Session II- Clinical Overview of PNDs , Andrea Gropman-Chair

The disorders known collectively as "pediatric neurotransmitter disorders" consists of several possibly under-recognized, recently identified errors of metabolism that affect the production of neurotransmitters. Neurotransmitters have vast CNS effects, controlling aspects of memory and cognition, temperature regulation, pain control, and motor function to name a few. The diseases within the category of PNDs include aromatic L-amino acid decarboxylase deficiency, tyrosine hydroxylase deficiency, GTP cyclohydrolase deficiency (Segawa disease), and succinic semialdehyde dehydrogenase deficiency. Many of the presenting features are non specific, or overlap with features seen in other disorders, thus delaying or preventing diagnosis. Appropriate diagnosis can be achieved by specialized testing of cerebrospinal fluid or urine. The mechanism of inheritance for these disorders is known, and for many of the PNDs, appropriate therapeutic options are available. Thus, it is critical to establish the correct diagnoses in these patients, not only to benefit those affected, but also to offer appropriate genetic counseling to at risk individuals.

This session, held on Saturday, May 18th presented an overview of the clinical features of pediatric neurotransmitter disorders, including their classification, presentation, metabolic features, diagnosis, and aspects of medical treatment and management.

Dr. Kathryn Swoboda spoke of her experience with the aromatic l-amino acid decarboxylase deficiency disorders (ALAAD). The major metabolic defect in this category of PNDs is deficiency of central and peripheral catecholamines and serotonin owing to a deficiency of the enzyme aromatic L- amino acid decarboxylase deficiency. The disorder is transmitted in an autosomal recessive manner. Major clinical features include generalized hypotonia, paroxysmal movement disorders (ie torticollis, limb dystonia, flexor spasms, myoclonic jerks, limb tremor, athetosis, blepharospasm, oral facial dystonia), oculogyric crisis, temperature instability, sleep disturbance, irritability, and developmental delay. In the newborn period, infants may present with hypothermia, lethargy, poor suck, ptosis and hypotension. Originally, the patients may be thought to have cerebral palsy, seizure disorders, mitochondrial disorders, myasthenia gravis, or hyperekplexia, A number of automic features are present including abnormalities of sweating, GERD, increased salivation, apnea and cardiorespiratory arrest. Dr. Swoboda showed a videotape demonstrating some of the major clinical features. Autonomic testing in two patients showed normal to high vagal tone and abnormal sympathetic responses to alterations of heart rate or blood pressure. Neuroimaging studies show no defining features. A PET study in one patient revealed complete absence of dopamine uptake. She presented data from David Goldstein and Keith Hyland, regarding patient plasma catecholamine and serotonin levels , plasma AADC activity/CSF neurotransmitter metabolites, which forms the basis for clinical diagnosis. With regard to medication use, her preliminary studies have revealed some success in reducing frequency and severity of spells and improved voluntary movement with dopamine receptor agonists (pergolide, pramipexole, ropinirole, bromocriptine), although small numbers of patients were used and many experienced dose related irritability or dyskinesias. The next group of agents showing benefit were the anticholinergics (artane, tranylcypromine), antiepileptics (topirimate, klonopin) and MAO inhibitors (selegiline). Also, the serotonergic agents showed some benefit in decreasing irritability (fluoxetine, ergotamine, buspirone, zolmitriptan). Phenylephrine reversed ptosis in about half of patients who were tried on this agent.

In general, the outcome for this group of patients appears to be non-satisfactory, with the majority of patients remaining non verbal and nonambulatory. A few patients in this series achieved assisted or independent ambulation. Lastly, Dr. Swoboda presented the possibility that there may be increased psychiatric disease in the family histories of patients with ALAAD. Whether this is related to the carrier status of AADC mutation remains to be investigated.

Dr. Georg Hoffman spoke of his experience with Tyrosine hydroxylase deficiency. He presented several slides of patients demonstrating the cardinal clinical features of this disorder: oculogyric crises, parkinsonian symptoms, tremor, hypokinesia, truncal hypotonia, irritability, and alterations in tone with hypotonia on one end of the spectrum to opisthotonous and spasticity at the other extreme. The metabolic defect in tyrosine hydroxylase results in decreased CNS catecholamine levels (including HVA and MHPG), while serotonin metabolism is unaffected (5-HIAA). The tetrahydrobiopterin and neopterin levels are normal, which allows for distinguishing THD from forms of GTPCH deficiency (see next). The disorder is transmitted in an autosomal recessive manner and three disease associated mutations (missense) have been identified. The features of dopamine deficiency include the tremors, oculogyric crises, akinesia, rigidity, and dystonia. The manifestations of norepinephrine deficiency include ptosis, miosis, increased oculopharyngeal secretions, and postural hypotension. In these patients, only some have responded to dopamine and those unresponsive to dopamine may respond to selegiline.

Dr. Masaya Segawa presented his experience with hereditary progressive dystonia with marked diurnal fluctuation/dopa responsive dystonia, dominant GTP cyclohydrolase I deficiency. First described in 1971, this disorder is a hereditary basal ganglia disease with diurnal fluctuation, inherited in an autosomal dominant manner. It is differentiated form other dopa responsive basal ganglia disorders by its early age of onset (typically 5-6 years of age), diurnal fluctuation (ie worse in the evening, improved in the morning) postural dystonia as a constant feature, later developing tremor, and the absence of cognitive or autonomic features. Characteristically it also demonstrates sustained response to L-dopa (exquisite sensitivity) without any side effects. Early development may be normal or patients may have hypotonia and difficulty in crawling, delayed language, or dystonia in early childhood.

GTP cyclohydrolase is the first enzyme required for the synthesis of tetrahydrobiopterin. Metabolic confirmation can be obtained by measuring biogenic amine metabolites and pterins in CSF. Tetrahydrobiopterin and neopterin concentrations in CSF will be low, along with reduced levels of HVA. Definitive diagnosis is made by mutation analysis of the GTPCH gene (chromosome 14q22.1-22.2). There are no common mutations, and in many cases, a mutation may not be found.

Patients who have undergone PET studies show normal or subnormal FDA PET. Histopathologic studies show absence of degenerative changes in the substantia nigra and basal ganglia. There is reduction of tyrosine hydroxylase in the substantia nigra and reduced dopamine in the ventral caudate nuclease where the D1 receptors are predominantly affected. In addition, there is a reduction of neopterin and biopterin in the striatum. Dopamine transporter activities in the striatum are normal.

Patients with heterogeneous mutations of the GTPCH gene show dominant inheritance with low penetrance, selective impairment of dopamine neurotransmission, preferential involvement of the D1 direct pathway, diurnal fluctuation, and female predominance. Patients with phenotypic

variations include those with focal dystonias (ie writer's cramp), paroxysmal dystonia, action dystonia, oculogyric crisis, and muscle hypotonia and developmental delays seen in patients who are compound heterozygotes. Patients with recessive inheritance of mutations in GTPCH gene have hyperphenylalaninemia with neopterin, biopterin, dopamine, and serotonin deficiency (tetrahydrobiopterin is a cofactor not only for tryptophan and tyrosine hydroxylases, but also phenylalanine hydroxylase in the liver) along with onset in infancy, epilepsy and mental retardation. Treatment with dopamine is effective and long lasting.

Lastly, Dr. Philip Pearl presented his experience with a small series of patients with Succinic semialdehyde dehydrogenase deficiency (SSADH). SSADH is a rare autosomal recessive disorder affecting the breakdown of GABA. Due to enzyme deficiency, GABA is not broken down to succinic acid (which then enters the Kreb cycle), but accumulates as gamma hydroxybutyrate. It is unclear whether decreased GABA, and/or elevations of GHB account for the phenotype. The gene has been identified to chromosome 6p22, where greater than 47 disease causing mutations have been identified (leading to absence of functional protein--slice site, missense, frameshift). The presenting features are non specific and include mental retardation, seizures, hypotonia, nonprogressive ataxia, disproportionate language impairment, autistic features, aggression, anxiety, hallucinations. Patients may be identified by excessive urinary excretion of gamma hydroxybutyrate (GHB) measured by specific ion monitoring on GCMS. Dr. Pearl then discussed imaging findings in the seven patients he studied: 5/5 demonstrated increased T2 weighted signal in the globus pallidi with normal 3H-MR spectroscopy. One patient showed cerebellar hypoplasia. Reviewing the literature of published cases of SSADH, he found evidence of T2 hyperintensities in globus pallidus, white matter, dentate nucleus, brainstem, as well as reports of delayed myelination, cerebral atrophy, and cerebellar atrophy. EEG results in one patient showed diffuse background slowing, sleep spindle asynchrony, sleep activated spike wave complexes, and central/temporal focal spike discharges. Literature review demonstrated similar findings with the addition of one patient with lack of REM stage sleep.

Of the seven patients he reported, about half have epilepsy, which is concordant with a seizure frequency of about 50% in the literature. All of his patients had generalized tonic clonic seizures, one with absence seizures, and two with history of convulsive status epilepticus. He had limited success with vigabatrin treatment (GABA transaminase inhibitor--ie should lead to improved GABA levels due to blocking breakdown), and found the benzodiazepines helpful for anxiety. He concluded that SSADH may be under-recognized and that cases of autism be screened for urinary excretion of GHB.