Achondrogenesis

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Abstract

Achondrogenesis is a lethal disorder characterized by deficient endochondral ossification, abdomen with disproportionately large cranium, and anasarca. Radiological features are characteristic, with virtual absence of ossification of the vertebral column, sacrum and pelvic bones. There are 2 types of achondrogenesis, and differentiation between those types is possible through clinical and radiological and histological studies. Type I achondrogenesis is of autosomal recessive inheritance with the subtype IB caused by mutations in the diastrophic dysplasia sulfate transporter DTDST gene, and type II achondrogenesis caused by de novo dominant mutations in the collagen type II-1 COL2A1 gene.

Keywords

endochondral ossification deficiency, lethal disorder, anasarca, absence of ossification in vertebral column, DTDST gene, COL2A1 gene

Disease name and synonyms

According to the current classification, there are 2 types of achondrogenesis:

**Achondrogenesis type I:**
IA: achondrogenesis Houston-Harris type
IB: achondrogenesis Fraccaro type

**Achondrogenesis type II:**
achondrogenesis Langer-Saldino type
chondrogenesis imperfecta

Prevalence

It remains unknown.

Diagnosis criteria / Definition

Association of:
- short-limbed dwarfism with short trunk, prominent abdomen with anasarca, and disproportionately large cranium;
- virtual absence of ossification of the vertebral column, sacrum and pelvic bones at radiological examination;
- lethal condition with death *in utero* or during the early neonatal period
- new dominant mutations within the collagen type 2 alpha1 gene COL2A1 in type II achondrogenesis, and autosomal recessive inheritance in type I achondrogenesis with...
mutations in the diastrophic dysplasia sulfate transporter gene \textit{DTDST} in type IB achondrogenesis.

**Clinical description**

Achondrogenesis is characterized by:
- short-limbed dwarfism with short trunk, narrow thorax, prominent abdomen, and disproportionately large cranium;
- limbs sometimes resemble flippers, and an articular crease at the hip or shoulder can be present;
- anasarca or fat appearance is given by the abundance of soft tissue relative to the short skeleton;
- characteristic craniofacial features include prominent forehead, flat face, short nose with anteverted nostrils, long philtrum, micrognathia, short neck;
- inconsistent clinical features include heart defects, umbilical or inguinal hernias, polydactyly in type II achondrogenesis.

**Differential diagnosis**

The main problem in establishing the diagnosis is to differentiate the type of achondrogenesis. Different features are helpful to accurately diagnose the type:
- the mode of inheritance;
- clinical features: the distinction between the different types of achondrogenesis is difficult on clinical grounds. Hands are almost normal in type II, whereas in types IA and IB, they are obviously shortened. Other minor criteria can be mentioned: compared to type I, type II achondrogenesis is characterized by fewer stillbirths, longer survival, longer gestational period, larger size of baby, longer limbs;
- X-ray features: ribs tend to be thin in type IA achondrogenesis, with multiple fractures;
- histological features: round, vacuolated chondrocytes with inclusion bodies in type IA achondrogenesis, collagenous rings around the chondrocytes in type IB achondrogenesis, with the characteristic image of sulfate incorporation into cultured fibroblasts or chondrocytes. In type II achondrogenesis, cartilage in all sites has an abnormal gelatinous texture and translucent appearance, with no detection of collagen type II.
- Molecular studies
  - The differential diagnosis includes other types of lethal osteochondrodysplasia, mainly lethal osteogenesis imperfecta, thanatophoric dysplasia and the short rib-polydactyly syndromes. In osteogenesis imperfecta, the skull is soft, the sclerae blue and the bones bowed but clearly not as short as in achondrogenesis.

In thanatophoric dysplasia, the limbs are longer, and the shape of the thorax is narrow but elongated. The short rib-polydactyly syndromes resembles thanatophoric dysplasia and are usually associated with hexadactyly.

**Diagnostic methods**

Diagnosis depends upon the clinical and the pathognomonic radiographic findings. Histological findings can be helpful, with the study of sulfate incorporation into cultured fibroblasts or chondrocytes for type IB. Molecular studies of \textit{COL2A1} or \textit{DTDST} can be performed depending on the subtype of achondrogenesis. X-ray findings include:
- the tubular bones are the most markedly affected, and are much shorter in type I than type II. Femurs and humeri are usually shortened to a degree where no major axis can be recognized. As some metaphyseal spurring occurs, these bones end up resembling thorn apples. The tibiae and fibulas are similarly misshapen, and the fibulas are not ossified in subjects with very early manifestations. In most cases, the ulna is amorphous. The carpals and phalanges are usually very poorly ossified and can rarely be identified;
- the iliac bones are smaller than usual and only their upper half is ossified in type I, often in an irregular fashion. The ischium is not ossified or only minimally;
- disproportion between the skull of almost normal size and the hypoplastic skeleton is noticeable. The skull can be slightly less ossified than expected for gestational age;
- the vertebral bodies are usually not ossified, at most, rudimentary calcification is seen in the central part. The vertebral lateral pedicles are generally ossified. Ribs are short.

**Etiology**

- Type II achondrogenesis is caused by a dominant mutation in the \textit{COL2A1} gene. Collagen II is also called cartilage collagen. Various types of chondrodysplasia are allelic, including spondyloepiphyseal dysplasia congenital type, Strudwick type and Namquandal type; osteoarthritis with mild chondrodysplasia; spondyloepiphyseal dysplasia with precocious osteoarthritis; Stickler syndrome; Kniest dysplasia; Wagner’s syndrome, and hypochondrogenesis.
- Type IB achondrogenesis is caused by recessive mutations in the \textit{DTDST} gene, which encodes the diastrophic dysplasia sulfate transporter.
Genetic counseling
Since type II achondrogenesis is caused by de novo dominant mutation, the risk of having another affected child is low for a couple who had a first affected child because of the low risk of gonadal mosaicism. Because type I achondrogenesis is an autosomal recessive disorder, the risk of having another affected child is 25% for a couple who had a first child with this condition. Genetic counseling must rely on differentiation between type I and type II achondrogenesis.

Antenatal diagnosis
A recurrence of the disease can be suspected by the observation of short femora as early as gestational week 13 to 14 by experienced sonographers if a first child was born with Achondrogenesis. Other ultrasound signs may be nuchal oedema, reduced rump length, poor ossification of the vertebral bodies and of the limb bones, and polyhydramnios. Chorionic villi sampling can be proposed in early pregnancies if a mutation in DTDST have been found. Molecular prenatal diagnosis is not indicated in type II achondrogenesis because of the very low recurrence risk and the early ultrasound prenatal diagnosis. Analysis of sulfate incorporation in chorionic villi might theoretically be used for prenatal diagnosis but experience is lacking.

Management including treatment
No treatment can be proposed for this lethal disorder.

Unresolved questions
The gene responsible for type IA achondrogenesis has not been identified yet.

References


