Diagnosis and Treatment of Neurotransmitter Disorders

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Opinion statement

The neurotransmitter disorders represent an enigmatic and enlarging group of neurometabolic conditions caused by abnormal neurotransmitter metabolism or transport. A high index of clinical suspicion is important, given the availability of therapeutic strategies. This article covers disorders of monoamine (catecholamine and serotonin) synthesis, glycine catabolism, pyridoxine dependency, and γ-aminobutyric acid (GABA) metabolism. The technological aspects of appropriate cerebrospinal fluid (CSF) collection, shipment, study, and interpretation merit special consideration. Diagnosis of disorders of monoamines requires analysis of CSF homovanillic acid, 5-hydroxyindoleacetic acid, ortho-methyldopa, BH4, and neopterin. The delineation of new disorders with important therapeutic implications, such as cerebral folate deficiency and PNPO deficiency, serves to highlight the value of measuring CSF neurotransmitter precursors and metabolites. The impressive responsiveness of Segawa fluctuating dystonia to levodopa is a hallmark feature of previously unrecognized neurologic morbidity becoming treatable at any age. Aromatic amino acid decarboxylase and tyrosine hydroxylase deficiency have more severe phenotypes and show variable responsiveness to levodopa. Glycine encephalopathy usually has a poor outcome; benzoate therapy may be helpful in less affected cases. Pyridoxine-dependent seizures are a refractory but treatable group of neonatal and infantile seizures; rare cases require pyridoxal-5-phosphate. Succinic semialdehyde dehydrogenase deficiency is relatively common in comparison to the remainder of this group of disorders. Treatment directed at the metabolic defect with vigabatrin has been disappointing, and multiple therapies are targeted toward specific but protean symptoms. Other disorders of GABA metabolism, as is true of the wide spectrum of neurotransmitter disorders, will require increasing use of CSF analysis for diagnosis, and ultimately, treatment.

Introduction

The neurotransmitter disorders refer to an inherited group of neurometabolic syndromes attributable to a primary disturbance of neurotransmitter metabolism or transport. This represents an enlarging group of recognized disorders requiring specialized diagnostic procedures for detection. This review considers clinical disorders of monoamine (catecholamine and serotonin), glycine, pyridoxine, and γ-aminobutyric acid (GABA) metabolism. The disorders of monoamine synthesis discussed in this paper are distinguished by the necessity of cerebrospinal fluid (CSF) analysis for diagnosis [1••]. These are GTPCH1 deficiency, also known as Segawa disease or classical dopa-responsive dystonia, aromatic amino acid decarboxylase (AADC) deficiency, and tyrosine hydroxylase (TH) deficiency. This paper also covers disorders of glycine and GABA metabolism. Although pyridoxine-dependent epilepsy was formerly considered a disorder of GABA synthesis because of
the role of pyridoxine as a cofactor for glutamic acid decarboxylase (GAD), recent findings have disclosed that pyridoxine- and pyridoxal-5-phosphate (P5P)–dependent seizures are related to other metabolic pathways. These entities are included in this paper given the prominent therapeutic considerations involved.

The inherited disorders of dopamine and serotonin synthesis that require CSF for detection of abnormal metabolites are GTPCH1, AADC, and TH deficiency. In these, increased peripheral phenylalanine, the precursor to tyrosine that is ultimately converted to dopamine, may not be detected in blood specimens owing to intact phenylalanine metabolism in the liver. Phenylalanine is normally hydroxylated to tyrosine, which is the precursor to levodopa, and subsequently dopamine (Fig. 1).

GTPCH1 deficiency was first described by Dr. Masaya Segawa in 1971 as a hereditary basal ganglia disease with marked diurnal fluctuation. Typically, patients have dystonia that worsens during the latter part of the day. The syndrome was ultimately recognized as an autosomally dominant inherited partial deficiency of GTPCH1 activity. This enzyme represents the rate-limiting step in BH4 synthesis. The responsible gene has been mapped to chromosome region 14q22.1-q22.2, spanning a 30-kb region and containing six exons. A disparate collection of mutations with variable penetrance has been reported [2].

The cardinal clinical features of GTPCH1 deficiency, or “Segawa dopa-responsive dystonia,” are fluctuating dystonia and tremor in the presence of normal cognition. Both the dystonia and tremor may have a prominent postural component. Isolated toe gait, a female predominance, and presentation with only prominent postural tremor in adulthood have all been described. Eventually the phenotype involves progressive postural dystonia and worsening tremor. The response to levodopa in this syndrome may be overwhelming and profoundly life altering at any age.

The diagnosis is typically made by the clinical presentation and assay of CSF neurotransmitters. There is selective impairment of dopaminergic transmission, and CSF neurotransmitters reveal low homovanillic acid (HVA), neopterin, and BH4. Genetic analysis of patients with true GTPCH1 gene mutations will only yield positive results approximately 50% of the time because not all mutations are known [3].

The other disorders of monoamine synthesis are less common and have a more severe phenotype. AADC deficiency is an autosomal recessive disorder that combines serotonin and catecholamine deficiency. The gene locus is 7p11. This reveals a CSF profile of low HVA and 5-hydroxyindoleacetic acid, high levodopa, 5HT, and ortho-methyldopa (a levodopa metabolite), and normal perilin levels. The associated clinical features are hypotonia and extrapyramidal movement disorders such as torticollis, dystonia, blepharospasm, athetosis, and myoclonus. Other manifestations are profound developmental delay, irritability, sleep disturbances, and autonomic manifestations such as temperature instability, impaired diaphoresis, hypersalivation, recurrent syncope, or cardiorespiratory arrest. Impaired sympathetic responses, with maintenance of systemic blood pressure after nitroprusside infusion, are demonstrable [4]. The syndrome may present in the neonate with hypothermia, lethargy, poor sucking, ptosis, and hypotension. Typically, patients are initially diagnosed with cerebral palsy, epilepsy, suspected mitochondrial encephalopathies, myasthenia, or hyperekplexia. Neuroimaging is generally unremarkable but may reveal progressive cerebral atrophy.

TH deficiency leads to impaired synthesis of dopamine as well as epinephrine and norepinephrine. This is an autosomal recessive condition, with gene locus 11p15.5, represented by a progressive encephalopathy and poor prognosis. Clinical features include dystonia that is minimally or nonresponsive to levodopa, extrapyramidal symptoms, ptosis, miosis, and postural hypotension.

Glycine, a simple amino acid structurally but ubiquitous and vital, functions as a neurotransmitter with dual excitatory (through the glutamatergic N-methyl-D-aspartic acid [NMDA] receptor) and inhibitory (spinal cord and brainstem through the glycine inhibitory receptor) roles. Glycine has multiple properties because it is gluconeogenic via pyruvate, constitutes over 15% of amino acids of essential structural proteins such as collagen, elastin, and gelatin, is incorporated into purines, glutathione, and the heme protein, and is involved in important detoxifying conjugation reactions. Nonketotic hyperglycinemia was originally named to distinguish it from ketotic hyperglycinemia, which is now known to be propionic acidemia. Because the distinction is no longer required and clinical confusion between hyperglycinemia and hyperglycemia occurs, a more appropriate name for this disorder is glycine encephalopathy (GCE).

Defects of the glycine cleavage system are detected by a ratio of CSF to plasma glycine more than 0.08. GCE is a group of autosomal recessive conditions related to varying defects of the complex tetrameric protein that constitutes the glycine cleavage system. There have been more than 150 patients identified with the classic neonatal phenotype, often presenting with “hammering” sensations in the pregnant mother later recognized as in utero onset seizures. Although the precise incidence and prevalence are unknown, there is a founder effect in the northern part of Finland, with a resulting incidence of one per 12,000 live births. Secondary causes of GCE include valproate effect and D-glyceric acidemia.

In the classic neonatal form of GCE, associated clinical findings include refractory seizures from birth or