

Research Journal of Pharmaceutical, Biological and Chemical Sciences

A Case Report of Antenatal Diagnosis of Achondrogenesis Type I.

Ramya Shree TR *, and Saraswathi K.

Department of Obstetrics and Gynecology, Sree Balaji Medical College and Hospital, Chrompet, Chennai-14, Tamil Nadu, India.

ABSTRACT

Achondrogenesis is a lethal form of congenital dystrophy characterised by mixromelia. We reported a case of achondrogenesis type I, detected by prenatal ultrasonography at 20 weeks gestation. A dwarfed fetus with large head, short neck and chest and short limbs was terminated trans-vaginally. Radiologic examination revealed features of achondrogenesis type I. Though the case had no known risk factor and the phenotypic abnormality was mild, modern development in prenatal screening made the early detection possible.

Keywords: Achondrogenesis, Skeletal dysplasia, Type 1a and 1b achondrogenesis, Prenatal diagnosis.

**Corresponding author*

INTRODUCTION

Marco Fraccaro first described achondrogenesis in 1952 [1]. He used the term to describe a stillborn female with severe micromelia and marked histological cartilage changes. The term was later used to characterize the most severe forms of chondrodysplasia in humans, which were invariably lethal before or shortly after birth. By the 1970s, researchers concluded that achondrogenesis was a heterogeneous group of chondrodysplasias lethal to neonates; achondrogenesis type I (Fraccaro-Houston-Harris type) and type II (Langer-Saldino type) were distinguished on the basis of radiological and histological criteria. In 1983, a new radiological classification of achondrogenesis (types I-IV) by Whitley and Gorlin was adopted in the McKusick catalog [2]. Achondrogenesis type I was subdivided further in 1988 on the basis of convincing histological criteria. It was subdivided into type IA, which has apparently normal cartilage matrix but inclusions in chondrocytes, and type IB, which has an abnormal cartilage matrix. Classification of type IB as a separate group has been confirmed by the discovery of its association with mutations in the diastrophic dysplasia sulfate transporter (*DDST*) gene, making it allelic with diastrophic dysplasia. Currently, 3 variants of achondrogenesis have been defined based on radiologic and histopathologic features: type IA (Houston-Harris), type IB (Parenti-Fraccaro), and type II (Langer-Saldino). Achondrogenesis IA appears to be autosomal recessive, but the mutant gene is still unknown. Type IB is caused by recessive mutations of the diastrophic dysplasia sulfate transporter gene (*SLC26A2*), and type II is caused by autosomal dominant mutations of the type II collagen gene (*COL2A1*). Achondrogenesis II results from heterozygosity for a new dominant mutation in the *COL2A1* gene at the chromosomal locus 12q8.11–q13.2.

Intra-molecular heterogeneity has been recognized, and genotype–phenotype correlations have been demonstrated [3].

Case Report

A 21 years old female booked at us from first trimester, married for 3years, non-consanguineous marriage, who is gravida 3 , abortion 2 with gestational age of 21weeks and 3days came diagnosed with anomalous baby on USG. The USG showed single live intrauterine gestation of 20-21weeks with gross skeletal dysplasia-Achondrogenesis type 1. On USG there was absence of forearm bones in both upper limbs and absence of bones in the right lower limb. Her LMP- 19/12/14 with irregular menstrual cycles of 5/45-60days. Her obstetrical history was, 1st pregnancy- spontaneous conception soon after the marriage and had a spontaneous abortion at one and a half months of amenorrhea. 2nd pregnancy – spontaneous conception after 2months of previous abortion and patient again had a spontaneous incomplete abortion at one and a half months of amenorrhea, MTP was done. 3rd pregnancy – spontaneous conception after 6months of previous abortion, folic acid tablets was taken regularly soon after confirmation of pregnancy. There was history of urinary tract infection with pain abdomen which was treated and patient was added on progesterone supplement (C.Susten 200mg) and tablet aspirin 75mg. No history of radiation exposure, fever with rashes or any teratogenic drug intake.

Patient was diagnosed with subclinical hypothyroidism (TSH-8.83mU/l, FT4- 1.11ng/dL) for which she was started of tablet thyronorm 25mcg and was having mild anemia(Hb-9.5).

Patient had history of PCOS and treated for it at 15years of age. There was no other significant past history. There is a family history of patient's mother having pre-auricular tag with hearing deficit since her childhood. On examination patient had polydactyly of left hand.

At 21weeks and 3days medical termination of pregnancy was done with T. Mifepristone 600mg orally and T.Misoprostol 200mcg per vaginum. Patient was given adequate antibiotic coverage. Under aseptic precautions ,a dead born female fetus of 300gm and a healthy placenta of 50gm with clear liquor was delivered trans-vaginally. The fetus was dwarf with large head, short neck and chest and short limbs along with club foot of right leg which is directly arising from pelvis. X-ray of the fetus showed absence of ulnar and radius bones of right upper limb, absence of femur ,tibia and fibula bones in the right lower limb, absence of femur in left lower limb where tibia and fibula arising directly from pelvis, crowding of ribs and no fractures were found which differentiate type1b from type 1a. On 3rd post delivery day patient developed herpetic lesions near her lips and was treated with T. Acyclovir 400mg TDS for 7days. Patient was given genetic counselling and advised for pre-conceptional counselling. She was discharged on 5th post delivery day.

DISCUSSION

Achondrogenesis is the severe form of congenital chondrodysplasia where there is malformation of bones and cartilages. It is inherited and is an autosomal recessive pattern which means both the parents carry the defective gene but do not show any signs and symptoms of the condition and there is 25% chance of subsequent child being affected [4]. It occurs in approximately 1 in 40,000 births [5]. The prevalence of this disease is 0.23/10,000 live births, and lethality among peri-natal deaths is 1:539.[6] The features of this disease are very short trunk, arms, legs, and neck, head appears large in relation to the trunk, small lower jaw, narrow chest, a prominent rounded abdomen and clubfeet . Infants born with this disorder usually are born prematurely, still births or die immediately after the birth because of respiratory problems .Histological, achondrogenesis Type 1 is probably a primary disorder of connective tissue and shows severe retardation of chondrocytic proliferation in the physéal cartilage [7]. Achondrogenesis is of two types- type 1 and type 2. Type 1 is further divided into two types, type1a and type 1b.

Achondrogenesis type 1A is caused by a defect in the microtubules of the golgi apparatus. In mice, a nonsense mutation in the thyroid hormone receptor interactor 11 gene (Trip11), which encodes the Golgi microtubule-associated protein 210 (GMAP-210), resulted in defects similar to the human disease. When their DNA was sequenced, human patients with achondrogenesis type 1A also had loss-of-function mutations in GMAP-210. GMAP-210 moves proteins from the endoplasmic reticulum to the Golgi apparatus. Because of the defect, GMAP-210 is not able to move the proteins, and they remain in the endoplasmic reticulum, which swells up.

The loss of Golgi apparatus function affects some cells, such as those responsible for forming bone and cartilage, more than others. Achondrogenesis type 1B is caused by a similar mutation in SLC26A2, which encodes a sulfate transporter.

[8] Similar to the other lethal short limb dysplasia, achondrogenesis is lethal due to pulmonary hypoplasia. Achondrogenesis may be differentiated from other skeletal dysplasias by having the most severe degree of limb shortening. The demineralization is only a differential diagnosis in osteogenesis imperfecta and hypophosphatasia, which do not present with the same degree of limb shortening.

Types I and II are distinguished based on clinical, radiologic, and histopathologic features. When the demineralization affects the skull and iliac wings the presumptive diagnosis is type I. When demineralization is present on sonography, an X-ray may confirm it. [9] Many cases of fetal skeletal dysplasias can be detected antenatally with ultrasonography. A final diagnosis may be obtained in most cases by fetopathological examination and radiographic studies and molecular testing as deemed necessary [10]. Therefore, the pregnancy can be managed as other pregnancies with fatal outcome and the option of pregnancy termination may be offered at any time after a definitive diagnosis [9]. There is no current therapy and genetic counselling can be given.





CONCLUSION

Though the case had no known risk factor and the phenotypic abnormality was mild, modern development in prenatal screening made the early detection possible. In such cases a detailed family history of the patient and her husband should be elicited along with clinical, genetic, radiographic and morphological examination. As in this case achondrogenesis was diagnosed by ultrasonography in the pre-natal period and its early detection, it throws the light on the importance of ultrasonography in such cases of skeletal dysplasia, where the decision of termination of pregnancy can be taken early. The family should be advised for genetic counselling and also pre-conceptual counselling for subsequent pregnancies.

REFERENCES

- [1] Fraccardo M. Folia Hered Path. 1952. 1:190-208.
- [2] Whitley CB, Gorlin RJ. Radiology 1983;148(3):693-8.
- [3] Mortier GR, Weis M, Nuytinck L, et al. J Med Genet 2000;37(4):263-71.
- [4] Horton WA, Hecht JT. Disorders involving ion transporters. In: Kliegman RM, Behrman RE, Jenson HB, Stanton BF, eds. Nelson Textbook of Pediatrics.
- [5] Spranger J, Beighton P, Giedion A, Hall J, Horton B, Kozlowski K et al. Eur JPediatr 1992; 151:407-15.
- [6] Romero R, Pilu G, Jearly P, Ghidhini A, Hobbins JC. Prenatal Diagnosis of Congenital Anomalies. Norwalk, Connecticut: Appleton & Lange; 1988. p. 311-82.
- [7] Yang SS, Heidelberger KP, Brough AJ, Corbett DP, Bernstein J. Lethal short limbed chondrodysplasia in early infancy. Perspective in Pediatric Pathology. Vol 3 Chicago: Yearbook; 1976. p. 1-40
- [8] Patrick Smits et al. N Engl J Med 2010;362:206.
- [9] Knowlton S, Graves C, Tiller G, Jeanty P. The Fetus 1992, 2:7564.
- [10] Witters I, Moerman P, Fryns JP. Genet Couns 2008;19:267-275.