Pediatric Neurology: Autism, Cerebral Palsy and More

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This article covers a lot on the topic of pediatric neurology. It explores embryological deficits which are fully covered in the etiology section. It will also cover definitions of intellectual disability, autism, developmental regression, and neurocutaneous disorders. Etiology, diagnosis, and management of these conditions are also discussed. This article runs complementary to Dr. Rangaraj's lecture on pediatric neurology.

Definition of Neurologic Disorders in Children

Mental retardation (intellectual disability)**:** below average intellectual function (usually full-scale IQ <70) and below average adaptive behavior.

Autism: a developmental disorder where patients do not develop a theory of mind. This manifests as abnormal language, poor social skills, behavioral abnormalities, and repetitive and stereotyped behaviors.

Developmental regression: loss of previously attained developmental milestones with almost always a bad prognosis.

Neurocutaneous disorders: broad term for neurologic disorders that are lifelong conditions. These include:

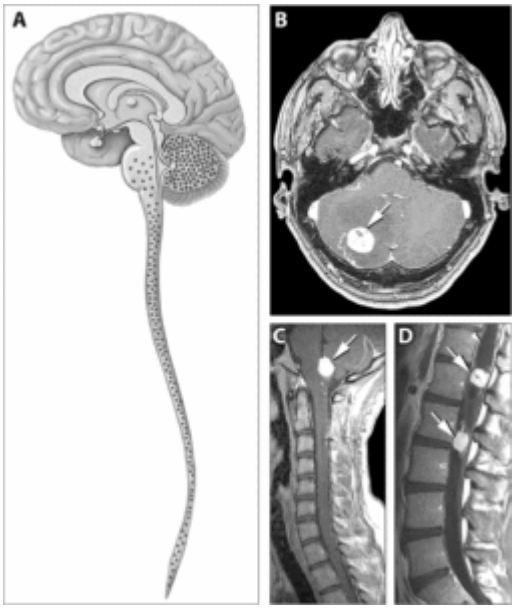

Image: “Distribution of Hemangioblastomas in the Central Nervous Systems of Study Patients with Von Hippel-Lindau Disease.” License: CC BY 2.5

- Tuberous sclerosis complex
- Neurofibromatosis type 1 and type 2
- Sturge-Weber syndrome
- Familial telangiectasia
- Von Hippel-Lindau disease
- Incontinentia pigment
- Ataxia-telangiectasia

Not all disorders are discussed in detail in this article.

Hypotonia: reduction in postural tone (floppy infant). Not necessarily associated with significant weakness.

Epidemiology of Neurologic Disorders in Children

Cerebral palsy: incidence of around 3 in 1000 live births

Autism spectrum disorders: incidence and prevalence of autism have increased rapidly in recent years. Around 1 in 100 children are diagnosed with some form of autism spectrum disorder.

Neurocutaneous disorders:

- Tuberous sclerosis – an autosomal dominant disease with an incidence of 1 in 10,000
- Neurofibromatosis type 1 – an autosomal dominant disease with an incidence of 1 in 3,000
- Neurofibromatosis type 2 – an autosomal dominant disease that is far less common than neurofibromatosis type 1

Etiology of Neurologic Disorders in Children

Brain tissue begins to differentiate from the **ectoderm** at around 3 weeks. Between

week 3 and 4, **neurulation** (the formation and closure of the neural tube) takes place. The anterior (rostral) neural tube closes at around 24 days. Failure of this process leads to **anencephaly** or **encephalocele**. Infants with anencephaly have no forebrain and as such have an open **calvarium**.

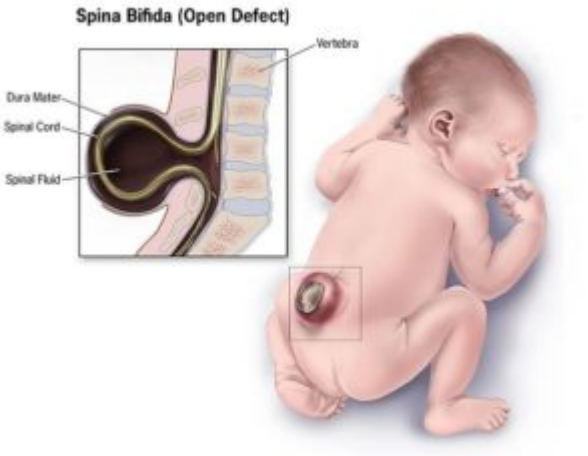

Image: "An illustration of an infant with spina bifida." by Centers for Disease Control and Prevention – Centers for Disease Control and Prevention. License: Public Domain

The posterior or caudal neural tube closes at around 27 days. Failure can lead to **myelomeningocele**, **meningocele** and **spina bifida**. In a spina bifida, the bony spinal canal fails to close. It can often be seen as a "tuft" of hair on the lower back of the patient with a minor deficit.

A **meningocele** is when the meninges outpouch, or herniate, through the bony defect.

A **meningomyelocele** occurs when both the meninges and nervous system tissue bulge through the defect.

Around weeks 5-6 the **vesicle** forms. The prosencephalon forms the telencephalon and diencephalon. The mesencephalon remains undivided. The rhombencephalon forms the metencephalon and myelencephalon.

Holoprosencephaly can occur due to a failure of prosencephalon cleavage. Holoprosencephaly is associated with **mutations in the "sonic the hedgehog" gene**. In severe instances, patients will have **cyclopia**.

Between weeks 8 and 32, **cellular proliferation and migration** take place. The **sulci** and **gyri** form.

- **Lissencephaly** is a smooth cortical surface due to poor migration.
- **Pachygyria** is defined as large gyri.
- **Microgyria** is defined as small gyri.
- **Schizencephaly** is defined as a crack in the brain where a cleft exists due to defective morphogenesis (stroke can often be the cause).

Etiology of intellectual disability (mental retardation)

This can be caused by a number of factors including **prenatal or postnatal trauma**, **hypoxic-ischemic encephalopathy**, **perinatal infections** (TORCH, HIV), **chromosomal abnormalities** as in Down's or Fragile X, **metabolic disorders** as in

hypothyroidism or Tay-Sachs disease. **Toxins** (e.g. alcohol in fetal alcohol syndrome) and **perinatal hypoxic-ischemic insult**.

Developmental regression (the loss of previously attained developmental milestones) usually has an onset before age 2. It is caused by a number of disorders including:

- Mitochondrial disorders (MELAS – mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes)
- Hypothyroidism
- Neurocutaneous disorders: neurofibromatosis
- Gray matter disorders
- White matter disorders: metachromatic leukodystrophy
- Amino acid metabolism disorders: phenylketonuria
- Enzymatic disorders

Neurocutaneous disorders are genetic disorders. **Tuberous sclerosis** is caused by an autosomal dominant mutation in 2 genetic loci. Either TSC1 on chromosome 9 which codes for the protein hamartin or TSC2 on chromosome 16 which codes for tuberin.

Neurofibromatosis type 1 is an autosomal dominant disease caused by a mutation on chromosome 17 in the gene that codes for the protein neurofibromin.

Neurofibromatosis type 2 is an autosomal dominant disease that is caused by a mutation of chromosome 22 that codes for the protein Merlin.

Sturge-Weber syndrome is a somatic non-inherited mutation developmental abnormality in the neural crest. This is caused by activation of a gene called GNAQ. This affects small blood vessels and patients typically present with a classic “port wine” stain on the face.

A number of underlying conditions can cause **hypotonia** (floppy baby syndrome). These can either be congenital or acquired.

There are a number of causes of **cerebral palsy** and as such the disorder has multiple etiologies. Antenatal factors like **premature birth** and **thyroid disease** can lead to cerebral palsy. Perinatal factors like **asphyxia** have also been linked to the development of the condition.

Risk Factors for Neurologic Disorders in Children

Risk factors are events associated with the development of a disease. The underlying etiology of how the risk events cause the disorder is not always known. Below are a number of risk factors for common pediatric neurological conditions.

In cerebral palsy, risk factors include:

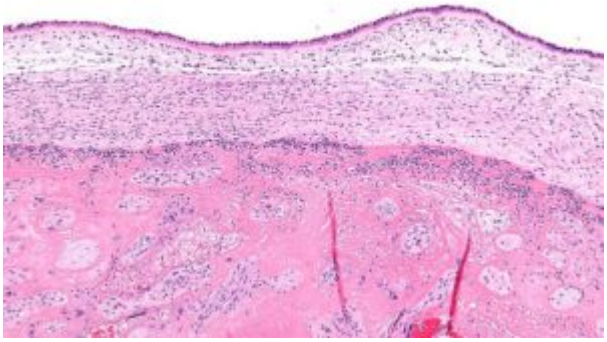

Image: “Intermediate magnification micrograph chorioamnionitis. H&E stain.” by Nephron – Own work. License: CC BY-SA 3.0

- Prematurity
- Low birth weight
- Chorioamnionitis
- Prenatal viral infection
- Prenatal strokes
- Perinatal hypoxic-ischemic insult

Risk factors for autism spectrum disorders are:

- Being of the male sex
- Positive family history
- Some genetic variant
- Chromosomal abnormalities

Classification of Neurologic Disorders in Children

A number of the disorders discussed in this article can be further classified into subtypes. These subtypes are discussed in more detail below.

Classification of **cerebral palsy**: There are a number of classifications of cerebral palsy. The classification is based on the **type of motor abnormalities** and their distribution in the patients. These include:

- Spastic (hypertonic) – most common
- Flaccid (hypotonic)
- Ataxic
- Dystonic (athetoid)
- Mixed

Classification of **hypotonia** (floppy baby syndrome): hypotonia can either be **central** or **peripheral**.

Pathophysiology of Neurologic Disorders in Children

Pathophysiology of cerebral palsy

Cerebral palsy has a number of underlying pathophysiological mechanisms dependent on

the etiology of the condition. In the event of **oxygen compromise** during or just after birth, there is a **hypoxic-ischaemic encephalopathy** that may cause damage **to the periventricular white matter** (particularly the internal capsule, leading to motor deficits).

As such, **neural projections from the motor cortex** are disrupted in the **internal capsule** and **skeletal muscle response** is hence affected. Fine motor control is often lost.

Pathophysiology of autism spectrum disorders

The complete pathophysiology of autism is not known. There are **genetic factors**, but their association is weak and defining pathophysiology has not been deciphered. We do know that the disorder is **neurodevelopmental** and much research has been done on the **altered function of the hippocampal and amygdala brain structures** (that are intimately tied to our emotions and empathy).

There are a few theories although they do not have much significance. They include the **theory of mind explanation** of autism whereby autistic individuals are hypothesized as not having a “theory of mind” i.e. an understanding of the internal agency of others.

Complications of neurological disorders

There is a wide range of complications varying from physical to behavioral and pathological. Some of them are Seizures, perinatal injuries, neurodevelopmental disorders, movement disorders, control and coordination disorders, psychological ailments, hemorrhages, and even stroke.

Diagnosis of Neurologic Disorders in Children

A **clinical diagnosis of autism** is not expected to be made in the USMLE step 1 but it is good to understand the general principles. Diagnosis of autism spectrum disorders is typically made clinically and by pediatricians. Most patients will have behavioral signs that affect their home and school life by the age of 2 years. Babies are either quiet and placid or irritable and throw frequent tantrums.

Diagnosis is difficult because the severity of the disorder varies and many children without autism spectrum disorders also display these types of symptoms. Many patients will fail theory of mind tests (e.g. the Sally Anne test).

Diagnosis of cerebral palsy is typically clinical. The examination will look at the range of motion, the power of movement and voluntary motor control. Thorough history should be taken and risk factors like **teratogen exposure in pregnancy** or **asphyxiation during birth** should be identified.

Patients with **tuberous sclerosis** typically present with the classic **“Vogt’s” triad of symptoms**. These are **skin lesions**, **convulsive seizures**, and **intellectual disability**. Patients with tuberous sclerosis will have **adenoma sebaceum**, **ungual fibroma**, **cortical tubers**, **subependymal nodules,** and **multiple retinal astrocytomas**. They then go on to develop **infantile spasms**, **ash leaf spots** (hypomelanotic macules), **cardiac rhabdomyoma** and **renal angiolipomas**.

Patients with **neurofibromatosis type 1** will have **Café au lait spots**, **axillary freckles** and **Lisch nodules** (iris hamartomas). On investigation, they have **plexiform**

simple neurofibromas, **optic gliomas**, **obstructive hydrocephalus**, and **pheochromocytomas**.

Patients with **neurofibromatosis type 2** will, on an investigation, have **bilateral acoustic neuromas** and can also develop **multiple meningiomas**.

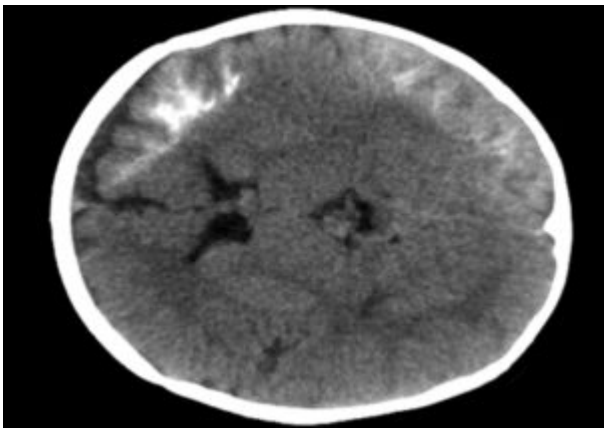

Image: "CT (without contrast) of the brain of a 20 month old child with Sturge-Weber syndrome demonstrating prominent subcortical white matter calcification." by Frank Gaillard – Own work. License: CC BY-SA 3.0

Sturge-Weber syndrome can often be noticed through the **"port wine" stain**, or **"nevus flammeus" stain** that typically has a **cranial nerve V distribution**. Patients develop **leptomeningeal angiomas** and will suffer from **seizures** and intellectual disability. They may have early onset **glaucoma**.

Remember – **hypotonia** is not a diagnosis of a disease but a syndrome. When examining a patient with hypotonia, it is important to identify underlying causes. **Central hypotonia** is typically associated with other signs of CNS dysfunction like **seizures**, **developmental delay**, **microcephaly,** and **dysmorphic features**. **Peripheral hypotonia** has a lack of central sign; **weakness** is prominent.

Therapy of Neurologic Disorders in Children

Treatment of cerebral palsy is tailored for the individual patient. In children with cerebral palsy, current therapies include **anticonvulsants**, **botulinum toxin**, **diazepam**, **fitness training,** and **goal-directed training** among others.

There is **no treatment for neurocutaneous disorders** like neurofibromatosis and Von Hippel-Lindau syndrome. When tumors form, **surgery** is often the only option. Apart from surgery, most management will come from **support and general counseling**.

There is **no cure for autism** and therapy is based mainly on **improving social communication**.

Prognosis of Neurologic Disorders in Children

The **prognosis of cerebral palsy** is highly dependent on the level of motor deficit and the intellectual ability of the sufferer. In most cases, cerebral palsy sufferers survive into adulthood and live to senior age. Life expectancy has improved significantly in the last 10-20 years.

Autism spectrum disorders are lifelong and have a variable course often dependent on the severity of the disease in childhood. Many (around 15 %) will live independent lives. Another 15 to 10 % will need community living support. The most prognostic factors for independent living are cognitive and verbal capacity.

Those with **neurofibromatosis type 1** rarely live beyond 50. Poor prognostic factors include childhood learning difficulties and optic gliomas among others.

Prognosis in patients with **spina bifida** depends on the severity of the defect. Milder the symptoms better the prognosis. However, medications, physical rehabilitation, recommended surgical intervention improves quality of life to a greater extent.

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Notes