Differential Diagnosis of Pediatric Neurodisorders

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Predominant Ethnic Background

| **Ashkenazi Jews**  | **Nova Scotia**  |
| --- | --- |
| Classic Tay-Sachs disease | Type D Niemann-Pick disease |
| Infantile Niemann-Pick disease | **Japan** |
| Juvenile Gaucher disease | Sialidosis with chondrodystrophy |
| Recessive dystonia musculorum deformans | **Scandinavia** |
| Mucolipidosis IV | Finnish (infantile) variant of ceroid lipofuscinosis |
| Canavan disease | Juvenile neuronopathic Gaucher disease |
| Dysautonomia | Krabbe disease |
| Juvenile non-neuronopathic Gaucher disease | Aspartylglucosaminuria |
| **Saudi Arabia** | Baltic myoclonus epilepsy (Unverricht-Lundborg syndrome) |
| Canavan disease  |

Typical Age at Onset

| ***Neonatal or Early Infantile*** | ***Preschool Years***  |
| --- | --- |
| Aminoacidurias and organic aciduriasUrea cycle disorders | Aminoacidurias, organic acidurias, urea cycle disorders with partial enzyme deficiency |
| Galactosemia | Aspartylglucosaminuria |
| Connatal Pelizaeus-Merzbacher syndrome | Marinesco-Sjögren syndrome |
| Connatal Alexander disease | Alexander disease |
| Congenital sialidosis | Ataxia telangiectasia |
| Early onset mitochondrial diseases | Xeroderma pigmentosum |
| Spongy degeneration (Canavan) (some cases) | Chediak-Higashi disease |
| Aicardi-Goutieres syndrome | Metachromatic leukodystrophy |
| Infantile Gaucher disease | Late infantile gangliosidoses |
| Infantile adrenoleukodystrophy | Niemann Pick--Nova Scotia variant |
| Zellweger syndrome and variants | Late infantile ceroid lipofuscinosis |
| Neonatal adrenoleukodystrophy | Sanfilippo syndromes |
| Chondrodysplasia punctata | Maroteaux-Lamy disease |
| Infantile Refsum syndrome | Mild Hunter disease |
| GM1 gangliosidosis (infantile variant) | Leigh syndrome and other mitochondrial cytopathies |
| I-cell disease (mucolipidosis II) | Kearns-Sayre syndrome |
| Trichopoliodystrophy (Menkes) | Disintegrative psychosis |
| Neurocutaneous syndromes | Other autistic regression |
| Progressive spinal muscular atrophy (Werdnig-Hoffmann disease) | ***School Age or Adolescence*** |
| Seckel bird-headed dwarfs | Acute intermittent porphyria |
| ***Infantile*** | Juvenile ceroid lipofuscinosis |
| Aminoacidurias, organic acidurias, urea cycle disorders with partial enzyme deficiency | AdrenoleukodystrophyLate variants of gangliosidoses |
| Many sphingolipidoses, mucopolysaccharidoses, mucolipidosesInfantile ceroid lipofuscinosis | Niemann-Pick with vertical ophthalmoplegia |
| Leigh syndrome (early types) | Fabry disease |
| Other mitochondrial cytopathies | Cerebrotendinous xanthomatosis |
| Lesch-Nyhan syndrome | Leigh syndrome (some variants) |
| Sjögren-Larsson syndromeSpongy degeneration | Other mitochondrial cytopathies (e.g., MERFF, MELAS) |
| Wolman disease | Refsum disease |
| Alexander disease | Friedreich ataxia |
| Pelizaeus-Merzbacher disease | Bassen-Kornzweig disease |
| Neuraxonal dystrophy | Other spinocerebellar degenerations |
| Infantile Hallervorden-Spatz disease | Dystonia musculorum deformans |
| Infantile fucosidosis | Juvenile Huntington disease |
| Nephrosialidosis | Juvenile parkinsonism |
| Sialidosis | Classic Hallervorden-Spatz syndrome |
| Pompe disease | Lafora 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  |  |

Clues in Physical Examination

|  |  |
| --- | --- |
| *Big Head* | *Skin Abnormalities*  |
| Tay-Sachs disease | **Thin atrophic skin**: |
| Alexander disease |   Ataxia telangiectasia |
| Spongy degeneration (Canavan) |   Cockayne disease |
| Hurler disease |   Xeroderma pigmentosum |
| Other mucopolysaccharidoses with hydrocephalus |   Progeria |
| *Small Head* | **Thick skin**: |
| Krabbe disease |   I-cell disease |
| Infantile ceroid lipofuscinosis |   Mucopolysaccharidoses I, II, III |
| Some infantile mitochondrial disorders |   Infantile fucosidosis |
| Neuraxonal dystrophy | **Subcutaneous nodules**: |
| Incontinentia pigmenti |   Farber disease |
| Cockayne disease |   Neurofibromatosis |
| Rett syndrome |   Cerebrotendinous xanthomatosis |
| Bird-headed dwarfs | **Xanthomas**: |
| *Hair Abnormalities* |   Niemann-Pick disease |
| **Stiff, wiry**: | **Blotching**: |
|   Trichopoliodystrophy (Menkes) |   Dysautonomia |
| **Frizzy hair**: | *Enlarged Nodes* |
|   Giant axonal neuropathy | Farber disease |
| **Hirsutism**: | Niemann-Pick disease |
|   Infantile GM1 gangliosidosis | Juvenile Gaucher disease |
|   Hurler, Hunter, Sanfilippo syndromes | Chediak-Higashi disease |
|   I-cell disease | Ataxia telangiectasia (lymphoma) |
| **Gray**: | *Stridor, Hoarseness* |
|   Ataxia telangiectasia | Infantile-onset peroxisomal disorders |
|   Cockayne disease | Farber disease |
|   Chediak-Higashi disease | Infantile Gaucher disease |
|   Progeria | Pelizaeus-Merzbacher disease |
| *Skin Abnormalities* | *Enlarged Orange Tonsils* |
| **Telangiectasia**: | Tangier disease |
|   Ataxia telangiectasia | *Severe Swallowing Problems* |
| **Angiokeratoma**:  Fabry disease | (Present late in course of all patients with severe bulbar, pseudobulbar, cerebellar, or basal ganglia pathology) |
|   Juvenile fucosidosis | Infantile 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 syndrome | Hurler disease and other mucopolysaccharidoses |
|   Tuberous sclerosis (ash leaf spots) | Fabry disease |
|   Hypomelanosis of Ito | Infantile fucosidosis |
|   Prader-Willi | Refsum disease |
|   Phenylketonuria | Friedreich ataxia |
| **Hyperpigmentation**: | Zellweger syndrome |
|   Niemann-Pick disease | Tuberous sclerosis |
|   Adrenoleukodystrophy | Progeria |
|   Farber disease | Abetalipoproteinemia (Bassen-Kornzweig disease) |
|   Neurofibromatosis (cafe au lait spots) |
|   Xeroderma pigmentosum |  |
|   Incontinentia Pigmenti |  |
| *Heart Abnormalities* | *Bone and Joint Abnormalities* |
| Disorders of carnitine metabolism | **Stiff joints**: |
| Duchenne muscular dystrophy |   Mucopolysaccharidoses (all but type I-S) |
| Kearns-Sayre syndrome |   Mucolipidoses (most types) |
| *Strokes* |   Fucosidosis |
| Fabry disease |   Farber disease |
| Trichopoliodystrophy (Menkes) |   Sialidoses (some forms) |
| Progeria |   Zellweger syndrome |
| MELAS |   Rhizomelic chondrodysplasia punctata |
| Homocystinuria |   Cockayne disease |
| Sickle cell diseases | **Scoliosis**: |
| *Organomegaly* |   Friedreich ataxia |
| Mucopolysaccharidoses (most types) |   Ataxia telangiectasia |
| Infantile GM1 gangliosidosis |   Dystonia musculorum deformans |
| Niemann-Pick disease |   All chronic diseases with muscle weakness, especially anterior horn cell involvement |
| Gaucher disease |   Rett syndrome |
| Generalized peroxisomal disorders | **Kyphosis**: |
| Galactosemia |   Mucopolysaccharidoses |
| Pompe disease | *Endocrine Dysfunction* |
| Mannosidosis | **Adrenals**: |
| *Gastrointestinal Problems* |   Adrenoleukodystrophy |
| **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 |   Morquio 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 | Neurofibromatosis |
|   Nephrosialidosis | Von Hippel-Lindau disease |
| Cysts: | Tuberous sclerosis |
|   Zellweger syndrome | *Hearing Loss* |
|   Von Hippel-Lindau disease | Hunter disease |
|   Tuberous sclerosis | Other mucopolysaccharidoses |
|   Neonatal OPCA | Generalized peroxisomal disorders |
|   Joubert syndrome | Refsum disease |
| Stones: | Cockayne disease |
|   Lesch-Nyhan disease | Kearns-Sayre and Leigh syndromes |
| Aminoaciduria: | Other mitochondrial cytopathies |
|   Aminoacidurias | Some spinocerebellar degenerations |
|   Lowe syndrome | Usher syndrome |
|   Wilson disease |  |

Prominent Seizures or Myoclonus

|  |
| --- |
| Acute intermittent porphyria  |
| Gangliosidoses (infantile types especially)  |
| Ceroid lipofuscinoses (late infantile variant especially)  |
| MERFF, MELAS  |
| Trichopoliodystrophy (Menkes)  |
| Zellweger syndrome  |
| Generalized peroxisomal disorders  |
| Infantile Alexander disease  |
| Krabbe disease  |
| Lafora disease  |
| Baltic myoclonus  |
| Sanfilippo disease  |
| Juvenile Huntington disease  |
| Tuberous sclerosis  |
| Juvenile neuropathic Gaucher disease  |
| SSPE |

Motor Signs

|  |  |
| --- | --- |
| *Floppiness in Infancy* | *Prominent Cerebellar Signs*  |
| Progressive spinal muscular atrophy | Neuraxonal dystrophy |
| Congenital myopathies | Metachromatic leukodystrophy |
| Zellweger syndrome | Ataxia telangiectasia |
| Pompe disease | Leigh syndrome |
| Trichopoliodystrophy | Niemann-Pick disease (Nova Scotia variant) |
| Neuraxonal dystrophy | Some late-onset gangliosidoses |
| Gangliosidoses (early variants) | Some sialidoses |
| 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 | Chediak-Higashi disease |
| Metachromatic leukodystrophy | Usher syndrome |
| Fabry disease | Neonatal OPCA |
| Krabbe disease | DeSanctis-Cacchione |
| Neuraxonal dystrophy | *Abnormal Posture or Movements* |
| Refsum disease | Wilson disease |
| Tangier disease | Lesch-Nyhan disease |
| Bassen-Kornzweig disease | Hallervorden-Spatz syndrome |
| Sialidosis (some variants) | Familial striatal necrosis |
| Mucolipidosis III | Dystonia musculorum deformans |
| Cerebrotendinous xanthomatosis | Juvenile Niemann-Pick with ophthalmoplegia |
| Ataxia telangiectasia | Chronic GM1 and GM2 gangliosidoses |
| Adrenomyeloneuropathy | Pelizaeus-Merzbacher syndrome |
| Levy-Roussy syndrome | Crigler-Najjar disease |
| Mucopolysaccharidoses I, II, VI, VII (entrapment) | Ataxia telangiectasia |
| Cockayne syndrome | Juvenile ceroid lipofuscinosis |
| Some mitochondrial cytopathies | Juvenile Huntington disease |
| Giant axonal neuropathy | Juvenile Parkinsonism |
| *Prominent Cerebellar Signs* | Gilles de la Tourette syndrome |
| Wilson diseaseLate infantile ceroid lipofuscinosis | DeSanctis-Cacchione (Xeroderma pigmentosum with endocrine dysfunction) |
| Pelizaeus-Merzbacher disease | Dentato-rubro-luysial atrophy |

Eye Findings

|  |  |
| --- | --- |
| *Conjunctival Telangiectasia* | *Macular and Retinal Pigmentary Degeneration*  |
| Ataxia telangiectasia | Other mitochondrial cytopathies |
| Fabry disease | Hallervorden-Spatz syndrome (some types) |
| *Corneal Opacity* | Cockayne disease |
| Wilson disease (Kayser-Fleischer ring) | Sjögren-Larson syndrome (not always) |
| Mucopolysaccharidoses I, III, IV, VI | Usher syndrome |
| Mucolipidoses III, IV | Some Other spinocerebellar syndromes |
| Fabry disease | Neurocutaneous syndromes |
| Galactosialidosis | *Optic Atrophy* |
| Cockayne disease | Krabbe disease |
| Xeroderma pigmentosum | Metachromatic leukodystrophy |
| Zellweger syndrome (inconstant) | Most sphingolipidoses late in their course |
| *Lens Opacity* | Adrenoleukodystrophy |
| Wilson disease | Alexander disease |
| Galactosemia | Spongy degeneration |
| Marinesco-Sjögren syndrome | Pelizaeus-Merzbacher disease |
| Lowe disease | Neuraxonal dystrophy |
| Cerebrocutaneous xanthomatosis | Neonatal mitochondrial cytopathies |
| Sialidosis (rarely significant clinically) | Leber congenital amaurosis |
| Mannosidosis | Some spinocerebellar degenerations |
| Zellweger syndrome | Diseases with retinal pigmentary degeneration |
| *Glaucoma* | *Nystagmus* |
| Mucopolysaccharidosis I--Scheie | Disease with poor vision (searching nystagmus) |
| Zellweger syndrome (infrequent) | Pelizaeus-Merzbacher syndrome |
| *Cherry-Red Spot* | Metachromatic leukodystrophy |
| Tay-Sachs disease | Friedreich ataxia |
| Sialidosis (usually) | Other spinocerebellar degenerations and cerebellar atrophies |
| Infantile Niemann-Pick (50% of cases) | Neuraxonal dystrophy |
| Infantile GM1 gangliosidosis (50% of cases) | Ataxia telangiectasia |
| Farber disease (inconstant) | Leigh syndrome (inconstant) |
| Multiple sulfatase deficiency (metachromatic leukodystrophy   variant) | Marinesco-Sjögren syndrome |
| *Macular and Retinal Pigmentary Degeneration* | Opsoclonus-myoclonus syndrome |
| Ceroid lipofuscinosis (most types) | Chediak-Higashi syndrome |
| Mucopolysaccharidoses I-H and I-S, II, III | *Ophthalmoplegia* |
| Mucolipidosis IV | Leigh syndrome |
| Bassen-Kornzweig syndrome (abetalipoproteinemia) | Kearns-Sayre and Leigh syndromes |
| Peroxisomal disorders | Niemann-Pick variant with vertical ophthalmoplegia (type C) |
| Olivopontocerebellar variant | Bassen-Kornzweig syndrome |
| Refsum disease (all types) | Ataxia telangiectasia |
| Kearns-Sayre syndrome | Infantile Gaucher disease |
| Leber congenital amaurosis  | Tangier disease |

Useful Laboratory Tests

|  |  |
| --- | --- |
| **Urine**  Amino acids, organic acids  Galactose, other sugars  Mucopolysaccharides, sialylated oligosaccharides   *N*-Acetyl aspartic acid  Copper excretion  Porphyrins  Metachromatic granules  Oxalate, cysteine crystals**Blood Chemistry**  Ammonia (urea cycle disorders)  Lactate-pyruvate ratio (Leigh syndrome, other mitochondrial cytopathies)  Amino acids, organic acids and other special metabolites  C26/C22 very long chain fatty acid ratio (adrenoleukodystrophy, Zellweger disease, infantile Refsum disease)  Phytanic acid  Pipecolic acid**White Blood Cells**  Lysosomal enzymes and other enzymatic assays  DNA tests for genetic mutations  Lipid and other inclusions (ceroid lipofuscinoses, gangliosidoses)**Red Blood Cells**  Enzymatic assays for galactosemia, porphyria | **Cultured Skin Fibroblasts**  Enzymatic assays for most diseases with known deficits  Lipid and other inclusions (in mucolipidosis IV, I-cell disease, mucopolysaccharidoses, Chediak-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, 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 genetic mutations**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 lipofuscinosis; 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

| **Skin** | **Nerve** |
| --- | --- |
| Ceroid lipofuscinosis |  Neuraxonal dystrophy |
| Mucopolysaccharidoses |  Metachromatic leukodystrophy |
| Mucolipidosis IV |  Other diseases with neuropathies |
| Neuraxonal dystrophy | **Liver** |
| Lafora disease |  Wilson disease (copper content) |
| **Conjunctiva** |  Generalized peroxisomal disorders (absent peroxisomes, cirrhosis) |
| Mucopolysaccharidoses |
| Mucolipidoses |  Lafora disease |
| Neuraxonal dystrophy |  Glycogenesis |
| **Bone Marrow** | **Brain**(rarely needed except possibly for following) |
| Niemann-Pick disease | Atypical ceroid lipofuscinosis |
| Gaucher disease | Alexander disease |
| Mucopolysaccharidoses | Neuraxonal dystrophy |
| Sea-blue histiocyte syndrome | Undiagnosed disease with probable cortical involvement |
| **Muscle** |
| Lafora disease | **Rectum** |
| Glycogenoses  | Sphingolipidoses |
| Other myopathies | Ceroid lipofuscinoses |
| Neuraxonal dystrophy | Sialidoses |
| Mitochondrial myopathies (Kearns-Sayre, Leigh syndrome) |  |

Bibliography for ch. “Pediatrics” → follow this [link >>](http://www.neurosurgeryresident.net/Ped.%20Pediatrics%5CPed.%20Bibliography.pdf)

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