Biogenic amines and pterins in cerebrospinal fluid: some pitfalls with interpretation

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The quantification of neurotransmitters or their metabolites in cerebrospinal fluid (CSF) can provide valuable clues for the detection of (often treatable) genetic disorders or their biosynthesis or salvage pathways. These analyses are technically demanding since the concentrations to be assessed are in the nanomolar range. To date, only a few laboratories worldwide offer these analyses. Since some metabolites are unstable at room temperature and sensitive to light or oxygen, special preparation of sampling tubes is helpful and the samples should be immediately frozen at the bedside. Furthermore, due to a craniocaudal gradient, a sampling protocol with numbered tubes should be adhered to. In addition to the technical difficulties, interpretation of the biochemical findings in lumbar CSF is much more complex than the interpretation of results in urine or blood. This article will focus on some pitfalls associated with the interpretation of analyses of dopamine, serotonin and pterin metabolites, and examines clinical data from pediatric patients to further illustrate those pitfalls.

A mainstay for the interpretation of cerebrospinal fluid (CSF) results is a valid reference range for each metabolite. While appearing simple in practice, this is a challenge and has provoked some debate. First, there is a craniocaudal gradient from ventricular to lumbar CSF to take into account substances that are produced mainly in the brain, such as the dopamine and serotonin metabolites. The concentrations of homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5-HIAA) in CSF have been shown to be an overall estimate of dopamine and serotonin turnover, respectively. Unfortunaelty, more subtle imbalances between some receptor subpopulations or supersensitivity of receptors, which may also cause significant clinical problems, cannot be mirrored reliably in lumbar CSF.

In addition to the craniocaudal gradient, a marked, nonlinear, age-dependency has to be considered, which is especially pronounced during the first year of life. The establishment of age-related reference ranges is therefore essential. For several reasons, the reference ranges given by different laboratories refer to different sampling protocols and different age groups. Bräutigam and colleagues have investigated this issue in a study enrolling 12 laboratories from six countries [1], and they found that the technical quality of analyses was comparable for most of the laboratories (nine of 12), whereas the age-related reference ranges and sampling protocols differed, sometimes substantially.

However, clinical practice teaches us that the reference ranges are not the only criteria for the interpretation of CSF metabolites, as will be illustrated by some authentic examples. Therefore, the conflict between the two opposing stand points – that 'overly broad' reference ranges will lead to missing a genetic defect, and 'overly narrow' ranges will produce too many false-positive results – needs to be revised since errors occur in both directions.

Analysis of biogenic amines & pterins in children with unexplained neurological disorders

Abnormal metabolites of dopamine, serotonin and pterins are detectable in CSF when their biosynthesis is disturbed (**Figure 1**). Disorders of this kind are genetic deficiencies of tyrosine hydroxylase, aromatic-L-amino acid decarboxylase, guanine tiphosphate (GTP) cyclohydrolase I, 6-pyruvoyltetrahydropterin synthase, sepiapterin reductase and dihydropteridine reductase. These disorders are presented in more detail in another article in this issue of *Future Neurology*. Dopamine and serotonin are also referred to as 'biogenic amines'.

Identification of the defect relies on the interpretation of the CSF concentrations of neopterin, 5-hydroxytryptophan (5-HTP), levodihydroxyphenylalanine (levodopa; L-dopa), 3-orthomethyldopa (OMD), 5-HIAA, HVA, their ratio HVA/HIAA, and sometimes sepiapterin (STP). As with most metabolic diseases, metabolites before the enzymatic block accumulate whereas downstream metabolites are reduced. HVA is the stable end product of dopamine and has been shown to reflect dopamine turnover, whereas 5-hydroxyindoleacetic acid reflects serotonin

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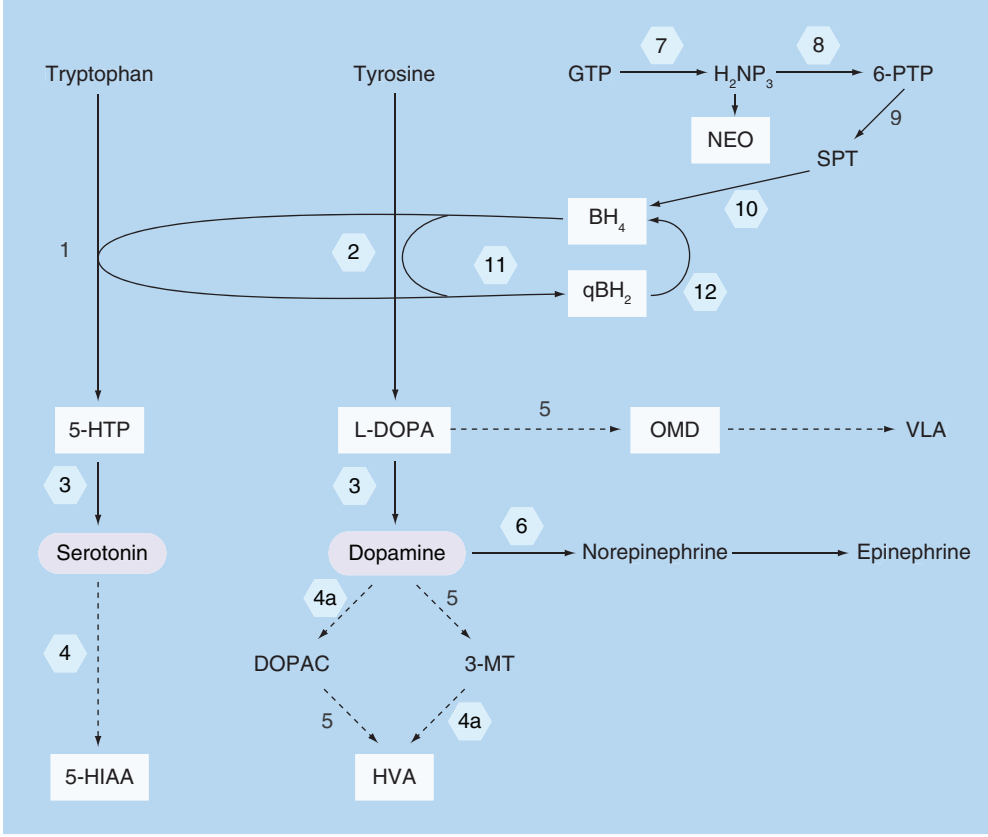
Figure 1. Metabolic pathway of serotonin and dopamine biosynthesis (solid arrows) and catabolism (broken arrows).



BH_4 is the essential cofactor for the rate-limiting enzymes tyrosine hydroxylase (TH) and tryptophan hydroxylase. **(1)** Tryptophan hydroxylase, **(2)** TH, **(3)** aromatic L-amino acid decarboxylase, **(4)** monoamine oxidase **(4a)** monoamine oxidase plus aldehyde dehydrogenase, **(5)** catechol-O-methyltransferease, **(6)** Dopamine β-hydroxylase, **(7)** GTP-cyclohydrolase I (GTPCH I), **(8)** 6-pyruvoyltetrahydropterin synthase, **(9)** aldose reductase, **(10)** sepiapterin reductase, **(11)** pterin-4α-carbinolamine dehydratase, **(12)** dihydropteridine reductase. The circled numbers refer to enzymes in which monogenic defects have been described; the metabolites in the white boxes are those analysed for differentiation and diagnosis of the monogenic defects.
5-HTP: 5 hydroxytryptophan; 5-HIAA: 5-hydroxyindoleacetic acid; 6-PTP: 6-pyruvoyltetrahydropterin; BH4: Tetrahydrobiopterin; GTP: Guanosine triphosphate; H_2NP_3: Dihydroneopterin triphosphate; HVA: Homovanillic acid; L-DOPA: Levodihydroxyphenylalanine (levodopa); NEO: Neopterin; OMD: 3-ortho-methyldopa; qBH_2: Quinonoid dihydrobiopterin; SPT: Sepiapterin; VLA: Vanillyllactic acid.

turnover. The neurotransmitters themselves only have very short half-lives. Pterin metabolism is slightly more complex since the tetrahydrobiopterin (BH_4) concentration is maintained by a biosynthesis pathway as well as a salvage pathway, and the concentration of BH_2 is negatively correlated to the activities of tryptophan and tyrosine hydroxylases. Dihydropteridine reductase deficiency produces reduced concentrations of 5-methyltetrahydrofolate (5-MTHF), which is also analyzed when the biogenic amines are investigated in most of the laboratories.

However, in contrast to metabolic defects of amino acid, organic acid or sterol metabolism, the concentration of metabolites found in CSF is dependent not only on genetic enzyme deficiencies, but also complex interactions between neurons of various brain regions. Abnormalities of these can lead to abnormal concentrations of neurotransmitter metabolites, which are termed 'secondary changes' as opposed to 'primary' changes, which are caused by the genetic deficiencies of enzymes involved in their biosynthesis or breakdown pathways.

Some secondary changes are caused by other defined metabolic diseases, such as a mild decrease of dopamine and serotonin metabolites in phenylketonuria. This is caused by the inhibition of tyrosine and tryptophan hydroxylases by accumulated phenylalanine, and the inhibition of precursor transport through the blood–brain barrier, as well as unknown factors. For example, neopterin is known to be enhanced by activation of macrophages or monocytes [2,3]. In the following section, some clinical examples will be presented with a focus on whether the CSF results are likely to be caused by a genetic deficiency of one of the enzymes of biogenic amine metabolism. The lumbar punctures were performed in the morning in fasting patients so that the potential influences of food were minimized. Samples where blood staining or thawing of CSF had occurred prior to analysis – nonbiological factors that are known to produce secondary changes – are not considered in this article. Results can be found in **Table 1**.

Symptoms typically found in genetic disorders of dopamine or serotonin metabolism are:

- Hypotonia in babies
- Seizures (age of onset variable)
- Dystonia
- Sometimes tremor and distal chorea
- Ptosis
- Miosis
- Reduced facial expression
- Drooling
- Instability of temperature
- Psychomotor retardation if untreated

Most of those symptoms are not specific for inborn errors in biogenic amine metabolism.

Examples for pitfalls in CSF neurotransmitter interpretation

Patient A

A 2-year old girl with severe developmental delay and a hypotonic–dystonic movement disorder was investigated for her neurotransmitter metabolites (**Table 1**).

Both metabolites were within their respective reference ranges. Pterins were normal. Therefore, at first glance, one could conclude that, in this case, there is no inborn error and no secondary disturbance of biogenic amine metabolism. However, the reduced ratio HVA/HIAA (dopamine metabolite/serotonin metabolite) suggests dopamine deficiency. In this patient genetic tyrosine hydroxylase deficiency was proven. The patient is an exception to the rule that most patients with tyrosine hydroxylase deficiency show HVA concentrations far below the reference ranges. This case illustrates that the ratio HVA/HIAA is a tool to discover imbalances between the dopaminergic and the serotoninergic systems and therefore should always be considered for the interpretation of results. (However, a normal ratio is also found when both pathways are involved, such as in pterin defects or AADC deficiency.)

Patient B

A baby was born prematurely by cesarean section after 34 weeks of gestation because of intrauterine growth retardation. She had good initial adaptation and development for the first 4 weeks. During the fourth week of life, the baby was entirely bottle fed. Shortly thereafter, she developed a progressive encephalopathy with severe hypotonia alternating with opisthotonus, temperature instability and blood pressure instability. There was no evidence of an infectious disease (**Table 1**).

As shown in **Table 1**, this combination of metabolites could be thought to result from a primary pterin defect, especially GTPCH I deficiency. However, besides other findings, there were high homocysteine and low methionine levels in the plasma and the child was diagnosed with cobalamin E deficiency (methionine-synthase reductase deficiency). This defect causes an accumulation of 5-MTHF (methyl-folate trap [4]). The complex interactions between folate and pterin metabolism are not fully understood. Systematic studies in these extremely rare disorders are not available; however, anecdotal cases of reduced biogenic amines in cobalamin deficiency syndromes have been observed.

Patient C

Another premature (dizygotic twin) baby was investigated following birth at 33 weeks of gestation as a result of abnormal fetal heart rate monitoring. His twin was fit and well, whereas this patient immediately showed severe multisystemic disease with seizures and very low voltage electroencephalograms, lactic acidemia, hepatomegaly, elevated transaminase levels and transient polyuria. The child was then very rigid with choreic movements and showed an abnormal breathing pattern, in addition to swallowing difficulties. Brain magnetic resonance imaging (MRI) on the second day of life was normal (**Table 1**).

Table 1. Neurotransmitter metabolites of clinical cases.

Neurotransmitter	Concentration	Age-related reference range	Neurotransmitter	Concentration	Age-related reference range
Patient A			***Patient H***		
HIAA	301 nmol/l	(130–360)	HIAA	99 nmol/l	(90–250)
HVA	319 nmol/l	(310–820)	HVA	127 nmol/l*	(240–710)
HVA/HIAA	1.1*	(1.5–4.1)	HVA/HIAA	1.3*	(1.8–4.1)
			Neopterin	69 nmol/l*	(7–27)
Patient B			***Patient Ia***		
HIAA	257 nmol/l*	(300–950)	HIAA	99 nmol/l*	(100–240)
HVA	258 nmol/l*	(480–1450)	HVA	187 nmol/l*	(285–560)
HVA/HIAA	1.0	(1.0–2.6)	HVA/HIAA	1.9	(1.7–3.7)
5-MTHF	329 nmol/l*	(60–290)			
BH_4	13 nmol/l*	(25–121)			
BH_2	5 nmol/l*	(<18)			
Neopterin	5 nmol/l*	(6-59)			
Patient C			***Patient Ib***		
HIAA	192 nmol/l*	(300–950)	HIAA	134 nmol/l	(100–240)
HVA	29 nmol/l*	(480–1450)	HVA	459 nmol/l	(285–560)
HVA/HIAA	0.15*	(1.0–2.6)	HVA/HIAA	3.4	(1.7–3.7)
BH_4	117 nmol/l	(25–121)			
BH_2	16 nmo/l	(<18)			
Neopterin	178 nmol/l*	(6–59)			
Patient D			***Patient J***		
HIAA	102 nmol/l*	(130–360)	HIAA	603 nmol/l*	(155–360)
HVA	69 nmol/l*	(310–820)	HVA	1020 nmol/l*	(360–870)
HVA/HIAA	0.7*	(1.5–4.1)	HVA/HIAA	1.7	(1.6–3.9)
BH_4	30 nmol/l	(20–61)	5-HTP	31 nmol/l*	(<10)
BH_2	60 nmol/l*	(<18)	OMD	59 nmol/l*	(<50)
Neopterin	229 nmol/l*	(5–53)	BH_4	72 nmol/l*	(20–61)
			BH_2	43 nmol/l*	(<18)
			Neopterin	61 nmol/l*	(5–53)
Patient E			***Patient K***		
HIAA	710 nmol/l*	(130–360)	HIAA	56 nmol/l*	(100–240)
HVA	2516 nmol/l*	(310–820)	HVA	144 nmol/l*	(285–560)
HVA/HIAA	3.5	(1.5–4.1)	HVA/HIAA	2.6	(1.7–3.7)
Patient F			***Patient La***		
HIAA	1130 nmol/l*	(160–530)	HIAA	148 nmol/l*	(170–410)
HVA	2327 nmol/l*	(430–990)	HVA	150 nmol/l*	(400–920)
HVA/HIAA	2.1	(1.2–2.9)	HVA/HIAA	1.0*	(1.8–3.0)
Patient G			***Patient Lb***		
HIAA	91 nmol/l*	(100–240)	HIAA	176 nmol/l	(130–360)
HVA	378 nmol/l	(285–560)	HVA	517 nmol/l	(310–820)
HVA/HIAA	4.1*	(1.7–3.7)	HVA/HIAA	2.9	(1.5–4.1)

**Abnormal values.*

5-MTHF: 5-methyltetrahydrofolate; BH_2: Dihydrobiopterin; BH_4: Tetrahydrobiopterin; 5-HIAA: 5-hydroxyindoleacetic acid; HVA: Homovanillic acid; OMD: 3-ortho-methyldopa.

As shown in **Table 1**, increased neopterin indicates an increased cellular immune response, as can be found after hypoxic insults [5]. The most likely explanation in this patient is severe antenatal hypoxia. A definite etiology to his hypoxia was not found, but this combination of clinical and biochemical findings is unknown in inborn errors of the biogenic amines' biosynthesis.

Patient D

A previously healthy 2-year-old boy presented with fever and vomiting at day 1 of his illness, focal seizures and progressive somnolence followed by coma and frequent seizures on day 2. Computed cranial tomography was normal on day 3, as were ophthalmological and metabolic findings. Neurotransmitters were analyzed on day 4 of the illness (**Table 1**).

There is no inborn error of the biogenic amines' biosynthesis, which would produce either such a pattern of abnormal findings or a similar clinical history. The abnormal pterin results are especially compatible with this patient's clinical diagnosis of encephalitis.

Patient E

The next case is a 2-year-old boy with a chronic neurological disorder characterized by hypotonia and hyper-reflexia, severe developmental delay, failure to thrive, camptodactyly, microcephaly and ptosis. MRI revealed hypomyelination (**Table 1**).

Although no definite diagnosis was found, this pattern of abnormalities, with marked elevation of both biogenic amines, is not compatible with any of the inborn errors in the pathways discussed here (pterins and 5-MTHF were normal).

Patient F

The next patient showed remarkable similarities and was very likely to suffer from a mitochondrial disorder.

This case is that of a 6-month old girl who was investigated for hypotonia and developmental delay with a history of normal development during the first few months of life. Cerebral imaging had shown abnormal myelin, which was interpreted as dysmyelination, and she had lactic acidosis after meals (**Table 1**).

All other metabolites were normal. Once again, this profile is not compatible with any enzyme deficiency concerning biosynthesis or breakdown of the biogenic amines, and the recurrent lactic acidosis after meals is very suggestive of a primary mitochondrial disorder.

Patient G

However, elevated biogenic amines are not always found with mitochondrial disorders. A 10-year-old boy presented with delayed psychomotor development, hypotonia and ataxia as well as elevated lactate in plasma. He was found to have complex I and IV deficiency of the respiratory chain. In the course of diagnostic work-up, neurotransmitter metabolites had been investigated (**Table 1**).

This reflects mildly reduced serotonin turnover, which probably results from some imbalance in synthesis or regulation of release as part of the patient's encephalopathy.

Patient H

Another group of secondary changes is one in which the movement disorder itself can be classified as secondary. A 7-year-old girl with progressive loss of skills from the second year of life and the development of 'massive chorea' was investigated. Cerebral imaging had shown signal changes in the corpus striatum (especially the putamen) and, therefore, by definition, this patient had a secondary movement disorder – regardless of the underlying defect that was unidentified. Her neurotransmitter levels were tested (**Table 1**).

All other metabolites, including BH_4, were normal. The region with signal changes on cerebral imaging is an essential part of the dopaminergic system and, therefore, reduced dopamine turnover appears to be a plausible finding caused by general disturbance of the dopaminergic neurons, rather than by a monogenic defect of dopamine synthesis. The only monogenic defect in the biosynthesis of dopamine and serotonin with elevation of neopterin is 6-pyruvoyltetrahydropterin synthase deficiency, which leads to hyperphenylalaninemia in addition to reduced BH_4 and biogenic amines. The increased neopterin concentration observed in this case could be the result of tissue reorganization involving macrophages.

Patient I

A 10-year-old girl with a progressive encephalopathy including dementia, epilepsy, dysarthria and 'dyskinesia' was investigated with the following neurotransmitter results in **Table 1, Patient Ia.**

Thus, dopamine turnover was slightly more reduced than the borderline-reduced serotonin turnover. Pterins and 5-MTHF were normal. The child was referred to a different hospital and a second lumbar puncture for the investigation

of neurotransmitters was performed (according to the identical protocol and analyzed in the same laboratory) 2 months later (**Table 1**, **Patient Ib**).

Subsequently, storage cells were found in her bone marrow biopsy, the workup of which is not yet completed (Filipin staining was negative). This case illustrates that neurotransmitter concentrations may vary, perhaps as a result of fluctuating seizure activity, and that repeat lumbar punctures may be helpful in some cases.

Patient J

A 17-month-old girl with absent psychomotor development from birth additionally presented with an extreme opisthotonus, which was occasionally alternating with severe hypotonia. There were mild dysmorphic features. Mildly increased phenylalanine concentrations in plasma and CSF, together with hyperprolactinemia, were the reason for an investigation of the biogenic amines' metabolites. There were further abnormal results, such as low T3 evolving to hypothyroidism with autoantibodies. The opisthotonus turned out to be epileptic in origin (**Table 1**).

This pattern of metabolites is not compatible with any inborn error of metabolism (**Table 1**). Here the very active epilepsy is likely to have produced many of the abnormal biochemical findings.

Patient K

Active seizures are a crucial point in this patient: a nearly 8-year-old boy with active epilepsy was investigated for neurotransmitter metabolites because a formerly spastic–ataxic movement disorder had evolved into predominantly parkinsonism–dystonia with marked hypokinesis. His epilepsy had been treated with homeopathic and nonpharmacological treatments during the preceding years (**Table 1**).

His clinical symptoms, which appeared to be caused by dopamine deficiency, did not respond to L-DOPA/carbidopa treatment, but the patient remarkably improved with phenobarbitone. This suggests that the active epilepsy had impaired his dopaminergic and serotoninergic systems.

Patient L

Another example for secondary changes in neurotransmitter metabolites during active epilepsy is a 10-month-old infant with West syndrome and cortical dysplasia. The infant was found to have dystonic posturing of his hands and was therefore investigated for dopamine and serotonin metabolites (**Table 1**, **Patient La**).

In addition to vigabatrin treatment, L-dopa/carbidopa was prescribed. At 16-months of age, with nearly 4 mg/kg/day of L-DOPA and without overt seizures since 5 months, the HVA concentration was still slightly below the reference range whereas HIAA and all other metabolites were normalized. Thus, it was recommended to increase the L-DOPA dosage. No mutation was found in the tyrosine hydroxylase gene, and at 33 months of age, the L-DOPA/carbidopa therapy was stopped. Lumbar puncture was performed 3 weeks later (**Table 1**, **Patient Lb**).

Thus, the abnormal results in the acute phase of the illness were not caused by a genetic enzyme deficiency. Cortical dysplasias are well known to cause West syndrome. Therefore, the underlying disorder in this child was well defined, and once again, the evidence indicates that an active seizure disorder may disturb the production or release of biogenic amines.

Conclusion

The analysis of biogenic amines and their related metabolites is important for the detection of inborn errors, which, in some cases, are treatable with dramatic effects. For some patients, the specific treatment from infancy onwards makes the difference between leading a normal life and the fate of being wheelchair bound, cognitively impaired and having seizures. Therefore, this investigation should always be considered in patients with a clinical picture compatible with defects in serotonin or dopamine metabolism. (Patients with genetic tryptophan hydroxylase deficiency have not yet been found. Thus, the clinical symptoms of isolated severe serotonin deficiency are not exactly known. It is conceivable that significant tryptophan hydroxylase deficiency is a fatal disorder.) Furthermore, some patients with secondary deficiencies of dopamine, for example patients with encephalitis lethargica, also benefit from a treatment with L-DOPA/carbidopa. Alternatively, some patients with reduced dopamine metabolites do not respond to L-DOPA treatment, even if a genetic defect in their biosynthesis has been proven [6]. The discussion of this phenomenon, which is only partially understood, is beyond the scope of this article.

Here, the pitfalls associated with the interpretation of CSF results are discussed, with specific illustrative examples. Some of these secondary changes, such as those that occur in the presence of active epilepsy, hypoxia or infection, have been the subject of prospective or retrospective case

studies, experiments with human brain slices or experiments with animal models. In practice, it is important to know about the phenomenon of secondary changes in CSF in order to be able to advise physicians and families correctly.

Future perspective

Functional imaging techniques for *in vivo* exploration of brain metabolism and animal models will likely shed light on further mechanisms for secondary neurotransmitter changes. While sosphisticated, the current method to explore lumbar CSF for the evaluation of complex neuronal interactions in the brain has inherent limits. Furthermore, I believe that analysis of CSF neurotransmitters is an important tool, but only a limited window into understanding the complexity of the brain and the diversity of neurological diseases and systemic disorders involving the CNS.

Executive summary

Introduction

- The analysis of neurotransmitter metabolites in lumbar cerebrospinal fluid (CSF) is technically demanding and complex to interpret.

Pitfalls

- Beside abnormalities attributable to genetic disturbances of neurotransmitter biosynthesis, secondary changes occur with active seizures, hypoxia or infections, as well as unresolved etiologies. It appears to be plausible that seizures result in general overstimulation or, in a chronic state, general reduction of neuronal function and neurotransmitter synthesis and release. In such cases, reduced or increased metabolite concentrations may be found.
- Whether increased neurotransmitter concentrations in CSF, with and without seizures, are the result of enhanced release, reduced availability of postsynaptic receptors, reduced clearance mechanisms, leaking vesicles or combinations of these mechanisms remains speculative, and probably varies from case to case.

Message

- For the interpretation of CSF neurotransmitter results, it is necessary to be familiar with the biochemical pathways, the technical problems of the analyses and the clinical symptoms and differential diagnoses. It is a comprehensive view of the metabolite profile – not only individual metabolites – together with the clinical picture, which should be considered for advice to referring physicians and patients. Secondary alterations in CSF neurotransmitters must be considered in the evaluation of complex neurological diseases.

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