Perioxisomal Disorders

Biochemical Defect	Peroxisomes = site for β-ox of VLCFAs, H_2O_2 degradation, and pipecolic, phytanic, and pristanic acid metabolism, also of bile acid synthesis, plasmalogen formation (for membranes and myelin).
Presentation	**Dysmorphic facies** (as below)) alongside shortened proximal limbs, epiphyseal stippling, hypotonia, seizures, encephalopathy, cataracts, retinopathy, hepatomegaly, and cholestasis.
Diagnosis	Elevated levels of substrate in question (see below), enzyme assays

Disorder	Enzyme Blockade	Accumulated Substrate(s)	Presentation (AR inheritance unless specified)	Treatment
Zellweger Syndrome	Several peroxisomal genes; often *PEX1*	VLCFAs and branched- chain FAs	Early neuromotor arrest, seizures, ID, craniofacial anomalies (large fontanel, midface hypoplasia, short pf, incr. neck fat),chondrodysplasia punctata (calcification of cartilage), renal cysts, liver failure - **cerebrohepatorenal** syndrome, death w/in 1 yr	Supportive care only; no disease-modifying rx
Refsum Disease	Defective phytanoyl-CoA -hydroxylase	Phytanic acid	Later onset (adolescence / adulthood) of ataxia, retinitis pigmentosa, ichthyosis, cataracts/ night blindness, anosmia, and hearing loss	Restrict phytanic acid intake (found in dairy, beef, lamb, seafood) Cardiac & ophtho surveillance
Adrenoleuko-dystrophy	*ABCD1* gene - issues shuttling VLCFAs in to peroxisomes	VLCFAs	*XLR. Seizures, intellectual disability, neuromotor arrest, adrenal insufficiency, hypogonadism, beginning with behavioral changes around **age 4-10.**	Lorenzo's oil (special preparation of FAs)- NOT PROVEN Treat adrenal disease HSCT

Differential Diagnosis by Clinical Manifestations

Presenting in **Neonatal period** or **early infancy**

History	Consanguinity (increased inc of AR disorders), ethnicity (e.g., tyrosinemia in French-Canadians of Quebec), SIDS or intellectual disability in family (all from possible undiagnosed IEMs), relation of symptom to introduction of new food, NBS results
Presentation	**Acute** and **severe**, simulating sepsis (lethargy, vomiting, tachypnea, seizures, poor perfusion) • classically ex FT, prev healthy, deterioration despite support, usu neg sepsis workup • d/t **deficiency of a product** or **excess of toxic substrate**, so called "intoxications" - organic acidemias, aminoacidopathies, and UCDs **Indolent** w/ **early** and **persistent neurological deterioration** • nl pregnancy, no interim healthy pd, d/t energy def: mitochondrial + peroxisomal disorders

Encephalopathy	Seizures	Hepatic	Cardiac	Hypoglycemia
MSUD MMA PA IVA MCD UCD	B6 responsive seizures MCD (biotin) Folinic acid responsive GLUT1 3PGD	Galactosemia Fructosemia Tyrosinemia Bile acid synthesis defects Glycosylation defects Ib LCHAD	FAOD Pompes	GSD FAOD Primary hyperinsulinemia

Differential Diagnosis by Clinical Manifestations

Physical Exam

Usually non-spec - **hepatomeg + HD instability** in metabolic crises; **dysmorphisms** are usu absent (though not always); **auditory** + **ophthalmologic** evaluations are an important part of workup

Dysmorphisms	
Peroxisomal disorders (Zellweger)	Trisomy 21 like facies
Pyruvate dehydrogenase deficiency	FAS like facies
Lysosomal disorders (I cell disease)	Hurler-like coarse facies
Glycosylation defects	Inverted nipples, fat pads/ lipodystrophy
Hydrops	
Storage disorders	Mucopolysaccharidosis, Niemann-Pick
Disorders affecting erythropoiesis	G6PD deficiency, pyruvate kinase deficiency
Disorders affecting liver	Neonatal hemochromatosis, galactosemia
Skin and hair manifestations	
Acrodermatitis enteropathica (Zn def)	Vesiculobullous/eczematoid lesions on perioral/ perineal areas
Hartnup	Pellagra like features
PKU	Blonde, fair, blue eyes
Hepatoerythropoetic & Congenital Erythropoetic Porphyrias	Photosensitivity with vesiculobullous Lesions and resulting scarring
Biotinidase deficiency	Rash and alopecia
Cataracts: Lowe, galactosemia, Zellweger and variants	
Hepatomegaly: Galactosemia, hereditary fructose intolerance, GSD type Ia & III, LCHAD, Tyrosinemia, hemochromatosis, Zellweger	

Initial Lab Workup and suggested diagnosis

Lab test	Common associations
VBG + chem 10	Acidosis and increased anion gap in organic acidemias
Blood glucose	Hypoglycemia in FAOD, glycogenolysis and glycosylation defects
LFTs and coags	Jaundice/hepatitis in tyrosinemia, galactosemia, hemochromatosis
Plasma ammonia	Increased in urea cycle defects and organic acidemias
Plasma lactate (L), pyruvate (P), and ketoacids (3OHB, AcAc)	Some IEMs have pathognomonic L/P / 3OHB/AcAc ratios
CBC w/diff	Neutropenia and thrombocytopenia with IVA, MMA, PA; neutropenia in GSD Ib
Blood Culture	Galactosemia a/w increased incidence of *E. coli* sepsis.
Urine pH	>5 in setting of acidosis suggests distal RTA.
Urine (non-glucose)reducing substances	Suggestive of galactosuria or fructosuria
Urine ketones (if acidosis or hypoglycemia)	See below

Secondary Workup (after talking w/

- **Urine**: Organic acids, acylglycines, mucopolysaccharides, oligosaccharides
- **Plasma**: AAs (quantitative), carnitine + acylcarnitine, Peroxisomal tests (VLCFA), bile acid analysis
- **CSF**: for amino acids (glycine), lactate, pyruvate, and neurotransmitters
- **Imaging**: Brain MRI/MRS, HIDA scan for biliary atresia
- *In general pre-prandial samples should be sent for most tests (at least 2-4 hours after last feed)

Differential Diagnosis continued on next page →