

Utility of the Measurement of Monoamine Neurotransmitter Metabolites and Other Specific Biomarkers in CSF from Infants and Children with Early Onset Epilepsy [P05.087]

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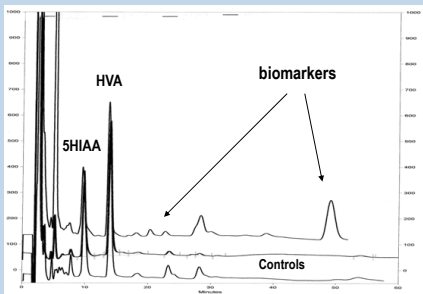
Background

The measurement of cerebrospinal fluid (CSF) neurotransmitter metabolites and related compounds in movement disorders and the inborn errors of metabolism that affect serotonin and dopamine has obvious utility. There is however also great utility in collection of spinal fluid for the analysis of neurotransmitter metabolites and related compounds in infants and children with early-onset epilepsy in childhood. Over the last 20 years we have learnt to recognize 'normal' biomarker profiles when analyzing CSF for disorders of monoamine neurotransmitter metabolism. During this period we have also recognized 'abnormal' biomarker profiles which have now been linked to specific conditions associated with epileptic disorders.

Pyridoxine Responsive Seizures

The classic form of pyridoxine responsive seizures is now known to be due to mutations in alpha aminoacidic semialdehyde (AASA) dehydrogenase (antiquitin/ALDH7A1), an enzyme located on the lysine degradation pathway. It has also recently become apparent that folinic acid responsive seizures and pyridoxine responsive seizures are the same disorder (Gallagher et al, *Ann Neurol* 2009). We described the first cases of folinic acid responsive seizures in 1995 and demonstrated that two unknown compounds appeared on our chromatographic system used for the measurement of neurotransmitter metabolites. With the realization that the two disorders are allelic we now have biomarkers for pyridoxine responsive seizures. In the last year we have found 13 cases of pyridoxine/folinic acid responsive seizures in patients who have had intractable seizures. In all cases the two biomarkers have been found and pathogenic mutations in the ALDH7A1 gene have been demonstrated.

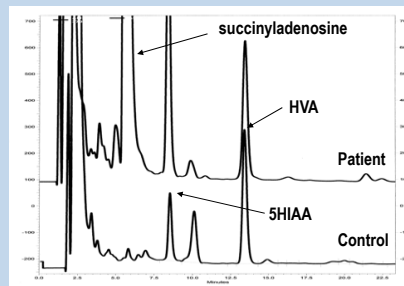
Biomarkers seen following HPLC separation of CSF neurotransmitter metabolites in pyridoxine responsive seizures



Adenylosuccinate Lyase Deficiency

Adenylosuccinate lyase deficiency is a disorder of purine metabolism. Patients normally present with seizures (early or later onset) and/or autism and occasionally a lack of myelination or cortical blindness. The condition leads to accumulation of succinyladenosine and succinylaminoimidazole carboxamide riboside. Succinyladenosine is the major metabolite and this compound is electrochemically active and can also be seen on the chromatogram used for the analysis of neurotransmitter metabolites in CSF. The region where this compound elutes is also the region where many drugs may appear. A subsequent specific test for succinyladenosine is always required for positive identification of this metabolite.

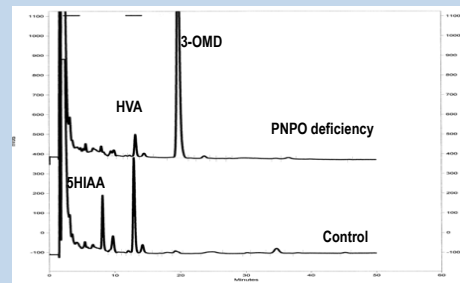
Succinyladenosine can be seen on the CSF neurotransmitter metabolite chromatogram



Pyridoxamine Phosphate Oxidase (PNPO) Deficiency

Pyridoxamine phosphate oxidase (PNPO) deficiency is a disorder that leads to a deficiency of pyridoxal 5'-phosphate (PLP) within the central nervous system. CSF PLP levels are reduced (Ormazabal A, et al. *Mol Genet Metab.* 2008). The lack of PLP within the brain in the neonatal period leads to presentation of neonatal seizures. PLP is required as a cofactor for a multitude of enzymes including those required for the transamination of threonine and glycine and these amino acids can accumulate in CSF in this disorder. PLP is also required for the activity of aromatic L-amino acid decarboxylase (AADC) which is an enzyme required for the synthesis of both dopamine and serotonin. PNPO deficiency can therefore mimic a primary defect in AADC and lead to a characteristic profile of neurotransmitter metabolites in CSF which consists of elevated 3-O-methyldopa (3-OMD) and decreased concentrations of homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5HIAA).

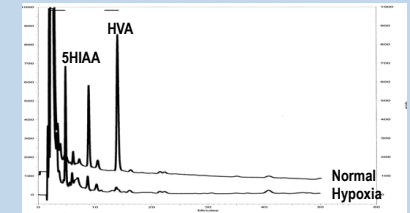
CSF Neurotransmitter metabolite profile seen in PNPO deficiency



Hypoxia

A period of hypoxia, particularly in the neonatal period can lead to profound decreases in HVA, 5-HIAA and tetrahydrobiopterin (BH4) which is the cofactor required for dopamine and serotonin synthesis.

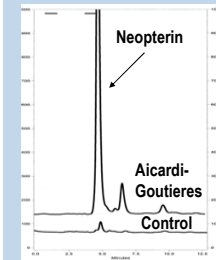
CSF Neurotransmitter metabolite profile seen in a neonate following hypoxia



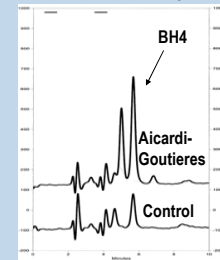
CSF Neopterin in CNS Immune System Stimulation

Neopterin is released from astrocytes and macrophages following stimulation by interferon gamma. Elevations of neopterin in CSF provides evidence that a neurological disorder has an immune based mechanism rather than a metabolic/structural cause. Particularly high levels of neopterin, together with tetrahydrobiopterin are found in the Aicardi-Goutieres syndrome and elevations of both in CSF are diagnostic for this condition.

Fluorescence



Electrochemistry



Summary

Testing of CSF for neurotransmitter metabolites, neopterin and tetrahydrobiopterin not only allows detection of primary monoamine neurotransmitter defects it also allows detection of pyridoxine responsive seizures, PLP responsive seizures and adenylosuccinate lyase deficiency. The same testing can also help determine if a hypoxic event has occurred or if neurological dysfunction is related to an infectious/immune related process.