New subtype of familial achondrogenesis type 1A (Houston-Harris)

Nuevo subtipo de acondrogénesis familiar tipo 1A (Houston-Harris)

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Abstract

Background: Achondrogenesis is a skeletal dysplasia characterized primarily by short stature, severe micromelia, short and narrow chest, prematurity, polyhydramnios, fetal hydrops, and in utero or neonatal death. Based on the radiological and histopathological findings, there are three types of achondrogenesis: type 1A (Houston-Harris), type 1B (Fraccaro) and type 2 (Langer-Saldino). **Clinical case:** A premature female product was studied whose clinical, radiological and histopathological characteristics were compatible with achondrogenesis Type 1A. The family information allowed us to conclude that the 4 products of the 6 previous pregnancies were affected. Statistical analysis in at least 4 families previously described, including this family case showed significant differences between expected and observed number of members, being incongruent with an autosomal recessive mode of inheritance previously reported. **Conclusions:** therefore, it could be considered a new subtype of achondrogenesis type 1A due to the presence of a preferential germline mutation.

KEY WORDS: Achondrogenesis type 1A. Germinal mutation. Skeletal dysplasia.

Resumen

Introducción: La acondrogénesis es una displasia esquelética que se caracteriza principalmente por talla baja, micromelia grave, tórax corto y estrecho, prematuridad, polihidramnios, hidropesía fetal y muerte fetal in utero o neonatal. Según los hallazgos radiológicos e histopatológicos existen tres tipos de acondrogénesis: tipo 1A (Houston-Harris), tipo 1B (Fraccaro) y tipo 2 (Langer-Saldino). **Caso clínico:** Se sometió a estudio a un producto femenino prematuro cuyas características clínicas, radiológicas e histopatológicas fueron compatibles con acondrogénesis tipo 1A. La información familiar permitió concluir que los cuatro productos de los seis embarazos previos se encontraban afectados. El análisis estadístico en por lo menos cuatro familias previamente descritas, incluyendo este caso familiar, mostró diferencias significativas entre el número de miembros esperado y el observado, siendo incongruente con el modo de herencia autosómico recesivo previamente reportado. **Conclusiones:** Podría considerarse un nuevo subtipo de acondrogénesis tipo 1A debida a la presencia de una mutación germinal preferencial.

PALABRAS CLAVE: Acondrogénesis tipo 1A. Mutación germinal. Displasia esquelética.

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Introduction

Skeletal dysplasias are a heterogeneous group of disorders with abnormal development of the skeleton (in size and shape of the limbs, trunk and skull). Those resulting from problems in ossification normal process have been designated as osteochondrodysplasia^{1,2}. In this group, achondrogenesis (ACG) are found, which are identifiable during fetal life or at birth, and are accompanied by polyhydramnios, fetal hydrops and pulmonary hypoplasia, which cause neonatal mortality or stillbirth³. Patients with these dysplasias have a short neck and trunk, narrow chest, prominent abdomen, short height, severe micromelia and facial dysmorphism (exophthalmia, flat nasal bridge, short nose with anteverted nostrils, low set ears and lingual protrusion). Main radiological findings include virtual ossification absence of the cranial vault bones and vertebral bodies of sacrum, and short ribs with horizontal orientation. The ilium is shortened, in the shape of a half moon. Long bones are small, arched and occasionally stellate, with longitudinally oriented metaphyseal spurs^{3,4}.

Thus far, three types of ACG have been described: type IA (ACG1A, Houston-Harris, MIM # 200600), caused by mutation of the TRIP11 gene at locus 14q32; type IB (ACG1B, Fraccaro; MIM # 600972), caused by a mutation of the SLC26A2 gene at locus 5q32 (both types are described with autosomal recessive inheritance mode); and type II (ACG2, Langer-Saldino; MIM # 200610), due to mutation of the COL2A1 gene at locus 12q13.11, with an autosomal dominant pattern. ACG has a global frequency of 1-50,000. In the case of ACG1A, mutations in the TRIP11 gene have been reported, but without being conclusive as a single cause³⁻⁸. These three variants are lethal in utero. Radiological and histopathological characteristics enable differential diagnosis; between types I and II it is easier, since they are clinically different³⁻⁶. The present work aims to be the first report of a new ACG1A subtype with a previously unreported mode of inheritance, which is not autosomal recessive, as well as some not previously observed histopathological findings.

Clinical case

Female newborn resulting from a seventh pregnancy. Parents were not consanguineous (Fig. 1). Since week 12 of gestation, abdominal ultrasound revealed short limbs. Since week 28, there was fetal hypoactivity, with probable dropsy and severe polyhydramnios.

Delivery occurred at 30 weeks by cesarean section. At birth, she had a body weight of 1600 g, crown-heel length of 23 cm, head circumference of 22 cm, chest perimeter of 18.5 cm, abdominal perimeter of 21 cm and a lower segment of 6 cm. There were also findings consistent with rhizomelic and mesomelic dwarfism, macrocrania, mild orbital hypertelorism, auricular pavilions low implantation, short nasal bridge, short and wide nose, microretrognathia, short neck, thoracolumbar dorsal hypertrichosis, significant shortening of the trunk with costal hypoplasia, prominent abdomen and micromelia of the four limbs. The patient died 15 minutes after birth.

Family and genetic study

Parents were healthy, 35 years (father) and 33 years (mother) of age at birth of the case. Karyotype of the parents was obtained with GTG banding, which was normal in both. Genealogical analysis revealed the presence of other affected siblings, with the same clinical characteristics II-1, II-2, II-3, II-5 and II-7; II-4 was a miscarriage; II-6 was clinically and radiologically healthy (Fig. 1). Family member's clinical characteristics are shown in Table 1.

Imaging studies

Full skeletal survey radiological findings are shown in table 2 and figure 2 B. Overall, axial and appendicular skeleton bones poor ossification is observed, with predominance in vertebral bodies, as well as pelvic bones hypoplasia and shortening of all four limbs long bones, with stooping thereof.

Anatomopathological study

Macroscopic description reported extensive maceration, and generalized ascites and edema (Fig. 2). Histopathological study of the femoral epiphysis by biopsy was carried out using formic acid and paraffin embedding; macroscopically, it revealed decalcified bone. Different 7-mm-thick histological sections were stained with hematoxylin/eosin, Alcian blue/PAS and Masson's trichrome, and analyzed by light microscopy. The results were: normal cartilaginous matrix, with sparse, densely packed and vacuolated, PAS-positive chondrocytes, some of them with an aspect of bullseye (at the center of the biopsy with Alcian blue/PAS; Fig. 3); elongated bone lacunae and a pseudo-mesenchymal zone

Figure 1. Family tree.

Table 1. *Proposita* siblings clinical data

Gestation	II-1	II-2	II-3	II-4	II-5	II-6
Gender	Male	Female	Female	Not determined	Female	Female
Gestational age in weeks	29	23/24	28	8	30	39
Clinical findings	Short limbs	Multiple malformations	Cleft lip, short and flat nose, short neck, trunk and limbs, hydrops fetalis	Does not apply, it was a miscarriage	Cleft lip, short and flat nose, short neck, trunk and limbs, hydrops fetalis	Normal
Death age/continued hours	4	2	2	Does not apply	2	Does not apply
Birth height (cm)	Not recalled	Not recalled	Not recalled	Does not apply	23	50
Birth weight (g)	Not recalled	400	Not recalled	Does not apply	650	3000
Polyhydramnios	Data unknown	Data unknown	Present	Absent	Present	Absent
Placenta	Data unknown	Degeneration	Data unknown	Data unknown	Edematized and hypochromic	Normal

between cartilage and bone. No intrachondrocytic inclusion bodies were found, and extraskelatal cartilage was found to be involved.

Discussion

Pathognomonic data consistent with ACG1A were found in the *proposita*, as well as in several members of the family, including polyhydramnios in the second trimester of gestation and radiological abnormalities

(multiple dysostosis) (Table 1)^{3,6,9-13}. Most cases are premature and stillbirths; some remain alive for minutes after birth, as in the present case⁷. Information of the analyzed genealogy allowed concluding that four products of the six previous pregnancies were clinically affected with ACG1A. The *proposita* was more affected (she had serious facial dysmorphism) in comparison with her brother, who died with the same problem; this is due to hydrops fetalis and polyhydramnios, which are the cause of malformations.

Table 2. Comparative clinical and imaging data in achondrogenesis and the *proposita*

Clinical characteristics	Type IA*	Type IB†	<i>Proposita</i>
Polyhydramnios	18/22	5/24	+
Gestational age			
Full term	1/22	4/25	
Prematurity	20/22	16/25	+
Death age			
Stillborn	15/22	11/25	
Minutes	11/22	13/25	+
Birth length (cm)	22-30	23.5-30	23
Birth weight (g)	520-1840	1020-2200	1600
Gender ratio (male/female)	15:7	5:13	Female
Consanguinity	3	2	-
Member of a family with multiple affected siblings	9	5‡	+
Radiologic findings			
Poorly ossified skull	+	+	+
Rib fractures	+	-	-
Non-ossified vertebrae	+	-	+
Ossified posterior pedicles	-	+	-
Ilium	Arched	Crenated	Arched
Unossified ischium	-	+	-
Femur	Wedge-shaped, with metaphyseal spikes	Trapezoid	Wedge-shaped, with metaphyseal spikes
Tibia	Shortened, with metaphyseal flare	Stellate	Shortened, with metaphyseal flare
Fibula	Shortened, with metaphyseal flare	Unossified	Shortened, with metaphyseal flare

*Twenty-two analyzed cases from reference 17.

†Twenty-four cases reported in reference 14, and one case reported in reference 15.

‡Reference 20 reports a consanguineous family with two fetuses (after ultrasound examination, pregnancy was terminated).

ACG1A differential diagnosis is established by ruling out conditions of two nosological groups of diseases with high perinatal mortality: chromosomal defects that produce facial dysmorphism and malformations, which were ruled out, since cytogenetic evaluation in both parents was normal; and skeletal lethal dysplasias, including diastrophic dysplasia MIM # 222600 (caused by mutations in the SLC26A2 gene, at locus 5q32), short rib thoracic syndromes with or without polydactyly (there are several types with autosomal dominant or recessive inheritance patterns), osteogenesis imperfecta type II, MIM # 166210, with autosomal dominant pattern, caused by mutations in the COL1A2 gene, at locus 7q21.3, and by the COL1A1 gene at locus 17q21.33, “baby rattle” pelvic dysplasia, MIM # 605838 (still without a candidate gene),

fibrochondrogenesis type 1, MIM # 228520 (with an autosomal recessive pattern caused by mutations in COL11A1 locus 1p21.1), and type 2, MIM # 614524 (with both autosomal dominant and recessive inheritance, caused by mutations in COL11A2, locus 6p21.32), thanatophoric dysplasia MIM # 187600 (caused by mutations in the FGFR3 gene at locus 4p16.3), and especially ACG2, due to the autosomal dominant transmission pattern, similar to that found in the analyzed family⁸⁻¹³.

The diagnosis can also be established by sequencing. For patients with ACG2, mutations are found in COL2A1^{6,10}; in ACG1B, in the DTDST gene^{3,5,9,12-17}. In the search for an implicated gene for ACG1A, Smits et al.¹³ found that mice with GMAP-210 deficiency died with a phenotype similar to ACG1A. This gene is

Figure 2. A: post-mortem photograph of the patient. Notice the hydropic appearance and the neck, chest and short limbs. B: photograph of patient X-rays. Notice the poor ossification of the skull and vertebrae, short ribs, hypoplastic pelvis, arched ilium and wedge-shaped femur.

Figure 3. Femur biopsy. Notice the vacuolated chondrocytes.

homologous to TRP11 in humans, where 11 mutations have been found (most of them in the compound heterozygous state)¹³. Apparently, these mutations are inherited with an autosomal recessive inheritance pattern, and since those affected are compound heterozygotes, it is speculated that they may remain alive for minutes or days after birth, since homozygotes are

incompatible with life, and thus are rare, as it occurs in thanatophoric dysplasia¹⁴⁻¹⁶. Grigelioniene et al.⁴ also show evidence on the autosomal recessive pattern and in contrast they found dizygotic twins with an ACG1A clinical and radiological phenotype with a homozygous genotype for a new nonsense mutation in TRIP11⁴. They also found a patient who was compound heterozygous for a nonsense mutation and a deletion of the 3' end of the gene, with milder manifestations. Therefore, mutations of the TRIP11 gene may encompass a wider phenotypic range, but to date they are not the only cause of ACG1A¹³, as we can see in the family of the *proposita* analyzed in this report, since, clinically, they correspond to cases with ACG1A, but the genealogy is not consistent with an autosomal recessive inheritance pattern.

In view of the above, the frequency of expected (E) and observed (O) affected members was analyzed in three families with ACG1A clinical characteristics reported by Borochowitz, et al.¹⁷ (Table 1), together with that of the present report (n = 22, E = 6 and O = 16). Differences were found between E and O affected members; O cases are three times higher than E

cases ($X^2 = 26.68$, $p < 0.001$). If we consider that in diseases with autosomal recessive inheritance pattern there is a risk of recurrence of 25% in the siblings of an affected subject, this is not met in the *proposita* genealogy and neither in those three genealogies, and therefore not all ACG1A cases are explained by this inheritance pattern. Taken as a whole, these data suggest that there may be a parental *de novo* preferential germline mutation, whereby the patients' parents are asymptomatic carriers of a mutation in the heterozygous state, inherited by their offspring with an autosomal dominant pattern, which is supported by the present case report, since in the family there were deaths, and some affected subjects died minutes after birth, as the *proposita* did. In cases with this pattern, the risk of recurrence is 50% or higher (as observed in the analyzed family), and this is the value that should be used in genetic counseling for this pathology in such cases. Risk is 25% when the condition occurs in families with an autosomal recessive pattern.

Germinal mosaicism for a dominant gene might be another possibility that would explain the ACG1A pattern discussed in this work, since it has also been reported in achondroplasia (ID MIM # 100800), pseudoachondroplasia (ID MIM # 177170) and ACG1B, which are autosomal dominant dysplasias where cases have been reported with the same transmission pattern, as in the present family, where recurrence is associated with germinal mosaicism¹⁶⁻²⁰.

Germline mutation is another explanation, since the cell continues to divide into a somatic cell before separation into germ cell lines. Considering that in the *propositi*'s parents (mosaicism carriers) some slight histopathological alterations in the connective tissue might be observed¹⁸, Superti-Furga, et al.¹⁴ postulated that ACG1 could be classified into different subgroups. Vargas²¹ also reported a rare sporadic case with ACG1A and B peculiar characteristics. A family has been reported where the parents had had undergone 3 pregnancies and did not have a single child alive; the last one, a stillborn, was a 24-week fetus with clinically-detected ACG1A²². These data support the hypothesis that the present case and other ACG1A recurrent cases presumably correspond to a non-described subgroup, due to germinal mosaicism or parental *de novo* preferential germline mutation.

The search for a germline mutation or a mosaic, or a parental *de novo* germline preferential mutation in TRIP11, requires molecular analysis of different tissues of all relatives, as well as a gene expression

analysis, with biopsy and immunohistochemistry¹⁴⁻²¹, which was not possible to be carried out, since affected subjects are deceased. For ethical reasons, since the mother is asymptomatic and had been able to bear a healthy child, biopsy taking was not approved, since these are also high-risk pregnancies. However, it can be part of the diagnostic workup for future ACG1A cases that exhibit an inheritance pattern such as that which is being reported. The results of these tests, when negative, open the hypothesis of another gene with dominant inheritance pattern mutations being the cause of ACG1A, either by a *de novo* or germline, and even mosaic mutation. Thus far, these theories cannot be ruled out, since, as in the case of diseases caused by lethal genes, it is difficult to arrive on time to take tissue samples for cytogenetic and molecular testing. As in the present case, when we were informed about the patient for evaluation, she had already died within minutes, and her siblings were already dead. For many skeletal dysplasias, molecular diagnosis is quite useful, but, in ACG, standards for their request are not well established, since the pathogenic mechanisms are not entirely demonstrated²¹.

There are few ACG studies in the Latin American population. Few cases have been described, among them a Mexican newborn girl who arrived at 38 weeks of gestation and died of bradycardia and respiratory failure; clinical and immunohistopathological diagnosis of ACG2 (Langer-Saldino) was established²³. In the Venezuelan population a 23-week female still-birth was reported, with hydrops fetalis, occipital cystic hygroma, hypertelorism, micromelia and polyhydramnios, where clinically, by imaging, cytogenetics and histopathology, ACG1B was concluded, as well as one case of a subtype with ACG and peculiar characteristics^{21,24}. With a very similar approach, another sporadic female-gender case was reported in the Colombian population, who was severely affected with ACG1A and whose gestation was interrupted at 23 weeks for being a high-risk pregnancy²⁵. The present case is the first one in the Mexican population with ACG1A and the first report in the literature to present an ACG1A with an inheritance pattern that is not autosomal recessive.

From the histopathological point of view, differential diagnosis can be established (Table 3). In transgenic murine models, the ACG1A skeletal phenotype has been shown to be exclusively caused by cartilage development defects, although bone development is also abnormal because of the cartilage defect, since chondrogenesis is closely related to bone formation²⁶.

Table 3. Achondrogenesis types morphopathological comparison

Achondrogenesis variants	Histopathological findings reported in achondrogenesis	Pathognomonic histopathological changes	Ref.
ACG1A, Houston-Harris/ highly lethal, rare achondroplasia	Densely packed chondrocytes with bullseye appearance, large round or oval inclusions, PAS-positive, with vacuoles attached to the cell membrane found within Normal monochromatic cartilaginous matrix, with moderate perivascular fibrosis and disorganized growth plates with hypertrophic chondrocytes, extending to the primary and secondary trabeculae Chondrocytes show histomorphologic signs of protein material intracellular retention, reduced amount of proteoglycans, with thinning of collagen fibers Columnar chondrocyte zones with poor organization in growth plates On electron microscopy, dilated endoplasmic reticulum and Golgi apparatus can be appreciated. Golgi apparatus cisternae expansion is also observed By immunohistochemistry, normal pattern of collagens, aggrecan, matrilins, oligomeric cartilage protein and type 10 collagen (COL10A1) reduced expression have been reported	Abnormal metaphysis PAS-positive chondrocytes with cytoplasmic inclusions Hypertrophic chondrocytes resemble bullseyes	20-23, 29
ACG1B, Fraccaro	Chondrocyte disorganization, which show an increase in size and number (hypercellularity) Marked cartilaginous matrix loss and irregularity in the endochondral ossification columnar line, multifocal sclerosis and matrix calcification Perichondrocytic collagen rings	Abnormal metaphysis Perichondrocytic collagen rings	19, 29
ACG2, Langer-Saldino/lethal achondrogenesis	Significant ossification loss and irregular ossification in different bones Chondro/osseous tissue shows high cell density and reduced extracellular matrix Metaphyses show disorganized endochondral ossification with balloon-shaped chondrocytes; periosteum with advanced ossification, chondroid matrix and elongated chondrocyte lacunae Chondrocytes are increased in number and size, growth zone columns are irregularly arranged Osteoid deposit without calcification, chondroid matrix exhibits vascular channels and cartilage hypervascularity Primary trabeculae are thin and irregular, and perivascular fibrosis No inclusions in chondrocytes Irregular vascular penetration in ossification line Immunohistochemistry for apoptosis: BAK 80%, BAX 80% and Bcl-X 10% Immunohistochemistry for cell proliferation: focally positive PCNA (cell proliferation antigen)	Abnormal metaphysis Chondrocytes are balloon-shaped Markedly enlarged chondrocyte lacunae	18, 29

This explains why in the femoral biopsy of the of the ACG1A index case, elongated bone lacunae and a pseudomesenchymal zone were found between the cartilage and bone tissue, as well as extraskeletal cartilage involvement. These findings have not been previously reported. Cartilage and bone have also been reported to be highly secretory tissues, with high traffic of molecules through the membranes, which affects the traffic of a subset of proteins expressed in chondrocytes and leads to a membrane traffic that

harms globally. Affected molecules include sulfated glycosaminoglycans²⁶ (which are part of chondrocytes extracellular matrix and capsule). This explains why the index case biopsy shows that the chondrocyte capsule is thinner (Fig. 3).

In biopsies of ACG1A cases, through immunohistochemistry, the matrix molecules have been also reported to have a normal distribution pattern, except for type X collagen, which results in alteration of the assembly of the cartilaginous matrix with sulfated

glycosaminoglycans²⁷. Presumably, the consequences of this event are the processes of maturation and differentiation of chondrocytes and endochondral bone formation, which are severely affected²⁷. Presence of inclusion bodies, hypertrophic vacuolated chondrocytes and disorganized chondrocyte plaques has also been described²⁵⁻²⁹; all these findings are similar to those observed in the *proposita's* biopsy, except that inclusion bodies were not observed, a finding that has not been previously described. The absence of inclusion bodies can be explained by the reduced amount of intracellular collagen and proteoglycans, which is conclusive of the severe endochondral formation disorder. Considering all these histopathological findings, the COL10A1 gene (which encodes collagen 10) could be proposed as the possible gene involved in ACG1A with non-recessive or recurrent pattern, as in the family analyzed in the present case, which is supported if we consider that mutations in COL10A1 are transmitted with a dominant pattern (inheritance where germline or mosaic mutation, or preferential de novo parental germline mutation cases fit) and produce metaphyseal chondrodysplasia, Schmid type.³⁰ In this sense, recurrent non-recessive ACG1A might be an allelic variant of the COL10A1 gene, a very similar case to achondroplasia (produced by mutations in the FGFR gene) and thanatophoric dwarfism, which is an allelic variant of the same gene. In this work, it was not possible to continue with TRIP11 and COL10A molecular study or histopathological analysis, due to the non-bioavailability of tissues. Masson's trichrome stain was applied to different sections of the index case femur, which allowed us to scan the structure of the cartilaginous matrix collagen fibers in general, which did not show alterations, but, with this stain, type-10 collagen cannot be particularly explored, which is a limitation of this work.

Conclusions

By means of clinical, imaging and pathology examination, the first report of a new ACG1 subgroup that corresponds to ACG1A, but with an alternative inheritance pattern is presented. Certainly, autosomal recessive inheritance has been reported in ACG1A, but it was ruled out in the present report. In future ACG1A cases with this alternative inheritance pattern, or in recurrent cases, it shall be convenient to search for mutations in the COL10A1 gene by means of exome sequencing. This way, this is the first work in the Mexican population with ACG1A and the first one in the

literature to present an ACG1A with an inheritance pattern that is not of the autosomal recessive type. Concluding whether it corresponds to an exclusively germline defect or rather to somatic/germline mosaicism in TRIP11 and COL10A, or in some other gene was not possible, given that availability of several tissues of the family is required (of those affected, both deceased and healthy asymptomatic subjects) in order to make the detection of mutations, as well as to carry out gene expression analysis, which was limited by hospital ethical issues related to patient benefit.

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Ethical responsibilities

Protection of people. The authors declare that the followed procedures were in agreement with the responsible human experimentation committee ethical standards and in accordance with the World Medical Association and the Declaration of Helsinki.

Confidentiality of data. The authors declare to have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained informed consent from the patients and/or subjects referred to in the article. This document is in possession of the corresponding author.

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Conflict of interests

None of the authors has any conflicts of interests.

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