Clinical Genetics: Characterization of Disorders *(continued)*

858

Twin study in familial Mediterranean fever (FMF) - a genetic disorder with marked variability in clinical expression. M. Shohat*, A. Livneh, D. Zemer, M. Pras. Beilinson Medical Ctr, Shiba Medical Ctr and Tel-Aviv Univ., Israel.

Familial Mediterranean Fever (FMF) is a recurrent inflammatory disorder characterized by short episodes of fever, peritonitis, pleuritis or arthritis. The majority of patients are from the Mediterranean area; non Ashkenazi Jews, Armenians and Arabs. It was suggested that FMF is a genetic disorder probably autosomal recessively inherited, but lower "observed" than "expected" FMF patients were found in all segregation studies. Although many families have been described, no twin study has been carried out. The purpose of this study was to evaluate the cosegregation and clinical spectra of the disease in di and monozygotic twin sets. From a total of 2500 FMF patients seen in the major Israel FMF referral Center, we identified 18 sets of twins where at least one was diagnosed as having FMF, based on standard criteria. All these twins were reexamined. Identity, as tested by DNA fingerprints, was determined in nine. While in the 9 dizygotic twins concordance for the FMF disease was found in only 3 pairs, full concordance was observed in all the 9 monozygotic twin sets. However, marked variability in the clinical manifestations and degree of severity within twins has been noticed. In two occasions, one of the twins had only few (2-3), but confirmed, episodes of peritonitis or pleuritis, and had not been diagnosed as affected prior to this study. These findings provide strong evidence that FMF is a genetic disease, probably transmitted in autosomal recessive mode of inheritance with marked variability in expression.

859

Usefulness of the Axial Mesodermal Dysplasia Spectrum concept as a pathogenetic diagnosis. I. Simoneau*, Y. Lacassie. Louisiana State University Medical Center, New Orleans, LA, U.S.A.

In 1981, Russell et al. suggested the existence of a spectrum of anomalies derived from the mesoderm that would explain the association of caudal regression and craniofacial anomalies syndromes. They named it the axial mesodermal dysplasia spectrum. In 1990, Wulfsberg and Grigbsy reported a patient with Rokitansky sequence associated with the Facio-Auriculo-Vertebral Sequence which could be part of this mesodermal dysplasia spectrum, and reviewed several cases reported of associations of mesodermally derived sequences. We report 3 patients in whom we raised this diagnostic possibility. Patient 1 presented with features of the FAV spectrum, Treacher-Collins, Wildervanck, Femoral hypoplasia-unusual facies, and Hay-Wells syndromes. Patient 2 presented with short stature, severe MR, microphthalmia, sclerocornea, striking urogenital anomalies, kyphoscoliosis, short femurs, absent tibias, postaxial polydactyly left hand. MR was present in the maternal family. Patient 3 presented with small ears, bilateral sclerocornea, short neck, cardiac anomalies and hydronephrosis. These patients support the existence of this pathogenetic concept.

860

Huntington's Disease in North East Scotland: Predictive Testing and Sex Ratio. Sheila A. Simpson* (1), John Besson (2), David Alexander (2), Alan W. Johnston (1). (1) Medical Genetics and (2) Dept. Mental Health, Medical School Buildings, Foresterhill, Aberdeen, U.K.

Grampian region in North East Scotland has the highest prevalence of Huntington's Disease in Europe. The Presymptomatic Predictive Test Programme has been in operation for 30 months and 38 results have been given. Exclusion testing has been requested by another 13 couples, and 10 have been completed. The follow up of these patient groups has shown no significant psychiatric morbidity, using Beck's Inventory, Beck's Hopelessness Scale, as well as an assessment of lifestyle changes and psychiatric interview.

The sex distribution of those receiving results, whether they had the gene or did not carry it, was approximately equal in both groups. This is in contrast to the affected population in Grampian, where an excess of females exist (58%). This unexpected ratio was also found in the affected individuals in Scottish psychiatric and general hospitals and in those dying with the diagnosis of Huntington's Disease over the last decade. This has not been explained by the local general population sex ratio, early death in affected males, early diagnosis in females, or a longer lifespan in affected females, nor does it appear to be a reflection of sample size. Five years of study has not revealed undiagnosed males in the population.

861

Genetic heterogeneity of skeleton dysplasia in Roberts syndrome. A.K.Sinha*(1) and R.S. Verma(2). (1) Booth Memorial Medical Center, Flushing,N.Y. and (2) Long Island College Hospital-SUNY Health Science Center at Brooklyn, New York.U.S.A.

Roberts-SC phocomelia syndrome is a rare autosomal recessive disease with variable expression. Phocomelia or 'seal limb' in which hands or feet of unusual size even excessively short limb was first described in 1838 by Geoffroy Saint-Hilaire. Later,J.B. Roberts (1919) reported double cleft and lip palate, protrusion of the intermaxillary portion of the upper jaw with improper development of all four extremities in siblings.Cytogenetic and clinical diagnosis have been vigorously persued and todate 43 cases has been reported. Present study reviews 18 cases. In general, 14 cases had short and deformed humerus and 4 had absent humerus Six cases had short and deformed and 12 had absent radius. A relationship of deformaties exists between humerus vs femur, radius & ulna vs tebia & fibula. Only six cases had club foot. The number of fingers and toes were variable. The longest follow up survival was 13 years. The sex was 1:1. Though the condition may be caused by a single gene, the clinical manifestation is highly heterogeneious.

862

Late-infancy globoid cell leukodystrophy. S. Sklower Brooks(1)*, R. DeCarlo(2), K. Wisniewski(1), S. Kurzion(1) and D. Deshmukh(1). (1) OMRDD New York State Institute for Basic Research in Developmental Disabilities, Staten Island, NY and (2) St. Vincents Medical Center at Richmond, Staten Island, NY, USA.

Globoid-cell leukodystrophy (Krabbe Disease) usually presents between 3-6 month of age with rapid psychomotor regression. While other clinical forms have been described with later onset, only rare cases have been noted between 9 mo and 2 yrs and in only one case was MRI reported. We describe the clinical phenotype in two unrelated patients with onset at 10 and 15 months. Diagnosis was confirmed enzymatically using labelled galactocerebroside and lactosylceramide. Spasticity and loss of previously attained motor milestones were the first observed findings and occurred over a period of about 2 months. In one child these symptoms developed following measles immunization after the development of a maculopapular rash and fever. Periodic extensor posturing and irritability were then noted. Neither child had visual disturbance at the onset. CSF protein was elevated. The older child had mild dilatation of the ventricular system demonstrated on 2nd generation CT scan. The younger child had circumscribed and well defined bilateral regions of low density in the mid corona radiata from the lateral ventricles to the convexity on CT scan and 2-3 cm ovoid, poorly defined hyperintensities in the T2 weighted images in the deep white matter of the frontal and parietal lobes on MRI. These cases further delineate the phenotype and clinical heterogeneity in late-infantile Krabbe disease.

863

Association of autism and tuberous sclerosis. S. Smalley (1)*, P. Tanguay (1), and M. Smith (2). (1) Department of Psychiatry, UCLA, Los Angeles, CA and (2) Department of Pediatrics, UC Irvine, CA.

Tuberous sclerosis (TSC) is an autosomal dominant disorder characterized by hamartomas of multiple organs including skin and brain. Autism is a behavioral disorder that has been noted to co-occur with TSC. We are investigating the association of autism and TSC in an ongoing family/genetic study. In our first 22 families, 11 ascertained through TSC probands and 11 through autistic probands, we have preliminary data on behavioral disorders in probands and their relatives. In this clinically based sample, 36% of TSC probands and 27% of all TSC subjects (11 probands and 4 affected relatives) meet DSMIIIR criteria for autism, a frequency significantly greater than the population frequency of .05%. These data support a significant association of TSC and autism. The mechanism of this association is under investigation by our group. Using a family history interview, among 215 relatives of autistic probands, 5% have speech delay, 10% have cognitive deficits including mental retardation, and 4% have social deficits. Among 264 relatives of TSC probands, 3% have speech delay, 5% cognitive deficits, and none have social deficits. These findings suggest familial differences may exist between autism co-occurring with and without TSC.