2315 Niemann-Pick Disease Type C: Phenotypic variability often leads to delay in diagnosis. C. Prasad 1, C. Pushpanathan 1, R. Morris 2, A. J. Davies 2 and F. E. Dougherty 2, Division of Genetics 1, Pathology 2 and Pediatrics 3, Janeway Child Health Centre, St. John's, Newfoundland, Canada, and the Division of Genetics and Metabolism 1 Children's Hospital, Boston, MA.

Niemann-Pick Disease Type C (NPC- C) is a lipidosis, caused by a unique block in cholesterol esterification, which results in intracellular storage of protein manifestations of the condition often cause diagnostic confusion in the early stages. We present 3 cases highly characteristic of the clinical and biochemical findings, which defined the disease.

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, indicating a possible diagnosis of NPC.

Case 2: A 14 year old boy presented with chronic megaloblastic anemia, hepatosplenomegaly and short stature. There were no neurological symptoms. Electron microscopic examination of muscle tissue showed complex lipid storage and cholesterol ester 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 for 2 years and 3 months. She had delayed development, generalized hypotonia and weakness. A muscle, skin and nerve biopsy showed lamellar inclusions suggestive of NPC.

In each of the three cases the definitive diagnosis was established by demonstration of impaired choleseryl 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, but were observed in our patients despite early intensive respiratory support. The child died on day 21 of life of diffuse uncontrolled cutaneous and mucous bleeding. Post mortem examination revealed significant iron deposits in the liver as well as in other main organs.

Identification of two novel polymorphisms in the glucocerebrosidase gene region: the first one consists of a tetranucleotide (AAAT) repeat upstream to the glucocerebrosidase gene, and the second is a series of a dinucleotide (GT) repeat in the intergenic region between the glucocerebrosidase gene and its pseudogene. These two polymorphisms, along with the previously reported $P v u l$ 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 B48G mutations. We also found exceptions to previous reports that the N370S/B48G genotype is always associated with a PV1+1, PV1+1 genotype. Several unusual cases of patients with unexpected haplotypes led us to reevaluate our understanding of the origin of glucocerebrosidase mutations. The study of these patients might reveal possible ancestral chromosomes which led to affected alleles, and that might be diagnostically useful in Gaucher patients when the specific mutations have not been identified.

2319 Maternal hyperhomocysteinemia and occurrence of orofacial clefts in offspring. R.P.M. Stuengers-Thouinsson 1,2, W.Y. Wong 1, A.Kuljapers-Jagim 1, P.H.M. Spauwen 1, B.C.J.H. Harrell 2, J.B. Bioni 2, C.M.G. Thomas 2, T.K.A.B. Eisele 1, Department of Obstetrics/Gynecology 1 and Epidemiology 2, Orthodontics and Dentistry 2, Plastic and Reconstructive Surgery 2, Clinical Genetics 2, Laboratory of Pediatrics and Neurology 2, Laboratory of Endocrinology and Reproduction 1, University Hospital St Radboud, Nijmegen, The Netherlands.(Intro by M.M.Tolraova).

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 twin studies indicate that genes play a major role in the etiology of OCF. Several orofacial cleft supplements including folic acid, reduces the recurrence risk of OCF. However, the fundamental biological processes that underly the preventer action of folic acid remains to be identified. Folate and the vitamin B6 and B12 are involved in the metabolism of homocysteine.

In order to investigate the folate-dependent homocystein 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 a OCF child and 2 controls - in the absence of an antenatal kidney function - hyperhomocysteinemia was established. In general, the folate, vitamin B12 and B6 levels were within the normal range. Therefore, this preliminary finding suggests a disorder in the enzymes involved in the metabolism of homocysteine or in the metabolism of folate end/ vitamin B12.


Wilson's Disease is an autosomal recessive disorder of copper accumulation in various organs of the body. Wilson's disease is characterized by liver damage, serum copper and ceruloplasmin in control subjects (141 cases of different types of liver cirrhosis) which are significantly higher than compared to Wilson's disease (51) and their relatives (59) while marked hyperuricemia (145 ± 7 mg/dl) 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 renal tubular acidosis.