Encephalomyelopathy of Leigh

It is exciting to follow the evolution of biochemical understanding in a disease, even one as uncommon as infantile subacute necrotizing encephalomyelopathy (sometimes described as Leigh's syndrome).[1] Over 50 cases have now been reported, and recently a test for it has been devised.

The syndrome presents usually in early infancy with impaired feeding, vomiting, failure to thrive, lethargy, progressive lack of movement, hypotonia, and a poor cry. There is usually severe psychomotor retardation, and some patients have had epileptic attacks, optic atrophy, deafness, abnormal pupillary reaction and extraocular movements, and spasticity of the lower limbs. The usual progress is steadily downhill, many dying within a month or two of onset. However, acute[2] and chronic[3] courses have been described in a number of cases, and relapses and partial remissions have been seen in a few. The disease appears in childhood, the oldest patient so far reported being 17 years.[4] Most cases have been sporadic, though a number have been siblings or products of consanguineous marriages, suggesting an autosomal recessive mode of inheritance.

The clinical picture is not pathognomonic of the disease, but the histopathological changes are characteristic. Frequently the diagnosis has been made in life only when a previous child has been found at necropsy to have died of the condition. The changes are strikingly similar to those of Wernicke's encephalopathy, particularly the hypervascularity of the lesions. There are multifocal areas of damage ranging in severity from necrosis with cavitation to simple degenerative changes in neurones and oligodendroglia, spongiform change in the white matter of the brain, and astrogliosis. These are accompanied by a conspicuous increase in the number of capillaries and small blood vessels. While the character of the lesions is similar to those in Wernicke's encephalopathy, the distribution is different.[4] In Wernicke's encephalopathy they are found in the mamillary bodies, hypothalamus, and thalamus, with a lesser involvement of the brain stem. In infantile subacute necrotizing encephalomyelopathy the mamillary bodies are usually spared, and the brunt of the disease falls on the mid brain and lower brain stem, with lesser involvement of the spinal cord, basal ganglia, cerebellum, optic nerve and tracts, and thalamus. The substantia nigra and periaquedectal grey matter are especially attacked. Peripheral nerves have been affected in some cases,[5] and occasional patients have had aminoaciduria.[5, 6] Lesions outside the nervous system are rare, though a patient recently described had nephrosis, with damage to the arteries and arterioles.[7]

The similarity to Wernicke's encephalopathy, which is due to a deficiency of thiamine, prompted D. Leigh[1] to suggest that the syndrome arose from some dietary deficiency. The findings in many cases of an acidosis with increased plasma pyruvate and lactate supported this idea.[6-9] However, with one possible exception,[10] blood levels of thiamine have been normal in patients with this syndrome. Moreover, treatment with thiamine has been without effect.

Just as the clinical and to a lesser extent pathological picture varies from case to case, it is possible that the biochemical basis may not be identical in all. H. E. Worsley and colleagues[6] found that red cells in this syndrome convert glucose to pyruvate abnormally rapidly, suggesting that the syndrome arises from the overproduction of an enzyme rather than the deficiency of a co-factor. The almost total absence from a patient's liver of pyruvate carboxylase,[9] the enzyme responsible for the conversion of pyruvate to oxaloacetate, would not prevent the metabolism of pyruvate to acetyl coenzyme A. The increased synthesis of alanine found in some patients[5] indicates that excess pyruvate may be removed by transamination.

However, recent work from Yale[11, 12] suggests that in patients with subacute necrotizing encephalomyelopathy an abnormal substance accumulates and inhibits the enzyme which phosphorylates thiamine pyrophosphate to thiamine triphosphate (TPP-ATP phosphoryl-transferase). By means of a test for this substance the Yale group have been also to diagnose five definite and three probable cases in the space of a year. The father of one of the cases and two of three infant siblings of another had the inhibitor in their urine. One false positive was found, but so far no false negatives are known. The test for this inhibitor is relatively straightforward, and its use is recommended in infants with progressive encephalopathy. It is becoming clear from both the work of the Yale group and elsewhere[7, 13] that the syndrome is more common than originally thought. So far the work on this inhibitor has not led to an effective treatment, though lipoate has slowed the progression of the disease in some patients.[9, 14]

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