femur. An X linked spondyloepimetaphyseal dysplasia with mental retardation was described by Bieganski *et al.*² In our opinion, our patients do not share the clinical and radiological symptoms of this entity.

The association of a spondyloepimetaphyseal dysplasia and abnormal dentition has been described by Rao *et al.*³ However, the spondylar and epimetaphyseal abnormalities in that condition are much milder and the tubular bones of the hands are slender. Dental anomalies in the Goldblatt syndrome are associated with spondylar and metaphyseal abnormalities but not with such severe epiphyseal changes as seen here.⁴⁻⁵

The clinical and radiographic signs of the disorder described here are sufficiently characteristic to differentiate it from other rare spondylometaphyseal dysplasias including SMED, short limb-abnormal calcification type,⁶⁻⁸ spondyloepimetaphyseal dysplasia (SEMD) with eczema and hypogammaglobulinaemia,⁹ micromelic SMED,¹⁰ micromelic dwarfism, humerus, femur, tibia type,¹¹ SEMD Irapa type,¹² SEMD Shohat type,¹³ or SEMD caused by ATP sulphurylase kinase 2 deficiency.^{14,15}

In conclusion, the observation of two affected sibs confirms and expands the identity of a bone dysplasia which we propose to name anauxetic dysplasia on the basis of the extreme dwarfism resulting from a severe pre- and postnatal disturbance of skeletal growth and differentiation.

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Adducted thumb-club foot syndrome in sibs of a consanguineous Austrian family

EDITOR—An adducted thumb-club foot syndrome was originally reported by Dunder *et al.*¹ in 1997 (MIM 601776).² The patients presented with facial dysmorphism comprising a broad and bossed forehead, widely patent anterior fontanelle, telecanthus, downward slanting palpebral fissures, deep set ears, arachnodactyly, severely adducted thumbs, and club feet. Dunder *et al.*¹ discussed several known conditions featuring adducted thumbs, such as the Freeman-Sheldon syndrome (MIM 193700 and 277720), multiple pterygium syndrome (MIM 265000), congenital contractural arachnodactyly (MIM 121050), the Christian adducted thumb syndrome (201550), and the MASA syndrome/X linked hydrocephalus (MIM 307000). They considered the combination of adducted thumbs, club foot, arachnodactyly, and distinct facial dysmorphism present in their patients to constitute a "new" syndrome. The occurrence of this striking phenotype in male and female cousins, the offspring of consanguineous Turkish parents, indicated autosomal recessive inheritance to them. Very recently, two sibs of healthy Japanese parents with a previously unrecognised combination of distal

arthrogryposis with other congenital anomalies were reported by Sonoda and Kouno.³ The parents of these patients were first cousins once removed. However, although there are striking similarities between their patients, the authors did not refer to the report of Dunder *et al.*¹ We report two male sibs with the same condition, the product of a fourth cousin marriage of an Austrian family. We are tempted to identify the same dysmorphogenetic syndrome in all three families, thereby confirming the existence of a distinguishable syndrome. Autosomal recessive inheritance of the condition is suggested by parental consanguinity in the three kindreds.

Patient 1, a boy, was delivered at 32 weeks of gestation and died shortly after birth from respiratory failure. Birth weight was 1250 g (10th centile), body length was 40 cm (25th centile), and head circumference was 28.5 cm (25th centile). The infant had dysmorphic features including an anteriorly enlarged fontanelle, premature sagittal synostosis, brachycephaly, a low anterior hairline, a broad, bossed forehead, telecanthus, downward slanting palpebral fissures, prominent, deep set ears, and a short neck (fig 1). Clapsed fingers, adducted thumbs, and arachnodactyly as well as bilateral talipes equinovarus deformity, scoliosis, hirsutism, cryptorchidism, and a sacral skin tag were noted. There were no additional large joint contractures, dislocations, or skin webs. Postmortem radiographs showed scoliosis, thin ribs, and a thin, high diaphragm (fig 2A) as well as laterally ascending orbital roofs and premature sagittal

synostosis (fig 2B). Cranial ultrasound examinations showed minor degrees of third and lateral ventricular enlargement. Furthermore, necropsy identified a large secundum type atrial septal defect, mild coarctation of the aorta, a horseshoe kidney, and a common mesentery.

Patient 2 is the brother of patient 1. He was born at 38 weeks of gestation. Birth weight was 3070 g (25th centile), body length was 50 cm (50th centile), and head circumference was 35 cm (50th centile). He also had a wide open fontanelle, brachycephaly, a deep set anterior hairline, broad, bossed forehead, telecanthus, and downward slanting palpebral fissures. He had bluish sclerae, dysplastic, posteriorly rotated ears, a preauricular tag on the right side, short neck, arachnodactyly, adducted thumbs, bilateral

simian creases, narrow chest, umbilical hernia, cryptorchidism, and a bilateral talipes equinovarus deformity (fig 3). Generalised joint laxity was observed. There were no additional large joint contractures, dislocations, or skin webs. X rays of the chest and the skull showed thin ribs (fig 2E) and ocular hypertelorism (fig 2C). Ultrasound examinations identified ventricular asymmetry, absence of the left septum pellucidum (fig 2D), and a tethered cord. Ultrasound examinations of the heart and the kidneys were normal. While hearing tests were repeatedly normal, ophthalmological examination identified circumferential corneal pannus when last seen at the age of 12 months. Muscle tone was slightly decreased. Psychomotor development was not retarded. Routine laboratory screening including

Figure 1 Postmortem appearance of case 1 showing the general aspect, face, and hand of the preterm infant.

Figure 2 (A) Postpartum thoracoabdominal x ray of case 1. Note severe thoracolumbar scoliosis and thin ribs. (B) Skull x ray of case 1. Note marked sclerosis of the sagittal suture and laterally ascending orbital roofs. (C) Skull x ray of case 2 shows marked hypertelorism. (D) Coronal ultrasound scan showing moderately dilated lateral ventricles and absence of the left leaf of the septum pellucidum in case 2. (E) Chest x ray of case 2 aged 5 days: note thin ribs.

liver function tests and thyroid hormone estimation as well as metabolic screening gave normal results. Chromosome analysis showed a normal male karyotype in both sibs.

The striking similarities between the patients of Dundar *et al.*,¹ those reported by Sonoda and Kouno,³ and our cases, consisting of dysmorphic facial features, widely patent anterior fontanelle, brachycephaly, shortish neck, arachnodactyly, adducted thumbs, and bilateral talipes equinovarus deformity leads us to conclude that they all have the same syndrome. Moreover, the Turkish and Austrian patients had ventricular abnormalities, such as mild ventricular enlargement, ventricular asymmetry, or absence of the left septum pellucidum in one case. Interestingly, out of the six patients reported three had an atrial septal defect, two had bilateral hydronephrosis not further specified, and one had a horseshoe kidney, whereas the other three patients had no such organ involvement. Undescended testes were a common finding in the male patients in all families.

Some findings are suggestive of an underlying myopathic process in the Austrian and Turkish families. These include the reduced amplitude muscle action potentials with normal distal latency time and nerve conduction velocity in the 18 month old Turkish patient, and the underdeveloped diaphragm, severe scoliosis, and thin ribs in our first case, as well as thin ribs in our second case. Neurological investigation with special regard to tendon reflexes and muscle tone did not show significant abnormalities in our patient examined at the age of 12 months. Generalised joint laxity

observed in the Turkish and the Austrian patients indicates a connective tissue disorder in adducted thumb-club foot syndrome. This is emphasised by the presence of bilaterally dislocated hips in both and dislocated elbows in one of the Japanese patients, but no such comment was explicitly made by Sonoda and Kuono.³

Importantly, mental development is not significantly impaired in patients with the adducted thumb-club foot syndrome and psychomotor development in our surviving patient was found to be normal at the age of 12 months. This is in line with the findings in both Japanese patients. While global psychomotor developmental delay was evident in both Turkish patients, in the girl at the age of 3.5 and in the boy at the age of 1.5 years, follow up of the boy showed an IQ of 91 and 86 scoring points (Porteus test and Goodenough test, respectively) at 7 years 2 months of age (M Dundar, personal communication). However, further follow up of the patients is indicated since only one of the patients has been examined after the age of 2 years and two affected patients died in infancy, with a connection to the syndrome not conclusively being ruled out.

The differing cardiac and urogenital phenotypes as well as the severe scoliosis in the affected Austrian sibs might be explained by a pleiotropic effect of the disease gene or differences in the genetic and environmental background. This concept might be applied to other phenotypic differences between the Turkish, Japanese, and Austrian patients, notably the more severe degree of the distal arthrogryposis, the growth retardation, and the cleft palate

in the Japanese patients. Another noteworthy difference between the three pairs of patients reported by Dundar *et al*,¹ Sonoda and Kouno,³ and us is the presence of anterior synechiae associated with raised intraocular pressure in the Turkish patients and normal ophthalmological findings in the Japanese patients. However, close ophthalmological follow up showed otherwise unexplained circumferential corneal pannus in our patient at the age of 12 months.

To classify the phenotype of their patients, Dundar *et al*¹ discussed and excluded several known disease entities including Christian-type adducted thumb syndrome, Escobar syndrome, congenital contractural arachnodactyly (CCA), as well as unclassified published cases, some of which were connective tissue disorders or myopathies.^{1,2}

Though some of the facial dysmorphism as well as club foot are found in autosomal recessively inherited Escobar syndrome or the rare type of autosomal recessively inherited Freeman-Sheldon syndrome, these syndromes can be excluded in our case because of absence of major features like pterygia across the large joints or severe microstomia. The same holds true for CCA typically presenting with flexion contractures of all fingers. MASA syndrome/X linked hydrocephalus can be excluded in our case because of the lack of aqueductal stenosis and the presence of distinctive facial dysmorphism. Furthermore, Sonoda and Kouno³ reviewed the most important classifications of distal arthrogryposis when discussing their patients. They excluded the known types of distal

Figure 3 Appearance of case 2. (A-D) General aspect and face of the patient aged 3 months. (E) The patient aged 12 months.

arthrogryposis as well as otopalatodigital syndrome types I and II (MIM 311300 and 304120), Larsen syndrome (MIM 150250), frontometaphyseal dysplasia (MIM 305620), and Freeman-Sheldon syndrome, based either on the probable mode of inheritance in their family, the lack of mental retardation, deafness, or broad distal digits with short nails, and the distinctive facial appearance, finger/toe abnormalities, and radiographic findings in their patients.

Adducted thumbs and club foot as well as downward slanting palpebral fissures, telecanthus, and abnormal ear placement were reported in autosomal recessively inherited Christian-type adducted thumb syndrome.⁴ These features as well as hirsutism, craniosynostosis, and a fatal course of the disease in our first patient are shared in our cases. Therefore, a significant overlap of the adducted thumb syndrome and the adducted thumb-club foot syndrome exists. Most patients classified with this diagnosis, however, presented with additional non-specific findings, such as microcephaly, bifid uvula/cleft or highly arched palate, generalised severe muscular hypotonia, myopathic face, and impaired swallowing.^{4,5} Myopathic changes in a muscle biopsy were observed in a patient with Christian-type adducted thumb syndrome by Kunze *et al*⁶ and dysmyelination was observed in one of the patients originally reported by Christian *et al*.⁴ Information as to the aetiology of the disorder is not available in the other cases with that syndrome or in our patients. The existence of a distinctive adducted thumb-club foot syndrome is largely emphasised by the reports of this recognisable dysmorphic condition in three consanguineous families of different ethnic origin. Moreover, the disorder differs significantly from similar established disease entities by the absence of mental retardation and most likely autosomal recessive inheritance. On the other hand, some intra- and interfamilial variability of the syndrome is described.

Finally, our very recent review of published reports, the London Dysmorphology Database,⁶ and the POSSUM Database did not show up any other known syndrome equalling or approximately matching the adducted thumb-club foot syndrome proposed by Dundar *et al*¹ or the syndrome present in the patients reported by Sonoda and Kouno³ and considered to represent a new type of distal arthrogryposis. There were some similarities with the patients reported by Moore and Weaver,⁷ who presented with probably autosomal dominant inherited distal arthrogryposis and craniofacial abnormalities and who were considered to have a new subtype of type II arthrogryposis.

We conclude that adducted thumb-club foot syndrome most likely presents a distinct clinical entity. Parental consanguinity observed in our family as well as in the Turkish and Japanese families, strongly supports autosomal recessive inheritance of this syndrome, although we cannot exclude X linked inheritance or parental germline mosaicism, which has been shown in CCA.⁸ Genome scans in the families with the adducted thumb-club foot syndrome might enable the mapping of the disease causing gene that exerts pleiotropic effects at least in organogenesis and prenatal development.

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Diaphragmatic hernia, hydrocephalus, and cardiac malformations in four pregnancies of a non-consanguineous couple

EDITOR—Diaphragmatic hernia occurs with an incidence of 1/4000-1/5000 newborns.^{1,2} About half of the cases occur as isolated malformations; anomalies of the central nervous system are well known associated defects, as are midline malformations such as cleft lip and palate and heart defects.^{1,2} Among syndromic causes of diaphragmatic hernia are numerous chromosomal imbalances (4p deletion, trisomy 18, i(12p)), and some single gene defects such as the autosomal recessive Fryns syndrome³ and an X

linked form, the thoracoabdominal syndrome.^{4,5} Fryns syndrome is probably the most frequent non-chromosomal malformation syndrome associated with diaphragmatic hernia,^{3,6} but this disorder presents with typical dysmorphic features, and both heart and CNS malformations are infrequent in Fryns syndrome.

The family reported here, along with several other published reports, combining CNS, heart, and diaphragmatic defects, may help to delineate a distinct syndromic form of diaphragmatic hernia.

Healthy, non-consanguineous parents, of French origin and with unremarkable family histories, had six unsuccessful pregnancies. Two resulted in first trimester spontaneous abortion. The other four led to pregnancy terminations between 15 and 23 weeks' gestation because of malformations detected on ultrasound (table 1). Left diaphragmatic hernia was the earliest observed and most constant feature. Cardiac malformations, present in all cases, were of varying