A new probably autosomal recessive cardiomegaly dysplasia with mesosaxial hexadactyly

SUMMARY A distinct probably autosomal recessive syndrome was ascertained in a 17-year-old boy and his deceased sister. The main features were cardiac dysplasia, peculiar facies, central bilateral (mesosaxial) hexadactyly, synmetacarpalia, short stature, ocular torticollis, and delayed puberty.

We describe a patient with multiple congenital anomalies, some of which were indirectly ascertained in his deceased sister, suggesting autosomal recessive inheritance.

Case report

The proband, born in 1962, was the product of a term gestation and normal delivery. Birthweight and length were not recorded; however, he was smaller than his normal sibs. Bilateral hexadactyly, broad right hallux, acrocyanosis, the presence of teeth, and dyspnoea were observed at birth. Psychomotor retardation was evident from early infancy and he tilted his head to the left when he started walking at about 4 years of age. Excision of the supernumerary right finger was performed at 10 years of age. Physical examination at 13½ years (fig 1) showed delayed development, a weight of 28·7 kg, a height of 134 cm (both below the 3rd centile), an upper-to-lower-segment ratio of 0·97 (66/68), an arm span of 127 cm, and a head circumference of 53 cm. Other features included normocephaly, wide and flat forehead, hypertichosis of the eyebrows distally (ulerythema ophryogenes), telecanthus, ocular torticollis as a result of alternate exophoria-tropia, a winking tick, long prominent nose with lateral bossing, tented nares, lateral pits in the nasal alae, short philtrum,macrostomia, everted lower lip, downturned mouth, multiple dental diastemata and malocclusion, large pinnae, prominent antihelix, two right Darwinian tubercles, short neck, prominent trapezius muscles, cylindrical thorax, hypoplastic nipples, underdeveloped external genitalia, normal spine, mesosaxial hexadactyly in both hands, digital clubbing and cutaneous syndactyly between digits 2 and 3, thenar and hypothenar hypoplasia, genu and pes valgus, right hallux polydactyly, and mild flattening of toe nails. Dermatoglyphic analysis did not reveal extra triradii at the base of the supernumerary fingers.

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References

The proband aged 17 years. Note the infantile genitalia and the peculiar facies. In the upper left photograph the patient had already had operations on both hands. In the lower left photograph the left hand still shows the mesoaxial hexadactyly. Also note the right hallucal polysyndactyly.

Results of routine laboratory examinations, including blood cell count, glucose, urea, creatinine, plasma proteins, alkaline phosphatase, Ca and P, urine analysis, and screening tests for inborn errors of metabolism, were either normal or negative. The karyotype processed for G bands was normal, 46,XY. Endocrinological studies included the following normal results: T₃, T₄, 17-ketosteroids, 17-hydroxycorticoids, TSH and prolactin release after TRH stimulation, as well as basal and post-stimulation (insulin induced hypoglycaemia) HGH levels. At 17 years of age, the plasma values of testosterone, dihydrotestosterone, total oestrogens, LH, and FSH (before and after stimulation with LH-RH) correspond to a prepubertal male.

X-ray examination disclosed a bone age delayed by about 3 years (Greulich-Pyle), osteopenia, cervical dextroconvex scoliosis, thinning of cortices, metacarpophalangeal dysrhythmic growth, distal central synmetacarpalia and bilateral type A mesoaxial hexadactyly, right hallucal polysyndactyly, and enlarged first podal ray (fig 2). Urography was normal.

Cardiological evaluation, including haemodynamic studies and direct visualisation during surgery, revealed pulmonary stenosis, persistent ductus arteriosus, single atrium, ventricular septal defect (20 mm), lower vena cava and persistent left upper vena cava draining into coronary sinus, and hepatic veins draining into left auricle (fig 3). Cardiac surgery at 11 years of age consisted of atrial and ventricular septal repair, pulmonary valvulotomy, and closure of the persistent ductus arteriosus. Cardiac failure was present for about one year after
surgery and required medical therapy. Neuroophthalmological evaluation supported a peripheral origin for the exophoria-tropia.

At the age of 14, he had a mental age of 8 (IQ 57). At 17 years of age, mild mental retardation, short stature, and infantile genitalia were observed.

**FAMILY DATA**

The father and mother, aged 36 and 25 years, respectively, at the proband's birth, were clinically and radiologically normal. It was not possible to assess consanguinity. One sister, born with low birthweight and distally bifid 3rd fingers, who died 6 days after birth with cardiopulmonary dysplasia, was considered to have had the same condition as the proband. Six other sibs, one female and five males, were normal. No relative as far as the fourth degree was found to have this syndrome or constitutional short stature.

**Discussion**

The association of mental retardation, short stature, delayed puberty, mesoaxial polydactyly with central synmetacarpalia, ocular torticollis, oral and facial dysmorphism, and the cardiac malformations present in the proband have not been previously reported. Although indirectly ascertained, the proband's deceased sister was also considered to have been affected, since she had mesoaxial hexadactyly (distally bifid 3rd fingers), which is a very rare malformation, as well as low birthweight and probable cardiac dysplasia as the cause of death. Differential diagnosis ruled out the cardiomelic dysplasias and the Ellis-van Creveld and Kaufman-McKusick syndromes.

The lack of exposure to teratogenic factors, the normal karyotype, the finding of the disease in two of eight children of both sexes, and the lack of phenotypic manifestations in the parents or relatives, strongly suggest autosomal recessive inheritance of this cardiomelic dysplasia.

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Prenatal diagnosis for adenosine deaminase deficiency

SUMMARY Amniocentesis was performed in two successive pregnancies of the mother of a child with adenosine deaminase (ADA) deficient severe combined immunodeficiency. Assay of ADA in amniotic fluid fibroblasts showed the pregnancies to be normal and homozygous deficient, respectively. These findings were confirmed by the demonstration of a normal level of erythrocyte ADA in the cord blood of the healthy male born of the first pregnancy and by the demonstration of undetectable ADA activity in cord erythrocytes, spleen, liver, and kidney of the abortus of the second pregnancy. Prenatal diagnosis of ADA deficiency appears to be a reliable procedure.

Deficiency of the purine catabolic pathway enzyme ADA represents the first inborn error of metabolism to be associated with an immunodeficiency disorder.1 The clinical significance of this association has been exploited in a number of ways. Where a family has had a child with severe combined immunodeficiency, the finding of ADA deficiency can be useful for genetic counselling, since it indicates an autosomal recessive mode of inheritance. Enzyme replacement appeared feasible since the enzyme is abundant in erythrocytes and successful correction has been achieved,2 3 though such success is not invariable.4 5 Intrauterine diagnosis is possible since ADA is widespread in tissues. Hirschhorn et al6 reported the diagnosis of this deficiency in a 28-week fetus. The pregnancy proceeded and the deficiency7 was confirmed at delivery. The purpose of this communication is to report that prenatal diagnosis has been performed successfully in two pregnancies of a woman who had previously born an ADA deficient child.

Case report

The case history, clinical and laboratory findings, and details of management of the proband have been reported elsewhere.6 Briefly, a first-born male was referred at 14 weeks with failure to thrive, recurrent bacterial infection, thrush, diarrhoea, and cough with respiratory distress. Tonsillar and peripheral lymphoid tissue were deficient. X-rays showed absent thymic shadow, interstitial pneumonitis, and skeletal findings suggestive of ADA deficiency. Immunological studies showed severe combined immuno-deficiency, ADA deficiency was shown in red blood cells and leucocytes, and the parents were found to be heterozygous deficient. A family study has been reported elsewhere.7 Therapy included gammaglobulin replacement, erythrocyte and plasma infusions, and fetal liver transplants, but was unsuccessful and the patient died at age 17 months of a parainfluenza pneumonitis. The mother of this child has since had two pregnancies and prenatal diagnosis was offered for both (see below). The first of these proceeded to term and produced a healthy infant. The second was terminated at 22 weeks’ gestation.

Methods

Amniotic fibroblast cultures were performed as described.8 Amniotic fluid was collected at 14 to 16 weeks’ gestation and set up in 25 cm² flasks (Falcon Plastics) in Ham’s F10 medium buffered with 25 mmol/l Hepes. For ADA assay, cells were lysed directly from the flask.

ADA assay on all tissues examined was determined by an isotopic method previously described in detail.9 Tissue homogenate or cell suspensions in 10 mmol/l

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