- Neurodegenerative disorders (NDD) are characterized by Neuro regression.Neuroregression in children is associatedwith loss of memory, Ability to think, understand and recognize along with personality changes or distressing behavior. Vision loss, hearing loss, tone abnormalities and epilepsy are other common symptoms. This neurological deterioration is not explainable by any other concurrent systemic illness.
- Never miss out a treatable cause of neuroregression like hydrocephalus, HIV infection, hypothyroidism,lead toxicity
- There may be regression in static encephalopathy.Increasing spasticity (usually during the firstyear) New onset movement disorders (usually during the second year) New onset seizures,Parental misperception of attained milestones,Progressive hydrocephalus
- Many neurodegenerative disease are treatable

Disease	Therapeutic agent
Gaucher disease	Enzyme replacement, Miglustat
Fabry disease	Enzyme replacement
Attenuated variants of Mucopolysaccharidosis type I (MPS I)	Enzyme replacement
Pompe disease	Enzyme replacement
Ataxia (Co-Q deficiency)	Coenzyme Q10
Ataxia with vitamin E deficiency	Vitamin E
Minimally symptomatic X-linked adrenoleukodystrophy	Bone marrow transplant
MPS 1H-Hurler disease	Bone marrow transplant
Glycogen storage disease	Liver transplant
Glutaric aciduria–II, Biotinidase deficiency	Co-factor replacement

-

Evaluation

- The objective of a careful initial evaluation is to ascertain the age of onset, extent and evolution of the disease (white matter, gray matter, cerebellum, As a first step to clinical evaluation, pseudoregression should be excluded in all cases.
- Regression can occur without an underlying neurodegenerative process due to poorly controlled seizures, over-medication with anticonvulsants,intercurrent systemic illness and secondary neurological problems in a static encephalopathy, e.g. loss of mobility due to development of joint contracture, seizures, movement disorder, etc. or depression or other emotional problems especially in older children
-

Feature	Gray matter	White matter
Dementia	Early	Late
Seizures	Early and prominent	Late
Psychological symptoms	May be present	Uncommon
Basal ganglia signs and symptoms	Often present	Absent
Retinitis pigmentosa	May be present	Absent
Primary optic atrophy	Rare	May be seen
Primary neuropathy	Rare	May be seen
Imaging (MRI)	Cortical atrophy, abnormalities in basal ganglia, cerebellum	Clearly identifies abnormalities in white matter
Electroretinogram	May be abnormal	Normal
Visual evoked response	May be abnormal	Normal
Brainstem auditory evoked responses	Usually normal	Abnormal

History and Examination

- A detailed history is aimed at ascertaining the age of onset,and the spheres of development affected—motor, cognitive,vision and hearing. Family history of three generations isimportant to identify the possible modes of transmission.There are certain specific clues in general physical and systemic examinations, which give an indication to thenature of disorder. After a careful history and examination, one is generally able to decide about therange of pathology within the nervous system and whetherother organ systems are involved or not.
- Broadly, if one is able to assign the patient into one of the following groups,the further evaluation is easier.
- **Gray matter degenerations:** poliodystrophies
- **White matter degeneration:** leukodystrophies
- Progressive ataxias
- Basal ganglia disorders
- Multisystem disorders with neuroregression

Clinical features

| Head	Microcephaly	NCL, Krabbe disease, Rett syndrome
	Macrocephaly	MPS, Alexander disease, Canavan disease, GM1 gangliosidosis, Tay-Sachs disease, MLSC
Hair	Alopecia	Biotinidase deficiency
	Pigmentary changes	PKU, Menkes disease
	Wooly, kinky hair	Menkes disease (Fig. 6.3.7)
Skin	Rash	Biotinidase, holocarboxylase deficiency
	Subcutaneous nodules	Farber disease
	Angiokeratomas	Fabry disease
	Fat pads, focal atrophy	Congenital disorders of glycosylation
	Hyperpigmentation	Adrenoleukodystrophy
Eyes	Cataract	Galactosemia, Zellweger disease, Wilson disease
	Retinitis pigmentosa	Peroxisomal disorders, NCL, mitochondrial encephalomyopathies, MPS, PKAN, ABLP
	Cherry red spot	Tay-Sachs disease, Niemann-Pick disease, GM1 gangliosidosis
	Optic atrophy	NCL, MLD, Krabbe disease, Canavan disease, GM2 gangliosidosis
Ears	Deafness	MPS, ALD, mitochondrial disorders, peroxisomal disorders
	Hyperacusis	Krabbe, Tay-Sachs disease
Abdomen	Hepatosplenomegaly	MPS, GM1 gangliosidosis, Gaucher disease, Niemann-Pick disease
	Hernia	GM1 gangliosidosis, MPS
Nervous system	Peripheral neuropathy	MLD, Krabbe disease, mitochondrial disorders
	Hydrocephalous/raised intracranial pressure	MPS, infantile Alexander disease
Cardiac	Cardiomyopathy	FAOD, mitochondrial disorders, Friedreich ataxia, AVED, Pompe disease
	Valvular defects	MPS, Zellweger syndrome, Fabry disease

Abbreviations: NCL, Neuronal ceroid lipofuscinosis; MPS, Mucopolysaccharidosis; MLSC, Megalencephalic leukodystrophy with subcortical cysts; PKU, Phenylketonuria; PKAN, Pantothenate kinase associated neurodegeneration; ABLP, Abetalipoproteinemia; MLD, Metachromatic leukodystrophy; ALD, Adrenoleukodystrophy; FAOD, Fatty acid oxidation defects; AVED, Ataxia with vitamin E deficiency

Regression in a child below two years

- During infancy delayed milestones are common manifestation of neuroregressive disorders. Since the child has not gained many distinctive abilities, the loss of abilitiesis difficult to quantify or localize. Commonly, the infant lacks visual interest or socialization has poor head control and inability to use hands. Other common symptoms are developmental retardation with severe hypotonia especially with feeding difficulties and/or vomiting and failure to thrive.
- Many disorders that present in the second year of lifeare frequently recognizable by the obvious loss of motor abilities. This may result from corticospinal, cerebellar,extrapyramidal or peripheral nerve involvement. The second year of life is also the age for disorders with gradually increasing dysmorphism, skeletal abnormalities and cognitive decline

[mucopolysaccharidosis (MPS) and mucolipidosis]. Some children may present with progressive mental deterioration, seizures and vision loss. Yet another group of children, presents with recurrent neurological deterioration interspersed with apparent recovery (organic aciduria, mitochondrial disorders, urea cycle disorders, etc.).

- In girls with regression in cognitive spheres starting in infancy, microcephaly and associated with loss of purposeful hand movements "Rett syndrome" should be considered.
- Additionally, a possibility of HIV encephalopathy should always be kept in mind and a systematic evaluation for risk factors should be undertaken.
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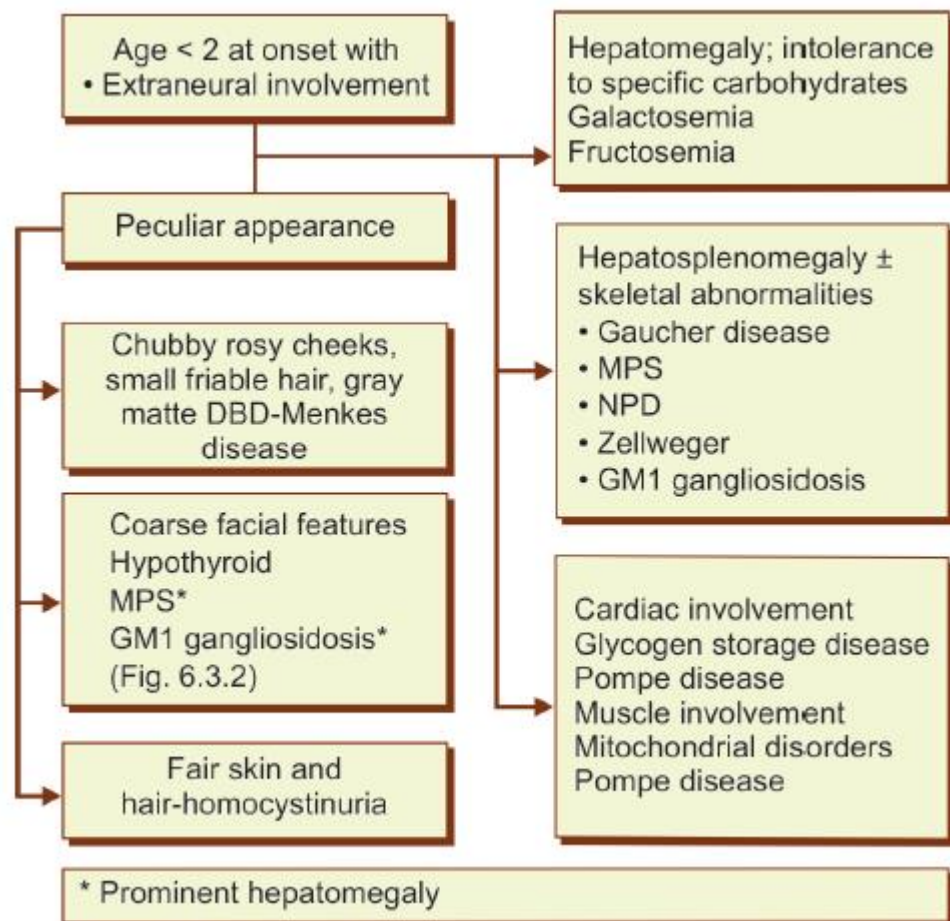
- presents at birth or during the neonatal period with anorexia, poor sucking, and inadequate weight gain. Development is globally retarded, and generalized seizures are prominent. The phenotype is striking and shares many characteristics with Hurler syndrome.
- The **facial features are coarse**, the forehead is prominent, the nasal bridge is depressed, the tongue is large (macroglossia), and the gums are hypertrophied. Hepatosplenomegaly is present early in the course as a result of accumulation of foamy histiocytes, and **kyphoscoliosis is evident because of anterior beaking of the vertebral bodies**. The neurologic examination is dominated by apathy, progressive blindness, deafness, spastic quadriplegia, and decerebrate rigidity. **A cherry red spot in the macular region is visualized in approximately 50% of cases**.
- The **cherry red spot** is characterized by an opaque ring (sphingolipid-laden retinal ganglion cells) encircling the normal red fovea Children rarely survive beyond age 2-3 yr, and death is due to aspiration pneumonia
- **Hurler Disease**
- This form of MPS I (MPS I-H) is a severe, progressive disorder with multiple organ and tissue involvement that results in premature death, usually by 10 yr of age. An infant with Hurler syndrome appears normal at birth, but inguinal hernias are often present. **Diagnosis is usually made between 6 and 24 mo of age with evidence of hepatosplenomegaly, coarse facial features, corneal clouding, large tongue, prominent forehead, joint stiffness, short stature, and skeletal dysplasia** Acute cardiomyopathy has been found in some infants <1 yr of age.
- Most patients have recurrent upper respiratory tract and ear infections, noisy breathing, and persistent copious nasal discharge. Valvular heart disease with incompetence, notably of the mitral and aortic valves, regularly develops, as does coronary artery narrowing. Obstructive airway disease, notably during sleep, may necessitate tracheotomy. Obstructive airway disease, respiratory infection, and cardiac complications are the common causes of death
- **Gaucher disease type 2** is much less common and does not have an ethnic predilection. It is characterized by **a rapid neurodegenerative course with extensive visceral involvement and death within the first years of life. It presents in infancy with increased tone, strabismus, and organomegaly. Failure to thrive and stridor caused by laryngospasm are typical**. After

a several-year period of psychomotor regression, death occurs secondary to respiratory compromise
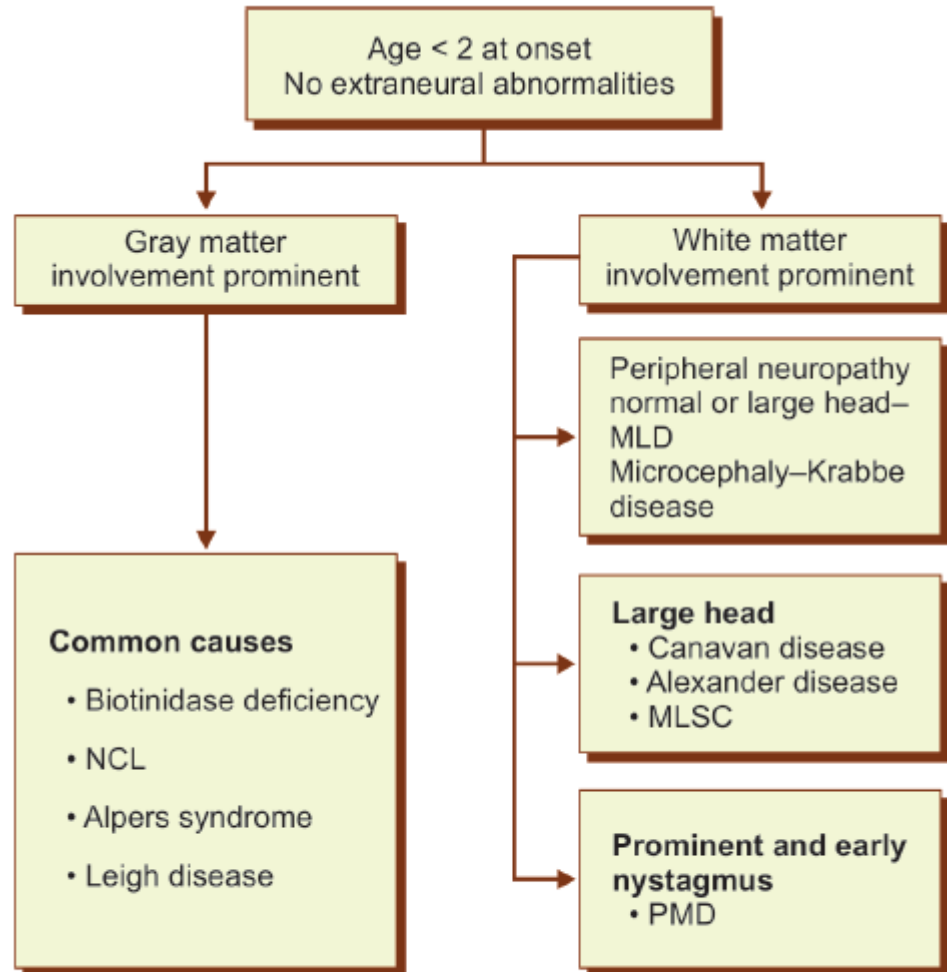
- **Nieman pick disease:**
- The clinical manifestations and course of type A NPD is uniform and is characterized by a normal appearance at birth. **Hepatosplenomegaly, moderate lymphadenopathy, and psychomotor retardation are evident by 6 mo of age, followed by neurodevelopmental regression and death by 3 yr**. With advancing age, the loss of motor function and the deterioration of intellectual capabilities are progressively debilitating; and in later stages, spasticity and rigidity are evident. Affected infants lose contact with their environment
- **Pompe:**
- The disorder encompasses a range of phenotypes, each including myopathy but differing in age at onset, organ involvement, and clinical severity. **Infantile Pompe disease** was uniformly lethal without enzyme replacement therapy. Affected infants present in the 1st few months of life with **hypotonia, a generalized muscle weakness with a "floppy infant" appearance, neuropathic bulbar weakness, feeding difficulties, macroglossia, hepatomegaly**, and a hypertrophic cardiomyopathy followed by death from cardiorespiratory failure or respiratory infection usually by 1 yr of age
- **Galactosemia:**
- The diagnosis of uridyl transferase deficiency should be considered in newborn or young infants with any of the following features: jaundice, hepatomegaly, vomiting, hypoglycemia, seizures, lethargy, irritability, feeding difficulties, poor weight gain or failure to regain birth weight, aminoaciduria, nuclear cataracts, vitreous hemorrhage, hepatic failure, liver cirrhosis, ascites, splenomegaly, or mental retardation. Symptoms are milder and improve when milk is temporarily withdrawn and replaced by intravenous or lactose-free nutrition. Patients with galactosemia are at increased risk for *Escherichia coli* neonatal sepsis; the onset of sepsis often precedes the diagnosis of galactosemia. Pseudotumor cerebri can occur and cause a bulging fontanel. Death from liver and kidney failure and sepsis may follow within days. When the diagnosis is not made at birth, damage to the liver (cirrhosis) and brain (mental retardation) becomes increasingly severe and irreversible

Age < 2 at onset
No extraneural abnormalities

Gray matter involvement prominent

White matter involvement prominent

Peripheral neuropathy normal or large head–MLD
Microcephaly–Krabbe disease

Common causes

- Biotinidase deficiency
- NCL
- Alpers syndrome
- Leigh disease

Large head
- Canavan disease
- Alexander disease
- MLSC

Prominent and early nystagmus
- PMD

Abbreviations: NCL, Neuronal ceroid lipofuscinosis; MLD, Metachromatic leukodystrophy; MLSC, Megalencephalic leukodystrophy with subcortical cysts; PMD, Pelizaeus-Merzbacher disease

MLD:

Late infantile MLD begins with insidious onset of gait disturbances between 1 and 2 yr of age. The child initially appears awkward and frequently falls, but locomotion is gradually impaired significantly and support is required in order to walk. The extremities are hypotonic, and the deep tendon reflexes are absent or diminished. Within the next several months, the child can no longer stand, and deterioration in intellectual function becomes apparent. The speech is slurred and dysarthric, and the child appears dull and apathetic. Visual fixation is diminished, nystagmus is present, and examination of the retina shows optic atrophy. Within 1 yr from the onset of the disease, the child is unable to sit unsupported, and progressive decorticate postures develop. Feeding and swallowing are impaired

due to pseudobulbar palsies, and a feeding gastrostomy is required. Patients ultimately become stuporous and die of aspiration or bronchopneumonia by age 5-6 yr. Neurophysiologic evaluation shows slowing of peripheral nerve conduction velocities (NCVs) and progressive changes in the VEPs, ABRs, and somatosensory-evoked potentials (SSEPs). CT and MRI images of the brain indicate diffuse symmetric attenuation of the cerebellar and cerebral white matter, and examination of the CSF shows an elevated protein content. Bone marrow transplantation is a promising experimental therapy for the management of late infantile MLD. As with Krabbe disease, favorable outcomes have been reported only in patients treated very early in the course of the disease

KRABBES DISEASE:

The symptoms of KD become evident in the 1st few months of life and include excessive irritability and crying, unexplained episodes of hyperpyrexia, vomiting, and difficulty feeding. In the initial stage of KD, children are often treated for colic or "milk allergy" with frequent formula changes. Generalized seizures may appear early in the course of the disease. Alterations in body tone with rigidity and opisthotonos and visual inattentiveness due to optic atrophy become apparent as the disease progresses. In the later stages of the illness, blindness, deafness, absent deep tendon reflexes, and decerebrate rigidity constitute the major physical findings. Most patients die by 2 yr of age. MRI and magnetic resonance spectroscopy are useful for evaluating the extent of demyelination in Krabbe disease. Umbilical cord blood (stem cell) transplantation from unrelated donors in asymptomatic babies may favorably alter the natural history but will not help patients who already have neurologic symptoms

NCL:

CLINICAL AND GENETIC CHARACTERISTICS OF THE NCLs*

NCL TYPE	GENE[†]	PROTEIN[†]	AGE OF ONSET	CLINICAL PRESENTATION
Congenital	CLN10	Cathepsin[‡]	Birth (but can present later)	Severe seizures, blindness, rigidity, early death Can also present similar to late infantile forms
Infantile	CLN1	Palmitoyl-protein	6-24 months	Early onset, often rapid progression of seizures;

NCL TYPE	GENE[†]	PROTEIN[‡]	AGE OF ONSET	CLINICAL PRESENTATION
		thioesterase-1 (PPT1)[‡]		cognitive and motor decline with visual loss
Variant infantile	CLN1		3 years to adulthood	Chronic course Initial visual loss followed then by slow mental and motor decline and seizures
Late infantile	CLN2	Tripeptidyl peptidase-1 (TPP1)[‡]	2-8 years	Seizures, often severe and intractable; cognitive and motor decline; and visual loss
	CLN5	Partially soluble protein		
	CLN6	Membrane protein		
	CLN8	Membrane protein	5-10 years	Severe epilepsy, progressive with mental retardation (EPMR)
Juvenile	CLN3	Membrane protein	4-10 years	Visual loss is usually the initial presenting complaint Also have mental, motor disorder and seizures

* Note that all the NCL genes have the prefix *CLN*. The adult form (also called Kufs disease, with locus *CLN4*) is not well characterized and is not included.

† Direct genetic testing is available.

Neuroregression in Later Childhood and Adolescence

In older children, the presentation of neuroregression begins after a considerable period of normal evelopment.
The onset and course of the disorder can also be more accurately determined. It is now much easier to view individual patients as having the predominant involvement of a particular area of the nervous system. The major clinical problem one faces is the varied ways in which the same disorder can present.

This is particularly so for autosomal dominant disordersSubacute sclerosing pan-encephalitis (SSPE), though not a hereditary NDD is a common cause of neuroregression in our country. It should be considered in all children with behavioral changes, cognitive deterioration with or without myoclonic jerks.

Approach to progressive neurological deterioration in 2–5 years age group
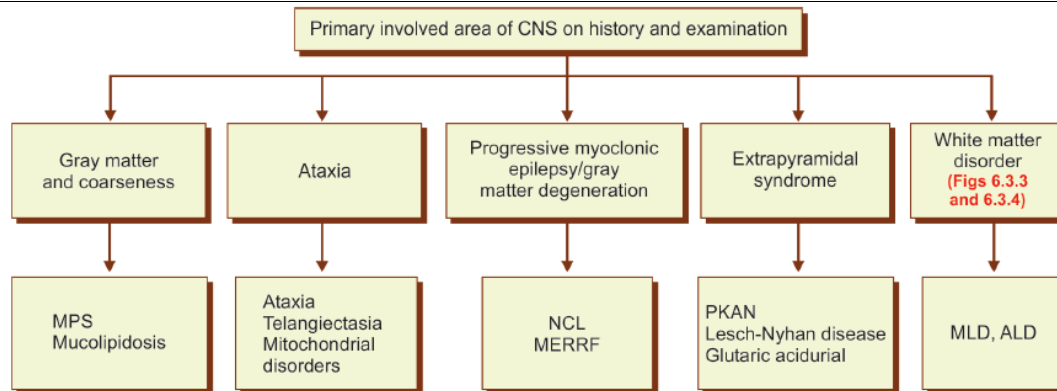
Abbreviations: MLD, Metachromatic leukodystrophy; ALD, Adrenoleukodystrophy; PKAN, Pantothenate kinase associated neurodegeneration; NCL, Neuronal ceroid lipofuscinosis; MERRF, Myoclonic epilepsy with ragged red fibers; MPS, Mucopolysaccharidosis

Mitochondrial diseases

are a clinically heterogeneous group of disorders that arise as a result of dysfunction of the mitochondrial respiratory chain. They can be caused by mutations of nuclear or mitochondrial DNA (mtDNA). Some mitochondrial disorders only affect a single organ (e.g., the eye in Leber hereditary optic neuropathy [LHON]), but many involve multiple organ systems and often present with prominent neurologic and myopathic features. Mitochondrial disorders may present at any age. Many affected individuals display a cluster of clinical features that fall into a discrete clinical syndrome, such as the Kearns-Sayre syndrome (KSS), chronic progressive external ophthalmoplegia (CPEO), mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS), myoclonic epilepsy with ragged-red fibers (MERRF), neurogenic weakness with ataxia and retinitis pigmentosa (NARP), or Leigh syndrome (LS). However, considerable clinical variability exists and many individuals do not fit neatly into one particular category. Common clinical features of mitochondrial disease include ptosis, external ophthalmoplegia, proximal myopathy and exercise intolerance, cardiomyopathy, sensorineural deafness, optic atrophy, pigmentary retinopathy, and diabetes mellitus. Common central nervous system findings are fluctuating encephalopathy, seizures, dementia, migraine, stroke-like episodes, ataxia, and spasticity. A high incidence of mid- and late pregnancy loss is a common occurrence that often goes unrecognized.

Diagnosis/testing. In some individuals, the clinical picture is characteristic of a specific mitochondrial disorder (e.g., LHON, NARP, or maternally inherited LS), and the diagnosis can be confirmed by molecular genetic testing of DNA extracted from a blood sample. In many individuals, such is not the case, and a more structured approach is needed, including family history, blood and/or CSF lactate concentration, neuroimaging, cardiac evaluation, and muscle biopsy for histologic or histochemical evidence of mitochondrial disease, and molecular genetic testing for a mtDNA

Clinical Syndromes of Mitochondrial Diseases

Disorder	Primary Features	Additional Features
Alpers-Huttenlocher syndrome	• Hypotonia • Seizures • Liver failure	• Renal tubulopathy
Chronic progressive external ophthalmoplegia (CPEO)	• External ophthalmoplegia • Bilateral ptosis	• Mild proximal myopathy
Kearns-Sayre syndrome (KSS)	• PEO onset at age <20 years • Pigmentary retinopathy • One of the following: CSF protein >1g/L, cerebellar ataxia, heart block	• Bilateral deafness • Myopathy • Dysphagia • Diabetes mellitus • Hypoparathyroidism • Dementia
Pearson syndrome	• Sideroblastic anemia of childhood • Pancytopenia • Exocrine pancreatic failure	• Renal tubular defects

Infantile myopathy and lactic acidosis (fatal and non-fatal forms)	• Hypotonia in 1st year of life • Feeding and respiratory difficulties	• Fatal form may be associated with a cardiomyopathy and/or the Toni-Fanconi-Debre syndrome
Leigh syndrome (LS)	• Subacute relapsing encephalopathy • Cerebellar and brain stem signs • Infantile onset	• Basal ganglia lucencies • Maternal history of neurologic disease or Leigh syndrome
Neurogenic weakness with ataxia and retinitis pigmentosa (NARP)	• Late-childhood or adult-onset peripheral neuropathy • Ataxia • Pigmentary retinopathy	• Basal ganglia lucencies • Abnormal electroretinogram • Sensorimotor neuropathy
Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS)	• Stroke-like episodes at age <40 years • Seizures and/or dementia • Ragged-red fibers and/or lactic acidosis	• Diabetes mellitus • Cardiomyopathy (initially hypertrophic; later dilated) • Bilateral deafness • Pigmentary retinopathy • Cerebellar ataxia
Myoclonic epilepsy myopathy sensory ataxia (MEMSA) [1]	• Myopathy • Seizures • Cerebellar ataxia	• Dementia • Peripheral neuropathy • Spasticity
Myoclonic epilepsy with ragged-red fibers (MERRF)	• Myoclonus • Seizures • Cerebellar ataxia • Myopathy	• Dementia • Optic atrophy • Bilateral deafness • Peripheral neuropathy • Spasticity • Multiple lipomata

Leber hereditary optic neuropathy(LHON)	• Subacute painless bilateral visual failure • Males:females ~4:1 • Median age of onset 24 years	• Dystonia • Cardiac pre-excitation syndromes

ADRENOLEUCODYSTROPHY

Classic adrenoleukodystrophy (ALD), also called cerebral ALD (CERALD) is considered to be the most common leukodystrophy. Boys present between 5 and 15 yr of age with evidence of academic difficulties, behavioral disturbances, and gait abnormalities. ALD is caused by accumulation of very long chain fatty acids in neural tissue and adrenals due to mutations in the *ABCD1* gene coding for the ALD protein, an adenosine triphosphate (ATP)-binding cassette half transporter on Xq28.

The incidence of ALD approximates 1/20,000 boys. In 40% of male hemizygotes, the disease presents in its classic form, CERALD, as an inflammatory demyelinating disease. Generalized seizures are common in the early stages. Upper motor neuron signs include spastic quadriparesis and contractures, ataxia, and marked swallowing disturbances secondary to pseudobulbar palsy. These dominate the terminal stages of the illness. Hypoadrenalism is present in approximately 50% of cases, and adrenal insufficiency characterized by abnormal skin pigmentation (tanning without exposure to sun) may precede the onset of neurologic symptoms. CT scans and MRI studies of patients indicate periventricular demyelination beginning posteriorly; this advances progressively to the anterior regions of the cerebral white matter. ABRs, VEPs, and SSEPs may be normal initially but ultimately show prolonged latencies and abnormal waveforms. Death occurs within 10 yr of the onset of the neurologic signs

Ataxia-telangiectasia

- an autosomal recessive condition, is the most common of the degenerative ataxias and is heralded **by ataxia beginning at about age 2 yr and progressing to loss of ambulation by adolescence** Ataxia-telangiectasia is

caused by mutations in the *ATM* gene located at 11q22-q23. ATM is a phosphytidylinositol-3 kinase that phosphorylates proteins involved in DNA repair and cell cycle control.

- **Oculomotor apraxia of horizontal gaze**, defined as having difficulty fixating smoothly on an object and therefore overshooting the target with lateral movement of the head, followed by refixating the eyes, is a frequent finding, as is strabismus, hypometric saccade pursuit abnormalities, and nystagmus.
- Ataxia-telangiectasia **may present with chorea rather than ataxia**. The **telangiectasia becomes evident by mid-childhood** and is found on the bulbar conjunctiva, over the bridge of the nose, and on the ears and exposed surfaces of the extremities.
- Examination of the skin shows a loss of elasticity. Abnormalities of immunologic function that lead to frequent sinopulmonary infections include decreased serum and secretory IgA as well as diminished IgG_2, IgG_4, and IgE levels in more than 50% of patients.
- Children with ataxia-telangiectasia have a 50- to 100-fold greater chance over the normal population of developing lymphoreticular tumors (lymphoma, leukemia, and Hodgkin disease) as well as brain tumors. Additional laboratory abnormalities include an increased incidence of chromosome breaks, particularly of chromosome 14, and elevated levels of α-fetoprotein. Death results from infection or tumor dissemination
- PANTOTHENATE KINASE

Pantothenate kinase associated neurodegeneration (formerly Hallervorden-Spatz syndrome)	AR	PANK2, 20p	Pantothenate kinase 2	Childhood, but also adult-onset subtype	Chorea, dystonia, parkinsonian features, pyramidal tract features; MR abnormalities with decreased T2 signal in the globus pallidus and substantia nigra, "eye of the tiger" sign (hyperintense area within the hypointense area); sometimes acanthocytosis,

					abnormal cytosomes in lymphocytes

Approach to progressive neurological deterioration in 5–15 years age group
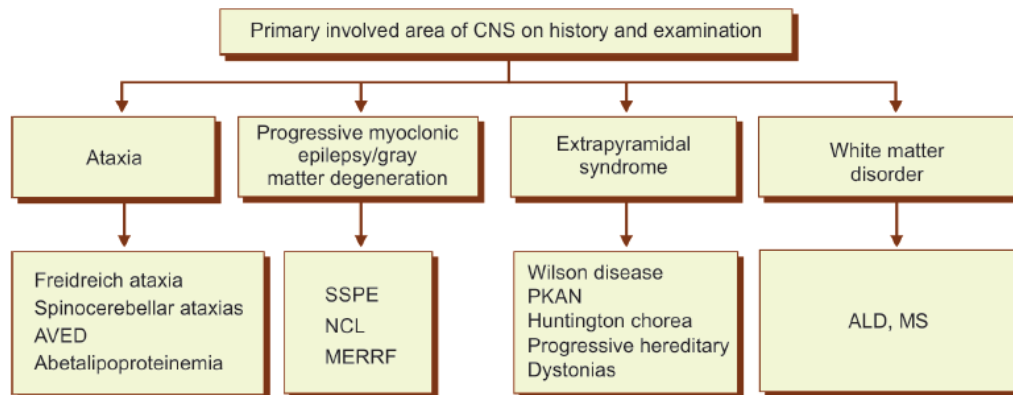
Abbreviations: ALD, Adrenoleukodystrophy; MS, Multiple sclerosis; PKAN, Pantothenate kinase associated neurodegeration; SSPE, Subacute sclerosing panencephalitis; NCL, Neuronal ceroid lipofuscinosis; MERRF, Myoclonic epilepsy with ragged red fibers; AVED, Ataxia with vitamin E deficiency

Friedreich ataxia

- is inherited as an autosomal recessive disorder involving the spinocerebellar tracts, dorsal columns in the spinal cord, the pyramidal tracts, and the cerebellum and medulla. The majority of patients are homozygous for a GAA repeat expansion in the noncoding region of the gene coding for the mitochondrial protein frataxin. Mutations cause oxidative injury associated with excessive iron deposits in mitochondria.
- The **onset** of ataxia is somewhat later than in ataxia-telangiectasia but **usually occurs before age 10 yr**. The ataxia is **slowly progressive and involves the lower extremities to a greater degree than the upper extremities**. The Romberg test result is positive; the deep tendon reflexes are absent (particularly the Achilles), and the plantar response is extensor.
- Patients develop a **characteristic explosive, dysarthric speech**, and nystagmus is present in most children. Although patients may appear apathetic, their intelligence is preserved. They may have significant weakness of the distal musculature of the hands and feet.

- Typically noted is a marked loss of vibration and position sense caused by degeneration of the posterior columns and indistinct sensory changes in the distal extremities.
- Friedreich ataxia is also characterized by skeletal abnormalities, including high-arched feet (pes cavus) and hammertoes, as well as progressive kyphoscoliosis. Results of electrophysiologic studies including visual, auditory brainstem, and somatosensory-evoked potentials are often abnormal. Hypertrophic cardiomyopathy with progression to intractable congestive heart failure is the cause of death for most patients. Antioxidant therapy with coenzyme Q10 and vitamin E has been reported to slow progression in some patients

SSPE

- Clinical manifestations of **SSPE begin insidiously 7-13 yr after primary** measles infection. Subtle changes in behavior or school performance appear, **including irritability, reduced attention span, and temper outbursts**. This initial phase (stage I) may at times be missed because of brevity or mildness of the symptoms.
- **Fever, headache, and other signs of encephalitis are absent**. The hallmark of the second stage is massive myoclonus, which coincides with extension of the inflammatory process site to deeper structures in the brain, including the basal ganglia.
- Involuntary movements and repetitive myoclonic jerks begin in single muscle groups but give way to massive spasms and jerks involving both axial and appendicular muscles. Consciousness is maintained.
- In the third stage, involuntary movements disappear and are replaced by **choreoathetosis, immobility, dystonia, and lead pipe rigidity that result from destruction of deeper centers in the basal ganglia**. Sensorium deteriorates into dementia, stupor, and then coma.
- The fourth stage is characterized by loss of critical centers that support breathing, heart rate, and blood pressure. Death soon ensues. Progression through the clinical stages may follow courses characterized as acute, subacute, or chronic progressive.
- The diagnosis of SSPE can be established through documentation of a compatible clinical course and at least 1 of the following supporting findings: (1) measles antibody detected in CSF, (2) characteristic electroencephalographic findings, and (3) typical histologic findings in

and/or isolation of virus or viral antigen from brain tissue obtained by biopsy or postmortem examination.

- CSF analysis reveals normal cells but elevated IgG and IgM antibody titers in dilutions >1:8. Electroencephalographic patterns are normal in stage I, but in the myoclonic phase, suppression-burst episodes are seen that are characteristic of but not pathognomonic for SSPE. Brain biopsy is no longer routinely indicated for diagnosis of SSPE.

WILSON

Clinical Manifestations

- Forms of Wilsonian hepatic disease **include asymptomatic hepatomegaly (with or without splenomegaly), subacute or chronic hepatitis, and acute hepatic failure (with or without hemolytic anemia).** Cryptogenic cirrhosis, portal hypertension, ascites, edema, variceal bleeding, or other effects of hepatic dysfunction (delayed puberty, amenorrhea, coagulation defect) can be manifestations of Wilson disease.
- Disease presentations are variable, with a tendency to familial patterns. The younger the patient, the more likely hepatic involvement will be the predominant manifestation. Girls are 3 times more likely than boys to present with acute hepatic failure. After 20 yr of age, neurologic symptoms predominate.
- **Neurologic disorders** can develop insidiously or precipitously, with intention tremor, dysarthria, rigid dystonia, parkinsonism, choreiform movements, lack of motor coordination, deterioration in school performance, or behavioral changes. Kayser-Fleischer rings may be absent in young patients with liver disease but are always present in patients with neurologic symptoms).
- **Psychiatric manifestations** include depression, personality changes, anxiety, or psychosis

Investigations

They are guided by history and examination.

• **Imaging:**

 A high resolution MR imaging with spectroscopy would be the best to pick up abnormalities. In certain patients it may provide a diagnostic clue, for e.g. pantothenate kinase associated neurodegeneration with "eye of tiger" sign in globus pallidi. MR imaging with spectroscopy helps in diagnosis of certain disorders such as Canavan disease, mitochondrial encephalopathies Iand creatine deficiency disorders

• **Radiographs:**

 A skeletal survey would be important to look for abnormalities in certain storage disorders such as MPS

Urine and blood assay for plasma ammonia, blood lactate and pyruvate, plasma amino acids:

These tests guide the course of further investigations in a suspected neurometabolic disorder to arrive at the diagnosis

• **Electrophysiological tests:**

Include *visual evoked potentials*, brainstem auditory evoked responses, *nerve conduction studies*, electroencephalography, electromyography and somatosensory evoked potentials. Helps delineate the extent of central and peripheral nervous system involvement in the patient

• **Histopathological and ultrastructural information from selected biopsies**

— *Bone marrow:* storage cells are seen in Niemann-Pick disease, Gaucher disease

— *Conjunctival, skin, rectal biopsy:* Neuronal ceroid lipofuscinosis

— *Hair microscopy:* Menkes Disease

• **Specific investigations are done based on clues obtained from preceding investigations**:

— *Serology:* HIV, SSPE

— *Urine copper, serum ceruloplasmin:* Wilson disease

— *Urine MPS:* mucopolysaccharidosis

— *Enzyme analysis:* lysosomal storage disorders, biotinidase deficiency

— *Urine organic acids:* organic acidemias

— *Very long-chain fatty acids (VLCFA) and plasmalogen levels:* peroxisomal disorders

— *Mutation testing:* this can be undertaken if the diagnosis is quite certain and the test is available

Type of Screening	Tests
General evaluation	Neuroimaging (MRI with and without contrast preferable to CT) Electroencephalogram (capturing wake and non-REM sleep) Comprehensive metabolic panel Complete blood count Ophthalmologic examination (by specialist if possible) Audiologic testing
ADDITIONAL SCREENING	
Autoimmune disorder	Serum sedimentation rate (Westergren), antinuclear antibody titer, complement levels
Autonomic disorder	Histamine skin test, sweat testing
Endocrinopathy	Serum T_4, TSH, ACTH, and cortisol
Genetic disorder	Genomic microarray (preferable to karyotype) *MECP2* mutation screening
Infection	CSF cell count, glucose, protein CSF bacterial, fungal, and viral cultures CSF HIV and HSV by polymerase chain reaction CSF fungal antigens CSF test for prion proteins CSF for viral antibodies (measles, mumps)
Intoxication	Serum lead and thin-layer chromatography Urine screen for drugs of abuse
Metabolic disorder	Serum amino acids, lactate, pyruvate, ammonia Serum carnitine (free and total) and acylcarnitines Serum cholesterol and lipid panel, very long-chain fatty acids Lymphocyte vacuolization, lysosomal enzyme analysis Urine organic acids, metabolic screen, porphyrins CSF lactate, amino acids, and neurotransmitter metabolites
Neoplastic disorder	CSF for cytologic analysis CSF and serum for paraneoplastic antibodies
Nutritional disorder	Serum niacin, thiamin, pyridoxine, cobalamine, vitamin E Serum homocysteine, methylmalonic acid

ACTH, adrenocorticotropic hormone; CSF, cerebrospinal fluid; CT, computed tomography; HIV, human immunodeficiency virus; HSV, herpes simplex virus, MRI, magnetic resonance imaging; REM, rapid eye movement; TSH, thyroid stimulating hormone.

Management

- Firstly, never miss out a treatable cause of neuroregression like hydrocephalus, HIV infection, hypothyroidism, lead toxicity, etc. It must be remembered that many NDD are amenable to treatment

Supportive Measures

- It is never wise or correct to say that the disease is "untreatable". Such statements only result in the parents feeling a profound sense of anguish, abandonment and loneliness. Something can almost always be done to help the child. Supportive treatment may add significantly to the quality of life of a child with neurodegenerative disorder.
- Measures to reduce spasticity, control seizures, control pain, improve nutrition, prevent constipation, prevent bed sores, and to enhance mobility, all contribute to the quality of life of the patient and indirectly to the quality of life of the parents and any unaffected siblings.

Prevention

- One of the very important aspects of management of a child with NDD is to accurately establish the diagnosis.This becomes important not only for proper care and prognostication but also for accurate prenatal diagnosis to prevent further children being affected by the same disease.
- The diagnosis may also help identify pauci or presymptomatic siblings or other family members who may benefit from early therapy, e.g. zinc therapy in Wilson disease. It would be wise to refer the parents for prenatal diagnosis to an equipped center before they plan any future pregnancies.

Prognosis

It is sensible to first confirm the diagnosis and then prognosticate.The prognosis in NDD depends on the underlying disorder. In general an earlier onset of disease predicts a poorer outcome. However, several late onset diseases can also rapidly progress, e.g. adrenoleukodystrophy

- A thorough clinical evaluation that includes a detailed history, family history, general physical and systemic evaluation forms an important starting point for further evaluation.
- If the history and examination are strongly indicative,more specific diagnostic testing can be undertaken,e.g. HIV testing, urine MPS, VLCFA, etc.
- Always keep the treatable causes in mind and exclude them systematically, based on the clinical presentation.
- Second line investigation is generally undertaken best at research and referral centers with expertise in handling these children.
- While managing these children, always focus on issues, which make the child's life comfortable, e.g. control seizures, spasticity, adequate nutrition and skin care, etc.