Atelosteogenesis type 2

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Atelosteogenesis type 2 (AO2) (MIM 256050) is a neonatally lethal chondrodysplasia characterised by severe limb shortening and deficient ossification of parts of the skeleton. Other features include facial dysmorphism, cleft palate, talipes, and abducted thumbs and toes. Phenotypic overlap with non-lethal diastrophic dysplasia (DTD) suggested a common aetiology and it has recently been confirmed that both syndromes result from mutations in the DTDST (diastrophic dysplasia sulphate transporter) gene.

(\textit{J Med Genet} 1998;35:49–53)

Keywords: atelosteogenesis type 2; diastrophic dysplasia; DTDST gene

\textbf{History}

Atelosteogenesis is one of a group of rare neonatal osseous dysplasias characterised by incomplete bone formation. The first case was described by Kozlowski et al\textsuperscript{12} and the syndrome was named atelosteogenesis (Greek: atelés=imperfect; osteon-genesis=bone formation) by Maroteaux et al\textsuperscript{2} in 1982. The condition was subdivided by Silence et al\textsuperscript{2} into types 1 and 2 when in 1987 he reclassified four cases referred to as severe diastrophic dysplasia as atelosteogenesis type 2 and recognised that these cases had features in common with cases described by McAlister et al\textsuperscript{3} (McAlister dysplasia), Spranger and Maroteaux,\textsuperscript{4} and Salonen.\textsuperscript{4} This latter case was subsequently rediagnosed as atelosteogenesis type 1 by Whitley et al\textsuperscript{5}. These, together with cases previously known as de la Chapelle dysplasia (DLCD),\textsuperscript{4} have come to be known as AO2 following recognition that the clinical and histopathological features overlap.\textsuperscript{1} Silence et al\textsuperscript{1} made the observation that cases of atelosteogenesis were “diastrophic-like” but the severe histological changes in AO2 distinguished the two syndromes. Schrander-Strumpel et al\textsuperscript{6} discussed the phenotypic overlap further and suggested a common aetiology. In total, 11 cases of AO2 have been published and in this review we add a further case. The cases of Bruer and Brudner\textsuperscript{7} would also be classified as AO2.

The syndromes are characterised by hypoplasia of the femora and humeri distally and absence of ossification in, for example, the fibula, which may be absent. Similarity to mesomorphic dwarfism, particularly the ulna, fibula, and mandible types, has been noted.\textsuperscript{1} Atelosteogenesis type 1 (AO1) includes cases previously described as giant cell chondrodysplasia or spondylohumeral dysplasia\textsuperscript{8} and there is a suggestion of overlap with boomerang dysplasia.\textsuperscript{9} Atelosteogenesis type 3 was recently delineated by Stern et al\textsuperscript{10} with features in common with otopalatodigital syndrome (OPD).

\textbf{Clinical features}

Table 1 summarises the clinical and radiological features. AO2 may be suspected prenatally because of short limbs. At birth all cases are disproportionately short owing to rhizomelic short limbs, which are bowed. Length falls way below the 3rd centile with relative macrocephaly. The condition is invariably lethal with death occurring as a consequence of a combination of pulmonary hypoplasia and tracheobronchomalacia. Cases may have laryngeal anomalies. The chest is narrow and bell shaped and the abdomen protuberant. All have cleft palate. Facial dysmorphism consists of a flat, depressed nasal bridge, prominent epicantthic folds, midfacial hypoplasia, and micrognathia. All have radial deviation of the thumb, the so called “hitch-hiker thumb”, and a gap between the first and second toes. There is usually ulnar deviation of the fingers and talipes equinovarus. Dislocations of the elbows and knees have been reported. The spine is curved owing to spinal scoliosis, cervical kyphosis, and lumbar hyperlordosis.

\textbf{Radiological features}

The long bones show metaphyseal and epiphyseal abnormalities characterised by short tubular bones with metaphyseal flaring and minimal irregularity of the epiphyses. The humerus shows some of the most characteristic abnor-

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Radiological features</th>
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<tr>
<td>Polyhydramnios</td>
<td>Wide flared metaphysis</td>
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<tr>
<td>Low birth weight</td>
<td>U or V depression distal humerus</td>
</tr>
<tr>
<td>Relative macrocephaly</td>
<td>Bowed tibia/fibula/radius/ulna</td>
</tr>
<tr>
<td>Cleft palate</td>
<td>Short, round metacarpals and metatarsals</td>
</tr>
<tr>
<td>Epicanthic folds</td>
<td>Short, small phalanges</td>
</tr>
<tr>
<td>Micrognathia</td>
<td>Short ribs</td>
</tr>
<tr>
<td>Depressed nasal bridge</td>
<td>Thin clavicles</td>
</tr>
<tr>
<td>Short stature</td>
<td>Small scapulae</td>
</tr>
<tr>
<td>Rhizomelic limb shortening</td>
<td>Platyspondyly</td>
</tr>
<tr>
<td>Bowed limbs</td>
<td>Cervical kyphosis</td>
</tr>
<tr>
<td>Hitch-hiker thumbs</td>
<td>Hypoplastic ilia</td>
</tr>
<tr>
<td>Small chest</td>
<td>Flat acetabular roofs</td>
</tr>
<tr>
<td>Scoliosis</td>
<td>Unossified pubic rami</td>
</tr>
<tr>
<td>Laryngeal anomalies</td>
<td>Small sacroiliac notches</td>
</tr>
</tbody>
</table>
malities including severe underossification and a "club shape" with rounded proximal end and tapered distal end. Also characteristic is a U or V shaped depression of the distal humerus. There may be premature ossification of the proximal epiphysis. The femora have a "dumb bell" shape similar to the humerus (fig 1). The hands show absent ossification of the proximal phalanges and better ossification of the distal phalanges (fig 2A). There is preaxial deviation of the thumbs and the metacarpals tend to be short and round (fig 2A). In the foot the metatarsals are broad and short with small phalanges (fig 2B). There is wide separation of the first and second toes (fig 2B). Characteristically there is bowing of the radius and tibia; the ulna is short and bowed and the fibula may be poorly ossified (fig 2). All have platyspondyly (fig 1B) and have hypoplastic or dysplastic vertebrae. There may be incomplete ossification or hypoplasia of the upper thoracic vertebrae and coronal clefts of the lumbar and lower thoracic vertebrae. The sacrum is either angulated or underdeveloped. The ilia tend to be round and hypoplastic with flaring of the iliac wings (fig 1A). All cases have flat acetabular roofs and small sacroiliac notches. The pubic rami are often incomplete (fig 1A) or unossified with additional ossification centres. The clavicles are thin and the ribs thin and short (fig 1A). The scapulae are short and the glenoid fossae small and shallow. The skull shows no abnormalities.

**Histology**

The primary abnormalities are radiating threads of fibrous material in the cartilage matrix giving a Swiss cheese appearance of acellular areas interspersed with areas of normal cellularity. Lacunar haloes consisting of concentric rings around the chondrocytes are characteristic in the resting zone. There may be large multinucleated "giant cells" in acellular areas, hence the name giant cell chondrodysplasia, but these are not pathognomonic for this condition. Secondary abnormalities consist of focal areas of hypocellularity and matrix degeneration in the resting zone, extending into the growth plate with disruption of column formation. The growth plate has a narrow proliferative zone and a wide, irregular hypertrophic zone showing irregular vascular invasion and fibrosis replacing hypertrophic and columnar zones. Other abnormalities include abnormal persistence of cartilage in the metaphysis. These abnormalities are seen in the cartilage of long bones, trachea, bronchi, and larynx.

The histology further distinguishes AO2 from AO1 in which the reserve zone cartilage is essentially normal but rather hypocellular with occasional giant cells.

Diastrophic dysplasia (DTD) shows similar histological changes to AO2 with cystic areas in the resting cartilage owing to irregular myxoid degeneration and also haloes around chondrocytes and occasional multinucleated cells. These abnormalities are found in the same

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**Figure 1** X rays of a baby boy with AO2 delivered by caesarian section for fetal distress. A single dating scan had been carried out at 13 weeks. Small size before delivery was thought to be the result of growth retardation, so labour was induced 12 days post-term. The baby lived for 45 minutes. (A) AP view showing short long bones, short ribs, curved spine, spinal scoliosis, round ilia with flat acetabular roofs, and incomplete pubic rami. (B) Lateral view showing platyspondyly, horizontal sacrum, and dumb bell shape of femora.
cartilage as in AO2, that is, trachea, vertebrae, and long bones. However, the growth plate has normal hypertrophic and proliferative zones and a normal columnar zone.

**Differential diagnosis**

The diagnosis of AO2 may be suggested radiologically but AO2 needs to be distinguished from other lethal dwarfing conditions. The lethal short rib polydactyly syndromes which also have short limbs, narrow thorax, and protruberant abdomen, for example, SRPDS type 2 Majewski,

![Figure 2](http://jmg.bmj.com/)

*Figure 2* The same child as in fig 1. (A) Right lower arm showing bowed ulna and radius, abducted “hitch-hiker” thumb, “semilunar” metacarpals, hypoplastic proximal phalanges, and relatively normal terminal phalanges. (B) Left foot showing curved tibia and short hypoplastic fibula, abducted hallux, and wide space between first and second toes.

Achondrogenesis type 1 (AO1) is distinguished from AO2 by better development of the distal humeri and femora and better ossification in vertebral bodies and pubic bones. Hitch-hiker thumbs and toes are not a feature of AO1 in which cleft palate is rare. AO1 has coronal clefts of the vertebrae and AO2 less marked vertebral anomalies. In AO2 the femora and humeri have a dumbbell shape with bifid distal ends. The fibula is usually hypoplastic whereas in AO1 it is often absent.

AO2 and DTD show greatest similarity; both have short limbs and mid thoracic spinal abnormalities, talipes equinovarus, abducted thumbs and big toes, and cleft palate. In many respects, clinically AO2 might be seen as a more severe variant of DTD. One major difference is that although Gustavson *et al.*

described lethal and non-lethal forms of diastrophic dysplasia, no survivors have been described with atelosteogenesis. Other differences include a normal trunk in DTD and cystic swelling of the ears. Radiologically both show major abnormalities in the femora and humeri. The skull is normal in both. Radiological differences include normal tubular bones in DTD apart from the long bones. As mentioned above, AO2 and DTD share the same histopathology and the diagnosis can rarely be certain until this has been analysed.

Achondrogenesis is the most severe form of chondrodysplasia. Limb shortening is extreme. Achondrogenesis type 1B (ACG1B) shows histological similarity to AO2 and DTD although it is phenotypically distinct. AO2, ACG1B, and DTD are now known to represent the spectrum of chondrodysplasias caused by mutations in the DTDST gene (see below).

A comparison of the clinical and radiological features of AO2, ACG1B, and DTD is shown in table 2.

**Aetiology and genetics**

Of 14 cases of AO2 described to date, five have been isolated. Evidence for probable recessive inheritance comes from three sets of sibs, of which one set of three sibs was born to con-
Table 2: Comparison of clinical and radiological features in ACG1B, AO2, and diastrophic dysplasia

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>ACG1B</th>
<th>AO2</th>
<th>DTD</th>
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<tr>
<td>Neonatal death</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Short limbs</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cleft palate</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hitch-hiker thumbs</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Gap toes I and II</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Radiological features</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Plastypondyly</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Rounded iliac bones</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Horizontal acetabula</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Distal femoral hypoplasia</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Distal ulnar hypoplasia</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>First metacarpal hypoplasia</td>
<td>+</td>
<td>+</td>
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sanguineous parents. Cases consist of equal numbers of males and females.

Defective sulphate transport and defective sulphation of proteoglycans have been shown in fibroblast cultures from patients with AO2, DTD, and ACG1B. Proteoglycan undersulphonation has a marked effect on the composition of the extracellular matrix of cartilage. The diastrophic dysplasia sulphate transporter gene (DTDST) has been identified by positional cloning.6 Following localization of DTD to chromosome 5q,26 the gene encodes a ubiquitously expressed sulphate transporter (DTDST). Mutations in DTDST have been identified in patients with DTD and ACG1B27 and in 1996 Hasbacka et al28 reported mutations in the DTDST gene in three patients with AO2. Evidence suggests that mutations in DTDST cause reduced DTDST expression in ACG1B, AO2, and DTD. The variable phenotype reflects the amount of residual activity of the sulphate transporter.29 ACG1B is produced by homozygosity or compound heterozygosity and appears to be the null phenotype. Mutations in both alleles occur invariably in the coding region leading to an early stop codon. In AO2 mutations occur in the coding region but may be frameshift or missense, causing partial loss of function. In DTD one mutation may be in the coding region but never both, the other mutation occurring in the extracellular loops or cytoplasmic tail, that is, AO2 and DTD may result from compound heterozygosity with a presumed reduced expression allele. Expression studies show low levels but not zero DTDST mRNA.29 An elegant diagram illustrating the sites of the various mutations is provided by Superti-Furga.30

In conclusion, the same mutation in DTDST may cause a different phenotype depending on the mutation on the other chromosome. Other factors also appear to be relevant since sibs with identical genotype (homozygous for the common Finnish ancestral mutation) have variable phenotypes, suggesting a role of modifier genes or epigenetic factors. Atelosteogenesis type 2, achondrogenesis type 1B, and diastrophic dysplasia appear to represent a phenotypic spectrum caused by mutations in the DTDST gene.

Prenatal diagnosis

Ultrasound may be useful in detecting AO2, as illustrated by Nores et al,31 who successfully diagnosed atelosteogenesis by ultrasound in a 21 week fetus with short limbs, coronal clefs, characteristic shaped humeri, abducted thumbs and toes, and talipes equinovarus. A second affected fetus was detected at 15 weeks. Usually, however, establishing the diagnosis in a case of short limb dwarfism requires detailed radiological assessment and histological confirmation and, in AO2, biochemical diagnosis based on defective sulphate transport in fibroblast cultures.

Identification of mutations in DTDST means that it is now possible to carry out DNA based prenatal diagnosis for AO2, DTD, and ACG1B. This reinforces the importance of obtaining DNA samples from all cases of lethal short limb dwarfism. Superti-Furga (personal communication) recently successfully undertook prenatal diagnosis for AO2 by DNA analysis of amniocytes at 15 weeks.

The author would like to thank Professor Ian Young and Dr Andrea Superti-Furga for their helpful comments.

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