Inherited neurotransmitter disorders: a rapidly enlarging field of neurometabolism in children and adults

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This issue of *Future Neurology* is devoted to the theme of the inherited neurotransmitter disorders. These neurometabolic syndromes comprise relatively obscure and rare diseases that, in aggregate, are assuming increasing importance in our understanding of the effects of neurotransmitter metabolism on the human nervous system. Their ramifications cut across the broadest of spectra in basic and clinical neuroscience. The articles in this volume are organized to cover the topic of the inherited neurotransmitter disorders by comprehensive clinical discussions on a range of these disorders. In order to provide balance and perspective on these seemingly disparate and rare conditions, special articles were selected to provide an overarching rubric: cerebrospinal fluid (CSF) examination and interpretation, emerging imaging modalities, animal models and how to incorporate the explosion of information in neurogenetics into medical practice.

Inherited neurotransmitter disorders encompass genetic disorders of neurotransmitter synthesis, catabolism or transport. While these have been commonly referred to as the pediatric neurotransmitter disorders or inherited disorders of neurotransmitter metabolism, the presently chosen term is preferred for a more global view that encompasses the irrefutable notion that there are affected adults who are undiagnosed or may benefit from available therapies. In addition, our expanded view of the disorders extends beyond neurotransmitter metabolism to transport across the blood–brain barrier, and, ultimately to vesicular storage, synaptic release and action, and termination of effect. This group of disorders represents potentially treatable conditions that were virtually unknown until recently and require a high index of clinical suspicion and laboratory expertise for diagnosis. While one could debate what disorders are most properly included, there is also recognition that there are likely undefined or undetected entities that involve the neurotransmitters in the present discussion, as well as others, for example, glutamate and melatonin.

The inherited neurotransmitter disorder story begins with some key observations by investigators who have made seminal and ongoing contributions to the field of neurometabolism. In 1971, Masaya Segawa and colleagues reported remarkable dopa-responsiveness in dystonia with diurnal fluctuation [1]. The biochemical and molecular basis of this autosomal dominantly-inherited mutation in GTP cyclohydrolase I has subsequently been identified. Moreover, the phenotypic spectrum of this condition is startling, with initial manifestations ranging from isolated toe gait in childhood to postural tremor in adults. The responsiveness of L-DOPA therapy persists throughout life. Clinical disorders stemming from mutations further downstream in the monoamine synthesis pathway have subsequently been identified, typically with more severe phenotypes and variable responsivity to therapy. These include disorders that, as with Segawa disease, do not feature peripheral hyperphenylalaninemia. These conditions include deficiency of aromatic amino acid decarboxylase (AADC), the enzyme that produces both dopamine and serotonin from their direct precursors, L-DOPA and 5-hydroxytryptophan, respectively, and tyrosine hydroxylase (TH), which converts tyrosine to L-DOPA. The first case of AADC deficiency was described in 1990 [2], and TH deficiency was described in 1996 [3]. Thus, a group of disorders along the monoamine synthesis pathway have been only recently recognized that require specialized CSF examination for precursors and metabolites of dopamine and serotonin.

In 1981, Cornelis Jakobs and colleagues reported the index case of 4-hydroxybutyric aciduria and deduced there must be accompanying deficiency of the enzyme succinic semialdehyde dehydrogenase, leading to accumulation of this metabolic byproduct of succinic semialdehyde [4]. This inborn error was subsequently confirmed by KM Gibson in the Nyhan laboratory at University of California at San Diego, CA, USA [5].

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Gibson and colleagues produced the initial clinical descriptions of the disorder and developed a transgenic mouse model. This has led to a series of basic studies involving molecular characterization, pharmacological trials [6], gene expression profiling [7], and characterization of use-dependent decreases in γ-amino butyric acid (GABA)-A and -B receptor function, which may explain the fundamental problems of epilepsy and mental retardation in this disorder [8,9].

There have been many productive meetings and symposia devoted to this topic. In May 2002, an International Symposium on Pediatric Neurotransmitter Diseases in Bethesda, MD, USA was sponsored jointly by the National Institutes of Health and the Pediatric Neurotransmitter Disease Association. Following two packed days of presentations, the investigators felt when discussing future directions that the material was sufficiently compelling to the entire neurological community that the discussions should be disseminated as widely as possible. This led to publication of the proceedings in a special supplement to the *Annals of Neurology* [10]. This has spurred further studies and an expanding spectrum, as evidenced by the recent publication of the proceedings of an international symposium covering not only monoamine and GABA disorders, but related topics and other disorders, including glycine encephalopathy, pyridoxine-dependent seizures and aspartoacylase deficiency (Canavan disease) [11].

This issue of *Future Neurology* attempts to integrate the clinical, laboratory, imaging and basic research aspects of the inherited neurotransmitter disorders in a manner that will be useful for today's clinical and basic neuroscientists. The lead article by Keith Hyland tackles the vexing problem of the technically complex acquisition and analysis of CSF, which is vital to the diagnosis of the monoamine disorders that do not demonstrate elevated blood levels of phenylalanine. For this reason, these disorders are emphasized, although the reader is referred to the work of Blau and others to explore, in particular, the often treatable disorders of tetrahydrobiopterin metabolism [11,12]. Hyland also provides an overview of the clinical manifestations associated with disorders identifiable from CSF neurotransmitter studies. These include folinic acid responsive seizures [13] and cerebral folate deficiency [14], conditions that are poorly understood, but have significant therapeutic implications.

Hyland's article is followed by clinical synopses of the disorders of monoamine synthesis and pyridoxine metabolism. The CSF examination is integral to the diagnosis of the former, and is becoming increasingly helpful in the latter as the pyridoxine story unfolds. Swoboda describes the clinical features of Segawa disease, AADC deficiency and tyrosine hydroxylase deficiency. Surtees addresses recent and innovative work that has expanded the notion of pyridoxine-dependent seizures from an enigmatic, poorly understood but eminently treatable cause of neonatal seizures to a group of disorders that incriminate a recently identified mutation affecting antiquitin, leading to sequestration of pyridoxine, as well as a distinct pyridoxal-5-phosphate dependency secondary to deficiency of pyridox(am)ine phosphate oxidase.

Hennermann discusses glycine encephalopathy, commonly referred to as nonketotic hyperglycinemia, but with the more simplistic and informative term chosen to avoid confusion with nonketotic hyperglycemia, an unrelated disorder. This disorder of the tetrameric glycine cleavage system is yet another metabolic cause of neonatal seizures, having an expanded molecular complexity and phenotypic spectrum.

The subsequent clinical descriptions are that of GABA metabolism disorders and creatine deficiency syndromes. The disorders of GABA metabolism emphasize the most common of the known neurotransmitter disorders, succinic semialdehyde dehydrogenase deficiency, as well as GABA-transaminase deficiency, homocarnosinosis, and the recently identified association of a mutation in the GABA synthesizing glutamic acid decarboxylase (GAD) enzyme and nonsyndromic cleft lip with or without cleft palate. The profound roles of GABA in CNS and embryonic facial development are manifest when one considers the ramifications of these metabolic errors. Salomons's laboratory has done the seminal work in identifying the creatine transporter deficiency, and she discusses the creatine synthesis disorders from the perspective of whether these entities are on our radar screen. Indeed, this is the pivotal question regarding this dizzying breadth of disorders.

These papers are then followed by selected topics and authors who provide key perspectives that bear on the preceding clinical descriptions. Assmann presents a series of cases where CSF neurotransmitter abnormalities were secondary to other factors, a real-world issue encountered regularly. Novotny invokes the appealing concept of a metabolic brain map *vis-a-vis* the valuable

role of magnetic resonance spectroscopy, which harks directly back to the creatine discussion. Thony and Gibson demonstrate the tremendous progress made with gene ablation technology in developing mouse models of the neurotransmitter diseases, transforming our ability to understand and potentially treat monogenic and ultimately multigenic diseases. Gropman winds up the issue with a thoughtful piece on translating the new neurogenetics into the clinical sector, with a methodical approach that applies a bedside-to-bench-to-bedside model while recognizing the considerable challenges in bringing this level of medicine to practice and policy.

This work has been propelled and sustained by many outstanding physicians and investigators. I apologize in advance for the incomplete list of researchers and topics cited here and in this issue. Special credit must be due a truly homemade parent support group, The Pediatric Neurotransmitter Disease Association, whose collective spirit and energy, led by President Nancy Speller, have made possible the progress that has been made to date, and that will surely come in the future.

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