Epigenetic insult drives clinical course of orphan disease with aberrant proteins and ceramides that may be attenuated with bioactive lipids

A single defective enzyme does not limit pathology to a single organelle. Rather, there a disruption of organelle interplay driven by epigenetic insult, as reflected in both aberrant lipids and rampant proteinopathies affecting all cellular fractions. We have isolated very-long-chain fatty acids (VLCFA's) forming lipid rafts, or ceramides, in patients suffering orphan diseases that result in membrane derangement per disturbance in peroxisomal respiration. Epigenetic insult to cellular components presents with nuclear and mitochondrial DNA adducts that compromise gene expression, thus explaining the intensely aggressive course of disease endured by those with metabolic distress as well as variations in the course of the disease progression. Captured images of distorted phospholipid membranes enable us to link toxic adducts to altered lipid metabolism and cellular dysfunction, recognized as typical to the diagnosis. Following administration of a phospholipids PC, PE and PI subjects have demonstrated marked clinical neurological improvement, with normalization of red cell lipid status, improved cardiolipin stores, clearance of DNA adducts improving neurometabolic status, and stabilized cellular structure and function, as observed through imaging of membrane phospholipid leaflets and mitochondrial membranes.

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