

Epilepsy as a pyridoxine-dependent condition: Familial disorders of vitamin B6 metabolism

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The study carried out in children with different forms of epilepsy (excluding absence and atonic forms) has confirmed our earlier assumption on epilepsy as an inborn error of pyridoxine (vitamin B6) metabolism. Kynurenine pathway of TRP degradation, which represents the strong sequence of pyridoxine -dependent reactions, was traced in epileptic children and control healthy group. In children of both group the urinary level of tryptophan (TRP), concentrations of compounds formed or metabolized in the course TRP degradation, as well as the level of 4-pyridoxic acid (the end product of Vitamin B6 metabolism) were detected. These parameters, as well as the ratios between some of them, turned out to be quantitative biomarkers of patient's state, which determine individual monitoring of antiepileptic treatment. The ratio of 4-pyridoxic acid to kynurenine is the biomarker of experienced seizure attack, while the ratio of 3-hydroxyanthranilic acid to 3-hydroxykynurenine (3-HOAA/3-HOKYN) reflects activity of kynureninase, the enzyme critically sensitive to PLP supply. Growing progressively worse, epilepsy is accompanied by aggravation of PLP-dependent disturbances of TRP metabolism and the expanding inhibition of kynureninase. The affected pyridoxine metabolism is evidently an inborn genetic trait in epilepsy in a whole, rather than a specific sign of only pyridoxine-dependent epilepsy.

Almost the same, sometimes even more severe, disorders of pyridoxine metabolism were revealed in asymptomatic first degree relatives of epileptic probands. The increased level of TRP and disrupted activity of the majority of PLP-dependent enzymes turned out to be the common hidden inborn traits in epileptic families. Activity of kynureninase, as the most vulnerable link of TRP degradation, was reduced in all asymptomatic first degree relatives of epileptic probands, confirming the notion of endophenotype as a heritable biochemical trait, which is "co-segregated" with illness within the family and manifests in an individual whether or not illness is active.

We assume that low activity of alkaline phosphatase, disrupts PLP transport through membranes, and is a heritable biochemical trait in epileptic families. At least our experiments in seizure-naïve epilepsy-prone (EP) and epilepsy-resistant (ER) mice, (selectively bred from BALB/c strain), have shown, that activity of alkaline phosphatase in the cortex and hippocampus of EP mice amounted to (accordingly) 77.2±6.7 and 74.1±6.1% activity of ER controls.

Disorders of pyridoxine transport affect production of PLP-dependent excitatory and inhibitory neurotransmitters, creating their imbalance. Thus, the disturbance of pyridoxine transport probably is the determining factor of familial seizure predisposition. According to our experience, the long-term pyridoxine treatment in pharmacological doses (10 mg/kg) started at early development and targeted at the correction of pyridoxine-dependent metabolic disturbances, is protective for children born in affected families.

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