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Hyperornithinemia with Gyrate Atrophy

Background

The first description of a patient with gyrate atrophy of the choroid and retina, as defined by the characteristic appearance of the ocular fundus and a typical history of visual deterioration, was probably made in 1888. Since that time numerous other case reports have confirmed this condition as a distinct entity. Hyperornithinemia and ornithinuria were recognized as the biochemical marker for this disorder in 1973. Elevations in Ornithine, a non-protein amino acid, are associated with complete or partial deficiency of Ornithine Aminotransferase (OAT) activity.

Clinical

The major clinical problem in these patients is a slowly progressive loss of vision leading to blindness, usually by the fifth decade of life. Myopia and decreased night vision are early symptoms, usually noted by the first or second decade. Reduced peripheral vision is typically present in the second decade, with nearly all patients ultimately developing cataracts. The combination of the cataracts and diminished visual fields results in progressive visual loss, which is frequently well established by the third decade of life in most patients. However, there is significant variability in vision and a few patients retain good visual function into their sixth or seventh decade.

Younger patients often come to the attention of the ophthalmologist in late childhood or around the time of puberty for evaluation of myopia or decreased night vision. Aside from visual impairment, patients with gyrate atrophy are for the most part asymptomatic. Some patients have mild muscle weakness with associated abnormalities on muscle biopsy and in electromyograms, although creatine phosphokinase activity is normal. Affected patients are developmentally normal.

Testing

Newborn screening of dried blood spots using tandem mass spectrometry (MS/MS) is capable of identifying and quantitating Ornithine. Diagnostic evaluation can show abnormal levels of ornithine in plasma, cerebrospinal fluid and urine. An ornithine methyl ester is found in the urine of patients with gyrate atrophy and other conditions associated with hyperornithinemia.

Deficiency of OAT has been documented in cultured skin fibroblasts, lymphocytes, skeletal muscle, and liver biopsy specimens. Activity of this enzyme is absent or markedly diminished and may explain the clinical heterogeneity of the disease. Numerous mutations have been found in the OAT gene in patients from around the world.

Treatment

A few gyrate atrophy patients will respond to pharmacologic doses of vitamin B6 (pyridoxine) with increase in residual enzyme activity, partial reduction in plasma Ornithine and stabilization of vision. The slow progression of the degenerative changes in vision and the difficulty in measuring small changes in ocular function make evalua-tion of any therapy difficult. Additional approaches to therapy may be efficacious, including dietary reduction in Ornithine and administration of creatine.

Because the diagnosis and therapy of Hyperornithinemia with Gyrate Atrophy is complex, the pediatrician is advised to manage the patient in close collaboration with a consulting pediatric metabolic disease specialist.

Inheritance

Hyperornithinemia with Gyrate Atrophy is inherited as an autosomal recessive trait. Both parents are carriers of one normal gene and one abnormal Hyperornithinemia gene. An affected child is born when both parents pass along the Hyperornithinemia gene at conception, resulting in every cell of the body having the two abnormal genes. The risk for carrier parents having an affected pregnancy is one chance in four with every conception. If not screened at birth, all previous siblings should be tested to rule out Hyperornithinemia. This disease has been found in several ethnic groups around the world with a particularly high incidence in Finland.

References

Valle, D. and Simell, O. The hyperornithinemias. In, The Metabolic and Molecular Basis of Inherited Disease. 8th Edition, 2001. Scriver, Beaudet, et al., eds. McGraw-Hill. Chapter 83:1857-1895.