2315 Niemann-Pick Disease Type C: Phenotypic variability often leads to delay in diagnosis, C. Prasad1, C. Pushparathan2, R. Morris3, A. J. Davie4 and F. E. Dougbery5. Division of Genetics1, Pathology2 and Pediatrics3, Jennerio Child Health Centre, St. John's, Newfoundland, Canada, and the Division of Genetics and Metabolism6 Children's Hospital, Boston, MA.

Niemann-Pick Disease Type C (NPC-C) is a lipidosis, caused by a unique block in acid sphingomyelinase posttranslational modification leading to the condition often cause diagnostic confusion in the early stages. We present 3 cases highlighting such phenomena in our clinical practice. NPC-C is characterized by accumulation of neutral lipids, particularly sphingomyelin, in the Kupffer cells of the liver, foam cells in the connective tissues and in the central nervous system. NPC-C is often diagnosed in infancy or early childhood with symptoms such as chronic diarrhea, failure to thrive, developmental delay, hepatosplenomegaly, and jaundice. The diagnosis is confirmed by demonstrating the absence of acid sphingomyelinase activity and is characterized by progressive neurodegenerative disorder. The disease is autosomal recessive, with symptoms ranging from severe to mild.

2316 A CRITICAL EVALUATION OF COPPER METABOLISM IN INDIAN WILSON'S CHILDREN WITH SPECIAL REFERENCE TO THEIR PHENOTYPES AND RELATIVES. R. Prasad, G. Kaur and B. N. S. W. Wallia. DEPARTMENT OF BIOCHEMISTRY AND PAEDIATRICS, POIEM, CHANDIGARH, INDIA

WILSON'S DISEASE IS AN AUTOSOMAL RECESSIVE DISORDER OF COPPER ACCUMULATION IN THE LIVER, KIDNEY, AND BRAIN. IT PRESENTS WITH NEUROLOGICAL MANIFESTATIONS SUCH AS CEREBRAL ATAXIA, MUSCULAR ATROPHY, AND Dementia. SACRAMENTO DAMAGE, SERUM COPPER AND CERULOPLASMIN IN CONTROL SUBJECTS (141 CASES OF DIFFERENT TYPES OF LIVER CIRRHOSIS) WERE SIGNIFICANTLY HIGHER THAN IN WILSON'S DISEASE (51) AND THEIR RELATIVES (59) WHILE MARKED HYPERCUPRURIA (145+/-18 mg/24h) WAS OBSERVED IN WILSON'S CHILDREN ONLY. THEREFORE, A GOOD CORRELATION (r=0.8) OBSERVED BETWEEN COPPER NOT BOUND TO CERULOPLASMIN AND URINARY COPPER EXCRETION IN WILSON'S PATIENTS. INTERESTINGLY, 24-HOUR URINARY EXCRETION OF COPPER AND C-AMP WERE SIGNIFICANTLY (P<0.01) ELEVATED IN WILSON'S CHILDREN ASSOCIATED WITH NEPHROTOXIC ACIDOSIS. DURING THE FAMILY SCREENING BY SERUM COPPER, CERULOPLASMIN AND URINARY COPPER AND HEPATIC COPPER, 10 SIBS WERE DISCOVERED TO HAVE PRESYMPTOMATIC WILSON'S DISEASE. THESE SUBJECTS WERE THEN STARTED THE D-PENCILAMINE THERAPY, BECAUSE PRESYMPTOMATIC TREATMENT PREVENTS PROGRESS OF THE DISEASE AND ITS COMPLICATIONS.


The female infant was the product of an uneventful 36-week pregnancy. Parents were non-consanguineous and healthy. At birth the child was jaundiced and had hepatomegaly with ascites. Laboratory studies revealed the following: total bilirubin 14.5 mg/dl (direct 0.5), albumin 1.7 mg/dl, prothrombin time 30%, Factor II 16%, V 22%, VII 16%, X 22%, fibrinogen 114 mg/dl; amniocenteses was normal. Serum ferritin concentration was 1,915 mg/ml. Urinary succinylacetone was absent. Alpha-antitrypsin deficiency was excluded. All viral and serologic studies and cultures were negative. The patient was treated conservatively and despite intensive management the child died on day 21 of life of diffuse uncontrollable cataractous and mucous bleeding. Post mortem examination revealed signs of iron deposits in the liver as well as in the other main organs. Extensive loss of parenchyma was evident; residual hepatocytes showed iron overload; gill cell transformation was also found. The pathologic picture was compatible with the diagnosis of Neonatal Hemochromatosis (NH). NH (OMIM 231100) is an uncommon polycyclic iron storage disorder of proratal onset. It is a phenotypically defined disease and it is believed that apoptosis in infants during fetal life may result in NH phenotype. NH is determined on the basis of a specific pathological diagnosis. Its genetic or environmental bases are still unknown. NH is generally related to hereditary hemochromatosis.


An unrelated disease, an inherited glycolipid storage disorder, is caused by a deficiency of the catabolic enzyme glucocerebrosidase. The gene for glucocerebrosidase is located on chromosome 1q21 and has a highly conserved pseudogene located 160kb upstream. We now report two novel polymorphisms in the glucocerebrosidase gene region: the first consists of a tetrancotide (AAAT) repeat upstream to the glucocerebrosidase gene and the second consists of a dinucleotide (CT) repeat in the intergenic region between the glucocerebrosidase gene and its pseudogene. These two polymorphisms, along with the previously reported CYP21 II polymorphism in intron 6 of the glucocerebrosidase gene, were analyzed in Gaucher patients (n=106) and two control populations (Akenaiz n=72 and non-Jewish n=46). Strong linkage disequilibrium was found between the common N370S mutation and particular haplotypes, but no significant linkage disequilibrium was found in patients carrying the L444P or 844G mutations. We also found exceptions to previous reports that the N370S/844G genotype is always associated with a PV1,1PV1,1 genotype. Several unusual cases of patients with unexpected haplotypes led to the recognition of common haplotypes. Our work will help in understanding the origin of glucocerebrosidase mutations. The study of these markers may reveal possible ancestral chromosomes which led to affected alleles, and that may be diagnostically useful in Gaucher patients when the specific mutations have not been identified.


Orofacial cleft (OFC), i.e. cleft lip with or without cleft palate, is a classical example of a multifactorial disorder. Evidence has been accumulated over the years that a majority of ORG results from an interaction between environmental factors, including nutritional deficiency or toxicity, and genetic factors. Results from case-control and population-based studies show that there is a positive association with folic acid and other B-vitamins, including folate, which reduces the recurrence risk of OFC. However, the fundamental biological processes that underly the preventive action of folic acid supplementation are yet unknown. Folate and vitamin B6 are involved in the metabolism of homocysteine. Therefore, this preliminary finding suggests a disorder in the enzymes involved in the remethylation of homocysteine or in the metabolism of folate and/or vitamin B12.

2320 Spectrum of Mutations In 21-hydroxylase deficient form of Congenital adrenal hyperplasia in Singapore. Agham Tay1, Kah-Yin Loke2, Larry Por1. 1Institute of Molecular and Cell Biology, 2Dpt of Paediatrics, National University of Singapore.

Congenital adrenal hyperplasia is due to a deficiency in cytochrome P450 enzymes, the most common of which is 21-hydroxylase. This enzyme is encoded by the CYP21 gene on chromosome 6p. Our aim was primarily to determine the spectrum of genetic abnormalities responsible for this disease; such analysis has not been previously reported in South-East Asia. In addition, we hope to develop rapid screening assays for mutations common in our local population.

Fourteen unrelated patients from the Endocrine outpatient clinic were studied. Each patient characterizes a set of mutations that may cause 21-hydroxylase deficiency, such as the 14 individuals. These included: intron 2 splice site mutation (3 patients), genomic DNA using the polymerase chain reaction and the products of these markers may reveal possible ancestral chromosomes which led to affected alleles, and that may be diagnostically useful in Gaucher patients when the specific mutations have not been identified.