

Atelosteogenesis I

Authors: Professor David Sillence¹ and Professor Kazimierz Kozlowski

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¹Academic Department of Medical Genetics, The Children's Hospital at Westmead, Westmead 2145, AUSTRALIA. DavidS@chw.edu.au

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Abstract

Atelosteogenesis I (AOI, incomplete formation of bone) is a perinatally lethal short-limb newborn skeletal dysplasia with distinctive faces and diagnostic radiographic appearances. The patients are stillborn or die soon after birth. Prenatal sonography can detect bone dysplasia. An exact diagnosis can be established postnatally from skeletal radiographs and chondro-osseous histopathology. There is a continuum in radiographic findings between Atelosteogenesis I and Boomerang dysplasia and the two disorders are nosologically grouped. Atelosteogenesis I/Boomerang Dysplasia results from heterozygous mutations in the gene encoding filamin B (FLNB). All cases of this autosomal dominantly inherited disorder have been sporadic presumably resulting from a de novo mutation in FLNB. This is a very infrequently described disorder.

Keywords

Atelosteogenesis – Spondylo-humero-femoral dysplasia - Boomerang dysplasia - Atelosteogenesis I/Boomerang Dysplasia - disharmonious phalangeal maturation - FLNB gene – giant cell chondrodysplasia

Disease name/synonyms

Atelosteogenesis I/Boomerang Dysplasia

Spondylo-humero-femoral dysplasia

Giant Cell Chondrodysplasia

Differential diagnosis

[Boomerang dysplasia](#) with boomerang shaped humeri and femora is thought to be

pathogenetically related with a more severe expression of skeletal anomalies. There is a wide range of humeral and femoral bone shapes including round, oval, and triangular humeral shapes suggesting a continuum of disorders.

[Atelosteogenesis III](#) with less dysmorphic facial features and well ossified but disharmonious short tubular bones is also thought to be pathogenetically related to AOI/Boomerang.

Oto-Palato-Digital Dysplasia type II also has similar pattern of clinical and skeletal anomalies but shows X-linked dominant inheritance and is due to mutations in the gene encoding filamin A (*FLNA*).

Atelosteogenesis type II (AOII) has similar humeral and femoral bone shapes but has distinctive and diagnostic chondro-osseous histopathology. AOII results from mutations in the Diastrophic dysplasia sulfate transporter (*DTDST*).

Piepkorn dysplasia shows a similar pattern of anomalies, but ossification of all bones is more decreased, and the configuration of arms and legs is stated to be flipper-like. The cause is unknown.

Etiology

Inheritance is due to heterozygous autosomal dominant mutations. All cases have been sporadic although sibling recurrence due to germinal cell mosaicism can possibly occur. The majority of cases of Boomerang dysplasia are 46XY phenotypic males whereas the sex ratio in Atelosteogenesis I cases is normal.

Clinical description

Shortening of the trunk and rhizomelic shortening of the extremities, dysmorphic face, short broad hands and talipes equinovarus are the major clinical abnormalities. The distinctive face is broad with prominent forehead, hypertelorism, saddle nose with bilateral grooves at the nasal tip and micrognathia. Non-skeletal malformations include cleft palate and undescended testes. Skeletal survey shows short, distally tapering humeri and femora. Alternatively humeri or femora may be absent or show one of a large number of unusual geometrical shapes e.g. spherical, segment or shark's tooth shapes. There may be bowing of the remaining long bones, absent fibulae, moderate platyspondyly with coronal cleft vertebrae and discordant ossification of the short tubular bones, specifically discordant ossification of distal phalanges with delay in ossification of middle and proximal phalanges.

Diagnostic methods

Both anteroposterior (AP) and lateral radiographs of the fetal spine are valuable. Specific views of hands and upper and lower limbs permit definitive characterization of each entity in the AOI/Boomerang spectrum of disorders. Disharmonious maturation of the tubular bones of the hands is an important diagnostic feature. Perinatal pathologic examination is mandatory as the pattern of chondro-osseous pathology permits definitive distinction between AOI/Boomerang, Atelosteogenesis II, Otopalatodigital syndrome,

Piepkorn dysplasia, and presently unclassifiable disorders with overlapping phenotype.

Epidemiology

About a dozen cases have been reported from various populations.

Genetic counseling

A recurrence risk should be given which recognises that the disorders in this group are sporadic but germinal cell mosaicism is possible with a (presumed) recurrence risk of about 5%.

Prenatal diagnosis

Prenatal sonography has a high likelihood of detecting bone dysplasia. An exact diagnosis can be made postnatally by the observation of the humeral/femoral tapering and discordant ossification of short tubular bones.

Management including treatment

These disorders are perinatally lethal and long term respiratory support is unlikely to lead to independent survival.

Unresolved questions

The overlap in phenotypes between Atelosteogenesis I and Boomerang dysplasia suggested that these two disorders are pathogenetically related, and result from mutations at the same gene locus. Heterozygous *FLNB* mutations have been reported in AOI. In both AOI and Boomerang dysplasia, chondro-osseous histopathology shows dysplastic reserve zone cartilage with giant multinucleated chondrocytes. Atelosteogenesis III is very rare but there are sufficient phenotypic similarities to suggest that AO III represents an allelic disorder with mild phenotypic expression. This is to be confirmed by the finding of heterozygous *FLNB* mutations in AO III.

References

- Krakow D**, Robertson SP, King LM, Morgan T, Sebald ET, Bertolotto C, Wachsmann-Hogiu S, Acuna D, Shapiro SS, Takafuta T, Aftimos S, Kim CA, and 13 others. Mutations in the gene encoding filamin B disrupt vertebral segmentation, joint formation and skeletogenesis. *Nature Genetics* 2004;36:405-410.
- Sillence D**, Kozlowski K, Rogers J, Sprague P, Cullity G, Osborn R. Atelosteogenesis: evidence for heterogeneity. *Pediatric Radiology* 1987;17:112-118.
- Sillence DO**, Worthington S, Dixon J, Osborn R, Kozlowski K. Atelosteogenesis syndromes. A review with comment on their pathogenesis. *Pediatric Radiology* 1997;27:388-39.