The following full text is a publisher's version.

For additional information about this publication click this link.
http://hdl.handle.net/2066/24367

Please be advised that this information was generated on 2019-02-04 and may be subject to change.
2315
Niemann-Pick Disease Type C: Phenotypic variability often leads to delay in diagnosis. C. Prasad, C. Pushpanathan, R. Morris, A.J. Davis and F.E. Dougherty. Division of Genetics, Pathology and Pediatrics, Janeway Child Health Centre, St. John's, Newfoundland, Canada, and the Division of Genetics and Metabolism, Children's Hospital, Boston, MA.
Niemann-Pick Disease Type C (NP-C) is a lipidosis, caused by a unique block in cholesterol esterification due to the lack of protein manifestations of the disease often cause diagnostic confusion in the early stages. We present 3 cases highlighting this with pathologic findings of pancreatic tissue.

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 feocary histiocytes, providing a diagnostic clue.

Case 2: A 14 year old boy presented with chronic megaloblastic anemia, hepatosplenomegaly and short stature. There were no neurological symptoms. Electron microscopical examination of muscle tissue showed complex lipid storage and cholesteryl esters in cytoplasm.

In each of the three cases the definitive diagnosis was established by demonstrating impaired cholesterol 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 NP-C, but hepatomegaly in infants may be infrequent. In NP-C, it is not uncommon. Skin biopsy is an effective screening tool, while demonstration of a cholesteryl ester storage is the most specific test for diagnosis. With limited treatment options, establishing an early diagnosis is invaluable.

2317
Neonatal Hemochromatosis. G. Serra, W. Bonacci, 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 small and had hepatomegaly with ascites. Laboratory studies revealed the findings described previously: total bilirubin 14.5 mg/dl (direct 0.5), albumin 1.7 mg/dl, prothrombin time 30 s, Factor II 16%, V 22%, VII 18%, X 22%, fibrinogen 114 mg/ml; ammonia was normal. Serum ferritin concentration was 1,915 mg/ml. Urinary succinylacetone was absent. Alphal-antitrypsin deficiency was also ruled out. The patient's condition progressively deteriorated and despite ventilation until 2 years & 3 months, she died. Electron microscopic examination of muscle tissue showed complex lipid storage and cholesteryl esters in cytoplasm.

Inclusions suggestive of NP-C. Extensive loss of liver parenchyma was evident; residual hepatocytes showed iron overload; giant cell transformation was also found. The pathologic picture was compatible with the diagnosis of neonatal hemochromatosis (NH), a disorder of prenatal onset. It is a phenotypically defined disease and it is determined on the basis of a specific pathological diagnosis.

In our local population, NH is determined on the basis of a specific pathological diagnosis. Its genetic or environmental bases are still unknown. NH is not genetically related to hereditary hemochromatosis.

2319

Orofacial cleft (OCF), 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 OCF results from an interaction between environmental factors, including nutritional deficiency or toxicity, and genetic factors. Results from case-control and inbred family studies indicate that periconceptional vitamin supplementation, including folic acid, reduces the recurrence risk of OCF. 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 are involved in the metabolism of homocysteine.

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

Surprisingly, in 8 mothers of an OCF child and 2 control - in the absence of folate and kidney transplantation - hyperhomocysteinemia 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 and/or vitamin B12.

2320
Spectrum of Mutations In 21-hydroxylase deficient form of Congenital adrenal hyperplasia in Singapore. Agnes Tay, Kah-Yin Loke, Larry Port, 1Institute of Molecular and Cell Biology, 2Duke 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 using a view to characterize 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 intron II where mutations have previously been described revealed mutations in 6 out of the 14 individuals. These included insertion, deletion, splice site, 8-bp deletion in exon 3 (1 patient), 1172 missense mutation in exon 4 (1 patient), and Q319X nonsense mutation in exon 8 (1 patient). For the intron 2 mutation, allele-specific oligonucleotide hybridization proved 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.