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2315
Niemann-Pick Disease Type C: Phenotypic variability often leads to delay in diagnosis.
Division of Genetics1, Pathology and Pediatrics2, Jenessay Child Health Centre, St. John's, Newfoundland, Canada, and the Division of Genetics and Metabolism3, Children's Hospital, Boston, MA.
Niemann-Pick Disease Type C (NPC-C) is a lipidosis, caused by a unique block in the de novo synthesis of ergosterol, a protein of the outer mitochondrial membrane, which manifests in the condition often cause diagnostic confusion in the early stages. We present 3 cases highlighting such phenomena and the biochemical findings in this disorder.

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

Case 2: A 14 year old boy presented with chronic megaloblastic anemia, hepatosplenoomegaly and short stature. There was 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 ventilatory support until 2 years and 3 months. She had delayed developmental, 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 may be observed in infants during early life. This case report is not uncommon. Skin biopsy is an effective screening tool, while demonstration of other biochemical abnormalities is the gold standard for diagnosis. With limited treatment options, establishing an early diagnosis is invaluable.

2317
Neonatal Hemochromatosis. G. Serra, W. Bonaccì, C. Bellini, Servizio di Patologia Neonatale, Università 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 jaundiced and had hepatosplenomegaly with ascites. Laboratory studies revealed the following: total bilirubin 14.5 mg/dl (direct 0.5), albumin 1.7 mg/dl, prothrombin time 30s, Factor II 16%, V 22%, VII 16%, X 22%, fibrinogen 114 mg/ml, amniocentesis was normal. Serum ferritin concentration was 1,915 mg/ml. Urinary succinylacetone was absent. Alpha-1-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 uncontrolled cataracts and mucous bleeding. Post mortem evaluation revealed significant iron deposits in the liver and 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 picture resembled the diagnosis of neonatal hemochromatosis (NH). NH (OMIM 231100) is an uncommon polyvisceral iron storage disorder of proratal onset. It is a phenotypically defined disease and it is believed that this iron in disorders during fetal life may result in the NH phenotype. NH is determined on the basis of a specific pathological diagnosis, its 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 genetically related to hereditary hemochromatosis.

2319
Maternal hypercholesterolemia and occurrence of orofacial clefts in offspring. R.P.M. Steegers-Theunissen1,2, W.Y. Wong, A.Kuligars-Kojan1, M.H.M. Stansfeld1, B.C.J. Hamel, H.J. Bont1, C.M.G. Thomas, T.K.A.B. Eskes1, Department of Obstetrics/Gynaecology1, Epidemiology, Orthodontics and Dentistry2, Plastic and Reconstructive Surgery, Clinical Genetics2, Laboratory of Pediatrics and Neurology0, Laboratory of Endocrinology and Reproduction1, University Hospital St Radboud, Nijmegen, The Netherlands. (Intro by M.M.Tolzawa).

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 showing that the majority of OFC results from interaction between environmental factors, including nutritional deficiency or toxicity, and genetic factors. Results from case-control and intensive family studies confirm the familial predisposition. Vitamin supplements 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 B6 and B12 are involved in the metabolism of homocysteine.

In order to investigate the folate-dependent homocysteinaemia metabolism, a standardized methylene loading test was carried out in 28 mothers of a child with OFC and 56 control women.

Surprisingly, in 8 mothers of a OFC child and 2 controls - in the absence of dietary and kidney function - hyperhomocysteaemia was established. In general, the folate, vitamin B12 and B6 levels were within the normal ranges. Therefore, this preliminary finding suggests a disorder in the enzymes involved in remethylation of homocysteine or in the metabolism of folate end/ or vitamin B12.

2320
Spectrum of Mutations In 21-hydroxylase deficient form of Congenital adrenal hyperplasia in Singapore. Agness Tay1, Kay-Yin Loke2, Larry Port3, Institute of Molecular and Cell Biology, 2Dekta 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 selected; a view to characterizing the mutations. DNA was extracted from peripheral leukocytes. The CYP21 gene amplified from genomic DNA using the polymerase chain reaction and the products of amplification were sequenced. Sequencing of six exons and one intron where mutations have previously been described revealed mutations in 6 out of the 14 individuals. The mutations included one site A to G change at nucleotide 582, 8-bp deletion in exon 3 (1 patient), IN172 missense mutation in exon 4 (1 patient), and Q319X nonsense mutation in exon 8 (1 patient). For the intron 2 mutation, allele-specific PCR amplification hybridization proved to be a reliable and rapid screening technique.

Sequencing of the remaining exons is ongoing and we hope to infer genotype-phenotype correlates when we have catalogued the mutations in all the affected patients.

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. Walia. Department of Biochemistry and Paediatrics, Postgraduate Institute of Medical Education and Research, Chandigarh, India.

Wilson's disease is an autosomal recessive disorder of copper accumulation in the liver and nervous system. Its clinical presentation is often varied and in most cases, the diagnosis is delayed. Serum copper and ceruloplasmin in control subjects are significantly higher in Wilson's disease patients. Serum copper, copper and ceruloplasmin in control subjects are significantly higher in Wilson's disease patients. Serum copper, 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 failure. Acidosis.

Therefore, 13 cases of Wilson's were confirmed by measuring hepatic copper (80+80ug wet tissue: mean +/- SD). During the family screening by serum copper, ceruloplasmin and urinary copper and hepatic copper, 10 siblings were proposed 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.

2318

In this 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. We now report two novel polymorphisms in the glucocerebrosidase gene region: the first consists of a tetrancleotide (AATT) repeat upstream to the glucocerebrosidase gene, and the second is a series of dinucleotide (GT) repeat in the intergenic 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 (Askenazi 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 84GG mutations. We also found exceptions to previous reports of the N370S/64G genotype is always associated with a PV1->PV1+ genotype. Several unusual cases of patients with unexpected haplotypes led to the recognition of a distinct class of patients that contributed 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.

2321

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