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Abnormal brain structure and function in adult males with isolated clefts of the lip and/or palate. P. Nopoulos[1], S. Berg[1], L. Richman[1], and J. Canady[1] - [1]Univ. of Iowa Hospitals and Clinics, Iowa City, IA.

Objective: The aim of this study was to determine if adult males with isolated clefts of the lip and/or palate (CLP) have aberrant cerebral morphology and/or cognitive dysfunction. Brain morphology (using MRI) and performance on a battery of cognitive tasks in a sample of 50 males with isolated CLP were analyzed and compared to 50 healthy controls matched for sex, age, and parental socioeconomic status.

Results: The males with CLP have significantly lower full scale (p=0.000), verbal (p=0.000), and performance (p=0.000) Intelligence Quotients (IQ). After controlling for full scale IQ, subjects had a significant deficit in a language production task (p=0.001), but no deficit in a visuospatial task (p=0.237). In regard to brain morphology, CLP subjects had a robust anterior to posterior tissue distribution shift. That is, CLP patients had significantly larger than normal frontal and parietal lobes, but significantly smaller than normal temporal lobes, occitipal lobes and cerebellar volume. Effect sizes for anterior "enlargement" were small (0.30 for frontal, 0.18 for parietal lobe) while effect sizes for posterior brain region "decrement" were more robust (range .57 for occipital lobe to .70 for cerebellum). Volume decrement in the CLP patients in the temporal lobe and cerebellum were more severe on the left side.

Conclusions: Adult males with CLP have significant cognitive deficits. Against the background of global cognitive dysfunction, language function is particularly disturbed. In addition, adult males with CLP have a significantly altered pattern of brain morphology compared to healthy controls, which is most likely due to aberrant cerebral development. Pathoetiologic mechanisms will be further discussed. This study highlights the complex interaction and interdependence of craniofacial and cerebral development.

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The clinical expression of Gaucher disease correlates with genotype: Data from 570 patients. CR Scott, G Pastores, H Andersson, J Charrow, P Kaplan, E Kolodny, P Mistry, B Rosenbloom, R Wappner, N Weinreb. The International Collaborative Gaucher Group (ICGG), Cambridge, MA.

Gaucher disease is the most common lysosomal storage disease and is caused by a deficiency of glucocerebrosidase. It is typically considered an adult disorder, manifest with hematologic changes and bone fractures. The five most common genotypes, consisting of 570 patients, were selected from the ICGG Registry (2000+ patients) and stratified according to clinical symptoms. Surprisingly, 50% of all patients in the registry were less than 10 years when diagnosed. The most common genotype was N370S/N370S (38%), followed by N370S/L444P (27%), N370S/84GG (20%), L444P/L444P (11%), and N370S/IVS2+1 (4%).

The age at diagnosis was 27.8 years for N370S/N370S, 17.9 years for N370S/L444P, 9.4 years for N370S/84GG, 8.9 years for N370S/IVS2+1, and 2.5 years for L444P/L444P.

All patients with the N370S allele were classified as type I and were free of neurologic symptoms. 78% of children with the L444P/L444P genotype had eventual neurologic symptoms and were classified as type III. Radiologic evidence of bone disease was present in 92% of N370S/N370S, but was rare in L444P/L444P patients at diagnosis. The largest spleen volumes were in L444P/L444P (40 x norm), followed by N370S/IVS2+1 (19.1 x), N370S/84GG (18.7 x), N370S/L444P (15.4 x), and N370S/N370S (12.1 x).

Some rare alleles present with unique clinical signatures. Patients homozygous for D409H are severe with aortic valve calcification. Infants homozygous for a rare recombinant allele, RecNciI, are born with "collodian" skin and severe neurologic symptoms.

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Focal abdominal wall hernias and pre-axial toe polydactyly define distinct phenotypes and etiologies for infants of diabetic mothers and the VATER Association. L.R. Shapiro,[1,2] P.A. Duncan,[1,2] D. Beneck,[1,2] B.F. Goldin[2], I. Legarda[1] and D. Kronn[1,2]. [1]New York Medical College and Westchester Medical Center, Valhalla, NY.

Three **newborn infants of mothers with insulin dependent diabetes mellitus (IDDMm) were found to have multiple congenital malformations consisting of 3 or more VATER ascertainment anomalies. In addition, each of the 3 infants also had left lateral abdominal wall hernias, not previously noted in VATER or IDDMm infants. The hernias had intact overlying skin, were easily reducible and approximately 5-8 cm in diameter. Abdominal wall hernias with intact overlying skin are unusual, especially on the left side. One infant came to autopsy and was found to have hypoplasia (amyoplasia) of the abdominal wall musculature. Each of these 3 infants also had bilateral toe pre-axial polydactyly which has been rarely reported in VATER or in IDDMm infants.**

While there is overlap in the anomalies of VATER Association and infants of IDDMm, these 3 infants of IDDMm suggest that the phenotypes are distinct with separate etiologies. In VATER, an early insult to the allantois and subsequent vascular consequences have been etiologically implicated. The pre-axial toe polydactyly and abdominal wall hypoplasias are related to mesenchyme. The presence of macrosomia and increase in number of cells with IDDM can result in excess mesenchyme at the time of limb bud development which has been linked to polydactyly. The focal abdominal wall amyoplasia derives from myotomal mesoderm which migrates from 3 directions to fuse in the midline. An excess of mesodermal cells can cause imperfect fusion and migration resulting in a focal defect.

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Aortic root dilatation complicates Ehlers-Danlos syndrome. R.J. Wenstrup[1], J. S. Lyle[1], P.S. Rose[2], H.P. Levy[2], L. Hoechstetter[1], R. A. Meyer[1], and C.A. Francomano[2]. [1]Children's Hospital Medical Center, Cincinnati, Ohio, and [2]National Human Genome Research Institute, NIH, Bethesda, MD.

Although aortic root dilatation (ARD) is a well-known complication of the Marfan syndrome, it has generally been believed to be a rare finding in Ehlers-Danlos syndrome (EDS). Based on experience with a few cases, we performed a prospective cohort study to determine the prevalence of aortic root dilatation in the Ehlers-Danlos syndromes. Aortic measurements by two dimensional echocardiography were performed on 77 consecutive children and adults in a clinic population who had Ehlers-Danlos syndrome types I, II, or III (1988 Berlin classification) or the *classical* or *hypermobile* types of EDS (1997 Villefranche Nosology). There were 32 males and 45 females. The average age at first echocardiogram was 24.7 years with a range of 1-62 years. Twenty-eight percent (22/77) of patients in the study population had ARD, as defined by a measurement > +2 S.D above population based norms (Roman et al., Am. J. Card. 64:507-512); the average age at the time of ARD diagnosis was 22.4 years with a range of 5-62 years. Thirteen of 46 individuals with the *classical* form of EDS (types I/II) and 9 of 31 individuals with the *hypermobile* form (type III) had ARD, with males and females being similarly affected. Prevalence of ARD was similar at both clinical centers. At one center (CHMC), 4 of the 12 individuals with ARD were referred on the basis of possible ARD, and the diagnosis of EDS was made subsequently. Removing these four cases as a possible source of ascertainment bias would reduce prevalence from 28% (12/45) to 20% (8/41). These results indicate that ARD is a relatively common finding in EDS. Larger cross-sectional studies and longitudinal studies are indicated to refine prevalence data, to correlate ARD with genotype, and to determine progression of ARD and its clinical significance.