Disorders of monoamine metabolism: 
inherited disorders frequently misdiagnosed as epilepsy

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Abstract

Pediatric neurotransmitter diseases are new emerging neurological diseases in children. They include tyrosine hydroxylase (TH) deficiency, aromatic L-amino acid decarboxylase (AADC) deficiency, succinic semialdehyde dehydrogenase (SSADH) deficiency, guanosine triphosphate cyclohydrolase I deficiency, sepiapterin reductase (SR) deficiency and cerebral folate deficiency. Of these, monoamine biosynthesis and metabolism disorders are one group of inherited disorders usually requiring specific diagnostic procedures. Children with disorders of neurotransmitters often present with psychomotor retardation, hypotonia and microcephaly. Although seizures may be more common in patients with SR deficiency, patients with TH or AADC deficiency only occasionally have non-epileptic myoclonus. However, the episodic dystonia and oculogyric crisis manifested in these patients are frequently misdiagnosed as epilepsy, and multiple anti-epileptic drugs (AEDs) may be given. In the present short review, the pathogenesis and diagnosis of these neurotransmitter disorders are discussed, with the hope that correct diagnosis of pediatric neurotransmitter diseases can reduce the unnecessary AED treatment.

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**Introduction**

Pediatric neurotransmitter diseases are new and important neurological diseases in children [1-3]. Several kinds of pediatric neurotransmitter diseases have been identified in the past years. Of these, monoamine biosynthesis and metabolism disorders are some of the very important diseases. The diagnosis of these disorders remains a challenge for clinicians, both in terms of conceptual and technological aspects. The major monoamine neurotransmitters include catecholamines (such as dopamine, norepinephrine and epinephrine) and serotonin. Several important enzymes are involved in the biosynthesis of the monoamines dopamine and serotonin, including tyrosine hydroxylase (TH), tryptophan hydroxylase, and aromatic L-amino acid decarboxylase (AADC) (Fig. 1). Dopamine and serotonin are then converted into homovanillic acid (HVA) and 5-hydroxyindolacetic acid (5-HIAA) by monoamine oxidase (MAO). Furthermore, dopamine can also be converted into norepinephrine by dopamine beta-hydroxylase. Although not common, deficiencies of TH, AADC, MAO and dopamine beta-hydroxylase have been found in the past years with different clinical manifestations. Patients with dopamine metabolism disorders such as AADC and TH deficiencies may present with different kinds of involuntary movements including oculogyric crisis and episodic dystonia, which are frequently misdiagnosed as epilepsy and consequently may be treated with multiple anti-epileptic drugs. To avoid unnecessary treatment in these patients, early and correct diagnosis of these diseases is very important.

In this brief review, the pathogenesis and diagnosis of these diseases are discussed to promote the understanding of these disorders of neurotransmitters.

\[\text{GTP} \quad \rightarrow \quad \text{GTPCH} \quad \rightarrow \quad \text{Dihydrolaric acid tetrohysolate} \quad \rightarrow \quad \text{Neopterin} \]

\[\text{6-pyruvyl-tetrahydropterin synthase} \quad \rightarrow \quad \text{SPR} \quad \rightarrow \quad \text{tryptophan} \]

\[\text{tyrosine} \quad \rightarrow \quad \text{TH} \quad \rightarrow \quad \text{BH}_4 \quad \rightarrow \quad \text{q-BH}_2 \quad \rightarrow \quad \text{5-HTP} \]

\[\text{3-O-MD} \quad \rightarrow \quad \text{AADC} \quad \rightarrow \quad \text{Dopamine} \quad \rightarrow \quad \text{Serotonin} \]

\[\text{MAO} \quad \rightarrow \quad \text{DBH} \quad \rightarrow \quad \text{NAO} \quad \rightarrow \quad \text{COMT} \quad \rightarrow \quad \text{MHPG} \rightarrow \text{VMA} \]

**Figure 1.** Biosynthesis and metabolism of monoamines.

GTPCH = guanosine triphosphate cyclohydrolase

PTS = 6-pyruvoyl-tetrahydropterin synthase

SPR = sepiapterin reductase

DHPR = dihydropteridine reductase

COMT = catechol-o-methyltransferase

MAO = monoamine oxidase

DBH = dopamine beta-hydroxylase
Tyrosine Hydroxylase Deficiency

TH catalyzes the hydroxylation of L- tyrosine to L-dopa, the rate limiting step in the biosynthesis of catecholamines (Fig. 1) [1, 3, 4]. Deficiency of TH, therefore, leads to impaired synthesis of dopamine and epinephrine. Patients with TH deficiency have been diagnosed in the past few years, and all cases reported so far have had an autosomal recessive inheritance. The first reported case of TH deficiency in humans was diagnosed in 1994 [5]. Thereafter, TH deficiency was identified sporadically around the world, sometimes known as recessive dopa-responsive dystonia [5-8].

The important role of TH in development had been demonstrated by the non-viability of TH-knockout mice [9], indicating that TH is important for the survival and development of humans. Several phenotypes for TH deficiency have been reported. Some patients have mild progressive gait disturbance or parkinsonism. Some have hypotonia and chorea since infancy, or even severe early-onset encephalopathy. The clinical presentations for patients with TH deficiency are also variable [1]. The initial manifestations may be psychomotor retardation with generalized hypotonia, which usually begin between 4 and 6 months of age. TH deficiency does not predominantly cause dystonia, but involuntary movements are not unusual, most patients suffer from choreic movements. Oculogyric crisis mimicking seizures is also not uncommon. The clinical presentations of patients with TH deficiency are often not characteristic, usually leading to a misdiagnosis of the conditions as cerebral palsy or sometimes epilepsy. Without correct diagnosis and treatment, the patients usually show severe psychomotor retardation, and may become bedridden.

The diagnosis of TH deficiency can be made based on the findings of CSF neurotransmitters [1]. After diagnosis, they can be treated with low doses of L-DOPA together with the decarboxylase inhibitor carbidopa. Improvement may be immediate in some cases, but sometimes it takes months or years to see significant improvement. The addition of selegiline has been shown to improve the clinical outcome [6, 10].

Aromatic Amino Acid Decarboxylase Deficiency

AADC is responsible for the decarboxylation step in monoamine biosynthesis [1]. Deficiency of AADC leads to decreased levels of biogenic monoamines including dopamine, norepinephrine, epinephrine and serotonin in the brain [1-3]. Therefore, patients with AADC deficiency have low levels of HVA and 5-HIAA, and increased levels of L-DOPA and 3-O-methyldopa (3-O-MD) in CSF.

The CSF neurotransmitter measurement remains a critical diagnostic tool in the diagnosis of patients with suspected AADC deficiency. Less than 70 cases of AADC deficiency have been reported in the world, including 20-30 cases in Taiwan (Dr. Lee, personal communication). In 1990, Hyland and colleagues [11, 12] diagnosed the first case of AADC deficiency by screening the CSF samples in patients with psychomotor retardation, and reported for the first time the characteris-
tic findings of neurotransmitters in children. Since then sporadic cases of AADC deficiency have been identified around the world.

Deficiency of AADC results in reduced synthesis of dopamine and serotonin, resulting in different clinical presentations. Dopamine is one of the monoamines that play important roles in modulating neuronal functions. There are three main dopaminergic pathways in the brain: (1) the nigrostriatal pathway from the substantia nigra pars compacta to the dorsal striatum, which is mainly implicated in motor function; (2) the mesolimbic pathway from the ventral tegmental area to the nucleus accumbens, which is implicated in reward and motivation; and (3) the mesocortical pathway from the ventral tegmental area to the frontal cortex, which is implicated in working memory. Impairment of dopamine biosynthesis in AADC deficiency may therefore lead to motor and cognitive dysfunction. In addition to dopamine, serotonin and norepinephrine may also play important roles in neuronal development [13]. Altered serotonergic and adrenergic functions may be related to some psychiatric conditions seen in patients with AADC deficiency.

Because of the reduced synthesis of monoamines, patients with AADC deficiency usually have profound developmental delay, microcephaly, and hypotonia since 2 to 6 months of age [1, 14-17]. They also frequently have irritability and feeding difficulties, tremor, episodic dystonia, oculogyric crisis and parkinsonian symptoms. The oculogyric crisis may last for several minutes to several hours, and can be stopped by sedative drugs. Autonomic manifestations such as temperature instability, excessive diaphoresis, hypersalivation, recurrent syncope and cardiorespiratory arrest are also very common presentations [18]. Only rarely do patients with AADC deficiency have myoclonus or other seizure disorders [1]. Flexor spasms or epilepsy can be observed [1], but are relatively rare compared with other involuntary movements.

Occasionally, patients with AADC deficiency may also present in the neonatal period with hypothermia, lethargy, poor sucking, ptosis and hypotension [19], which may lead to a misdiagnosis of sepsis or other neuromuscular diseases. Because children with AADC deficiency usually present with psychomotor retardation and oculogyric crisis, they are frequently misdiagnosed with cerebral palsy or mitochondrial diseases, and did not receive early and appropriate treatments. They are also frequently misdiagnosed with epilepsy, as in children with TH deficiency. Nearly 70% of patients with AADC deficiency in Taiwan were initially diagnosed with epilepsy as in western countries, and most received multiple antiepileptic drug treatment without response before diagnosis. These observations indicate that AADC deficiency may be much more frequently misdiagnosed as epilepsy compared with TH deficiency.

Patients with AADC deficiency are usually treated with dopamine receptor agonists, monoamine oxidase (MAO) inhibitors, and anti-cholinergic agents. High-dose Vitamin B6 and folinic acid are also frequently used. However, the treatment effect is highly vari-
able, and frequently unsatisfactory [12, 17]. Anti-epileptic drugs had been tried in some patients with AADC deficiency without definite benefits [1]. Clinical trial with serotonin agonist also revealed only limited improvements. Gene therapy for patients with AADC deficiency may be tried in the future, but more studies are needed to clarify the most optimal approach.

**Sepiapterin Reductase Deficiency**

Sepiapterin reductase (SR) catalyzes the final step in tetrahydrobiopterin (BH4) synthesis (Fig. 1). BH4 plays an important role in monoamine biosynthesis as shown in Fig. 1. Therefore, SR deficiency leads to impaired synthesis of neurotransmitters, and the diagnosis can also be made by analyzing the CSF levels of biogenic monoamines, dopamine and serotonin, as well as individual pterins [20]. Patients with SR deficiency usually have decreased concentrations of HVA, 5-HIAA, and elevated levels of 7,8-dihydrobiopterin in CSF.

Neurological abnormalities in patients with SR deficiency usually begin between 2 and 6 months of age. Patients also have developmental delay and generalized hypotonia [21]. Other clinical presentations include oculogyric crisis, action dystonia, Parkinsonian tremor and choreic movements. Patients with SR deficiency also have seizure disorders in addition to psychomotor retardation, choreoathetosis, temperature instability and hypersalivation, commonly seen in patients with other monoamine biosynthesis disorders [21, 22].

Treatment of SR deficiency following the diagnosis relies on L-DOPA in combination with carbidopa and 5-hydroxytryptophan. Rapid and favorable response to treatment with L-DOPA warrants the classification of SR deficiency into an autosomal recessive type of DOPA-responsive dystonia [21].

**Conclusions**

Disorders of monoamine biosynthesis and metabolism comprise one group of inherited neurological disorders having overlapping clinical presentations. Episodic dystonia and oculogyric crisis in these children are frequently misdiagnosed as epilepsy. Early and appropriate diagnosis of these neurotransmitter disorders may improve the prognosis and avoid unnecessary antiepileptic drug treatment.

**Reference**


