Acromesomelic dysplasia Grebe type

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Abstract
Acromesomelic dysplasia Grebe type (AMDG) is a rare autosomal recessive disorder belonging to the group of osteochondro-dysplasias. AMDG is characterized 1) clinically, by severe dwarfism with marked micromelia and deformation of upper and lower limbs, with a proximo-distal gradient of severity, and 2) radiologically, by short and deformed middle long bones, fusion of carpal and tarsal bones, absence of proximal and middle phalanges and several metacarpal and metatarsal bones. The facial appearance and intelligence are normal, and there are no vertebral abnormalities. The gene responsible for AMDG has been identified, it encodes cartilage-derived morphogenetic protein-1 (CDMP-1) and is located on human chromosome 20q11.2. The same gene is responsible for autosomal recessive acromesomelic dysplasia Hunter-Thompson type, autosomal recessive DuPan syndrome and autosomal dominant brachydactyly type C. Heterozygous carriers of the disease can manifest clinical features of the extremities.

Keywords
osteochondro-dysplasia, autosomal recessive inheritance, dwarfism, micromelia, 20q11.2 locus, AMDG gene

Disease name and synonyms
- Acromesomelic dysplasia, Grebe type (AMDG)
- Chondrodysplasia Grebe type
- Grebe dysplasia

Prevalence
The general frequency of the disease is unknown. There is a high frequency of AMDG in Brazil, with a gene frequency of 1/50 and a prevalence of affected individuals of 1/2000 live births.

Diagnosis criteria/Definition
Association of:
- severe dwarfism with marked micromelia and deformation of upper and lower limbs, with a proximo-distal gradient of severity at physical examination;
- short and deformed middle long bones, fusion of carpal bones and several
metacarpal and metatarsal bones, absence of proximal and middle phalanges at radiological examination;
- autosomal recessive inheritance.

Clinical description
AMDG is characterized by:
- dwarfism present at birth;
- adult height below 100 cm. While the axial skeleton is normal, there is severe micromelia with increasing severity in a proximo-distal gradient. In the upper limbs, the proximal segment is short, and the middle segment is even shorter and bowed. In the lower limbs, the proximal segment is short and the middle one is relatively shorter, with bulky muscles. Movement of the elbows, wrists, knees, ankles and fingers is limited, while movement of shoulders and ankles is normal;
- there are very severe abnormalities of hands and feet, with digits reduced to globular appendages which appear to be joined to the hand by a bridge of soft tissue, without apparent articulation of the metacarpophalangeal joints. There is no apparent development of the thumb and frequent hexadactyly. There is no apparent articulation of the toes with the foot, and no movement of the toes;
- the facial appearance is normal, with normal head circumference, and intelligence is normal.

Diagnostic methods
- Diagnosis can be made easily based on the characteristic clinical and radiographic findings.
- X-ray features include relatively normal but short humeri and femors, short and deformed radii-ulnas and tibia-fibulas, fusion of carpal and tarsal bones, absence of several metacarpal and metatarsal bones, absence of proximal and middle phalanges of fingers and toes while the distal phalanges are present. Postaxial polydactyly is found in several individuals. Several joints of the carpus, tarsus, hand and foot are absent.
- Mutations analysis of the CDMP-1 (cartilage-derived morphogenetic protein-1) gene can confirm the clinical and radiological diagnosis.

Differential diagnosis
The main differential diagnosis is acromesomelic dysplasia Hunter-Thompson type (AMDH) in which limb abnormalities are more marked in the lower limbs than the upper limbs and in which multiple dislocations of the large joints are common. Interestingly, progress in molecular genetics showed that these entities are allelic for the same gene. Similarly, AMDG is different from acromesomelic dysplasia Maroteaux type in which hands and feet involvement is less severe but axial skeletal abnormalities are found.

Etiology
In 1997, the gene responsible for AMDG was identified by a candidate gene approach; it encodes cartilage-derived morphogenetic protein-1 (CDMP-1) and is located on human chromosome 20q11.2. This is the same gene as that responsible for AMDH, but the mutations differ. CDMP-1 belongs to the transforming growth factor TGF-β superfamily, which comprises a number of functionally diverse growth-factors/signaling molecules, and elicits their response upon binding to serine-threonine kinase receptors. CDMP-1 is closely related to the subfamily of bone morphogenetic proteins (BMP), and is predominantly expressed at sites of skeletal morphogenesis. By studying the phenotypic features of patients with mutations in CDMP-1, the authors concluded 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. Pertinently, some heterozygous carriers present a variety of mild skeletal abnormalities of the extremities. CDMP-1 gene has been demonstrated to also be responsible for autosomal dominant brachydactyly type C.

Genetic counseling
AMDG is a disorder of autosomal recessive inheritance. The risk of having another affected child is 25% for a couple who had a first child with AMDG. Genetic counseling for other members of the family can be reassuring in light of the low frequency of the disease, unless the couple is consanguineous. Similarly, an affected individual does not run the risk of having an affected child, unless his/her partner is a blood relative. Heterozygous carriers are of average stature, but can have some mild clinical features in their hands and feet including: brachydactyly, postaxial polydactyly, delayed bone age, metatarsus adductus, valgus deviation of toes, and/or flexion contractures of fingers. Premature vertebral hand-plate disease (spondyloysis, spondyloolisthesis) has also been observed.

Antenatal diagnosis
Early molecular antenatal diagnosis can be performed for a couple who has had a first child with AMDG if the familial mutation has been
identified. Another child with the disease can also be suspected based on the ultrasonographic observation of intrauterine growth retardation and short limbs during pregnancy.

Management including treatment
The death rate of children affected with the disease is high in Brazil, accounting for 11% stillbirths and 38% infant mortality. Most of the living patients are fully independent and described as productive members of their community. They had adapted surprisingly well to the hand malformations by handling objects between their thumbs. One woman was a proficient house keeper and could even crochet. Her brother repaired small appliances. All were ambulatory, and one young boy even played soccer.

References