

## 2.1 Introduction

Monogenic defects of neurotransmission have become recognized as a cause of early onset, severe, progressive encephalopathies. The diagnosis is mostly based on the quantitative determination of the neurotransmitters or their metabolites in cerebrospinal fluid (CSF), i. e., the amino acids glutamate, glycine, and  $\gamma$ -aminobutyric acid (GABA), the acidic metabolites of the biogenic monoamines, and individual pterin species (Hoffmann et al. 1998). In contrast to inborn errors in catabolic pathways, neurotransmitter defects are reflected by the interplay of biosynthesis, degradation, and receptor status. Even borderline abnormalities can be diagnostic, but their recognition requires a strictly standardized sampling protocol and adequate age-related reference values. All laboratories have their own reference values that differ because of local variations in the technique of CSF sampling and the precise aliquot used for analysis. Because of these special logistics of sampling and transport, as well as demanding laboratory techniques due to very low metabolite concentrations, “neurotransmitter defects” are investigated in few specialized laboratories worldwide, and consequently only a small number of patients has been diagnosed. Therefore we suspect a substantial underdiagnosis.

This is in contrast to patients suffering from pterin defects that cause hyperphenylalaninemia, which are diagnosable by neonatal screening programs (see Chap. 1), or to patients with succinic semialdehyde dehydrogenase deficiency resulting in 4-hydroxybutyric aciduria, which is diagnosable by urinary organic acid analysis (see Chap. 3). For the diagnosis of the other defects, plasma or urine investigations are inadequate or even misleading and they require specific CSF analyses. Only elevated concentrations of prolactin in serum (the release of which is normally inhibited by dopamine via dopamine D<sub>2</sub> receptors), and of serotonin in whole blood point to genetic defects of dopamine biosynthesis or monoamine oxidase deficiency, respectively. In our experience neither is sensitive nor specific.

The clinical presentation of neurotransmitter diseases can be quite distinctive and these investigations should not routinely be performed in every child with an unexplained encephalopathy. Patients with *GABA-transaminase* deficiency or *nonketotic hyperglycinemia* usually present with early onset, severe

encephalopathy, dominated by seizures refractory to treatment. For neither is there a satisfactory specific therapy; they are discussed in Chap. 3. *Folinic acid-responsive seizures* (Hyland et al. 1995) or *defects in pyridoxine metabolism* (Baxter 2001; Clayton et al. 2003) can present similarly. For these diseases rational therapies have been developed with satisfactory or even excellent success.

Defects in the biosynthesis of dopamine result in progressive extrapyramidal movement disorders, especially parkinsonism, dystonia, and chorea. Nevertheless, the spectrum of individual symptoms and courses of disease is wide, ranging from intermittent focal dystonia to severe, lethal infantile encephalopathies. In very young infants, the symptoms can be less specific. They present with truncal hypotonia, restlessness, feeding difficulties, motor delay, or even hypoglycemia or signs of autonomic dysfunction, the latter two due to inadequate peripheral catecholamine production. Suggestive are ophthalmologic symptoms such as ptosis, miosis, and oculogyric crises.

*Tyrosine hydroxylase* and *aromatic L-amino acid decarboxylase* are the two biosynthetic enzymes converting tyrosine to the catecholamine dopamine, which in turn is the precursor for epinephrine and norepinephrine. Several patients with recessively inherited defects of these enzymes have been diagnosed. Most of them suffer from an early onset, severe progressive encephalopathy with hypotonia, hypokinesia, an extrapyramidal movement disorder, mostly dystonia, ptosis, miosis, and oculogyric crises, while some show the features of dopa-responsive dystonia (Surtees and Clayton 1998, Hoffmann et al. 2003, Swoboda et al. 2003).

Deficiency of *dopamine- $\beta$ -hydroxylase* results in a distinct autonomic disorder due to the deficiency of epinephrine and norepinephrine. The disorder should be suspected in infants presenting with delayed eye-opening, hypoglycemia, hypothermia, or hypotension. Severe orthostatic hypotension becomes the hallmark of this disease in late childhood. Careful examination may further reveal ptosis, nasal stuffiness, and retrograde ejaculation in adult males (Biaggioni and Robertson 1987; Biaggioni et al. 1990).

Only one defect in the catabolism of the biogenic monoamines has been identified so far. Complete deficiency of *monoamine oxidase A* has been demonstrated by biochemical and molecular analyses in several males of a large kindred presenting with borderline mental retardation and abnormal behavior, including aggression, arson, exhibitionism, and rape (Brunner et al. 1993). The enzyme is required for the degradation of serotonin and the catecholamines in the brain, and the gene is located on the X-chromosome. Additional, independent descriptions of the same condition delineated other major characteristics of chronic episodic flushing, diarrhea, headaches, psychiatric problems, increased blood serotonin, and altered urinary concentrations of the catecholamines, serotonin, and their metabolites (Cheung and Earl 2002).

Genetic defects of *neurotransmitter receptor subtypes* are rapidly emerging as a new group of disorders that cause a wide range of neurological and psychiatric symptoms. The first such defects include a defect in the  $\alpha_1$ -subunit of the

glycine receptor causing hyperekplexia (Becker 1995), defects in the GABA<sub>A1</sub>, the GABA<sub>B1</sub>, and the GABA<sub>G2</sub> receptors, and defects in the  $\alpha_4$ -subunit and the  $\beta_2$ -subunit of the nicotinic acetylcholine receptor, all of the latter causing familial seizure disorders. Diagnosis of these disorders by mutation analysis may be aided by specific abnormalities of neurotransmitter metabolites in CSF, e. g., reduced CSF levels of GABA in children suffering from hyperekplexia.

## 2.2 Nomenclature

No.	Disorder	Definition/comment	Gene symbol	OMIM No.
2.1	Pyridoxine-dependant epilepsy	Seizures that respond to pyridoxine and recur on withdrawal pyridoxine	–	266100
2.2	Pyridox(am)ine 5'-phosphate oxidase deficiency	Seizures do not respond to pyridoxine but to pyridoxal phosphate	<i>PNPO</i>	603287
2.3	Folinic acid-responsive seizures	Seizures that respond to folinic acid and recur on withdrawal		
2.4	Hyperekplexia	Clinical diagnosis. "Stiff baby" syndrome; nose tap causes an abrupt, exaggerated startle followed by a tonic spasm. Familial forms have mutations in $\alpha_1$ -subunit gene of the glycine receptor	<i>GLRA1</i> <i>GLRB</i>	138491 138492
2.5	Tyrosine hydroxylase deficiency	Inborn error of dopamine biosynthesis. Variable clinical severity (from severe progressive infantile parkinsonism-dystonia to Segawa disease) and variable response to treatment	<i>TH</i>	191290
2.6	Aromatic L-amino acid decarboxylase deficiency	As above	<i>DDC</i>	107930
2.7	Dopamine $\beta$ -hydroxylase deficiency	Syndrome of autonomic failure characterized by severe orthostatic hypotension, ptosis, but normal sympathetic cholinergic and parasympathetic function	<i>DBH</i>	223360
2.8	Monoamine oxidase-A deficiency	Episodic facial flushing, headache, diarrhea, borderline mental retardation and psychiatric symptoms, including impulsive aggression and inappropriate sexual behavior	<i>MAOA</i>	309850

## 2.3 Treatment

No.	Gene symbol	Medication	Dosage (mg/kg per day)	Dose/day ( <i>n</i> )
2.1	<i>EPD, PDE</i>	Pyridoxine	5–30	1
2.2	<i>PNPO</i>	Pyridoxal phosphate	10–50	3
2.3		Folinic acid	3–5	3
2.4	<i>GLRA1 GLRB</i>	Clonazepam	0.1 <sup>a</sup>	3

<sup>a</sup> Start dose in infants is 0.25 mg; gradually increase to maintenance of 0.1 mg/kg per day

### Dangers/Pitfalls

1. Both pyridoxine and pyridoxal phosphate may cause apnoea and prolonged cerebral depression after the initial dose (Baxter 2001; Clayton et al. 2003). Resuscitation equipment and intensive care facilities should be available.
2. Pyridoxine-responsive seizures may be heterogeneous in their presentation, and sometimes idiopathic epilepsies respond to treatment with pyridoxine. Typical patients present with an intractable seizure disorder within the first 2 days of life, the latest within 28 days. There are, however, three atypical presentations: (1) late onset, i. e., later than 28 days; (2) neonatal onset, but with an initial response to conventional anticonvulsant therapy; (3) neonatal onset with initially negative, but a later sustained positive response to pyridoxine. Because of these, one recommendation is that all patients with “difficult-to-treat” seizures starting before 2 years should have a trial of pyridoxine (usually given orally).
3. There is no universal protocol for a pyridoxine trial. The dose of pyridoxine required is variable and higher doses may be necessary to control seizures, at least initially. In classic cases we suggest a starting dose of 100 mg intravenously. If there is no response within 24 h, the dose should be repeated (and possibly increased up to 500 mg in total) before being sure about pyridoxine nonresponsiveness. If there is uncertainty about at least a partial response, pyridoxine should be continued at 30 mg/kg per day for 7 days before final conclusions are drawn.
4. Doses of folinic acid (Hyland et al. 1995), pyridoxine, and pyridoxal phosphate (Baxter 2001; Clayton et al. 2003) all need to be increased and adjusted to body weight during growth. Patients with these defects require lifelong supplementation. Obvious criteria to increase the doses are breakthrough seizures.
5. Neither pyridoxine nor pyridoxal phosphate will reverse preexisting brain damage caused by late diagnosis or treatment. Neurological disability (including seizures) requires treatment in its own right.
6. In hyperekplexia, duration of treatment is unclear and should be individually determined. One approach is to treat until stable walking is achieved and then slowly withdraw. Risks and benefits of treatment should be carefully reviewed as long as the patient continues treatment. Startle is reduced, but not stiffness usually.
7. Neurological disability needs treatment in its own right.

Sodium valproate may also be helpful in hyperekplexia. Vigabatrin has also been suggested but has been found not to be of benefit to adults with dominantly inherited hyperekplexia (Tijssen et al. 1997).

No.	Gene symbol	Medication	Dosage (mg/kg per day)	Dose/day (n)
2.5	<i>TH</i>	Levodopa (L-dopa) plus carbidopa	1–10 10% or 25% <sup>a</sup>	2–6 2–6
2.6	<i>AADC</i>	Bromocriptine or pergolide	0.25–0.5 4 mg/day <sup>b</sup>	1–2 2
		Trihexyphenidyl	Up to 10	3
		Tranlycypromine	8 mg/day <sup>b</sup>	2
		<i>DβH</i> <i>MAO</i>	DL-Dihydroxyphenylserine See Alternative Therapies/Experimental Trials	250–500 mg/day <sup>b</sup>

<sup>a</sup> Percentage of levodopa dose; use 25% with total daily dose levodopa less than 400 mg, otherwise 10%

<sup>b</sup> Reported doses used

### Dangers/Pitfalls

1. L-Dopa/carbidopa/5-hydroxytryptophan therapy should be introduced slowly and increased in steps of not more than 1 mg/kg over days or weeks.
2. Changes in dopamine receptor density can cause difficulties with treatment. Receptor hypersensitivity in early diagnosed, severe cases means that treatment with cocareldopa should start at very low doses (0.25–0.5 mg levodopa/kg per day) given frequently up to 6 times a day. Receptor downregulation in late-diagnosed severe forms means that treatment with cocareldopa in the maximally tolerated dose up to 10 mg levodopa/kg per day should be maintained for as much as 6 months before deciding it is unhelpful.
3. L-Dopa/carbidopa/5-hydroxytryptophan therapy may reduce CSF folate (5'-methyltetrahydrofolate in CSF is the major transport species for the brain folate pool and is utilized by the single carbon transfer pathway to methylate L-dopa to 3-O-methyl-dopa). Determine 5-methyltetrahydrofolate in CSF. Consider folinic acid (5-formyltetrahydrofolate) substitution (10–20 mg/day). This may occur “naturally” in AADC deficiency, again requiring folate supplementation (Surtees and Hyland 1990).
4. In AADC deficiency dopamine agonists can produce dyskinesia and increased irritability, and the dose needs to be carefully titrated.
5. The dose of trihexyphenidyl should start at 1 or 2 mg three times a day. The dose is then increased by 1 or 2 mg/day each week until one of three possibilities occur: (1) the child's condition improves; (2) troublesome side-effects occur (dry eyes or mouth, or gastrointestinal disturbance most commonly); or (3) a limit of 10 mg/kg per day is reached.

## 2.4 Alternative Therapies/Experimental Trials

No.	Gene symbol	Medication	Dosage (mg/kg per day)	Dose/day ( <i>n</i> )
2.5	<i>TH</i>	Selegiline	0.1–0.3	2–3
		Entacapone	30	2
		Bromocriptine	0.25–0.5	1
2.6	<i>AADC</i>	Pyridoxine	≤ 200	3
		L-Dopa	≤ 60	3
2.8	<i>MAO</i>	Cyproheptadine hydrochloride	Unreported	
		Sertraline hydrochloride	Unreported	

### Dangers/Pitfalls

1. Adjunctive treatment with a MAO-B inhibitor such as selegiline, COMT inhibitor such as entacapone, and dopamine agonists such as bromocriptine may be necessary in TH. When introducing a MAO-B inhibitor or a COMT inhibitor, L-dopa should be reduced by approximately 50–30%.
2. Pyridoxine is a natural cofactor of AADC. In most patients, no sustained clinical or biochemical effect is achieved. In one family, in whom kinetic studies showed the mutation to decrease the binding affinity for the substrate, an improvement was achieved by combined therapy of L-dopa, without carbidopa, and pyridoxine.
3. Sertraline hydrochloride should be introduced slowly because of the risk of causing the serotonin syndrome.

## 2.5 Follow-up/Monitoring

### ■ Defects in Pyridoxine Metabolism

There is some evidence that lower doses of pyridoxine, whilst controlling seizures, may allow the development of cognitive impairment. Serial cognitive assessment is recommended. High doses of pyridoxine carry the risk of developing skin photosensitivity and a peripheral sensory neuropathy, which must be weighted against the anticipated neurodevelopmental benefit. Doses up to 1 g/day can be regarded as safe in older children.

### ■ 2.4 Hyperekplexia

The condition is not entirely benign, because of episodes of apnea with the possibility of death as well as repeated falls. The attacks can be prevented by sudden flexion of the head and limbs. During infancy there is the necessity of constant supervision, including apnea monitoring.

### ■ 2.5 Tyrosine hydroxylase and aromatic - L-amino acid decarboxylase deficiency

Because of intolerable side-effects, mainly chorea, only very small doses of L-dopa may initially be tolerated. In such patients L-dopa can only be increased very slowly, sometimes over several years. During the 1st years of life, paroxysmal episodes with the possibility of death can occur.

The central pathophysiological mechanism is dopamine deficiency in the brain, which can be best assessed by following metabolite concentrations by consecutive lumbar punctures. In individual patients, serum prolactin concentrations may be used as an appropriate functional parameter of dopamine deficiency and to tailor therapy, allowing a reduction in lumbar punctures (Birnbacher et al. 1998). Determination of catecholamines and their products in urine are useless.

CSF investigations <sup>a</sup>	Age	Frequency	Comments
5-HIAA	< 1 year	Every 4-8 weeks	Close to normal ranges
HVA Folates	> 1 year	Monthly to yearly	Close to normal ranges

<sup>a</sup> Lumbar puncture in the morning before medication is given

### ■ 2.7 Dopamine $\beta$ -hydroxylase deficiency

Treatment is adjusted clinically to disappearance of orthostatic hypotension. In MAO, treatment is monitored clinically by improvement of symptoms as well as fall of serotonin levels in whole blood.

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