Disorders of Neurotransmitters

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Although there is a large number of (established and putative) neurotransmitters, the number of known diseases due to hereditary defects in the metabolism of these substances is rather small. The established neurotransmitter systems can be divided into aminoacidergic (mainly gamma aminobutyrate, GABA, glycine, aspartate, and glutamate), cholinergic (acetylcholine), monoaminergic (mainly adrenaline, dopamine, noradrenaline, and serotonin), and purinergic (adenosine and adenosine monophosphate, diphosphate, and triphosphate, AMP, ADP, and ATP), while a rapidly growing list of peptides are considered putative neurotransmitters. Possibly involved in neurotransmission and/or neuromodulation are N-acetyl amino acids and N-acetyl peptides.

This review deals with hereditary diseases in the metabolism of GABA, the monoamines, and N-acetylaspartate. Disorders in the metabolism of glycine are treated in the chapter by Tada (this volume). The recent discovery of a glycine receptor defect in hyperekplexia [1] indicates that the scope of this chapter should be broadened to disorders of neurotransmission in the next edition of this book!

Inborn Errors of Gamma Aminobutyrate Metabolism

Three genetic diseases due to a defect in brain GABA metabolism have been reported: glutamic acid decarboxylase deficiency and two defects in GABA catabolism, GABA transaminase deficiency and succinic semialdehyde dehydrogenase (SSADH) deficiency (Fig. 1).

Pyridoxine-Responsive and -Unresponsive Glutamic Acid Decarboxylase Deficiency

Pyridoxine-responsive glutamic acid decarboxylase deficiency (pyridoxine-responsive convulsions) was first reported in 1954 [2]. It is a rare cause of convulsions in early childhood [3]. Recently, indirect evidence was presented for pyridoxine-unresponsive glutamic acid decarboxylase deficiency in infants with a “stiff baby-like” syndrome and convulsions. This is not further discussed in this chapter.

Clinical Presentation

The clinical picture of typical pyridoxine-responsive convulsions has to be differentiated from the more recently identified atypical presentation. The typical form satisfies the following criteria:

- Onset of convulsions before or shortly after birth
- Rapid response to pyridoxine
- Refractoriness to other anticonvulsants
- Dependence on a maintenance dose
- Absence of pyridoxine deficiency

The disease may start as intrauterine convulsions as early as in the fifth month of pregnancy. Some patients suffered from peripartal asphyxia probably as a consequence of this disorder. The seizures are intermittent at onset, but may proceed to status epilepticus. All types of seizures can be
observed, mostly long-lasting seizures and repeated status epilepticus, but also brief convulsions (generalized or partial), atonic attacks, and infantile spasms. There is pronounced hyperirritability that can alternate with flaccidity. Abnormal eye movements are often reported (nystagmus, “rolling” eyes, miosis, and/or poor reaction of the pupils to light).

The atypical presentation [4] differs from the typical one as follows:

- Later onset of the attacks (up to the age of about 15 months)
- Prolonged seizure-free intervals without pyridoxine (as long as 5 months)
- Need of larger pyridoxine doses in some patients
- Higher incidence

Metabolic Derangement

Pyridoxine-responsive convulsions are considered to be due to brain GABA deficiency resulting from a genetic defect at the pyridoxal phosphate coenzyme-binding site of glutamic acid decarboxylase, the rate-limiting enzyme in GABA synthesis. Brain and cerebrospinal fluid (CSF) GABA have only rarely been measured and were found to be low [5, 6].

Diagnostic Tests

The diagnosis rests on the clinical response to pyridoxine. A trial of pyridoxine should be performed in all unclear seizure disorders with onset before the age of about 15 months. Results of CSF free GABA determinations and investigations at the DNA level should not be waited for, as these are mostly not readily available.

Treatment and Prognosis

The disease promptly responds to pyridoxine, but is refractory to other antiepileptic medications. The minimum effective daily dose is at least ten times the minimum daily amount recommended for healthy infants and usually varies between 2 and 15 mg. Treatment with isoniazid increases the minimum effective dose. The convulsions cease within a few minutes when pyridoxine is administered parenterally and within a few hours when it is given orally. The effect of a single dose remains constant in the same patient (mostly 2–5 days). When treatment is interrupted, the seizures return, although there might be exceptions to this rule (delayed maturation of enzyme activity?) [6]. In the case of (suspected) intrauterine convulsions, treatment of the mother with pyridoxine is effective (around 100 mg/day). In the later-onset pre-