretch of gravity
  - Phasic tone: Rapid contraction in response to high intensity stretch e.g. testing the deep tendon reflexes

Normal Muscle Tone

- Intact central and peripheral nervous system
  - Central: brain, spinal cord
  - Peripheral nervous system: Lower motor neuron
    - Anterior horn cell
    - Peripheral nerve
    - Neuromuscular junction
    - Muscle

The Hypotonic Infant

- Infantile hypotonia refers to inadequate resistance of the postural muscle to the stretch imposed by gravity
- Floppy baby – Infant with poor muscle tone affecting the limbs, trunk and the cranial-facial musculature
- Usually evident at birth or identified in early life
- Results in inability to maintain normal posture during rest and movement

Clinical History

- Birth History
  - Antenatal
    - Fetal movements in utero
    - Polyhydramnios/ oligohydramnios
    - Fetal ultra sound
    - Age of the mother, drug or teratogen exposure, neuromuscular disorder in mother
Clinical History

- Birth History
  - Natal
    - Birth weight, prematurity, delivery complications - asphyxia, trauma, sepsis, prolonged rupture of membranes, abnormal presentation (breech)
  - Postnatal
    - Respiratory or feeding difficulty, seizures
    - Exposure to anesthetics or sedatives, Magnesium
- Family History
  - Neuromuscular problems in the mother, siblings or other members

Clinical Features

- Lack of spontaneous movements
- Floppy, low tone
- Weak cry, poor feeding
- Regurgitation and aspiration - common
- Occipital plagiocephaly, loss of hair
- Weakness of respiratory muscle/diaphragmatic or paradoxical breathing, pectus excavatum

Clinical Examination

- Observation of posture - frog leg posture
- Myopathic Facies
- Look for fixed joint deformities/contractures (Arthrogryposis), dislocation of hips, pectus excavatum
- Assess phasic tone: resistance of muscles to rapid movement
- Traction response (pull to sit position): assess head lag
- Vertical (axillary) suspension - slips
- Horizontal suspension - 'ragged doll'
- Deep tendon reflexes

Frog leg Posture

Myopathic facies

Ragged Doll
Floppy Infant

Arthrogryposis/Congenital Contractures

Central v/s Motor Unit Hypotonia

- Central causes (UMN):
  - Cerebral hemispheres
  - Basal ganglia, cerebellum, brainstem,
  - Spinal cord
- Peripheral causes (LMN):
  - Anterior horn cell
  - Peripheral nerve
  - Neuromuscular junction
  - Muscle

Where is the problem?

- Is it central (brain and spinal cord) or peripheral (beginning at anterior horn cell)

Cardinal distinguishing feature is often WEAKNESS

Clues to Cerebral/Central Hypotonia

- Abnormalities of other brain function
  - Decreased consciousness
  - Seizures
- Weakness less striking for degree of hypotonia, facial and EOM sparing
- Dysmorphic features
- Fisting of the hands (Cortical thumb)
- Malformations of other organs
- Movement through postural reflexes
- Normal or brisk deep tendon reflexes
- Scissoring on vertical suspension
Central Causes of Hypotonia

- Hypoxic-ischemic encephalopathy
- Structural cerebral or cerebellar abnormalities including cerebral infarction and hemorrhage
- Traumatic brain or spinal cord injury
- Infection: Sepsis, meningitis, encephalitis
- Metabolic: hypoglycemia, electrolyte disturbance, jaundice, IEMs (urea cycle disorders, organic acidemia, aminoacidemia), Leukodystrophies, Peroxisomal disorders
- Drug intoxication
- Endocrine (hypothyroidism)
- Genetic/syndromic: Trisomy 21 (Down’s syndrome), Prader-Willi syndrome

Clues to Motor Unit Hypotonia

- Absent or depressed tendon reflexes
- Failure of movement on postural reflexes
- Fasciculations (tongue and other muscles)
- Muscle atrophy
- No abnormalities of other organs
- Joint deformities: hip dislocation, Arthrogryposis multiplex congenita (multiple joint contractures)

Causes of Motor Unit Hypotonia

- Anterior horn cell
  - Spinal muscular atrophy (SMA)
- Nerve
  - Metabolic neuropathy
  - Cong. hypomyelinating neuropathy
- Neuromuscular junction
  - Transient neonatal myasthenia
  - Congenital myasthenic syndromes
- Botulism
- Muscle
  - Congenital muscular dystrophy
  - Congenital myotonic dystrophy
  - Congenital myopathies

Investigations

- Serum CK
- Electrodagnostic studies: EMG, NCS, repetitive nerve stimulation (RNS)
- Muscle biopsy
- Nerve biopsy
- Tensilon (Edrophonium) test
- Genetic testing: DNA studies
- Metabolic studies and enzymatic assays
- Chromosomal studies
- Neuroimaging- MRI scan

Anterior Horn Cell Disorders

- Hereditary
  - Spinal muscular atrophies/ SMA
  - GM2 gangliosidosis
  - Pompe’s disease (Acid maltase deficiency)
- Acquired
  - Poliomyelitis and other enteroviral infections

Clues on Examination

- Hypotonia with weakness
- Decreased muscle bulk
- Normal sensation
- Fasciculations present—tongue, proximal muscles
- Absent deep tendon reflexes
Infantile Spinal Muscular Atrophy

- Werdnig Hoffman disease/ SMA type 1
- Decreased fetal movements in utero
- Hypotonic and weak infant at birth or early infancy
- Sparing of extraocular movements
- Presence of tongue fasciculations
- Bulbar and respiratory weakness- aspiration pneumonia and respiratory failure

Spinal Muscular Atrophy

- Progressive loss of anterior horn cells in the spinal cord & motor nuclei in the brain cells
- Autosomal recessive inheritance
- Genetic defect on chromosome 5q 11-13
- Genes : SMN (Survival motor neuron gene) NAIP (Neuronal apoptosis inhibitor protein)
- Classified by age of onset and severity

DNA Testing for SMA

- Rapid DNA diagnostic test for SMA
- Deletions of exon 7 affecting the SMN gene
- Caused by a gene deletion affecting the telomeric SMN gene
- 95%- homozygous
- approx.5% -heterozygotes
- <1%- subtle intragenic mutation

Peripheral Nerve Disorders

- Hereditary:
  - Congenital hypomyelinating neuropathies
  - Dejerine Sottas syndrome (DSS)
  - Refsum’s disease
  - Leukodystrophies
- Acquired
  - Guillain Barré syndrome
  - Infectious
  - Toxic- lead, arsenic, solvents

Peripheral Nerve Disorders

- Relatively rare etiology for floppy infant
- Clues on examination
  - Hypotonia and weakness
  - Muscle fasciculations
  - Normal or decreased sensation
  - depressed to absent reflexes

Work up for peripheral nerve disorders

- Elevated CSF protein
- NCS: marked slowing of nerve conduction velocities, EMG : findings of denervation
- Nerve biopsy: thinning or complete absence of myelin, onion bulb formation (DSS and congenital hypomyelinating neuropathy)
- Genetic testing: mutations in various gene products(PMP22, MPZ, EGR2, Connexin 32)
### Neuromuscular Junction Disorders

**Clinical Clues**

- Hypotonia and generalized weakness
- Facial diplegia
- Ptosis, extraocular movement deficits
- Feeding difficulties
- Progressively weakening cry, easy fatigability
- Apnea and respiratory difficulties
- Absent fasciculations
- Normal sensation

### Transient Neonatal Myasthenia

- Seen in 10-15% of offspring's born to myasthenic mothers
- Caused by passive transfer of AChR antibody from myasthenic mother to normal fetus
- Ptosis, extraocular movement limitation
- Respiratory insufficiency - rare
- Supportive management, neostigmine, exchange transfusion
- Complete recovery in 3 to 8 weeks

### Congenital Myasthenic Syndromes

- Pre-synaptic defect in acetylcholine resynthesis or packaging or postsynaptic defect in the AChR or acetylcholinesterase deficiency
- Ptosis, generalized weakness, arthrogryposis
- EOM and facial weakness
- Respiratory insufficiency, feeding difficulty
- Seronegative for antibodies to Ach receptor
- Tensilon test – decremental response to repetitive stimulation

### Infantile Botulism

- Onset: 2 weeks to 6 months
- Pre-synaptic blockade of Ach release by Clostridium botulinum toxin
- Dietary contamination with honey or corn syrup - in 20% cases
- Presentation:
  - Asymptomatic carriers of organisms
  - Mild hypotonia with failure to thrive
  - Severe progressive life-threatening paralysis and sudden infant death

### Muscle disorders

- Congenital muscular dystrophies
- Congenital myopathies
- Metabolic myopathies
- Congenital myotonic dystrophy

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**Infantile Botulism**

- Poor feeding, lethargy, constipation
- Progressive bulbar and skeletal muscle weakness
- Diffuse hypotonia, ptosis, dysphagia, weak cry, dilated pupils (react sluggishly to light), loss of tendon reflexes
- Self-limited illness lasting 2 to 6 weeks
- Repetitive stimulation-incremental response
- Stool culture for Clostridium botulinum
- Therapy: supportive care, Botulinum immune globulin
Clues on Examination

- Hypotonia and weakness
- Normal or decreased muscle bulk
- Normal sensation
- Absent fasciculations
- Intact DTRs, may be decreased in later stages of the disease

Congenital Myotonic Dystrophy

- Affected mother, autosomal dominant
- Polyhydramnios, reduced fetal movements
- Facial diplegia, inverted V shaped upper lip
- Joint deformities-club feet, arthrogryposis
- Feeding difficulties, gastrointestinal dysfunction
- Respiratory difficulty- inadequate diaphragmatic and intercostal muscle function

Congenital Myopathies

- Developmental /structural abnormalities in the muscle fibers, variation in size and number of fiber types, presence of inclusions on EM
- Flabby muscles, weakness, hyporeflexia, high arched palate, micrognathia,open bite, facial amimia ( lack of expressions).
- Muscle biopsy: with histochemical and EM analysis, most useful diagnostic test

Congenital Myopathies

- Central core disease
- Nemaline rod disease
- Myotubular (centronuclear) myopathy
- Congenital fiber type disproportion

Congenital Muscular Dystrophy

- Absence or deficiency of key structural muscle proteins
- Progressive wasting and weakness
- Significantly elevated Serum CK levels
- Merosin (laminin alpha 2) backbone for basement membranes
- Two broad categories: Merosin deficient and merosin positive
- Eg Fukuyama CMD, Walker-Warburg syndrome, Muscle Eye brain disease

Clinical Vignette 1

- 1 month old female infant
- Normal pregnancy and birth history
- Floppy at 1 month, diminished anti-gravity leg movement and poor head control
- Alert infant, generalized hypotonia, increased head lag, weak facial muscles, tongue fasciculations and areflexia
Clinical Vignette 1

- Investigations
  - Serum CK 291 IU/L
  - EMG/NCS
  - Muscle biopsy
  - DNA testing for Chromosome 5q deletion (exon 7)
- Diagnosis: Spinal muscular atrophy
- Management: Tube feeding, frequent suctioning, Genetic counseling
- Clinical Course: recurrent aspiration pneumonia, died 6 months later.

Clinical Vignette 2

- Floppy NB with Arthrogryposis, requiring ventilator support for first 5 weeks of life and feeding difficulty
- Severe hypotonia, with tenting of the mouth
- History of mother having difficulty opening bottles and jars, maternal grandfather having difficulty releasing his grip when shoveling snow

Clinical Vignette 2

- Examine the mother and grandfather
- EMG: on mother, as infant may not have myotonia on EMG
- Genetic testing: large expansion of trinucleotide CTG repeats in the myotonin-protein kinase gene on Chromosome 19q13.

Clinical Vignette 3

- 5 month old infant with 4 day history of poor feeding and irritability
- Normal birth and early motor development
- Weak cry and suck, expressionless face, ptosis, sluggish pupils, diffuse hypotonia and hypoactive reflexes
- History of constipation

Summary

- Clinical history and examination of floppy infant
- Upper motor neuron (Central) vs. lower motor neuron (peripheral) hypotonia
- Etiologies of LMN hypotonia
- Workup of floppy infant
1- Abnormal movements in a 9 month old baby

History:
A 9-month-old baby boy is brought to the clinic with the following history:
3 weeks ago the mother noted the baby to demonstrate twisting movements of the body.
Initially she did not think much of it but reported it to the family physician as the baby appeared to be in discomfort and frequently cried with the events. Mom was asked to come back in 2 weeks.
- there are a lot of reasons for babies to be irritable, transient viral irritability for example

The baby now has similar episodes many times a day where the baby seems to twist the neck in a jerky fashion to the right, then flexes the right arm at the elbow and extends the left leg as he emits a cry. This occurs over a 2-3 second period and is followed by relaxation of the body to be repeated again shortly
- similarity of the episodes suggests it’s a discrete entity, not just random baby movements
- it requires investigation
- possible causes:
  o infantile spasm
  o benign infant myoclonus
  o colic
  o myoclonic seizures
. The baby seems to be babbling less these days per mom.
- regression
  o suggests a neurological process
  o or some kids regress during an acute illness (viral illnesses for example)

She also thinks that these events are related to sleep since they happen frequently when he wakes up and she is wondering whether the baby has nightmares!
- infants don’t have nightmares

Past medical history, history of pregnancy, birth, delivery and developmental history is all normal.
- evidence of some cause of neurological damage like encephalitis, hypoxic-ischemic damage, for example
- important to get baseline for development,
  o part of giving comprehensive care,
  o evaluate other reasons for presentation
  o follow the baby’s progress

Physical exam shows a well-nourished baby with a normal weight, height and head circumference for age.
- numbers are plotted – follow growth parameters from birth

General exam shows a non-dysmorphic facies and no neurocutaneous stigmata.
- set of diseases that are typically genetic and classically affect the skin and the brain
- skin lesions are fairly innocent on their own but signify underlying disease

Neurological exam is completely normal.
Identify the seizure type
- **infantile spasm**
- **other might be myoclonic seizure, colic, benign myoclonus of infancy (though would not have eeg changes like this one)**

List the common causes of new onset of such a seizure type in this child
- **really anything that causes brain injury of any sort**
- **infection related damage**
- **tuberosclerosis**
- **inborn errors of metabolism**
- **structural abnormalities/brain dysgenesis**
- **hypoxic ischemic damage**

What diagnostic tests would you recommend?
- EEG
- MRI
- routine biochemistry, metabolic workup

Please analyze the EEG provided
- **hypsarrhythmia** – pattern in interictal period
  - chaotic high amplitude slow waves
  - multifocal spikes and sharp waves
- ictal EEG would show flat lines

What is the diagnosis?
- infantile spasm

What would be the treatment of choice?
- **ACTH injections** – theory that it might modulate neurotransmitters somehow?
- this produces great changes in EEG pattern and may not seize again
- **vigabatrin is particularly helpful in tuberosclerosis**

What would you tell parents in terms of prognosis?
- kids who do well with ACTH become seizure free and may do well developmentally if brain is otherwise normal, or may revert back to their baseline development
  - this is not the norm
- if they continue to seize then ongoing deterioration developmentally may occur
- also if they have underlying bad etiology, or cannot be controlled with drugs, they don’t do well.
  - this is more typical
  - often evolve into a lennox-gasteau picture later in life
Case 2 - Staring and guttural sounds in a 10-year-old child

**History**
A 10 year old girl; was brought for evaluation of many episodes characterized by staring, asymmetric facial grimace, production of guttural sounds lasting 1 minute. This was followed by lethargy for about 30 minutes and many times there was evidence of right facial paresis. The girl had no memory for the events but sometimes recalled a funny taste in her mouth prior to the onset of symptoms.

Past medical history is unremarkable. Review of the family history reveals that the patients’ maternal aunt had similar episodes as a child, which then disappeared when she went to college.

General and neurological exam (including fundoscopic exam) looking for evidence of increased intracranial pressure suggestive of a mass lesion, hydrocephalus etc. papilledema (hemorrhages, engorgement of the vessels, loss of the optic cup, fuzzy disk margins) are normal.

**What is the seizure type?**
- complex partial seizure
  - begins with aura of a funny taste in her mouth
  - post-ictal state of lethargy and right facial paresis for about 30 min
  - facial movements and guttural sounds asymmetric (one spot involved)

**What are the likely causes of a new onset seizure in a child this age?**
- causes may be
  - idiopathic (genetic) – often passed on in dominant fashion
    - with family history of seizures that regressed in adulthood in a person with above average intelligent (went to college)
    - suggests a positive prognosis
  - cryptogenic
    - very common
  - symptomatic
    - history of head trauma in past (even if not apparently a significant trauma)
    - encephalitis.meningitis in past leaving a deficit
even if not apparently a significant trauma
  - tumor
  - never too old to rule out inborn errors of metabolism
  - electrolyte, glucose, metabolic abnormality
  - structural CNS abnormality – small areas of dysplasia can give you partial seizures
  - psychogenic non-epileptic
Differential diagnosis?
- metabolic abnormalities
- structural abnormality, tumor
- migraine – movements are atypical, sometimes people will have both migraine and epilepsy
- muchousen (by proxy)

What diagnostic tests would you recommend?
- MRI, EEG, metabolic workup (electrolytes, glucose, metabolites, LFT’s etc)

Comment on the EEG findings
- Left posterior temporal and parietal
- the rest of the EEG s normal
- consistent with complex partial seizures exhibiting right face twitch

Recommend appropriate treatment
- the post ictal phase is long, and they are frequent, so she should benefit from treatment
- suggested treatment: carbemazepine is first line for partial
  - look for rashes and other side effects

What is the prognosis?
- good prognosis, especially if control can be achieved
- treat her for a year or two and take her off the drugs, and she will likely “outgrow” her seizures
- resistance to seizures increases with age