

Acromesomelic dysplasia Hunter-Thompson type

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Abstract

Acromesomelic dysplasia Hunter-Thompson type (AMDH) is a very rare autosomal recessive disorder belonging to the group of acromesomelic dysplasias. AMDH is characterized :

1) *clinically by severe dwarfism with abnormalities limited to the limbs. The middle and distal segments are the most affected, the lower limbs are more affected than the upper limbs, and dislocation of the large joints frequently occurs.*

2) *radiologically by missing or fused skeletal elements within the hands and feet while axial skeleton is normal. The facial appearance and intelligence are normal, and there are no vertebral abnormalities. The AMDH gene is identified as cartilage-derived morphogenetic protein-1 (CDMP-1) on human chromosome 20q11.2.*

The same gene is responsible for autosomal recessive acromesomelic dysplasia Grebe type, autosomal recessive DuPan syndrome and autosomal dominant brachydactyly type C.

Keywords

dwarfism, AMDH gene, CDMP-1 protein, 20q11.2 locus

Disease name and synonyms

- Acromesomelic dysplasia, Hunter-Thompson type (AMDH)
- Acromesomelic dwarfism, Hunter-Thompson type

Frequency

The prevalence is unknown. This type of acromesomelic dysplasia seems to occur more rarely than the other types of autosomal

recessive acromesomelic dysplasias. Less than 10 cases have been reported in the literature to date.

Diagnosis criteria / Definition

Association of:

- Severe dwarfism with abnormalities limited to the limbs. The middle and distal segments are the most affected, the lower limbs are more affected than the upper limbs, and dislocation of the large joints is

frequently observed at clinical examination.

- Missing or fused skeletal elements within the hands and feet while axial skeleton is normal at radiological examination
- Autosomal recessive inheritance

Clinical description

AMDH is characterized by:

- Dwarfism present at birth
- Adult height is about 120 cm. The trunk is normally proportioned. The upper and lower limbs are markedly shortened with the middle and distal segments more affected than the proximal segments. Movement of all the large joints are limited with frequent dislocations. The patients sometimes walk on their knees.
- Fingers are generally short and of unequal length, but are generally symmetric between both hands. Thumbs are generally very short. Feet are very short and often everted, with some of the toes being ball-shaped and functionless.
- The facial appearance is normal with normal head circumference, and intelligence is normal.

Diagnostic methods

Diagnosis can be easily made by the combination of characteristic clinical and radiographic findings.

X-ray features show that the radii and ulnae are short compared to the humeri, and the ulnae are relatively shorter than the radii. The radial heads can be dislocated. Metacarpals are short, with the first being shorter than the others. The distal phalanges are normal in all fingers, but the proximal and middle phalanges are short or absent. The large joints are dislocated.

Mutations analysis of the *CDMP-1* gene can confirm the clinical and radiological diagnosis.

Differential diagnosis

The main differential diagnosis is [acromesomelic dysplasia Grebe type](#) (AMDG) in which dwarfism and hypomelia are more severe but proportionate between upper and lower limbs, all fingers and toes are ball-shaped, and joint dislocations occur less frequently. It is worth noting that progress in molecular genetics showed that both entities were allelic for the same gene.

Similarly, AMDH is different from acromesomelic [dysplasia Maroteaux type](#) in which hands and feet involvement was less important with axial skeleton abnormalities.

Etiology

In 1996, the gene for AMDH was identified as being cartilage-derived morphogenetic protein-1

(*CDMP-1*) on human chromosome 20q11.2 by a candidate gene approach. Indeed, there were phenotypic similarities with murine brachypodism where mutations in growth/differentiation factor-5 are known, the mouse homologue of human *CDMP-1*. Only one family was studied and affected individuals are homozygous for a 22-bp tandem duplication frameshift mutation in the mature region of *CDMP-1*. It is the same gene but different mutations found in autosomal recessive Acromesomelic dysplasia Grebe type, autosomal recessive DuPan syndrome (fibular hypoplasia and complex brachydactyly) and autosomal dominant brachydactyly type C. *CDMP-1* is derived from the superfamily of the TGF- β , which comprises a number of functionally diverse growth-factors/signaling molecules and elicit their response upon binding to serine-threonine kinase receptors. *CDMP-1* is closely related to the sub-family of bone morphogenetic proteins, and is predominantly expressed at sites of skeletal morphogenesis. By studying the phenotypic features of patients with mutations in *CDMP-1*, authors conclude that this gene is involved in determining the shape and size of the digits and joint dysplasia, but that the development of the craniofacial and axial skeleton is influenced by other factors.

Genetic counseling

AMDH is a disorder of autosomal recessive inheritance. A couple who had a first child with AMDH has a 25% risk of transmitting the disease. Genetic counseling for other members of the family is reassuring taking into account the low frequency of the disease, unless the couple is consanguineous. Similarly, an affected person does not run the risk of transmitting the disease to a child, unless he is mating with a blood relative. Heterozygous carriers do not show any mild features of the disease.

Antenatal diagnosis

Early antenatal molecular diagnosis can be performed in a couple with a first child with AMDH if the familial mutation is identified. Recurrence of the disease can be also suspected by the observation of intrauterine growth retardation and short limbs during pregnancy.

Management including treatment

The reported patients are described as independent and well accepted. Arthrodesis is often necessary because of joint dislocation.

Unresolved questions

As only a few cases with AMDH and AMDG have been molecularly studied, it is not clear whether these two diseases are allelic or due to

variable expression of the same entity. In the report of Langer in 1989, some affected members of the family resemble more to the description of Hunter and Thompson, while others resemble more to the description of Grebe. Furthermore, it is not known whether there is allelic heterogeneity in the *CDMP-1* gene in patients with AMDH.

References

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