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Niemann-Pick Type Disease C: Phenotypic variability often leads to delay in diagnosis. C. Prasad1, C. Pushpamathan, R. Morris1, A. J. Davies and F. E. Dougerty4. Division of Genetics1, Pathology2 and Pediatrics, Jeneva Child Health Centre, St. John’s, Newfoundaland, 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 blockage of the lysosomal esterification of glucocerebroside, with protein manifestations of the condition often cause diagnostic confusion in the early stages. We present 3 cases highly suggestive of such phenotype with characteristic pathological findings, that finally led to the diagnosis.

Case 1: A 2 year and 9 month old boy presented with neonatal hepatitis, hepatopancreaticomegaly 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, hepatopancreaticomegaly and short stature. There were no neurological symptoms.

Electron microscopy examination of muscle tissue showed complex lipid storage and cholesteryl esters in cytoplas.

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 were observed in two of our cases. Although NPC-C is not uncommon, skin biopsy is an effective screening tool, while demonstration of defective cholesteryl esterification remains the gold standard for diagnosis. With limited treatment options, establishing an early diagnosis is invaluable.

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Neonatal Hemochromatosis. G. Serra, W. Bonacci, 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 asplenic 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 18%, X 22%, fibrinogen 114 mg/dl, ascorbic acid was normal. Serum ferritin concentration was 1,915 mg/ml. Urinary succinylacetone was absent. Alphal-antitrypsin was normal. Hypothyroidism, hypoglycemia, hypothermia, hyponatremia were not present.

Hemochromatosis is the most frequent form of iron storage disease. NH is not necessarily at increased risk of Iron storage disease. NH is not considered an autosomal recessive disorder. Parents and sibs of patients with NH are not at increased risk of Iron storage disease. NH is not 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 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 necessarily at increased risk of Iron storage disease. NH is not necessarily at increased risk of Iron storage disease. NH is not necessarily at increased risk of Iron storage disease. NH is not necessarily at increased risk of Iron storage disease. NH is not necessarily at increased risk of Iron storage disease. NH is not necessarily at increased risk of Iron storage disease. NH is not necessarily at increased risk of Iron storage disease. NH is not necessarily at increased risk of Iron storage disease. NH is not necessarily at increased risk of Iron storage disease. NH is not necessarily at increased risk of Iron storage disease. NH is not necessarily at increased risk of Iron storage disease. NH is not necessarily at increased risk of Iron storage disease. NH is not necessarily at increased risk of Iron storage disease. NH is not necessarily at increased risk of Iron storage disease. NH is not necessarily at increased risk of Iron storage disease. NH is not necessarily at increased risk of Iron storage disease. NH is not necessarily at increased risk of Iron storage disease. NH is not necessarily at increased risk of Iron storage disease. NH is not necessarily at increased risk of Iron storage disease. NH is not necessarily at increased risk of Iron storage disease.

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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 past decade showing that the majority of OFC results from an interaction between environmental factors, including nutritional deficiency or toxicity, and genetic factors. Results from case-control and longitudinal studies have been contradictory. In our study we compared the incidence of maternal hyperhomocysteinemia (MHH) and OFC in two main groups. Maternal hyperhomocysteinemia was defined as total homocysteine levels above 15 µmol/l, including folate, and the vitamin B6 and B12 were involved in the metabolism of homocysteine.

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

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

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Spectrum of Mutations In 21-hydroxylase deficient form of Congenital adrenal hyperplasia In Singapore. Agnes Tay1, Kah-Yin Loke2, Larry Poh1, 1Institute of Molecular and Cell Biology, 2Dept 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 in 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 of intron three mutations have previously been described revealed mutations in 6 out of the 14 individuals. These included: intron 3 splice site mutation, 8-bp deletion in exon 3 (1 patient), INN7 missense mutation in exon 4 (1 patient), and Q315X nonsense mutation in exon 8 (1 patient). For the intron 2 mutation, allele-specific polymerase chain reaction proved to be 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.

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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, PRIMROVE, CHANDIGARH, INDIA.

WILSON'S DISEASE IS AN AUTOSOMAL RECESSIVE DISORDER OF COPPER ACCUMULATION IN ORGAN TISSUES LEADING TO NEUROLOGICAL DAMAGE. Serum Copper and Ceruloplasmin in Control Subjects (141 Cases) Listed in the Table are Significantly Higher than in Wilson's Disease (51) and Their Relatives (58) While Marked Hypercupriuria (14.5±4.7 mg/24 h) Was Observed in Wilson's Children Only. There Was 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 NEURAL TUBE DEFECTS.

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