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2315
Niemann-Pick Disease Type C: Phenotypic variability often leads to delay in diagnosis. C. Prasad1, C. Pushpanathan2, R. Morris3, J. A. Davies4 and F. E. Dougherty5 | Division of Genetics1, Pathology2 and Pediatrics3, Jennerow Child Health Centre, St. John’s, Newfoundland, Canada, and the Division of Genetics and Metabolism4 Children’s Hospital, Boston, MA.

Niemann-Pick Disease Type C (NPC-C) is a lipidosis, caused by a unique block in the intracellular cholesterol esterification, leading to protein manifestations of the condition often causing diagnostic confusion in the early stages. We present 3 cases highly compatible with such phenotypes, which to the best of our knowledge find no mention in the literature.

Case 1: A 2 year and 9 month old boy presented with neonatal hepatitis, hepatosplenomegaly and developmental delay. Initial investigations failed to establish a cause. A repeat study of the bone marrow showed foamy histiocytes, providing a diagnostic clue.

Case 2: A 14 year old boy presented with chronic megaloblastic anemia, hepatospleno megaly and short stature. There were no neurological symptoms. Electron microscopic examination of muscle tissue showed complex lipid storage and cholesterol crystals in cytoplasm.

Case 3: A female infant born at 38 weeks gestation developed neonatal hepatitis. At 4 months of age she developed respiratory failure requiring mechanical ventilation until 2 year and 3 months. She had delayed developmental delay, generalized hypotonia and weakness. A muscle, skin and nerve biopsy showed lamellar inclusions suggestive of NPC-C.

In each of the three cases the definitive diagnosis was established by demonstration of impaired cholesteryl esterification in skin fibroblasts. In conclusion, these cases illustrate the diverse, but common presentations of a rare disorder. Pulmonary manifestations (as in case 3) are rarely described in classical NPC-C, but have been observed in other NPC-C phenotypes.

2317
Neonatal Hemochromatosis. G. Serra, W. Benacchi, C. Bellini, Servizio di Patologia Neonatale, Universita' di Genova, Italy.

The female infant was the product of an uneventful 36-week pregnancy. Parents were non-consanguineous and healthy. At birth the child was icteric 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; ammonia 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 intubated and despite intensive management the child died on day 21 of life of diffuse uncontrollable cutaneous and mucous bleeding. Post mortem evaluation revealed signs of iron deposition in the liver as well as in other organs. In other main organs, extensive loss of parenchyma was evident; residual hepatocytes showed iron overload; giant cell transformation was also found. The pathologic examination confirmed the diagnosis of neonatal hemochromatosis (NH). NH is an uncommon polyvisceral iron storage disorder of proratal onset. It is a phenotypically defined disease and it is believed there is no risk of liver failure during fetal life or after. NH phenotype is not uncommon. Skin biopsy is an effective screening tool, while demonstration of massive iron overload in other organs, such as heart and point, provide a diagnostic clue. Despite the genetic or environmental bases are still unknown. NH is usually considered an autosomal recessive disorder. Parents and sibs of patients with NH are not necessarily at increased risk of Iron storage disease. NH is not an autosomal recessive disorder. Parents and sibs of patients with NH are not necessarily at increased risk of Iron storage disease. NH is not genetically related to hereditary hemochromatosis.

2319
Maternal hyperhomocysteinemia and occurrence of orofacial clefts in offspring. R.P.M.Steegers-Theunissen1,2, W.Y.Wong1, A.K.Julsen3, J.P.H.M.Visser4, B.C.J.Hamal5, H.J.Boni1, C.M.G.Thomas1, T.K.A.B.Emes1, Department of Obstetrics/Gynaecology1, Epidemiology2, Orthodontics and Dentistry3, Plastic and Reconstructive Surgery4, Clinical Genetics5, Laboratory of Pediatrics and Neurology6, Laboratory of Endocrinology and Reproduction7, University Hospital St Radboud, Nijmegen, The Netherlands.(Intro by M.M.Tolarova).

Orofacial clefts (OFC), i.e. cleft lip with or without cleft palate, is a classical example of a multifactorial disorder. Evidence has been accumulated over the last decades showing the majority of OFC results from an interaction between environmental factors, including nutritional deficiency or toxicity, and genetic factors. Results from case-control and in vitro studies of cleft lip palate patients indicate an association with maternal folate and vitamin B12 deficiency, including folic acid, reduces the recurrence risk of OFC. However, the fundamental biological processes that underly the preventive action of folic acid supplementation are as yet unknown. Folate and the vitamin B12 and B6 levels were within the normal ranges. Therefore, this preliminary finding suggests a disorder in the enzymes involved in methylation of homocysteine or in the metabolism of folic acid or vitamin B12.


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 6. 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 with a view to characterize the spectrum of mutations. DNA was extracted from peripheral leukocytes. The CYP21 gene amplified from genomic DNA using the polymerase chain reaction and the products of amplification sequenced. Sequencing of six exons and 1 intron where mutations have previously been described revealed mutations in 6 out of the 14 individuals. These included: intron 2 splice site mutation (4 patients), 3 bp deletion in exon 3 (1 patient), 11722 nonsense mutation in exon 4 (1 patient), and Q316X nonsense mutation in exon 8 (1 patient). For the intron 2 and intron 3, allele-specific oligonucleotide hybridization proved to be a reliable and rapid screening technique. Sequencing of the remaining exons is ongoing and we hope to infer genotype-phenotype correlations when we have catalogued the mutations in all the affected patients.

2321 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. S. Walia. DEPARTMENT OF BIOCHEMISTRY AND PAEDIATRICS, PIMIER, CHANDIGARH, INDIA.

WILSON'S DISEASE IS AN AUTOSOMAL RECESSIVE DISORDER OF COPPER ACCUMULATION IN LIVER, KIDNEY, BRAIN, EYES, AND EARDRUM. MANAGEMENT INVOLVES CHOLINE, SERUM COPPER AND CERULOPLASMIN IN CONTROL SUBJECTS [141 CASES OF DIFFERENT TYPES OF LIVER CIRRHOSIS ] WHOSE SIGNIFICANT INCREASED COMPARES TO WILSON'S DISEASE [51] AND THEIR RELATIVES [29] WHILE MARKED HYPERCUPRURIA [141+171] (mg/24 Hr) WAS OBSERVED IN WILSON'S CHILDREN ONLY. THEREFORE WAS A GROSS CORRELATION (r=0.77) 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 RENAL TUBULAR ACIDOSIS.

DURING THE FAMILY SCREENING BY SERUM COPPER, CERULOPLASMIN AND URINARY COPPER AND HEPATIC COPPER, 10 SIBS AND 7 RELATIVES WERE CHOSEN TO HAVE PRESYMPTOMATIC WILSON'S DISEASE. THESE SUBJECTS WERE THEN STARTED THE D-PENCILLAMINE THERAPY, BECAUSE PRESYMPTOMATIC TREATMENT PREVENTS PROGRESSION OF THE DISEASE AND ITS COMPLICATIONS.


Gaucher disease, an inherited glycolipid storage disorder, is caused by a deficiency of the catalytic enzyme glucocerebrosidase. The gene for glucocerebrosidase is located on chromosome 1q21 and has a highly conserved pseudogene situated 160kb downstream. We now report two novel polymorphisms in the glucocerebrosidase gene region: the first one consists of a tetrancuadert (AAAT) repeat upstream to the glucocerebrosidase gene, and the second is a series of a dinucleotide (CT) repeat in the intragenic region between the glucocerebrosidase gene and its pseudogene. These two polymorphisms, along with the previously reported Pvu II polymorphism in intron 6 of the glucocerebrosidase gene, were analyzed in Gaucher patients (n=105) and two control populations (Akinen n=72 and non-Jewish n=46). Strong linkage disequilibrium was found between the common haplotypes (Pvu II+ and Pvu II-), and the second is a series of a dinucleotide (CT) repeat in the intragenic region between the glucocerebrosidase gene and its pseudogene. Several unusual cases of patients with unexpected haplotypes led to the recognition of two additional haplotypes. Our findings add to our understanding of 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.