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De Barsy Syndrome (DBS): First Case Reported in Colombia

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Abstract: ***De Barsy syndrome (DBS) is an infrequent autosomal recessive disease, where a relationship has been identified in ALDH18A1 and PYCR1 mutations, mainly producing cutis laxa in the affected patient. Other clinical characteristics are similar to patients with Progeria Syndrome. Diagnosis is usually difficult due to the few cases reported worldwide. In order to identify patients with DBS molecular and/or histopathological studies are necessary. There is no specific treatment in these patients, and management is done according to the associated alterations. Probably, the first case described in Colombia with DBS is described.***

Keywords: Progeria - like syndrome; Cutis laxa; Intellectual disability; De Barsy Syndrome; Case report

1. Introduction

DBS, also known as: ARCL - III, Progeroid Syndrome de Barsy or cutis laxa - corneal opacity and mental retardation syndrome [1], is an infrequent autosomal recessive syndrome, with physical characteristics similar to progeria (Progeria - like syndrome) [2]; its most distinctive feature is the presence of cutis laxa, which is characterized by abnormal elastic fibers, resulting in loose and hypoelastic skin (especially on the dorsal acral surfaces and abdomen), as well as facial dysmorphia (wide nasal bridge, fissures descending eyelids, small mouth, among others), corneal opacification, progeroid appearance, reduction of subcutaneous fat and athetoid movements [1, 3]. There are also frequents some orthopedic and neurological abnormalities [3]. The genetic cause of DBS is not well defined, but mutations in the ALDH 18A1 and PYCR1 genes have been identified [4, 5]. Due to the low prevalence of the disease, it possibly goes under diagnosed; for this reason it is described, probably the first case described in Colombia of an adolescent with DBS.

2. Clinical Case

An adolescent male patient with multiple pediatric endocrinology visits, who was born preterm at 32 weeks; he has a prenatal diagnosis of intrauterine growth restriction (IUGR). Birth weight: 1100 g (- 3.2 Standard Deviation Score (SDS)); birth length: 37 cm (- 2.7 SDS); he required a stay for two months in a neonatal intensive care unitfor his low birth weight. Delays in reaching developmental milestones were observed: sitting at 2 years, walking at 3 years, language delay andpoor sphincter control. He had a hiatal hernia and required two surgical interventions. Others surgical interventions: bilateral inguinal hernia and a right hydrocele. Behavioral alterations of impulsive behavior were identified with irritability and difficulty in following orders; and with self - and hetero - aggressiveness. He was diagnosed in a neurological and a neuropsychological evaluation with a mild mental retardation.

On physical examination, sever short stature is observed; characteristic facies: with a prominent forehead and nasal bridge, strabismus, thin lips, large low - set ears; absence of adipose panniculus; joint stiffness; generalized muscle hypotrophy; visible veins; large hands and feet (see figure 1); anthropometric measurements at 13 years 8 months: weight 21 kg (-5.0 SDS); height 139 cm (-3.0 SDS); BMI 10.9 kg/m2 (-6.5 SDS). The patient receives multidisciplinary management with neurology, psychiatry, ophthalmology, gastroenterology and genetics; as well as occupational therapy and psychotherapy.

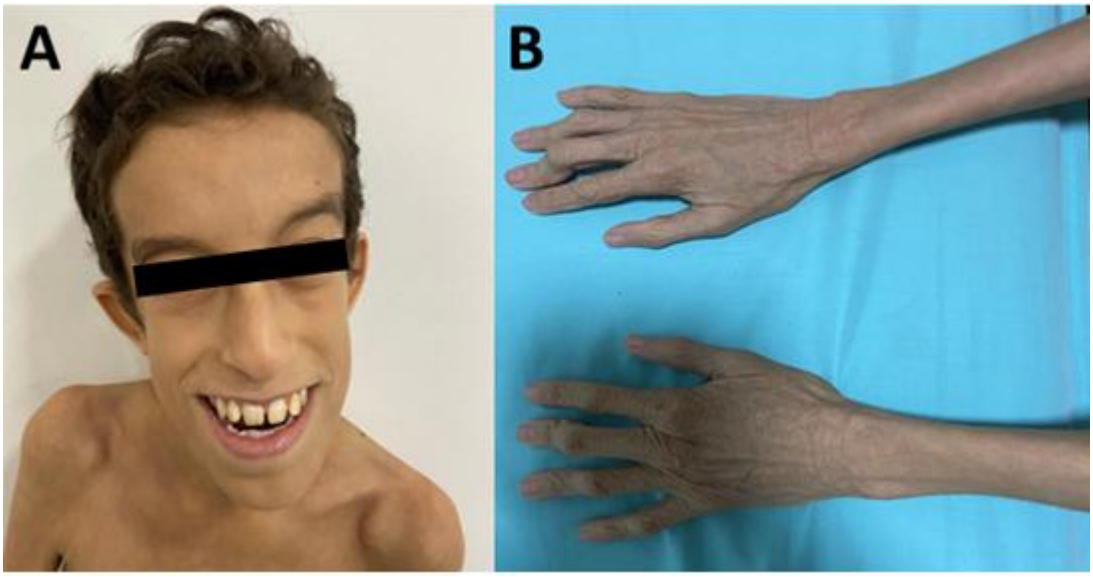

Figure 1: Case patient photos with DBS. A) Progeroid face: skull asymmetry, forehead and prominent nasal bridge, thin lips, large low - set ears, elongated lower jaw. B) Large hands, with lax skin and joint stiffness.

General and hormonal studies have been carried out and are summarized in Table 1. A whole - exome study was performed, and two alterations were found: **NM_006907.4 (PYCR1): c.535G>A p. (Ala179Thr); NM_052817.3 (MID2): c.1547A>G p. (Lys516Arg);** the firstone corresponding to DBS (PYCR1) and the second result is considered of uncertain clinical significance (MID2): related to X - linked mental retardation.

Table 1: Imaging studies and laboratories results

Date	Patient age	Imaging studies and laboratories
November - 2022	13 years	Brain MRI: Within Normal Limits. Simple and contrast - enhanced computed tomography of the abdomen and pelvis: sliding hiatal hernia, reduction of abdominal wall adipose tissue in relation to fatty lipodystrophy, deviation of the left convexity of the lumbar coronal axis.
April 2022	13 years	Leukocytes 8.2 x10 ^{3} / uL; HB 13.9 g/ dL; platelets 332 x 10 ^{3} / uL; Glycemia 101 mg/ dL; Triglycerides: 104 mg/ dl; Total chole: 239 mg/dl; LDL: 168 mg/dl; HDL: 71 mg/dl; TOG: 25 U/L; GPT: 16 U/L. free T4: 1.33 ng/dl; TSH: 1.15 uIU /ml. Prolactin: 71 ng/ml; Insulin 9.5 u/ml
November 2009	1 year	Leukocytes 11.8 x10 ^{3} / uL; HB 11.1 g/ dL; platelets 325 x 10 ^{3} / uL; Glycemia 77 mg/dl; creatinine 0.39 mg/ dL; BUN 5.42 mg/ dL; TOG: 37 u/L; GPT: 32 u/ L; cholesterol: 181 mg/dl; triglycerides 118 mg/dl; LDL 106 mg/dl; HDL: 51mg/dl; Insulin: 13.3 IU/ mL: TSH 1.67 IU / mL

Source: self - made.

3. Discussion

In 1967, Dr. De Barsy, a Belgian neurologist, described the first case of a patient with DBS: *progeroid facies*, *cutis laxa*, *mental retardation* and other ophthalmic, orthopedic and neurological complications [2]. DBS is a disease with an unknown prevalence; it is estimated that there are around 50 cases reported in the literature worldwide [4]. The reported cases are associated with parental consanguinity and it is considered with an autosomal recessive inheritance [2]. No ethnic influence has been reported in this syndrome, but a predominance has been noted in the male sex [4].

Clinically, DBS manifests itself in patients who have a history of pregnancies with IUGR (in up to 96%). There are patients with severe short stature, progeroid face with a prominent forehead and nasal bridge, thin lips, large low - set ears, absence of adipose panniculus, generalized muscle hypotrophy, visible veins, large hands and feet; 34% develop inguinal and umbilical hernias; 48% develop ophthalmological complications such as corneal opacities, myopia, strabismus and cataracts; 76% of the patients may have mild to moderate mental retardation, and 48% of them have severe mental retardation; regarding orthopedic alterations, the most frequent is joint hyperlaxity, followed by adducted thumb and joint dislocations [4, 6]. The patient in this case has a history of IUGR with low birth length and low birth weight; facies with the progeroid characteristics described in these patients; and, ocular alteration (strabismus); he has neurological alterations: cognitive deficit associated with behavioral alterations, and also a history of hiatal and inguinal hernias.

The diagnosis of DBS is initially based on clinical suspicion by observing the phenotypic characteristics: and this is confirmed by performing a molecular or a histopathological study [2]. DBS Mutations have been found in the ALDH18A1 and PYCR1 genes; the latter encoding a mitochondrial enzyme involved in proline metabolism [4, 7, 8] (this mutation was found in the exome performed in this patient). The mutation of this gene has also been related to alteration of fibroblasts, which at the histopathological level can show abnormal elastic fibers, reduction of C - fibers, which in histopathological studies were found to be thin, frayed and fragmented (there was also a reduction in elastin mRNA) [2]. These changes produce the clinical phenotype of patients with DBS.

There is no specific treatment for patients with DBS; symptomatic treatment is performed according to the alterations that each DBS patient presents [4, 5]. There are also no studies that evaluate the prognosis of these patients due to the few reported cases [4].

4. Conclusions

DBS is an infrequent syndrome, the result of a genetic alteration. Its diagnosis should be considered in patients with *cutis laxa*, facial, orthopedic and neurological alterations (progeria - like syndrome). There are very few cases reported in the literature, which is why the clinical characteristics of this case patient are described; and the importance of considering the differential diagnosis in patients with a progeria - like phenotype is highlighted. The prognosis of the patient in this reported case is not known, nor is there a specific treatment for the disease. In this case, the genetic study of the parents is recommended to determine the origin and segregation of the detected variants.

Acknowledgment
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