Session III- Diagnoses and Therapeutic Interventions for PND's Keith Hyland PhD- Chair

The session was designed to present and allow discussion of the clinical signs and symptoms and the analytical methods required to arrive at a diagnosis of a PND. In addition, treatment options were presented for the various conditions and the PND patient was discussed in terms of special nursing considerations and the long term impact on patient and family well being.

Dr. Georg Hoffmann overviewed the approach the clinician takes when considering the possibility of a pediatric neurotransmitter disease. He emphasized the need to exclude other diagnoses via blood or urine testing prior to resorting to cerebrospinal fluid collection and that the measurement of serum prolactin was useful as a peripheral marker of abnormal central dopamine metabolism. Symptoms associated with PND's can include tremor, other movement disorders, occular gyric crises, unstable temperature regulation and other autonomic signs. However, tyrosine hydroxylase deficiency can present as a severe encephalopathy and dopa responsive dystonia due to GTP cyclohydrolase deficiency has an extremely variable phenotype. The possibility of a PND should always be considered in a child who has been given the label of cerebral palsy where there is no obvious cause for the condition.

Dr. Keith Hyland outlined the importance of lumbar cerebrospinal fluid analysis for the diagnosis of the disorders of serotonin and catecholamine metabolism. Emphasis was placed on the critical importance of correct sample collection, handling and storage if meaningful results are to be obtained. Methodology was presented and example chromatograms were provided that indicated the possibility for a deficiency of GTP cyclohydrolase, sepiapterin reductase, tyrosine hydroxylase or aromatic L-amino acid decarboxylase. Problems with diagnoses were discussed and an overview of disorders yet to be discovered was presented. These included deficiencies of tryptophan hydroxylase, catechol-O-methyltransferase, hydroxyindole methyltransferase the vescicular amine transporter, the pre-synaptic amine transporters, post synaptic receptors, GABA defects and other receptor disorders.

Dr. Blair Ford provided an overview of the biochemistry, clinical features and treatment of dopa responsive dystonia (dominantly inherited GTP cyclohydrolase deficiency), tyrosine hydroxylase deficiency and aromatic L-amino acid decarboxylase deficiency. Emphasis was placed on the use of levodopa or dopamine agonists in the treatment of dopa responsive dystonia and tyrosine hydroxylase deficiency with the understanding that there may be receptor supersensitivity to dopamine agonists with accompanying drug-induced dyskinesias. Treatment of aromatic L-amino acid decarboxylase deficiency requires the use of dopamine agonists in conjunction with monoamine oxidase inhibitors. In addition, as the enzyme requires vitamin B6, trials with this cofactor should also be tried. Dr Ford summarized that the therapy for the defects of biogenic amine disorders is not optimum, that earlier diagnosis and initiation of therapy may be beneficial but in the long run gene replacement may be the optimal treatment approach.

Dr Andrea Gropman provided an overview of the biochemistry, clinical features and treatment of succinic semialdehyde dehydrogenase (SSADH) deficiency. Current therapeutic intervention has been limited to Vigabatrin that aims to prevent GABA breakdown and decrease succinic

semialdehyde and gamma hydroxybutyrate (GHB) levels. Efficacy of Vigabatrin has been limited possibly due to remaining high levels of GHB in the brain. Emphasis was placed on the SSADH-mouse model for exploring disease mechanisms, pathology and for the investigation of other potential therapeutic agents. Vigabatrin in the animal model elevated brain GABA but did not affect brain GHB. Using survival as an outcome marker, taurine and the GABAB receptor antagonist CGP 35348 increased survival and these pharmacological agents may prove beneficial to the human situation

Catherine Ascher RN, provided a poignant reminder that the long term care of a patient with a PND may be an arduous task both for health care providers and the affected families. Emphasis was placed on family and patient needs following diagnosis. These included the need for access to support groups and the necessity for referral to a pediatrician knowledgeable in this area. Physical, occupational, speech, feeding and behavioral therapies are required in many patients on a continuing basis and the problems and treatment issues relating to the profuse sweating, oculogyric crises, movement disorders, autonomic disregulation and gastrointestinal problems were all discussed.