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CLINICAL CASE

Peroxisomal disorder, rhizomelyc chondrodysplasia punctata type 1, case report

Enfermedad peroxisomal, condrodisplasia rizomelica punctata tipo 1, reporte de caso

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Abstract

Introduction: Peroxisomal diseases are a group of monogenic disorders that include defects in peroxisome biogenesis or enzyme dificiencies. Rhizomelic chondrodysplasia punctata type 1 (RCDP1) belongs to the first group, caused by autosomal recessive mutations on PEX7 gene, encoding for PTS2 receptor. The aims of this report are to describe a genetic disease of low prevalence, explaining its main characteristics and the importance of the diagnostic approach and genetic counseling. **Case report:** 13-month-old male infant with no medical history, family or consanguinity, demonstrate at birth upper limbs shortening. Surgery intervention at seven months old for bilateral cataract. Growth retardation, psychomotor retardation, minor craniofacial anomalies, rhyzomelic shortened upper limbs and lower limbs lesser degree. Punctata calcifications in patella cartilage. Also fatty acid phytanic and pristanic increased levels. Patient dead at age of 3 years. **Discussion:** RCDP1 is a rare disease, with a prevalence of 1/100,000. Different mutations of PEX7 gene have been described, with variations in phenotype. The treatment is basically symptomatic and depends on the severity of clinical manifestations. The rhizomelic type has poor prognosis, most patients do not survive before the first decade of live. Genetic counseling is essential because it is consider a 25% risk of recurrence.

Keywords:

Chondrodysplasia punctate, peroxisomal disorders, PEX7 gene, osteochondrodysplasia

Introduction

Peroxisomes are cellular organelles present in every cells of the body, except for some cells such as erythrocytes. They are made by simple membranes, and there are more than 50 enzymes involved in different metabolic processes, including biosynthesis of bile acids, phospholipids (plasmalogens) and oxidation of some very long fatty acids chains, among others¹⁻³.

The biogenesis of peroxisomes follows two basic procedures: the growth and division, or the process of assembly from pre-peroxisomal vesicles. PEX genes encode a series of proteins called peroxins, essential in the process of forming peroxisomes. These include peroxisomal targeting signal peptides, PTS1 and PTS2, which work as intermediaries in the importation of proteins into the peroxisome^{4,5}.

The matrix proteins incorporated into the peroxisome are synthesized in the cytosol, and imported simultaneously through an enzyme-receptor complex. There are two different pathways in this process that are dependent on peroxisomal signaling peptides: the first is a small peptide frequently attached to the end of the C-terminal region SKL sequence of most peroxisomal targeting signal type 1, (PTS1); The second is a degenerate nonapeptide (9 amino acid sequence) present at the amino terminal end of some peroxisomal targeting signal type 2 proteins (PTS2). The PTS2 receptor encoded by the PEX7 gene under normal conditions identifies the PTS2 sequence and it forms an enzymereceptor complex together with the PEX5 receptor (PEX5-PEX7-PTS2), which allows the translocation of the cytosol enzyme to the peroxisomal matrix, in order to be able to play their role. Although the process of translocation of the different peroxisomal proteins is similar, there could be mistakes in the reception of these pathways, which leads to different disorders. According to RCDP1, it is defined as a malfunction in the peroxin receptor number 7, because it generates its particular phenotype. Mutations in the PEX7 gene cause deficiencies in the enzyme phytanoyl coenzyme A (PAHX), failing its translocation to the matrix. This enzyme takes part of the oxidation of fatty acids, with the subsequent accumulation of its substrate, phytanic acid. Another enzyme, acyldihydroxyacetone phosphate synthase (ADHAPS), is also affected in the disease, causing the decrease of its product, plasmalogens⁴⁻⁶.

Peroxisomal diseases are classified into two major groups: one group created due to the deficiencies in biogenesis of the organelles or another group in which there is a deficiency of a single enzyme. The rhizomelyc chondrodysplasia punctata type 1 (RCDP1) (OMIM: # 215100) is an autosomal recessive genetic type disease, with a prevalence of 1 in 100,000^{7,8}, being classified in the first group of peroxisomal diseases⁹.

The main characteristics of the disease include punctate calcifications in hyaline cartilage, congenital cataracts, abnormalities in limb length, facial dysmorphism, severe growth delay, as well as delayed psychomotor development⁷. The mortality rate of this disease is focused on the first year of life¹⁰. The diagnosis is based on the clinical picture, also on laboratory tests given by biochemical tests such as determination of long fatty acids chains in plasma, plasmalogen levels, among others, and based on molecular diagnostic tests, if they are possible to perfom.

This research aims to make a detailed review of the main characteristics of the disease, as well as all the advises to be taken into account in the differential diagnosis, made for this low prevalence disease. We would like also to highlight the importance of early diagnosis in cases of dysmorphological alterations at birth, especially in those involving severe malformations, whether single or multiple. If we achieve an accurate diagnosis, it would allow parents to be advised about the prognosis and their possibility of recurrence in future pregnancies.

Clinical Case

A 13-month-old male patient (figure 1), with no history or background of major diseases in his family or relatives. Prenatal history of threatened abortion and preterm delivery. An ultrasound showed a intrauterine growth restriction (IUGR) at the sixth month of pregnancy. Cesarean delivery was performed at week 35, presenting an adequate weight and height for his gestational age, althouth he showed shortening of upper limbs and poor sucking reflexes, for he remained hospitalized, and a transfontanelar ultrasonography with verbal report of unspecified abnormality was performed.

The patient was taken to a surgery at 5 months of age for bilateral inguinal hernia and at 7 months of age for a bilateral cataract. Among all the studies performed prior to the first consultation by genetics are: x-rays of long bones, which it showed enlargement of metaphysis with diaphyseal shortening and presence of punctate type calcifications (figure 2); a brain nuclear magnetic resonance, that reported cortical atrophy; a renal ultrasound showing diminished kidneys; an echocardiogram showing atrial septal defect without hemodynamic repercussion; and a cariotipo with Gband analyzed in 20 metaphases, with report of 46, XY without numerical or structural alterations.

Due to these alterations, the patient was referred to the Medical Genetics service with a diagnosis of dysmorphic facial features and delayed psychomotor development. At his 13 months of age, his weight was identified: 4300 g (<-3 SD), low hight: 57 cm (<-3 standard deviation SD), small head circumference: 37 cm (percentile (p) <5), internal intercantal distance: 2.4 cm (p 50), Interpupillary distance: 3.5 cm (p <3), external intercantal distance: 6 cm (p <3), upper segment (US): 34.5 cm, lower segment (LS): 22.5 cm, ratio between UP/LS: 1.53; Filtrum: 1.5 cm (p 50-75); Craniofacial anomalies: microcephaly, alopecia, mediofacial hypoplasia, anteverted nostrils, depressed nasal bridge, long and flat filtrum, thin upper lip, unstable palate, low-set ears. Moveable neck without lesions. Rhizomelic shortening of upper limbs, in addition to camptodactyly and rhizomelic shortening in a lower degree of lower

limbs, contracture of limb joints (figures 1), hypotonia

According to all these measures, the diagnosis of rhizomelyc chondrodysplasia punctata type 1 was established. The quantification of long fatty acids chains in plasma, which reported high values of phytanic and pristanic acids was performed, confirming the diagnosis of RCDP1 at the age of 22 months, as shown in tables 1 and 2. The diagnosis was clarified and informed to his parents, indicating prognosis and genetic counseling. After the diagnosis, the patient had the natural evolution expected, in accordance with this disease, dying at the age of 3 years due to pneumonia.

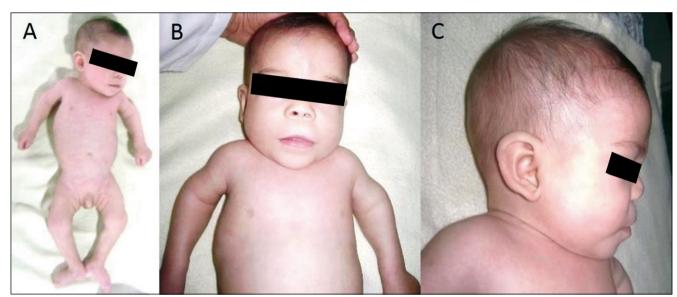


Figure 1. A. Symmetrical rhizomelic shortening of upper limbs and, to a lesser extent, lower limbs, in flexion. **B.** Alopecia, broad nasal bridge, anteverted nostrils, flat philtrum, thin upper lip. **C.** Medial facial hypoplasia, depressed nasal bridge, low implantation of auricular pavilions.



Figure 2. Comparative anteroposterior projection of limbs. **A.** Both humerus show significant shortening in relation to forearm bones and metaphyseal widening. **B.** Punctiform calcifications in the patella and distal femoral epiphysis, metaphyseal widening with femoral (rhizomelic) diaphyseal shortening.

Table 1. Total Lipids of Very Long Chain and Fatty Acids of Branched Chain in Plasma						
Fatty acids	Patients Results ug/ml	Normal Controls +/- 1 SD	X-Linked ALD Hemizygote +/- 1 SD	X-Linked ALD Heterozygote +/- 1 SD	Zellweger Syndrome +/- 1 SD	
C26:0 Hexacosanoic	0.490	0.23 ± 0.09	1.30 ± 0.45	0.68 ± 0.29	3.93 ± 1.50	
C26:1	0.230	0.18 ± 0.09	0.34 ± 0.16	0.23 ± 0.10	4.08 ± 2.30	
Phytanic Acid	119.0	< 3.00 ug/ml				
Pristanic Acid	3.350	< 0.3 ug/ml				
C22:0	7.370	20.97 ± 6.27	18.50 ± 5.10	19.41 ± 4.08	8.66 ± 4.97	
C24:0	8.070	17.59 ± 5.36	32.25 ± 8.20	24.89 ± 5.42	17.51 ± 8.64	
C22:1 (n-9)	0.660	1.36 ± 0.79	1.19 ± 0.66	1.33 ± 0.41	1.73 ± 0.65	
C24/C22	1.095	0.84 ± 0.10	1.71 ± 0.23	1.30 ± 0.19	2.07 ± 0.28	
C26/C22	0.066	0.01 ± 0.004	0.07 ± 0.03	0.04 ± 0.02	0.50 ± 0.16	

The values of phytanic and pristanic acid are very high, additionally we find high values of C26: 0 and an elevation of the relation C26: 22. The C24: 22 ratio is slightly elevated. ALD: Adrenoleukodystrophy. SD: Standar Deviation.

	Pipecolic acid in patient plasma at 22 months: 11.5 μmol/L					
Comparison Data	Plasma (μ	mole/L)	Urine (µmole/g creatinine)			
Normal	Mean ± SD	Normal Range	Mean ± SD	Normal Range		
Up to 1 month	2.4 ± 1.5 n = 54	(0.1 - 5.3)	26.8 ± 15.2 n = 10	(0.1 - 57.2)		
1 to 6 months	1.8 ± 1.0 n = 148	(0.1 - 3.9)	24.9 ± 18.7 n = 29	(0.1 - 62.3)		
7 months to 5 years	1.8 ± 1.2 n = 473	(0.1 - 4.2)	2.5 ± 1.9 n = 66	(0.1 - 6.3)		
> 5 years	1.7 ± 1.1 n = 230	(0.1 - 4.0)	1.5 ± 1.5 n = 26	(0.1 - 4.5)		

Discussion

The manifestation RCDP1 disease includes ocular problems, as cataracts¹¹, as well as weight and height with symmetrical rhizomelyc shortening⁴, seizures, cortical and cerebellar atrophy¹², congenital contractures and dysmorphic facial features. Regarding punctate calcifications of the cartilage, although they constitute a key radiological finding, they are temporary and they will not be evident after the first or second year of life¹³.

Other clinical findings are difficulties for breastfeedig, swallowing, a depressed nasal bridge, maxillofacial hypoplasia, anteverted nostrils, long filtrum. Some other abnormalities may occur in the eustachian tube, otitis media, and even hearing loss¹⁰. In addition, episodes of apnea and recurrent respiratory infections are common. Finally, although they are uncommon, structural congenital heart defects may occur as well.

The patient of this clinical case met the criteria with clinical and radiological pictures, being compatible with diagnosis of rhizomelyc chondrodysplasia punctata type 1. Certain characteristics of the syndrome were not present, such as seizures, ichthyosis or coronal clefts of the vertebral. It is important to take into account the variability of information reported in the literature, which allows us to notice differences in its clinical presentation. It has been attempted to link the genotype-phenotype correlation, according to the mutations found. However, there are patients who have the same mutation, but they vary in some clinical signs, thus, the cause of these differences are totally unknown yet^{5,7,9}.

In Latin America the reports of this disease are scarce, which makes difficult to make a correct diagnosis of each particular case^{14,15}, due to the variability of disease expression and the phenomena such as heterogeneity of loci.

The diagnosis is mostly based on clinical and radiological criteria, due to difficulties in the access of biochemical and molecular confirmatory tests¹⁶. If a correct diagnosis is established, it has a direct impact on prognosis, in addition to a proper treatment and genetic counseling to parents¹⁷.

Diagnostic confirmation exams show the metabolic effects of the deficiency of at least 4 peroxisomal enzymes; the main goal is to establish the biochemical concentration of plasmalogens in erythrocytes; and the concentration of phytanic acid in plasma or long fatty acids chains⁷.

Due to the mutation of the PEX7 gene, plasma erythrocyte concentration is decreased, together with plasma phytanic acid elevation (Tables 1 and 2); In this clinical case, a discrete elevation of C26: 0 was observed. This finding is rare, since the trend is to find normal values of these acids, which also showed increase of pipecolic acid, being described as a nonspecific finding in Peroxisomal alterations.

The molecular diagnosis consists of the sequencing of the PEX7 gene¹⁸. This study supports the diagnosis confirmed by biochemical studies and genetic counseling. This clinical case does not count on the molecular study, since their health insurer did not authorize its realization.

In the differential diagnosis, the peroxisomal defects of group 1 were highlighted, with the Zellweger spectrum consisting of Zellweger syndrome (# 214100), neonatal adrenoleukodystrophy (# 202370) and Refsum infantile disease (# 266510), which was the main one. These diseases have different clinical signs to RCDP1. Chondrodysplasia punctata type 2 (OMIM: # 222765), type 3 (OMIM: # 600121) and type 5 (OMIM: # 616716) should be considered as differential diagnoses. There are similar phenotype, but they have a low frequency (in less than 10% of cases); Chondrodysplasia punctata recessive X-linked or brachylophagous type (OMIM: # 302950) has the following different findings: ipoplasia of the distal phalanges, ichthyosis; X-linked dominant chondrodysplasia punctate or Conradi Hünerman syndrome (OMIM: # 302960), which it is usually fatal in men and the phenotypic presentation includes asymmetric limb compromise; Warfarin embriopathy and other vitamin K deficiencies; Maternal Erythematosus Systemic Lupus; Chondrodysplasia punctata type tibial-matacarpo (OMIM:% 118651), in this case there are no cataracts⁷.

Regarding the treatment, it is recommended to perform radiographic studies, ophthalmologic examination, to monitor growth and development, and magnetic resonance imaging with spectroscopy. The presence of congenital cataracts requires surgical correction. If the patient has swallowing disorders, gastrostomy is indicated. Respiratory function should be monitored, vaccination for pneumococcus and influenza is also suggested. Physical therapy improves joints mobility and hypotonia.

The treatment is basically supportive, since the disease has a poor prognosis. Restricting phytanic acid in the diet and its subsequent elevation has positive effects

only in those cases of mild presentation of the disease⁷. Those foods rich in phytanic acid include meats derived from ruminants or products derived from them (milk, cheeses, butter, cream); fish or oils devired from seafood are also included²⁰.

RCDP1 is an autosomal recessive type. The parents are heterozygous carriers of the disease, thus the probability for each pregnancy of forming a child with the disease is of a 50%, with a 25% of having an affected children and a 25% of having a healthy child¹⁰. Molecular diagnosis is recommended, if available. The survival rate up to 2 years of age is approximately of a 90%. Most individuals do not survive beyond their first decade of life.

Conclusions

The rhizomelyc chondrodysplasia punctata type 1 originates by disorders in the peroxisome biogenesis, being classified in the group 1 of the peroxisomal diseases. Clinically, facial malformations and rhizomelyc shortening of limbs, as well as respiratory, ocular, skeletal, otological and physical and mental development problems and delays are present. These characteristics should be known to the health team, in order to identify a patient from the moment of birth and to give advise to the family. The disease is fatal in all cases, presenting death in an early stage, in childhood. It does not have a cure, and the treatment is based on supporting the patients, which depends on the severity of the phenotype alterations, including dietary restrictions, surgeries, physical therapy, vaccines, gastrostomy and management of respiratory crises.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

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

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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