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