

Cerebral Folate Deficiency (CFD) and Mitochondrial Disease [P07.095]

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Background

Cerebral folate deficiency (CFD) is a recently described disorder in which the central nervous system (CNS) becomes deficient in folate in the face of normal peripheral folate levels. The mechanisms leading to CFD are varied. In many cases autoantibody formation against the folate transporter that carries 5-methyltetrahydrofolate (5MTHF) across the choroid plexus is involved.

In several inherited disorders such as dihydropteridine reductase deficiency and aromatic amino acid decarboxylase deficiency specific biochemical mechanisms have been proposed that lead to CFD. CFD has also been reported in the Kearns-Sayre syndrome and it has been suggested that ATP depletion might be involved in the development of CFD as 5MTHF transport across the choroid-plexus is ATP dependent. To investigate further this hypothesis we searched for evidence of CFD in patients with various forms of mitochondrial disease.

Methods

Cerebrospinal Fluid (CSF) 5MTHF Measurement:

CSF samples were collected in a standardized manner from 346 patients who were shown to have defective oxidative phosphorylation and the concentration of 5MTHF measured using HPLC with electrochemical detection.

Mitochondrial Disease Diagnosis

Diagnosis of mitochondrial disease requires a multifaceted approach. Criteria for mitochondrial diagnosis are reviewed in [Shoffner JM. Mitochondrial Diseases. In: Gilman S, ed. MedLink Neurology. San Diego: MedLink Corporation, 2008]. Patients were assessed using various testing which included muscle histology, oxidative phosphorylation (OXPHOS) enzymology (fresh muscle), OXPHOS protein chemistry (subunit levels, supercomplex formation, assembly of monomeric enzymes), high resolution respirometry of live muscle, and genetic testing of mtDNA and nuclear DNA OXPHOS genes.

Results

- ❖ Approximately 9% of mitochondrial disease patients have decreased cerebral folate levels. Of 346 patients with mitochondrial disease, 32 had 5MTH values less than 50 nmol/L.
- ❖ There is no consistent clinical phenotype, OXPHOS enzyme defect, or mutation group that is specific for a cerebral folate defect. Patients have a diverse array of clinical presentations that include Kearns-Sayre syndrome (mtDNA deletions), Chronic progressive external ophthalmoplegia Plus, Leigh disease (nuclear or mtDNA mutations), leukodystrophy (NDUFV1 mutation), mitochondrial myopathy (cytochrome b deletion), global developmental delays, fatigue, gastrointestinal dysfunction (cyclic vomiting, gastroparesis, pseudo-obstruction, autistic features, and seizures (controlled and intractable).
- ❖ Treatment of patients with levels at or below this value may respond to treatment with folinic acid.

ANY CATEGORY OF OXPHOS ENZYME DEFECT CAN BE ASSOCIATED WITH CEREBRAL FOLATE DEFICIENCY

	Number	5MTHF Range (nmol/L)
Single OXPHOS Enzyme Defects	18	8-49
Complex I	15	8-49
Complex III	1	49
Complex IV	1	46
Complex V	1	49
Multiple OXPHOS Enzyme Defects	14	26-49

OXPHOS enzymology was performed on fresh muscle. Defects were diagnosed by comparison of activity with the 5%-95% reference intervals calculated from 254 controls. Due to complexities in disease pathogenesis, OXPHOS enzyme defects are highly variable even among groups of individuals who harbor identical mutations. OXPHOS enzyme activity measurements depend in part on stability of individual OXPHOS enzymes, functioning of individual enzyme subunits, and presence of adequate supercomplex formation (aggregates of Complexes I, III, and IV).

CFD Treatment: Dramatic Response in Some Patients

14 year old male: Kearns-Sayre Syndrome

Normal early development

Ptosis, ophthalmoplegia, retinopathy, fatigue, cardiac conduction delay

No significant problems with ambulation, traveling with parents and attending school

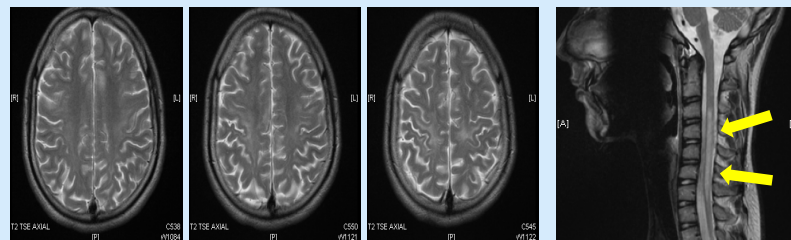
Over several weeks, he became bedridden and was hospitalized.

Progressive ataxia with weakness, proprioceptive and vibratory loss

CSF 5-MTHF 8 (Normal 50-120)

MRI on hospital admission below.

Treatment with folinic acid resulted in resolution of new neurologic symptoms and a return to baseline. Patient was able to attend school and hike with parents.



T2 Weighted Brain MRI images: Diffusely abnormal signal in hemispheric white matter. Central cervical cord signal abnormality (arrows).

Summary and Discussion

1. CSF 5MTHF was measured in a total of 346 patients with defective OXPHOS enzymology. Of these, 32 (9%) had values low enough to require initiation of folinic acid replacement therapy.
2. 91% of patients with OXPHOS defects did not have CFD at the time of testing
3. These data suggest that ATP deficiency is unlikely to be the cause of CFD in patients with OXPHOS defects.
4. It should be noted that CSF was only examined at a single time point in each patient. As mitochondrial disorders are often progressive CFD may develop with time.
5. The presence of CFD in multiple types of OXPHOS defects is important to recognize and treat. Some patients have a dramatic response to folinic acid therapy.
6. These results indicate that CSF 5MTHF measurement should be considered in any patient with mitochondrial disease.