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ORIGINAL ARTICLE

# Cerebrospinal fluid alterations of the serotonin product, 5-hydroxyindolacetic acid, in neurological disorders

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**Abstract** Although patients with low cerebrospinal fluid (CSF) serotonin metabolite levels have been reported, inborn errors of the rate-limiting enzyme of serotonin synthesis (tryptophan hydroxylase, TPH) have not been described so far. In this study we aimed to evaluate CSF alterations of the serotonin metabolite 5-hydroxyindolacetic acid (5-HIAA) in patients with neurological disorders and to explore a possible TPH deficiency in some of them. A total of 606 patients (286 males, 320 females, mean age 4 years and 6 months, SD 5 years and 7 months) underwent CSF analysis of neurotransmitter metabolites by reverse phase high performance liquid chromatography. Results were compared with values established in a control population. Patients' medical records were reviewed to determine diagnosis and clinical features. A primary defect of biogenic amines was genetically investigated in indicated patients. Low 5-HIAA was seen in 19.3%. Of these, 22.2% showed inborn errors of metabolism (mitochondrial disorders being the most frequent at 10.2% of low 5-HIAA patients) and neurogenetic conditions. Other relatively frequent conditions were pontocerebellar hypoplasia (4.3%), Rett syndrome (4.3%), and among congenital nonetiologically determined conditions, epilepsy including epileptic encephalopathies (26.4%), leukodystrophies (6.8%), and neuropsychiatric disturbances (4.2%). Mutational analysis of the *TPH2* gene, performed in five candidate patients, was negative. Although frequency of secondary alteration of 5-HIAA was relatively high in patients with neurological disorders, this finding was more frequently associated with some neurometabolic disorders, epileptic encephalopathies, and neuropsychiatric disturbances. No inborn

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errors of TPH were found. Due to serotonin's neurotrophic role and to ameliorate symptoms, a supplementary treatment with 5-hydroxytriptophan would seem advisable in these patients.

## Introduction

Serotonin (5HT) projections in the brain are broad and diffuse. The dorsal raphe nucleus contains the largest 5HT neuron group, which projects to the forebrain and mesostriatum. Furthermore, serotoninergic neurons are localized in the pineal gland, the substantia nigra, and the hypothalamus. 5HT is involved in the vegetative control of thirst, appetite, respiration, temperature control, and sleep-waking cycle, and modulates sensory and alpha motor neurons at the spinal cord. 5HT also affects neuronal proliferation, differentiation, migration, and synaptogenesis (Herlenius and Lagercrantz 2001).

5-Hydroxyindolacetic acid (5-HIAA) is the final metabolite of serotonin (5HT), and its measurement in cerebrospinal fluid (CSF) is thought to reflect the overall synaptic and extrasynaptic release activity of serotoninergic neurons of the central nervous system (CNS). In childhood, the analysis of 5-HIAA, together with homovanillic acid (HVA), is the first step in the diagnosis of several inborn errors of biogenic amines and pterins. Although to date 10 enzyme deficiencies in the biogenic amine metabolic pathway have been described (Pons 2009), no pathogenetic mutations of the *TPH2* gene have as yet been found, in contrast to the dopaminergic-limiting enzyme tyrosine hydroxylase.

Secondary dopaminergic deficiencies have been broadly reported in adult neurology. By contrast, and although serotoninergic innervation in the brain is more evenly distributed, its implication in different neurological disorders other than psychiatric diseases has scarcely been described. Previous studies showed secondary low 5-HIAA levels in infants with diverse neurological disorders and cortical brain atrophy (García-Cazorla et al. 2007), idiopathic adult-onset dystonia (Naumann et al. 1996), malignant epilepsies (Langlais et al. 1991), and dopa nonresponsive dystonia (Assmann et al. 2002). However, to date and to our knowledge, a large study determining the frequency and reviewing the possible causes of serotoninergic alterations in patients with diverse neurological problems has not been reported.

Our aims were to study children and young adults with low CSF 5-HIAA, to determine the frequency of this alteration, and to learn whether this finding could be suggestive of a particular diagnosis or clinical picture. Moreover, in order to detect possible primary alterations of the biosynthetic 5HT pathway, a mutational analysis of the *TPH2* gene, encoding tryptophan hydroxylase 2 (the rate-limiting enzyme for 5HT biosynthesis in CNS), was performed in some candidate children.

## Methods

### Patients

Over the last 7 years, 606 patients (286 males, 320 females; mean age 4.5 years; SD 5.6 years) presenting with neurological disorders whose etiology was initially unknown underwent a lumbar puncture at the Hospital Sant Joan de Déu, Barcelona.

Patients' medical records were reviewed to determine etiological diagnosis, the presence of epilepsy, EEG alterations, psychomotor delay, motor disturbances (including spasticity, ataxia, or movement disorders), micro- or macrocrania, and magnetic resonance imaging (MRI) findings. Patients with low 5-HIAA values and without a definite diagnosis were distributed into six clinical groups for descriptive purposes: (1) epilepsy, (2) epileptic encephalopathy, (3) motor disturbances, (4) leukodystrophy, (5) psychomotor delay, and (6) neuropsychiatric disturbances.

An epileptic encephalopathy was differentiated from a simple epileptic condition when frequent or severe seizures or subcontinuous paroxysmal interictal activity led to neurological deterioration. Patients with motor disturbances presented with the main clinical signs of spasticity, ataxia, or movement disorders, such as chorea or dystonia. Leukodystrophies were defined as cases characterized by diffuse involvement of the CNS white matter on MRI and with multiple neurological signs. In the group of patients affected by psychomotor delay, other neurological signs and symptoms could be present, but these features were mild or not specific. Finally, patients with neuropsychiatric disorders included those with severe autism spectrum disorders and behavioral disturbances.

All the patients underwent an exhaustive physical examination by an expert pediatric neurologist. Video recordings were obtained in subjects with motor disturbances. Brain MRI included T1- and T2-weighted images, and, when available, diffusion-weighted images and FLAIR (1.5 Tesla Signa EchoSpeed System, GE Medical Systems). Screening laboratory tests for diagnosis of inborn errors of metabolism (IEM) (lactate, pyruvate, ammonium, sialotransferrin, and amino acids in plasma or serum; organic acids, glycosaminoglycanes in urine) and karyotype were performed using standard procedures.

Samples were drawn in accordance with the Helsinki Declaration. The study was approved by the local ethics committee, and written informed consent was obtained from subjects or their parents.

CSF analysis

CSF samples were obtained by lumbar puncture according to previously described protocols (Hyland et al. 1993; Ormazabal et al. 2005). Biogenic amine metabolites (3-orthomethyldopa, 3-methoxy-4-hydroxyphenylglycol, HVA, 5-hydroxytryptophan, and 5-HIAA), pterins (neopterin and biopterin), and 5-methyltetrahydrofolate (5-MTHF) were analyzed by reverse phase high performance liquid chromatography (HPLC) with electrochemical and fluorescence detection, as previously reported. Results were compared with reference values established in our hospital (Ormazabal et al. 2005). Furthermore, glucose, proteins, lactate, and amino acids were determined by standard procedures.

Genetic analysis

A primary defect of biogenic amines or pterin metabolism was ruled out in patients with suggestive biochemical and clinical features by molecular analysis [tyrosine hydroxylase (TH), aromatic amino acid decarboxylase (AADC), and pterin deficiencies were investigated and are not included in the final study group if confirmed]. Regarding TPH deficiency, five patients with unexplained low values of 5-HIAA underwent direct sequencing of *TPH2* gene. The coding region, splice sites, 241 bp preceding the initiation codon, and 150 bp following the stop codon were amplified using a set of nine primer pairs (Bonsai Technologies Group; available upon request) and sequenced (ABI 3130 Genetic Analyzer, Applied Biosystems).

Statistical analysis

All analyses were performed using the SPSS 17.0 program. Chi-squared test was applied to search for the association between low CSF 5HIAA levels and other biochemical (HVA, folate, neopterins, lactate) or clinical (presence of epilepsy, microcephaly, psychomotor delay, movement disorders) and neuroradiological data (white matter disturbances, atrophy, deep grey matter abnormalities, cerebellar or brainstem anomalies). A $P$ value$<0.05$ was considered to be statistically significant.

## Results

One-hundred and seventeen patients (117/606; 19.3%) with different neurological disorders had low CSF 5-HIAA levels according to our reference values [62 (53%) were females and 55 (47%) males]. Mean age at lumbar puncture was 5.3 years (age range 1 month to 25 years; SD= 5.95 years). Low 5-HIAA levels were detected in every age group when compared with reference ranges for that group (Fig. 1)

Biochemical features of the low 5-HIAA study group

5-HIAA deficit was the only CSF abnormality in 49.1% of patients, while the rest also presented other biochemical CSF abnormalities. HVA deficiency was demonstrated in 54/117 patients (46.2%), denoting a combination of serotoninergic and dopaminergic disturbances. Low pterin levels were found in 15/114 patients and high levels in 9/114. Finally, CSF folate deficiency was present in 13 out of 112 cases with 5HT deficiency (11.6%). Seven out of 112 patients (6.3%) presented a combined deficiency of CSF 5-HIAA, HVA, and 5-MTHF values.

Clinical features of the 5-HIAA study group

Careful clinical follow-up of patients with low 5-HIAA allowed us to identify diverse diseases and conditions (Table 1). Eleven out of 117 patients (9.4%) turned out to have acquired CNS injuries. The other 106 patients (90.6%) presented genetic or congenital conditions: 31 (26.5%) had an epileptic condition of unknown etiology (19 had epileptic encephalopathy and 12 epilepsy), and 26 (22.2%) were affected with IEM and neurogenetic conditions. In particular nearly half of them (12 patients) were affected with mitochondrial disorders. The other half experienced diverse heterogeneous metabolic disorders. Other relatively frequent conditions were pontocerebellar

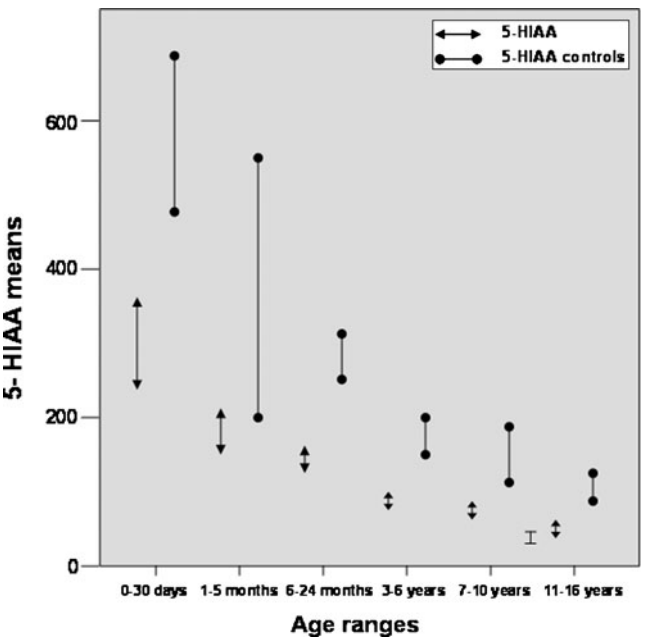


**Fig. 1** 5-HIAA levels in patients with neurological disorders compared with reference ranges for each age group

**Table 1** Etiological classification of patients and 5-HIIA concentrations in CSF

| Etiological classification | No. of patients | Cerebrospinal fluid 5-HIIA (nmol/l) individual values according to age range |
|---|---|---|
| Acquired CNS injuries | 11 | |
| Perinatal injury | 3 | A : 78; B: 149, 159 |
| Encephalitis | 2 | A: 378; D: 56 |
| Cerebrovascular disorder | 2 | A: 294; F: 58 |
| Connatal cytomegalovirus | 1 | C: 81 |
| Lymphoblastic lymphoma | 1 | E: 77 |
| Celiac disease–associated ataxia | 1 | D: 48 |
| Rheumatic chorea | 1 | D: 90 |
| Genetic or congenital conditions etiologically determined | 42 | |
| Inborn errors of metabolism | 26 | |
| Mitochondrial disorders | 12 | B: 144, 167; C: 158, 149, 115, 152; E: 71, 64; F: 51, 59, 62, 43 |
| Niemann Pick type C | 3 | C: 135; F: 45, 50 |
| Alexander disease | 3 | D: 91; F: 28, 33 |
| Organic acidurias (glutaric, argininosuccinic, urocanic) | 3 | C:99; D: 98; F: 60 |
| MHBD disorder | 1 | C: 133 |
| Hartnup disease | 1 | E: 69 |
| MTHFR deficiency | 1 | B: 67 |
| X-linked adrenoleukodystrophy | 1 | E: 72 |
| Aicardi-Goutieres syndrome | 1 | C: 163 |
| Other | 16 | |
| Pontocerebellar hypoplasia | 5 | A: 226; C: 102, 139; D: 96; E: 44 |
| Rett syndrome | 5 | C: 165; D: 95; E: 79; F: 46, 57 |
| Primary dystonia DYT negative | 2 | E: 72; F: 25 |
| Dravet syndrome | 1 | C: 141 |
| Cortical dysplasia | 1 | A: 363 |
| Steinert dystrophy | 1 | A: 210 |
| Congenital myasthenia | 1 | B: 193 |
| Congenital conditions not etiologically determined | 64 | |
| Epileptic encephalopathy | 19 | A: 398; B:189, 183, 154; C: 152, 121, 134, 164, 169, 149, 162, 110; D: 77, 73, 74, 83; F: 28, 32, 50 |
| Motor disturbances | 10 | C: 137, 111, 157, 104, 166; D: 97; F: 31, 36, 50, 6 |
| Epilepsy | 12 | A: 273; C: 114, 108, 115, 118; D: 90, 105, 95, 93, 97, 63 |
| Psychomotor delay | 10 | C: 122, 135, 146, 108, 130, 148, 133; D:102; F: 44, 50 |
| Leukodystrophies of unknown etiology | 8 | C: 144, 113, 160, 159; D: 90, E: 65 |
| Neuropsychiatric disturbances | 5 | C: 100; D: 103; E: 81, 74; F:58 |

Reference values: A (0–30 days): 428–1,122; B (1–5 months): 217–1,142; C (6 months–2 years): 170–490; D (3–6 years): 106–316; E (7–10 years): 87–366; F (11–16 years): 63–185

hypoplasia and Rett syndrome. Among patients with genetic and/or congenital conditions without a definitive diagnosis, 10 patients presented a clinical picture characterized predominantly by motor disturbances, 10 patients had a nonspecific psychomotor delay, another 8 patients had a complex clinical picture associated with MRI findings suggestive of leukodystrophy, and, finally, 5 patients presented neuropsychiatric disturbances including autism spectrum disorders and severe behavioral problems.

In Table 1, 5-HIAA values are expressed for each group of patients. Levels appeared to be extremely and particularly low in the first month of life and in patients presenting pontocerebellar hypoplasia or epilepsy.

## Molecular studies in the low 5-HIAA study group

Five patients were selected for TPH2 molecular analysis (Table 2) based on the following clinical criteria: (1)

**Table 2** Clinical and biochemical data of patients analyzed for *TPH2* gene mutations

| N/ Sex | Diagnostic group | Age (years) | HIAA mean (NV) | HVA mean (NV) | Ratio | Epilepsy | Psychomotor delay | Abnormal movements | Magnetic resonance imaging | Follow-up (months) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1/F | Psychomotor delay | 13 | 50 (63–185) | 208 (156–410) | 4.16 | N | Y | N | Normal | 18 |
| 2/F | Psychomotor delay | 0.75 | 130 (170–490) | 338 (344–906) | 2.60 | N | Y | N | Normal | 21 |
| 3/F | Epileptic encephalopathy | 2 | 77 (170–490) | 335 (344–906) | 4.35 | Y | Y | N | Normal | 17 |
| 4/M | Movement disorders | 1 | 104 (170–490) | 371 (344–906) | 3.57 | N | Y | Dystonia | Paramagnetic basal ganglia and deep white matter iron deposition | 33 |
| 5/F | Autism spectrum disorder | 2 | 100 (170–490) | 452 (344–906) | 4.52 | N | Y | N | Normal | 39 |

*NV* Normal values, *Y* yes, *N* no

absence of etiological diagnosis; (2) very severe unexplained symptoms; and (3) presence of striking neuropsychiatric/behavior abnormalities (behavior disturbances have been described in TPH2 knock-out mice).

Only previously reported single nucleotide polymorphisms and a 3-bp intronic deletion located more than 50 nucleotides upstream from the end of exon 1 in the *TPH2* gene (c.105+56_105+58delTCT) were found.

### Biochemical correlations

Biochemical data were available for the whole group of 606 patients that underwent lumbar puncture. The presence of low CSF 5-HIAA was significantly associated with low CSF HVA (chi-squared=58.69, $p$=0.0001), while it was not associated with low pterins and 5-MTHF, or high CSF lactate values.

### Clinical and neuroimaging correlations

When trying to establish an association between low 5-HIAA and clinical features (the presence of epilepsy, microcephaly, psychomotor delay, and presence of movement disorders), no significant relationship was found. Concerning neuroimaging analysis, in 236 patients, neuroimages were not available. Regarding the other 370/606, a significant relationship was demonstrated between 5-HIAA deficit and brainstem MRI abnormalities (chi-squared= 6.377; $p$=0.012).

## Discussion

To our knowledge, this is the first study describing the frequency of secondary 5-HIAA abnormality in CSF among patients with different neurological disorders. This biochemical feature was present in about 20% of patients who underwent lumbar puncture in our hospital, at different ages and with different clinical pictures and diagnoses. The majority (91%) represented congenital or genetically determined disorders. This finding reflects the high vulnerability of serotoninergic pathways due to their broad origins in the whole hindbrain and their diffuse innervation.

Our first study focused on secondary neurotransmitter deficiencies and involved 56 infants with different neurological disorders. We found that newborn patients with severe motor disturbances or disorders causing MRI abnormalities were more likely to have these alterations (García-Cazorla et al. 2007). In particular, 5-HIAA deficiency was associated with cortical brain atrophy. In the present study, we concentrated on 5-HIAA and analyzed a larger sample of patients with a wide age range.

Some clinical and diagnostic groups appeared to be particularly frequent. Patients with IEM accounted for 22.4% of the total. Most of them were affected by mitochondrial disorders, which are likely to produce abnormal neurotransmission given that this is an energetically demanding process. Indeed, we previously described five patients with mitochondrial disorders mimicking neurotransmitter disorders (García-Cazorla et al. 2008). 5HT is involved in the control of behavior and mood modulation. This particular vulnerability of serotonin in mitochondrial disorders could translate into the strong trend towards depression and mood disturbances that is found in these energetic deficiencies.

Other IEM found were quite heterogeneous and belong to different pathophysiological categories. Low levels of 5-HIAA could be due here to diverse neurobiological processes. Anatomical serotoninergic innervation could explain this finding in our patients with pontocerebellar hypoplasias, other brainstem abnormalities, and Niemann-Pick type C. In IEM presenting with white matter abnormalities such as X-linked adrenoleukodystrophy, Alexander disease, and MTHFR deficiency, dysfunctional oligodendrocytes could contribute to abnormal levels of serotonin metabolites at the synapse, as they participate in neurotransmitter homeostasis (Ohno et al. 2007). Low 5-HIAA levels were also found in different organic acidurias. In these disorders, impairment of brain

energy, blood-brain barrier transport, and astrogial communication might contribute to neurotransmitter imbalance (Kölker et al. 2008).

Concerning primary defects in biogenic amine metabolism, 10 enzyme deficiencies have been described to date (Pons 2009). However, no pathogenetic mutations of the *TPH2* gene have as yet been found. Studies on *TPH2* -/- mice confirmed that TPH2 is the major gene responsible for central serotoninergic projections, while peripheral 5HT is produced by TPH1. *TPH2*-derived 5HT is involved in the regulation of behavior and autonomic pathways but is not essential for adult life (Alenina et al. 2009).

A possible new neurodevelopmental syndrome related to 5HT pathway and responding to 5-hydroxytriptophan was described in 2001 (Ramaekers et al. 2001). However, *TPH2* gene analysis was normal in all five patients. We performed mutation screening of *TPH2* gene in five patients presenting a selective 5-HIAA deficit, but no pathogenic mutations were found. In all likelihood, other mechanisms such as regulatory genes, transcriptional factors, or 5HT transporters are involved in determining a reduced 5HT turn-over.

Beyond metabolic diseases, in our series, low CSF 5-HIAA values were found in different neurological conditions. Patients with epileptic encephalopathy and epilepsy constituted an important group. Alterations of 5-HIAA have been reported in progressive myoclonic epilepsies, infantile spasms, and burst suppression pattern–associated disorders (Duarte et al. 2008). However, these results have been controversial (Langlais et al. 1991; Airaksinen et al. 1992) and an association between biogenic amines and antiepileptic drugs has not been excluded in previous studies (García-Cazorla et al. 2007; Assmann et al. 2002).

Regarding movement disorders, results are also controversial. Reduced 5-HIAA levels were previously reported in idiopathic dystonia and dopa nonresponsive dystonia (Naumann et al. 1996; Assmann et al. 2002). In our study, patients with extrapyramidal disorder did not seem to be frequently affected by 5-HIAA deficiency. In particular, two of seven patients with DYT 1 negative primary dystonia showed HVA deficit and another patient with generalized progressive secondary dystonia showed very low HVA levels combined with HIAA deficiency. In our experience, secondary HVA deficiency is more frequently associated with severe motor impairment or perinatal asphyxia manifesting choreodystonia and basal ganglia abnormalities (García-Cazorla et al. 2007). However in a series of 448 young patients (Van Der Heyden et al. 2003), no correlation between low CSF HVA concentration and clinical symptoms or specific abnormalities at neuroimaging was found.

The close link existing between 5HT and dopamine in the brain, both at the biochemical and anatomical levels, may also explain the high association that we found between reduced 5-HIAA and reduced HVA. This result is in agreement with those previously reported (Hyland et al. 1993). Moreover, as already described (García-Cazorla et al. 2007), patients with low 5-HIAA levels often suffered from neurometabolic or progressive disorders, most likely impairing dopamine metabolism as well.

From a diagnostic point of view, patients with isolated 5-HIAA deficit did not seem to differ from patients with associated HVA/HIAA deficiency (data not shown). However, all the patients with neuropsychiatric disturbances presented an isolated 5-HIAA deficiency. This is an interesting fact, given that disturbance in 5HT metabolism in childhood has also been suggested in autism, impulsive disorders, and depression (Zhang et al. 2005; Walitza et al. 2005). Another interesting consideration is that in AADC deficiency, an inborn error affecting both the dopaminergic and serotoninergic pathway, patients may manifest with pervasive developmental disorders (Pons 2009). In adults, low CSF 5-HIAA concentration has been associated with suicidal behavior, schizophrenia, personality disorder, and certain impulse control disorders (Placidi et al. 2001). However, as psychiatric disorders in children do not constitute a clinical indication for lumbar puncture, the frequency of this biochemical alteration in these patients is not known.

In conclusion, low CSF 5-HIAA concentration was a common biochemical finding among patients with congenital and genetic neurological conditions. Regarding metabolic diseases, mitochondrial disorders seem especially vulnerable, as well as those involving the cerebellum, white matter, and organic acidurias. Due to serotonin's neurotrophic role, and in order to ameliorate neurological symptoms, a supplementary treatment with 5-hydroxytriptophan may be advisable in these conditions. Among patients without etiological diagnosis, epileptic encephalopathies and neuropsychiatric symptoms were commonly observed. No primary genetic deficiencies in 5HT metabolism (disease-causing mutations in the *TPH2* gene) could be demonstrated.

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## References

Airaksinen E, Tuomisto L, Riikonen R (1992) The concentrations of GABA, 5-HIAA and HVA in the cerebrospinal fluid of children with infantile spasms and the effects of ACTH treatment. Brain Dev 14:386–390

Alenina N, Kiric D, Todiras M et al. (2009) Growth retardation and altered autonomic control in mice lacking brain serotonin. Proc Nat Acad Sci USA 105:10332–10337

Assmann B, Kohler M, Hoffman G, Heales S, Surtees R (2002) Selective decrease in central nervous system serotonin turnover in children with dopa-nonresponsive dystonia. Pediatr Res 52:91–94

Duarte S, Sanmarti F, Gonzalez V et al. (2008) Cerebrospinal fluid pterins and neurotransmitters in early severe epileptic encephalopathies. Brain Dev 30:106–111

García-Cazorla A, Serrano M, Pérez-Dueñas B et al. (2007) Secondary abnormalities of neurotransmitters in infant with neurological disorders. Dev Med Child Neurol 49:740–744

García-Cazorla A, Duarte S, Serrano M et al. (2008) Mitochondrial diseases mimicking neurotransmitter defects. Mitochondrion 8:273–278

Herlenius E, Lagercrantz H (2001) Neurotransmitters and neuromodulators during early human development. Early Hum Dev 65:21–37

Hyland K, Surtees RA, Heales SJ, Bowron A, Howells DW, Smith I (1993) Cerebrospinal fluid concentrations of pterins and metabolites of serotonin and dopamine in a pediatric reference population. Pediatr Res 34:10–14

Kölker S, Sauer SW, Hoffmann GF, Müller I, Morath MA, Okun JG (2008) Pathogenesis of CNS involvement in disorders of amino and organic acid metabolism. J Inherit Metab Dis 31:194–204

Langlais PJ, Wardlow ML, Yamamoto H (1991) Changes in CSF neurotransmitters in infantile spasms. Pediatr Neurol 7:440–445

Naumann M, Gotz M, Reiners K, Lange KW, Riederer P (1996) Neurotransmitters in CSF of idiopathic adult-onset dystonia: reduced 5HIIA levels as evidence of impaired serotoninergic metabolism. J Neural Transm 103:1083–1091

Ohno Y, Hibino H, Lossin C, Inanobe A, Kurachi Y (2007) Inhibition of astroglial Kir4.1 channels by selective serotonin reuptake inhibitors. Brain Res 1178:44–51

Ormazabal A, García-Cazorla A, Fernandez Y, Fernandez-Alvarez E, Campistol J, Artuch R (2005) HLPC with electrochemical and fluorescence detection procedures for the diagnosis of inborn errors of biogenic amines and pterins. J Neurosci Methods 142:153–158

Placidi GP, Oquendo MA, Malone KM, Huang YY, Ellis SP, Mann JJ (2001) Aggressivity, suicide attempts, and depression: relationship to cerebrospinal fluid monoamine metabolite levels. Biol Psychiatry 50:783–791

Pons R (2009) The phenotypic spectrum of paediatric neurotransmitter diseases and infantile parkinsonism. J Inherit Metab Dis 32:321–332

Ramaekers VT, Senderek J, Häusler M et al (2001) A novel developmental syndrome responsive to 5-hydroxytryptophan and carbidopa. Mol Genet Metab 73:179–187

Van Der Heyden JC, RotteveelJJ, Wevers RA (2003) Decreased homovanillic acid concentrations in cerebrospinal fluid in children without a known defect in dopamine metabolism. Eur J Paediatr Neurol 7(1):31–37

Walitza S, Renner TJ, Dempfle A et al. (2005) Transmission disequilibrium of polymorphic variants in the tryptophan hydroxylase-2 gene in attention-deficit/hyperactivity disorder. Mol Psychiatry 10:1126–1132

Zhang X, Gainetdinov RR, Beaulieu JM et al. (2005) Loss-of-function mutation in tryptophan hydroxylase-2 identified in unipolar major depression. Neuron 45:11–16