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 acidurias Urea 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
GM_1 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	Adrenoleukodystrophy Late variants of gangliosidoses
Many sphingolipidoses, mucopolysaccharidoses, mucolipidoses Infantile 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 syndrome Spongy 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 GM_1 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 GM_1 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 GM_1 and GM_2 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 disease Late 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 GM_1 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

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,

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	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)	

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