Differential Diagnosis of Pediatric Neurodisorders

Last updated: April 21, 2019

**PREDOMINANT ETHNIC BACKGROUND**

<table>
<thead>
<tr>
<th>Ashkenazi Jews</th>
<th>Nova Scotia</th>
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<tr>
<td>Classic Tay-Sachs disease</td>
<td>Type D Niemann-Pick disease</td>
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<td>Infantile Niemann-Pick disease</td>
<td>Japan</td>
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<td>Juvenile Gaucher disease</td>
<td>Juvenile</td>
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<tr>
<td>Recessive dystonia musculorum deformans</td>
<td>Scandinavia</td>
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**Mucolipidosis IV**

- Finnish (infantile) variant of ceroid lipofuscinosis
- Canavan disease
- Juvenile neuroopathic Gaucher disease
- Krabbe disease

**Juvenile non-neuroopathic Gaucher disease**

- Aspartylglucosaminuria

**Saudi Arabia**

- Baltic myoclonus epilepsy (Unverricht-Lundborg syndrome)

**TYPICAL AGE AT ONSET**

<table>
<thead>
<tr>
<th>Neonatal or Early Infantile</th>
<th>Preschool Years</th>
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<tr>
<td>Aminoacidurias and organic acidurias</td>
<td>Aminoacidurias, organic acidurias, urea cycle disorders with partial enzyme deficiency</td>
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<tr>
<td>Urea cycle disorders</td>
<td>Galactosemia</td>
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<td>- Aspartylglucosaminuria</td>
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<td>Cononatal Pelizaeus-Merzbacher syndrome</td>
<td>Marinesco-Sjögren syndrome</td>
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<td>Cononatal Alexander disease</td>
<td>Alexander disease</td>
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<td>Congenital sialidosis</td>
<td>Ataxia telangiectasia</td>
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<td>Early onset mitochondrial diseases</td>
<td>Xeroderma pigmentosum</td>
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<td>Spongy degeneration (Canavan) (some cases)</td>
<td>Chediak-Higashi disease</td>
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<td>Aicardi-Goutieres syndrome</td>
<td>Metachromatic leukodystrophy</td>
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<td>Infantile Gaucher disease</td>
<td>Late infantile gangliosidoses</td>
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<tr>
<td>Infantile adrenoleukodystrophy</td>
<td>Niemann-Pick—Nova Scotia variant</td>
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<td>Zellweger syndrome and variants</td>
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<td>Neonatal adrenoleukodystrophy</td>
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<td>Chondrodysplasia punctata</td>
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<td>Infantile Refsum syndrome</td>
<td>Mild Hunter disease</td>
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<td>GM1 gangliosidosis (infantile variant)</td>
<td>Leigh syndrome and other mitochondrial cytopathies</td>
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<td>I-cell disease (mucolipidosis II)</td>
<td>Kearns-Sayre syndrome</td>
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<td>Trichopoliodystrophy (Menkes)</td>
<td>Disintegrative psychosis</td>
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<td>Neurocutaneous syndromes</td>
<td>Other autonomic regression</td>
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<td>Progressive spinal muscular atrophy (Werding-Hoffmann disease)</td>
<td>School Age or Adolescence</td>
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</tbody>
</table>

**Seckel bird-headed dwarfs**

- Acute intermittent porphyria
- Juvenile ceroid lipofuscinosis
- Adrenoleukodystrophy
- Late variants of gangliosidoses

**Many sialidoses, mucopolysaccharidoses, mucolipidoses**

- Infantile ceroid lipofuscinosis
- Niemann-Pick with vertical ophthalmoplegia

**Leigh syndrome (early types)**

- Fabry disease
- Other mitochondrial cytopathies
- Cerebrotendinous xanthomatosis

**Lesch-Nyhan syndrome**

- Leihg syndrome (some variants)
- Sjögren-Larsson syndrome
- Spiny degeneration

**Infantile**

- Juvenile ceroid lipofuscinosis
- Adrenoleukodystrophy
- Late variants of gangliosidoses

**Many sialidoses, mucopolysaccharidoses, mucolipidoses**

- Infantile ceroid lipofuscinosis
- Niemann-Pick with vertical ophthalmoplegia

**Infantile**

- Leigh syndrome
- Other mitochondrial cytopathies
- Cerebrotendinous xanthomatosis

**Lesch-Nyhan syndrome**

- Leigh syndrome (some variants)
- Sjögren-Larsson syndrome
- Spiny degeneration

**Infantile**

- Juvenile ceroid lipofuscinosis
- Adrenoleukodystrophy
- Late variants of gangliosidoses

**Infantile**

- Leigh syndrome
- Other mitochondrial cytopathies (e.g., MERRF, MELAS)

**Wolman disease**

- Refsum disease

**Alexander disease**

- Friedreich ataxia

**Pelizaeus-Merzbacher disease**

- Bassen-Kornzweig disease

**Neuroaxonal dystrophy**

- Other spinocerebellar degenerations

**Infantile Hallervorden-Spatz disease**

- Dystonia musculorum deformans

**Infantile fucosidosis**

- Juvenile Huntington disease

**Nephosphatidosis**

- Juvenile parkinsonism

**Sialidosis**

- Classic Hallervorden-Spatz syndrome

**Pompe disease**

- Lafra disease

**Xeroderma pigmentosum**

- Baltic myoclonus

**Cockayne disease**

- Subacute sclerosing panencephalitis (SSPE)

**Infantile galactosialidosis**

- Wilson disease

**Progeria**

- Sialidosis with cherry red spot-myoclonus (variants with and without chondrodystrophy)

**Rett syndrome**
# Differential Diagnosis of Pediatric Neurodisorders

## Big Head

<table>
<thead>
<tr>
<th>Skin Abnormalities</th>
<th>Common Causes</th>
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<tr>
<td>Tay-Sachs disease</td>
<td>Thin atrophic skin</td>
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<tr>
<td>Alexander disease</td>
<td>Ataxia telangiectasia</td>
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<tr>
<td>Spongy degeneration (Canavan)</td>
<td>Cockayne disease</td>
</tr>
<tr>
<td>Hurler disease</td>
<td>Xeroderma pigmentosum</td>
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<tr>
<td>Other mucopolysaccharidoses with hydrocephalus</td>
<td>Progeria</td>
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</tbody>
</table>

## Small Head

<table>
<thead>
<tr>
<th>Thick skin</th>
<th>Common Causes</th>
</tr>
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<tbody>
<tr>
<td>Krabbe disease</td>
<td>I-cell disease</td>
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<tr>
<td>Infantile ceroid lipofuscinosis</td>
<td>Mucopolysaccharidoses I, II, III</td>
</tr>
<tr>
<td>Some infantile mitochondrial disorders</td>
<td>Infantile fucosidosis</td>
</tr>
</tbody>
</table>

## Neuraxonal dystrophy

Subcutaneous nodules:  
- Ataxia telangiectasia
- Cockayne syndrome

## Incontinentia pigmenti

Farber disease

## Cockayne disease

Neurofibromatosis

## Incontinentia Pigmenti

Farber disease

## Hair Abnormalities

- Niemann-Pick disease
- Dysautonomia

## Stiff, wiry

- Trichopoliodystrophy (Menkes)
- Dysautonomia

## Frizzy hair

- Enlarged Nodes

## Gray

- Strider, Hoarseness

## Telangiectasia

- Enlarged Orange Tonsils

## Angiokeratoma

- Fabry disease
- (Present late in course of all patients with severe bulbar, pseudobulbar, cerebellar, or basal ganglia pathology)

## Juvenile fucosidosis

- Infantele Gaucher disease

## Galactosialidosis

- Dysautonomia

## Ichthyosis

- Hallervorden-Spatz syndrome

## Refsum disease

- Dystonia musculorum deformans

## Sjögren-Larsson syndrome

- Zellweger syndrome

## Hypopigmentation

- Heart Abnormalities

## Trichopoliodystrophy (Menkes)

- Pompe disease

## Chediak-Higashi disease

- Hurler disease and other mucopolysaccharidoses

## Tuberous sclerosis (ash leaf spots)

- Fabry disease

## Hypomelanosis of Ito

- Infantile fucosidosis

## Prader-Willi

- Refsum disease

## Adrenoleukodystrophy

- Friedreich ataxia

## Mannosidosis

- X-linked adrenoleukodystrophy

## Mucopolysaccharidoses (most types)

- Ataxia telangiectasia

## MELAS

- Friedreich ataxia

## Generalized peroxisomal disorders

- Enzymic deficiencies

## Sickle cell diseases

- Ataxia telangiectasia

## Mucopolysaccharidoses (most types)

- All chronic diseases with muscle weakness, especially anterior horn cell involvement

## Gaucher disease

- All chronic diseases with muscle weakness, especially anterior horn cell involvement

## Generalized peroxisomal disorders

- All chronic diseases with muscle weakness, especially anterior horn cell involvement

## Mannosidosis

- Enzymic deficiencies

## Gastrointestinal Problems

- Adrenoleukodystrophy

## Bone and Joint Abnormalities

- Disorders of carnitine metabolism
- Duchenne muscular dystrophy
- Mucopolysaccharidoses (all but type I-S)
- Kearns-Sayre syndrome
- Mucolipidoses (most types)
- Strokes
- Fabry disease
- Trichopoliodystrophy (Menkes)
- Progeria
- Rett syndrome
- Galactosialidosis
- Mucopolysaccharidoses (most types)
- All chronic diseases with muscle weakness, especially anterior horn cell involvement
- Rett syndrome
- X-linked adrenoleukodystrophy
- Mucopolysaccharidoses
- Pompe disease
- Endocrine Dysfunction
- Adrenal failure

## Skin Abnormalities

- Ataxia telangiectasia
- Enlarged Nodes

## Enlarged Tongue

- Infantele fucosidosis

## Heart Abnormalities

- Enlarged Nodes

## Bone and Joint Abnormalities

- Disorders of carnitine metabolism
- Duchenne muscular dystrophy
- Mucopolysaccharidoses (all but type I-S)

## Stiff joints

- Ataxia telangiectasia
- Enzymic deficiencies
- All chronic diseases with muscle weakness, especially anterior horn cell involvement

## Gastrointestinal Problems

- Adrenoleukodystrophy

## Enlarged Nodes

- Dysautonomia

## Mucopolysaccharidoses (most types)

- Ataxia telangiectasia

## Enzymic deficiencies

- All chronic diseases with muscle weakness, especially anterior horn cell involvement

## Adrenal failure

- Enzymic deficiencies

## Endocrine Dysfunction
Malabsorption: Wolman disease
Wolman disease: Hypogonadism
Bassen-Kornzweig disease: Xeroderma pigmentosum
Nonfunctioning gallbladder: Ataxia telangiectasia
Metachromatic leukodystrophy: Some spinocerebellar degenerations
Infantile fucosidosis: Diabetes
Jaundice: Ataxia telangiectasia
Infantile Niemann-Pick disease: Dwarfing
Zellweger disease: Marfan disease
Galactosemia: Other mucopolysaccharidoses
Niemann-Pick disease: Cockayne syndrome
Vomiting: Progeria
Dysautonomia: Diseases with severe malnutrition
Urea cycle defects: Hypothalamic dysfunction
Diarrhea: De Sanctis-Cacchione syndrome
Hunter syndrome: Neoplasms
Kidney Problems: Ataxia telangiectasia
Renal failure: Xeroderma pigmentosum
Fabry disease: Neurorrhaphatosis
Nephrosis/diabetes: Von Hippel-Lindau disease
Cysts: Tuberculous sclerosis
Zellweger syndrome: Hearing Loss
Von Hippel-Lindau disease: Hunter disease
Tuberosis sclerosis: Other mucopolysaccharidoses
Neonatal OPCA: Generalized peroxisomal disorders
Joubert syndrome: Refsum disease
Stones: Cockayne disease
Lesch-Nyhan disease: Krums-Sayre and Leigh syndromes
Aminoaciduria: Other mitochondrially cytopathies
Aminoacidurias: Some spinocerebellar degenerations
Lowe syndrome: Usher syndrome
Wilson disease

PROLIFERATIVE SEIZURES OR MYOCYCLONUS
Acute intermittent porphyria
Gangliosidosis (infantile types especially)
Ceroid lipofuscinoses (late infantile variant especially)
MERFF, MELAS
Trichopoliodystrophy (Menkes disease)
Zellweger syndrome
Generalized peroxisomal disorders
Infantile Alexander disease
Krabbe disease
Lafora disease
Baltic myoclonus
Santillipino disease
Juvenile Huntington disease
Tuberosclerosis
Juvenile neuropathic Gaucher disease
SSPE

MOTOR SIGNS
Floppiness in Infancy: Prominent Cerebellar Signs
Progressive spinal muscular atrophy: Neuronal dystrophy
Congenital myopathies: Metachromatic leukodystrophy
Zellweger syndrome: Ataxia telangiectasia
Pompe disease: Leigh syndrome
Trichopoliodystrophy: Niemann-Pick disease (Nova Scotia variant)
Neuronal dystrophy: Some late-onset gangliosidoses
Gangliosidosis (early variants): Some sialidases
Fucosidosis (infantile variant): Friedreich ataxia
Infantile ceroid lipofuscinosis: Bassen-Kornzweig disease
Spongy degeneration (early): Cerebrotendinous xanthomatosis
Leigh syndrome (early variant): Other spinocerebellar degenerations
Neonatal OPCA: Lafora disease
Peripheral Neuropathy: Baltic myoclonus
Acute intermittent porphyria: Chedlak-Hiagishi disease
Metachromatic leukodystrophy: Usher syndrome
Fabry disease: Neonatal OPCA
Krabbe disease: DeSanctis-Cacchione
Neuronal dystrophy: Abnormal Posture or Movements
Refsum disease: Wilson disease
Tangier disease: Lesch-Nyhan disease
Bassen-Kornzweig disease: Hallevorben-Spatz syndrome
Sludosis (some variants) Familial stratal necrosis
Mucolipidosis III Dystonia musculorum deformans
Cerebrotendinous xanthomatisosis Juvenile Niemann-Pick with ophthalmoplegia
Ataxia telangiectasia Chronic GM1- and GM2-gangliosidoses
Adrenomyeloneuropathy Pelizaeus-Merzbacher syndrome
Livy-Roussy syndrome Crigler-Najjar disease
Mucopolysaccharidoses I, II, VI, VII, (enypent) Ataxia telangiectasia
Cockayne syndrome Juvenile cerebellar atrophies
Some mitochondrial cytopathies Juvenile Huntington disease
Giant axonal neuropathy Juvenile Parkinsonism
Prominent Cerebellar Signs Guilles de la Tourette syndrome
Wilson disease Late infantile ceroid lipofuscinosis Defasciculus-Cachexia (Xeroderma pigmentosum with endocrine dysfunction)
Pelizaeus-Merzbacher disease Dentato-rubro-olivary atrophy

EYE FINDINGS

 Conjunctival Telangiectasia Macular and Retinal Pigmentary Degeneration
Ataxia telangiectasia Other mitochondrial cytopathies
Faby disease Hallervorden-Spatz syndrome (some types)
Coneal Opacity Cockayne disease
Wilson disease (Kayser-Fleischer ring) Sjogren-Larson syndrome (not always)
Mucopolysaccharidoses I, III, IV, VI Usher syndrome
Mucolipidoses III, IV Some other spinocerebellar syndromes
Faby disease Neuroaxonal syndromes
Galactosialidosis Optic Atrophy
Cockayne disease Krabbe disease
Xeroderma pigmentosum Metachromatic leukodystrophy
Zellweger syndrome (inconstant) Most sphingolipidoses late in their course
Leu Opacy Adrenoleukodystrophy
Wilson disease Alexander disease
Galactosemia Spongy degeneration
Marinesco-Sjogren syndrome Pelizaeus-Merzbacher disease
Low disease Neuraxonal dystrophy
Cerebrocutaneous xanthomatosis Neonatal mitochondrial cytopathies
Sludosis (rarely significant clinically) Leber congenital amauosis
Mannosidosis Some spinocerebellar degenerations
Zellweger syndrome Diseases with retinal pigmentary degeneration
Glioma Metachromatic leukodystrophy
Tay-Sachs disease Friedreich ataxia
Sludosis (usually) Other spinocerebellar degenerations and cerebellar atrophies
Infantile Niemann-Pick (50% of cases) Neuraxonal dystrophy
Infantile GM, gangliosidoses (50% of cases) Ataxia telangiectasia
Farber disease (inconstant) Leigh syndrome (inconstant)
Multiple sulfatase deficiency (metachromatic leukodystrophy variant) Marinsen-Sjogren syndrome
Macular and Retinal Pigmentary Degeneration
Metachromatic leukodystrophy
Ceroid lipofuscinosis (most types) Chediak-Higashi syndrome
Mucopolysaccharidoses I-H and I-S, II, III Ophthamoplegia
Mucolipidosis IV Leigh syndrome
Bassen-Kornzweig syndrome Juvenile (cerebrocutaneous lipomatosis)
Infantile Niemann-Pick (50% of cases) Neuraxonal dystrophy
Infantile GM, gangliosidoses (50% of cases) Ataxia telangiectasia
Farber disease (inconstant) Leigh syndrome (inconstant)
Multiple sulfatase deficiency (metachromatic leukodystrophy variant) Marinsen-Sjogren syndrome

 USEFUL LABORATORY TESTS

Urine
Amino acids, organic acids Galactose, other sugars
Mucopolysaccharides, sialylated oligosaccharides N-Acetyll aspartic acid
Acid Copper excretion
Porphyra Metachromatic granules
Oxalate, cystine cystines
Blood Chemistry
Lactate-pyruvate ratio (Leigh syndrome, other mitochondrial cytopathies)
Amino acids, organic acids and other special metabolites

Cultured Skin Fibroblasts
Enzymatic assays for most diseases with known deficits
Lipid and other inclusions (in mucolipidosis IV, I-cell disease, mucopolysaccharidoses, Chedhak-Higashi) DNA repair after ultraviolet or irradiation exposure (ataxia telangiectasia, Cockayne syndrome, xeroderma pigmentosum)
Restriction fragment length polymorphisms DNA tests for genetic mutations
CSF Protein Increased
Metachromatic leukodystrophy, Krabbe, infantile adrenoleukodystrophy (not always in classic variant), Friedreich ataxia and other spinocerebellar degenerations (inconstant), Zellweger disease (sometimes), Refsum disease.
DIFFERENTIAL DIAGNOSIS OF PEDIATRIC NEURODISORDERS

C26/C22 very long chain fatty acid ratio (adrenoleukodystrophy, Zellweger disease, infantile Refsum disease)
Phytanic acid
Pipolic acid
White Blood Cells
Lysosomal enzymes and other enzymatic assays
DNA tests for generic mutations
Lipid and other inclusions (ceroid lipofuscinoses, gangliosidoses)
Red Blood Cells
Enzymatic assays for galactosemia, porphyria
Cockayne syndrome
CSF Lactate/Pyruvate
Mitochondrial cytopathies
Amniotic Cells
Enzymatic assays for disease of known enzymatic defect
Abnormal inclusion in mucolipidosis IV
Karyotype in X-linked disease
C26/C22 very long chain fatty acid ratio
Restriction fragment length polymorphisms
DNA tests for genenotypations
Intradermal Histamine test
Dysautonomia

**ELECTRODIAGNOSIS**

**EMG and nerve conduction velocity**
To detect neuropathy, anterior horn cell disease, or muscle involvement

**Electroretinography**
To detect retinal degeneration

**Visual evoked responses**
Giant potentials in late infantile ceroid lipofuscinoses; delayed latency and decreased amplitude in leukodystrophies or optic atrophy.

**Brain stem auditory evoked responses**
Diagnosis of hearing loss; prolonged latency in leukodystrophies; delayed waves with decrease of amplitude in leukodystrophies and other disease of brain stem

**Somatosensory evoked responses**
Giant potentials in sialidosis with cherry-red spot myoclonus; decreased amplitude in peripheral neuropathy; delayed waves with decreased amplitude in diseases of white matter and peripheral nerves

**BIOPSIES**

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<tr>
<th>Skin</th>
<th>Nerve</th>
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<td>Neuronal dystrophy</td>
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<td>Mucopolysaccharidoses</td>
<td>Mitochondrial leukodysplasia</td>
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<td>Mucolipidosis IV</td>
<td>Other diseases with neuropathies</td>
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<tr>
<td>Neuronal dystrophy</td>
<td>Liver</td>
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<td>Lafora disease</td>
<td>Wilson disease (copper content)</td>
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<td>Conjunctiva</td>
<td>Generalized peroxisomal disorders (absent peroxisomes, cirrhosis)</td>
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<tr>
<td>Mucopolysaccharidoses</td>
<td>Neuronal dystrophy</td>
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<tr>
<td>Mucolipidosis</td>
<td>Lafora disease</td>
</tr>
<tr>
<td>Neuronal dystrophy</td>
<td>Glycogenesis</td>
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**Bone Marrow**

<table>
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<th>Bone Marrow</th>
<th>Brain</th>
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<tbody>
<tr>
<td>Niemann-Pick disease</td>
<td>Atypical ceroid lipofuscinoses</td>
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<td>Gaucher disease</td>
<td>Alexander disease</td>
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<td>Mucopolysaccharidoses</td>
<td>Neuronal dystrophy</td>
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<tr>
<td>Sea-blue histiocyte syndrome</td>
<td>Undiagnosed disease with probable cortical involvement</td>
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**Muscle**

<table>
<thead>
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<th>Muscle</th>
<th>Rectum</th>
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<tr>
<td>Lafora disease</td>
<td>Sphingolipidoses</td>
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<td>Glycogenoses</td>
<td>Other myopathies</td>
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<tr>
<td>Other myopathies</td>
<td>Cerebrite lipofuscinoses</td>
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<tr>
<td>Neuronal dystrophy</td>
<td>Sialidoses</td>
</tr>
<tr>
<td>Mitochondrial myopathies (Kearns-Sayre, Leigh syndrome)</td>
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