



## Trifunctional Protein Deficiency

### Background

Mitochondrial Trifunctional Protein (TFP) Deficiency is a defect in mitochondrial fatty acid  $\beta$ -oxidation. Three enzyme activities that act sequentially in the oxidation of fatty acids reside together on the TFP enzyme complex located on the inner mitochondrial membrane. The enzymes are Long-Chain-2-Enoyl-CoA Hydratase, Long-Chain Hydroxy-Acyl-CoA Dehydrogenase (LCHAD), and  $\beta$ -KetoAcyl-CoA Thiolase. The TFP complex consists of two different protein subunits ( $\alpha$ - and  $\beta$ ) coded for by two nuclear genes. The TFP complex has specificity toward fatty acids of ten carbons (C10) or longer.

### Clinical

Diverse clinical presentations have been reported in patients having TFP Deficiency. The usual presentation is in infancy and follows a period of fasting associated with a minor illness. Patients develop non-ketotic hypoglycemia, hypotonia, and lactic acidemia. Areflexia and cardiomyopathy is often found on physical exam, and sudden death can occur. Patients may have elevated CK levels and even rhabdomyolysis, and a few have had hyperammonemia. Low carnitine levels have been measured in serum and muscle. Hepatic steatosis is found at biopsy. Many of these patients succumb to severe muscular hypotonia with respiratory distress.

### Testing

Newborn screening of a dried blood spot using tandem mass spectrometry detects elevations of several long-chain and hydroxy acylcarnitines (i.e. C16-OH, C16:1-OH, C16, C18-OH, C18:1-OH, and C18). These findings are characteristic but not definitive of TFP Deficiency, because isolated LCHAD deficiency shows similar findings. Quantitative urine organic acid determination is usually not helpful, as elevation of C6 to C14 dicarboxylic and 3-hydroxy-dicarboxylic acids may or may not be present. Plasma acylcarnitine profile can demonstrate elevations of the above acylcarnitines noted in a dried blood spot. Definitive testing is performed by direct enzyme testing using leukocytes or fibroblasts or by probing cultured fibroblasts for the TFP activities using labeled fatty acid substrate.

TFP deficiency can be caused by mutations in either the  $\alpha$ -subunit or  $\beta$ -subunit genes for TFP. No common mutation in TFP deficiency has been reported, but prenatal diagnosis is theoretically possible if both mutations are known.

### Treatment

Supportive care for the acutely ill child involves treating hypoglycemia, lactic acidosis, and hyperammonemia with IV fluids containing glucose and bicarbonate. Administration of L-Carnitine should be considered. Avoidance of fasting is important to prevent symp-tomatic episodes.

Because the diagnosis and therapy of TFP Deficiency is complex, the pediatrician is advised to manage the patient in close collaboration with a consulting pediatric metabolic disease specialist. It is recommended that parents travel with a letter of treatment guidelines from the patient's physician.

### Inheritance

This disorder most often follows an autosomal recessive inheritance pattern. With recessive disorders affected patients usually have two copies of a disease gene (or mutation) in order to show symptoms. People with only one copy of the disease gene (called carriers) generally do not show signs or symptoms of the condition but can pass the disease gene to their children. When both parents are carriers of the disease gene for a particular disorder, there is a 25% chance with each pregnancy that they will have a child affected with the disorder.

## References

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