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Monoamine metabolism study in severe, early-onset epilepsy in childhood

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ABSTRACT – *Purpose*. To investigate the possible dysfunction of monoamine metabolism in patients with early-onset, epileptic encephalopathies. *Methods*. The CSF dopamine, serotonin and biopterin metabolites were studied in 37 patients with severe, mostly drug-resistant epilepsy. *Results*. No significant abnormality was found, whatever the type of epilepsy, cryptogenic or symptomatic. *Conclusions*. The present study failed to demonstrate that dysfunction of the main neurotransmitters pathways is a common phenomenon in children with early-onset, severe epileptic encephalopathy.

Key words: neurotransmitters, monoamines, epilepsy, childhood

Neurotransmitter disorders refer to a group of inherited neurometabolic syndromes attributable to disturbances of neurotransmitter metabolism or transport. Early-onset, severe epileptic disorders are frequently observed in several diseases affecting these metabolisms, *e.g.* in abnormalities of glycine, pyridoxal-phosphate, or gamma-aminobutyric acid (GABA) metabolism (Swoboda and Hyland 2002, Pearl *et al.* 2006). The incidence of epilepsy in disorders of monoamine dysfunction (catecholamine and serotonin) or in pterin metabolism is not very well known. Diagnosing these diseases requires investigation of cerebrospinal fluid (CSF), with special techniques that are only available in relatively few laboratories (Hyland 2006). This is a major reason why the complex spectrum of these diseases remains only partially understood.

The monoamine metabolism pathways covered by our study include those of guanosine triphosphate (GTP), pterins, serotonin, and dopamine *(figure 1)*. The corresponding enzyme deficiencies concern GTP cyclohydrolase 1 (GTPCH1), tyrosine hydroxylase (TH), aromatic L-amino acid decarboxylase (AADC), sepiapterin reductase (SR), 6-pyruvoyltetrahydrobiopterin synthase (PTPS), and dihydropteridin reductase (DR) *(figure 1)*. Most of the published cases correspond to patients with primary inherited deficiencies. However, secondary defects have also been reported in other conditions such as Menkes disease, Aicardi-Goutières syndrome, cerebral ischemia and neonatal hypoxia (Blau *et al*. 2003, Assmann 2006, Swoboda 2006), epileptic encephalopathies and early-onset neurological dysfunctions of unknown origin (Garcia-Cazorla *et al*. 2007). In some patients with pyridoxal-phosphate deficiency (pyridoxamine 5'-phosphate oxidase [PNPO] deficiency), CSF monoamine abnormalities have been described in neonates with severe drug-resistant

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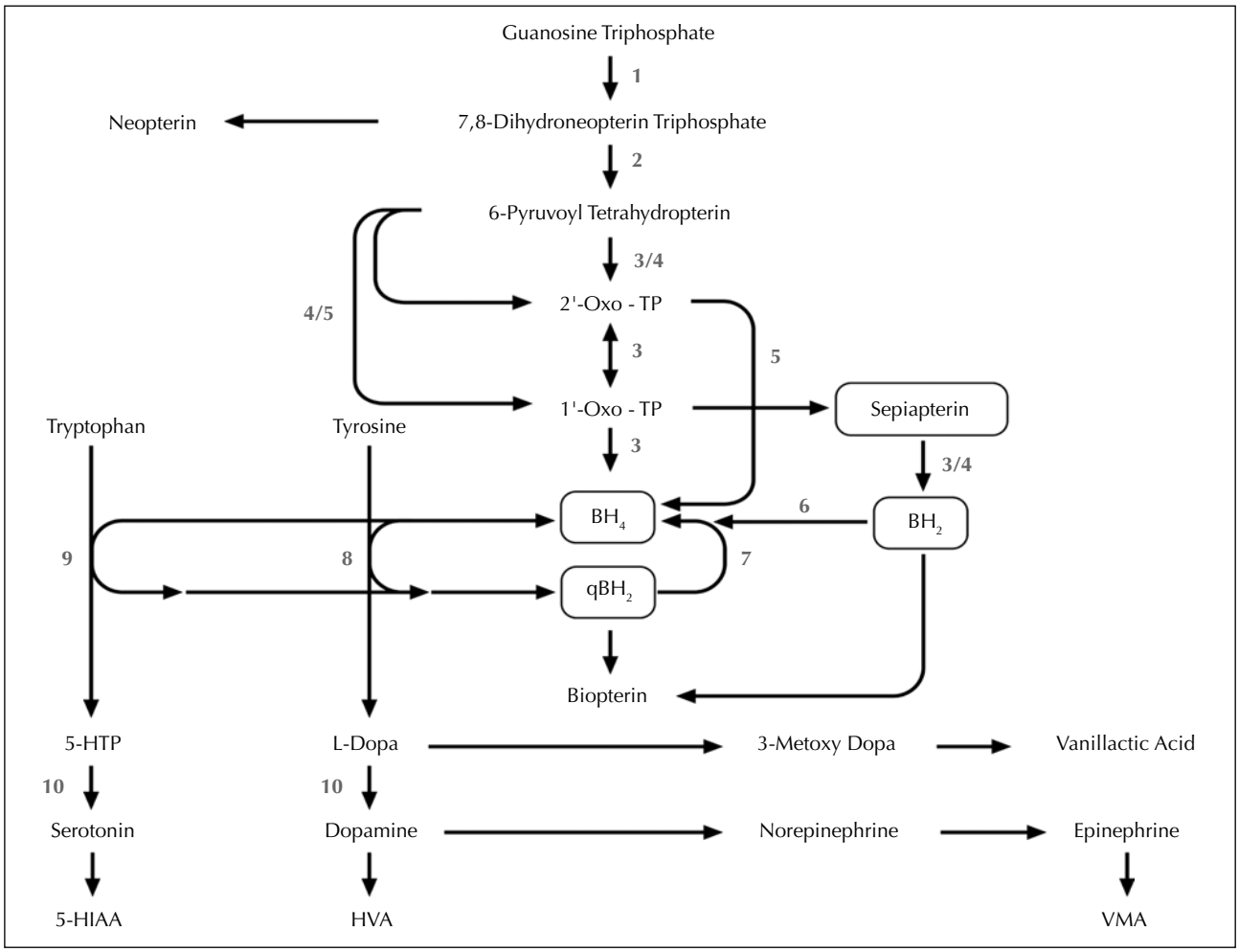

Figure 1. Pathways for biosynthesis and catabolism of the biogenic monoamine neurotransmitters serotonin, dopamine, norepinephrine and the pterins. 5HTP: 5 hydroxytryptophan; 5 HIAA: hydroxyindolacetic; HVA: homovanillic acid; 1 and 2-oxo TP: 1 and 2-oxo-hydroxytetrahydropterin; BH4: tetrahydrobiopterin; qBH2: quinonoid dihydrobiopterin; B H2: dihydrobiopterin; VMA: vanillylmandelic acid; 1: GTP cyclohydrolase 1; 2: 6-pyruvoyl-tetrahydrobiopterin synthase; 3: sepiapterin reductase; 4: carbonyl reductase; 5: aldose reductase; 6: dihydrofolate reductase; 7: dihydropteridine reductase; 8: tyrosine hydroxylase; 9: tryptophan hydroxylase; 10: aromatic L-aminoacid decarboxylase.

epilepsy: increases in 3-O-methyldopa, 5-HIAA, vanillactic acid and a decrease in HVA. The organic acid profile, (molecular study and the specific treatment), differentiates this very rare condition from the other, secondary forms of CSF monoamine disturbances (Clayton *et al.* 2003, Hoffmann *et al.* 2007, Ruiz *et al.* 2008). In cases of primary enzymatic defects, the clinical phenotypes correspond usually to cerebral palsy-like pictures, with dystonic movements, oculogyric crises, and mental delay, with or without diurnal fluctuations. However, the clinical picture may be non-specific, corresponding to a severe, early-onset encephalopathy of obscure origin.

Epileptic seizures have sometimes been reported in these diseases affecting monoamine metabolism (Hoffmann *et al.* 2003, Swoboda *et al.* 2003, Echenne *et al.* 2006, Assmann, 2006).

As a great number of these disorders probably remain undiagnosed (Neville 2007), we prospectively investigated, in an open study, together with the informed consent of parents, the CSF metabolites in children with early-onset, severe epilepsy, the results of which are presented here (in our department, the lumbar puncture and CSF analysis are systematically performed in these circumstances).

Patients and methods

Children presenting with seizures that were initially drug-resistant, needing several changes of treatment were in-

cluded in the investigation. Epilepsy was associated with persistent neurological abnormalities (motor delay, abnormal muscle tone or movements, mental delay). In most of these patients, the etiological investigations were negative, except for children who had only abnormal MRI. Patients with well-defined metabolic disorders, and storage or degenerative diseases were excluded from the study. All patients had repeated EEGs and cerebral MRI. Epilepsy was classified according to the ILAE classification (ILAE, 1989, Fisher *et al.* 2005). A biological investigation including urine and blood amino acid chromatography, urine organo-acid spectrometry, acid-base balance study, lactate and pyruvate levels was performed in each case. Chromosome studies were systematically done in patients with cryptogenic epilepsies, with special reference to chromosomes 15, 20, and 18. The main biological investigations involved the CSF monoamines and pterins metabolites: 5-hydroxyindolacetic acid (5-HIAA), homovanillic acid (HVA), 3-O-methyl dopa, and levodopa as well as tetrahydrobiopterin (BH_4), which were measured with high-performance liquid chromatography and electrochemical detection as described elsewhere (Blau *et al.* 2001). Dihydrobiopterin and neopterin were separated by reverse phase high-performance liquid chromatography using column switching and fluorimetric detection (Blau *et al.* 2001).

Results

In a prospective study lasting from 2002 to 2006, 37 children were included (20 boys and 17 girls).

The patients' age at the onset of epileptic seizures, varied from the neonatal period (eight cases), to infancy (19 patients aged from one to 12 months, seven others aged between one and three years). Only three patients were between five- and nine-years-old.

The type of epilepsy, according to the ILAE classification, included: focal symptomatic epilepsy (seven cases: ischemic stroke - one, cortical dysplasia - one, diffuse cortical atrophy or multiple focal lesions - five); focal cryptogenic epilepsy (seven cases); symptomatic infantile spasms (four cases: tuberous sclerosis - one, cortical dysplasia - two, diffuse cortical atrophy - one); cryptogenic infantile spasms (five cases); spasms associated with or followed by focal seizures (six cases, two of them symptomatic, subdural haematoma - one, diffuse cortical atrophy - one); astatic-atonic seizures (Doose syndrome) (four cases); cryptogenic Lennox-Gastaut syndrome (two cases); and complex unclassified epilepsies (two cases, one of them symptomatic, with diffuse cortical atrophy). Epilepsies were drug-resistant in 23 patients, and partially controlled in 14. With a follow-up lasting from six months to four years, we observed a severe encephalopathy with quadriparesis, and marked mental delay in 18 patients; four of whom had also dystonic and abnormal movement; one had abnormal ocular movements. Severe mental delay was present in 29 of 37 patients, three having a pervasive syndrome. A moderate mental delay was observed in the remaining eight patients; none of the 37 children had normal intellectual development (evaluated on Brunet-Lezine, MacCarthy or Wechsler scale according to age).

Cerebral MRI was normal in 23 patients, despite the severity of the motor deficit. It was found to be abnormal in the other 14 patients.

Considering the onset of epilepsy, CSF samples were analyzed at different times from one patient to another: during the first month following seizure-onset (15 cases), between 1 and 6 months (nine cases) or 6 to 18 months (eight cases) following seizure-onset, or more than 3 years later (five cases). At that moment, all patients were treated with anti-epileptic drugs (AED), most often under polytherapy. Several drugs were used, most often successively and/or in association; the combinations were different for each patient: sodium valproate, benzodiazepines, topiramate, levetiracetam, phenytoin, oxcarbazepine, and ACTH. Vagal stimulation and ketogenic diet were not used. The patients' age at the time of the investigation varied from one month to one year in 19 cases, and from one year to two years in eight cases. Six patients were between two and five years old. Four were older than five years (the oldest was nine years old).

The CSF analysis data are summarized in *table 1*. Whatever the age at epilepsy-onset, the type of epilepsy, the patient's age, and the results of the cerebral MRI study, the results were always within the normal range, according to age-matched, laboratory references. BH_4 levels were lower in three patients, but without any associated abnormality that might correspond to a metabolic disorder affecting biopterin (normal levels of dopa and serotonin metabolites, and normal levels of neopterins and dihydrobiopterin in these cases, apart from one disorder affecting one of these different pathways). CSF amino acids, 5-HIAA, HVA, 3-O-methyl dopa, L-dopa, 5-hydroxytryptophan and BH_2 were all found to be normal, as was 5 MTHF, which is also involved in neurotransmission.

Discussion

There are abundant data in the literature showing the inhibitory effects of dopamine and serotonin on epileptogenesis (Allan and Starr 1993, Clinckers *et al.* 2004, Clinckers *et al.* 2005). Generally, agents that elevate extracellular serotonin, such as 5-hydroxytryptophan and serotonin re-uptake blockers, inhibit both local and generalized seizures (Bagdy *et al.* 2007). Pharmacological and electophysiological data from animal models of epilepsy, and from humans, suggest that the basal ganglia and dopamine neurotransmission may function as a control circuit for some seizures (Deransart *et al.* 2001, Deransart and Depaulis 2002, Bouilleret *et al.* 2005). Furthermore,

Table 1. Results of CSF analysis according to epilepsy type.

Type of epilepsy	Age at CSF analysis (median)	Nb of patients	CSF analysis results						
			5-HIAA	HVA	3-O-M L	L-Dopa	5-HT	BH4	5-MTHF
Focal symptomatic	8.9m (extr : 1-16m)	7	190 (103-482)	612 (296-996)	23 (< 2-89)	< 2 (< 2)	3 (< 2-12)	72 (26-183)	106 (29-165)
Focal cryptogenic	13y (extr :1-40m)	7	270 (179-412)	537 (236-959)	16.4 (< 2-20)	< 2 (< 2)	2.9 (< 2-10)	39.7 (30-90)	110 (67-180)
Infantile spasms (sympt)	13.7m (extr : 7-27m)	4	375 (189-498)	753 (432-930)	34 (< 2-62)	< 2 (< 2)	3.2 (< 2-13)	10 (1-25)	127 (78-168)
Infantile spasm (crypt)	24m (extr :1m-7y)	5	230 (148-348)	418 (237-606)	14 (< 2-36)	< 2 (< 2-2)	11.6 (< 2-22)	30 (13-44)	261 (89-167)
Spasms + seizures	15m (extr :1m-5y7m)	6	252 (111-454)	579 (218-1030)	54 (< 2-169)	< 2 (< 2)	12 (< 2-46)	37.8 (11-88)	98.5 (54-175)
Doose syndrome	3y11m (extr : 19m-6y8m)	4	149 (119-175)	397 (279-501)	9.7 (< 2-37)	< 2 (< 2)	1.2 (< 2-5)	50 (24-95)	61 (36-85)
Lennox-Gastaut	8y6m 6y2m	2	75 294	317 724	< 2 56	< 2 < 2	< 2 16	16 11	58 54
Unclassified	4m 4y	2	356 154	691 432	< 2 16	< 2 < 2	< 2 5	37 88	134 96
Control ranges			87-247	270-713	< 50	< 15	< 15	20-49	

pharmacological activation of striatal neurons by dopaminergic receptor agonists suppress generalized seizures in different animal models (Turski *et al*. 1989, Deransart and Depaulis 2002), whereas blockade of striatal dopaminergic receptors aggravates absence seizures in a genetic model of absence epilepsy in rats (Deransart *et al*. 2001). Striatal dopamine dysfunction has been demonstrated in some forms of human epilepsy (Henry *et al*. 1990, Biraben *et al*. 2004). In the same way, several antiepileptic drugs increase extracellular levels of dopamine and/or serotonin in brain areas involved in epileptogenesis (Biggs *et al*. 1992, Murakami *et al*. 2001).

Epileptic seizures have been observed in different forms of genetically determined enzyme deficiencies involving the metabolic pathways of dopamine and serotonin, but with an incidence that varies from one disease to another.

To our knowledge, epilepsy has not been described in classical GTP cyclohydrolase deficiency (Segawa *et al*. 2003, Segawa *et al*. 2004). Epilepsy is not usually associated with tyrosine hydroxylase deficiency, in which non-epileptic myoclonic jerks are frequently seen (Hoffmann *et al*. 2003). However, epilepsy is a constant feature of PTBS deficiency in its severe forms (Chien *et al*. 2001, Scriver *et al*. 2001, Lee *et al*. 2006), which are associated with mental delay and motor impairment. Unfortunately, in these cases, the type of seizures and the EEG aspects are poorly described in the literature, and this is the case in other enzymes defects in which epilepsy may occur, for example SR deficiency (Neville *et al*. 2005, Echenne *et al*. 2006). In DR deficiency, seizures are frequent and non-specific, as are the EEG changes (interictal EEGs may remain normal despite the frequent occurrence of seizures, or they may show hypsarrhythmia, sharp waves, or generalised or focalised spike-waves) (Dhont 1993, Mikaeloff *et al*. 1999). Finally, seizures have been reported in AADC deficiency, but only as an unusual finding (Swoboda *et al*. 2003, Pons *et al*. 2004). It must be emphasised that in all these enzymes defects and diseases, abnormal ocular movements, tonic spasms, and non-epileptic myoclonic jerks may occur and mimic epileptic seizures, however, the ictal EEGs remain normal.

In our sample of severe, early-onset epilepsies in childhood, associated with mental and motor delay and most often with severe motor handicap, no abnormal results were detected concerning the main metabolites of monoamine pathways, dopamine, serotonin, and pterins. However, Assmann (2006) recently reported four patients with epilepsy and abnormal CSF monoamine levels (a 10-months-old infant with symptomatic infantile spasms, "active seizures" in an eight-year-old boy with spastic-ataxic movement disorders, a non-defined epileptic syndrome in a 17-month-old girl, and progressive encephalopathy, including epilepsy, in a 10-year-old girl), but without any primary defect affecting neurotransmitters metabolism. Recently, Garcia-Cazorla *et al*. (2007) reported the results of the CSF neurotransmitter study in different groups of early-onset neurological handicaps of various origin (the causes were not precisely described in the paper), with a definite diagnosis made in eight of 10 cases with a decrease in HVA. As a matter of fact, they found in 10 of their 56 patients, lower levels of HVA, and in four patients, a decrease in 5-HIAA; these abnormalities correlated to the neonatal onset of the neurological abnormalities, and patients with cortical atrophy seemed to have lower concentrations of 5-HIAA. However, the most important finding, closely related to our study, concerned

29 children who had early-onset epileptic encephalopathy, and who can be compared to our patients group: only three of them had HVA concentrations below the reference values, the other values being normal. No relationship was found between biogenic amine metabolites concentrations and drug intake.
This demonstrates that CSF changes may occur in the presence of active epilepsy. These secondary disorders improved in some cases under AED. This highlights the possibility of secondary, abnormal disorders of monoamine metabolism in childhood epileptic syndromes, a condition that probably remains infrequent, as we have shown in our study.

Conclusion

As far as genetically determined enzymatic defects of monoamine and pterin metabolism are concerned, epilepsy is a frequent feature only in PTBR and DR deficiencies, while they are rarely observed in SR and AADC deficiencies. They are not found in GTPCH1 or in TH deficiencies. Therefore, it is not really surprising to find no CSF monoamine metabolite abnormalities suggesting an enzymatic deficiency in cases of severe, early-onset, epileptic encephalopathies. Neurotransmitter disorders affecting GABA metabolism, glycine and 5-pyruvate phosphate may present with severe epileptic encephalopathy during the neonatal period. However, our results suggest that monoamine metabolism remains normal in most patients with severe, early-onset, cryptogenic, including symptomatic, epileptic syndromes in infancy and early childhood. □

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