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CASE REPORT

Rubinstein-Taybi syndrome: phenotypic characteristics and case report.

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Abstract

Introduction: Rubinstein-Taybi syndrome is a pathology of genetic origin that affects 1 out of every 100,000 to 125,000 live births, and it is characterized by growth retardation, delay in psychomotor development, and morphological abnormalities that include peculiar facial features (thick arched eyebrows, downward sloping palpebral fissures, convex nasal bridge with tip of nose below wings) and broad thumbs and halluxes. Its epigenetic origin in 60% of cases is due to an alteration in the CREBBP gene (coding for CPB protein), while in 10%, it is due to a change in the EP300 gene (coding for p300 protein), and in 30%, there is no identifiable cause.

Clinical case: An 8-year-old boy with a delay in psychomotor development had difficulties in adapting to school. On physical examination, facial features showed overpopulated and arched eyebrows, hirsutism in the forehead and upper lip region, downward sloping palpebral fissures, hypertelorism with convergent strabismus, wide nasal bridge, and flattened nose. The tip extends slightly below the nasal wings, with hirsutism in the cervical and interscapular region. In the hands, broad thumbs are identified. In the rest of the fingers, there are widened distal phalanges, and in the same way, in the region of the feet, a wide hallux and widened distal phalanges are identified.

Evolution: The patient continues to be observed by outpatient consultation. He was sent to speech, reading, and psychomotor therapy programs. He has not developed pulmonary infections until the close of follow-up at 6 months after diagnosis.

Conclusion: In this case report, we discuss the phenotypic alterations of the facial and limb characteristics of a child with Rubinstein-Taybi syndrome, which helped the clinical diagnosis.

Key words: Rubinstein-Taybi Syndrome, Chromosome Disorders; Craniofacial Abnormalities, Broad Thumb-Hallux Syndrome, Thumbs.

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Introduction

Rubinstein-Taybi syndrome (RSTS) is an extremely rare genetic disease first described clinically in 1963 [1], and its genetic origin was identified in 1991 [2]. The incidence of this genetic syndrome is 1 in every 100 to 125 thousand live births [3], and despite maintaining an autosomal dominant inheritance, most cases are due to de novo mutations [4, 5]. The epigenetic origin of this syndrome is attributed to alterations in two genes: the CREBBP gene in 50 to 60% of cases and the E1Ap300 (EP300) gene in 8 to 10%. In the remaining 30%, the site of the anomaly is not identified [6].

The CREBBP gene is located on chromosome 16p13.3 and encodes the CBP protein. The EP300 gene is located on chromosome 22q13.3 and encodes the p300 protein [3]. These two 70% homologous proteins [7] are characterized by being transcriptional coactivators that have histone acetyltransferase activity, so they have the ability to modify the chromatin structure and regulate gene expression. For this reason, they are known as epigenetic writers [5]. At present, 406 variants in the CREBBP gene [8] and 134 variants in the EP300 gene [9] that cause Rubinstein-Taybi syndrome have been identified.

This genetic syndrome is clinically characterized by delayed growth, delayed psychomotor development, intellectual disability (mild to moderate), peculiar facial features (including low front hairline, thick arched eyebrows, downward sloping palpebral fissures, Convex nasal bridge with septum below the wings of the nose, high palate, abnormal and low-set ears, grimacing smile), and broad thumbs and first toes [6, 10]. But despite being frequent, it has not been possible to identify specific phenotypic correlations for each gene, and even patients with alterations in the EP300 gene have less marked traits compared to those with CREBBP-gene alterations [11].

The complications described in the different descriptive studies range from dental problems to congenital cardiac problems, passing through alterations in the eye, hearing, the genitourinary system, the neurological level, and the skin (see Table 1) [6, 11]. Below, we present the phenotypic characteristics of a patient clinically diagnosed with Rubinstein-Taybi syndrome with the aim of conducting a review of the most important characteristics in the literature.

Table 1 Complications of Rubinstein-Taybi syndrome – Taybi

Pathology	Frequency
Ocular	
Squint	60 – 71%
Refractive errors.	41 – 56%
Tear duct obstruction	38 – 47%
Coloboma of Iris, retina or optic nerve.	9 – 11%
Cataract, eyelid ptosis, nystagmus, glaucoma, and corneal abnormalities.	ND
Hearing	
Sensorineural / conductive deafness, recurrent middle ear infections.	ND
Dental	
Claw cusps of upper incisors.	73%
Tooth crowding, malaocclusion, multiple cavities, enamel hypoplasia, hypodontia, and hyperdontia.	ND
Cardiac (congenital heart disease)	
Atrial-interventricular communication, patent ductus arteriosus, coarctation of the aorta, aortic stenosis, pulmonary stenosis, dextrocardium, vascular ring and conduction disorders	24 – 38%
Respiratory	
Recurrent upper respiratory infections	75%
Obstructive sleep apnea, aspiration asthma, and anesthetic complications.	ND
Gastrointestinal	
Constipation.	40 – 74%
Gastroesophageal reflux	68%
Megacolon (Hirschprung's disease)	ND
Genitorurinary	
Cryptorchidism	78 – 100%
Hydronephrosis and kidney malformations.	52%
Hypospadias, bladder reflux, nephrolithiasis and UTI	ND
Neurological	
Microcephaly	35 – 94%
Nonspecific EEG abnormalities.	57 – 66%
Seizures	25%
Craniovertebral junction stenosis, neuroradiological alterations (callus corpus dysgenesis, Chiari type I malformations, Dandy Walker malformations)	ND
Orthopedic	
Vertebral abnormalities (C1 –C2 instability), ligamentous laxity, femoral head prolongation.	ND
Skin	
Pilomatrixomas, ingrown nails, paronychia, tendency to form keloids and hirsutism.	24%

EEG: Electroencephalogram. ND: No Data. UTI: urinary tract infection.

Case report

An 8-year-old male patient was the product of the third pregnancy of non-consanguineous parents. During the anamnesis, a delay in psychomotor development was evidenced by a delay in reading (at 5 years), writing (7 years with difficulty until now), speaking (1 year 6 months, pronounces bisyllables), control of the sphincters (diaper use up to 3 years), and difficulties in school adaptation with low academic performance.

He had normal weight and height for his age. Physical examination revealed distinctive facial features characterized by overpopulated and arched eyebrows, hirsutism in the forehead and upper lip region, downward sloping palpebral fissures, hypertelorism with convergent strabismus (Figure 1 and 2), wide nasal bridge and flattened nose, and the tip of the nose extending slightly below the nasal wings (Figures 2 and 3). Hirsutism was evidenced in the cervical and interscapular region (Figure 4). At the musculoskeletal level, in the region of the hands, broad thumbs were identified, and in the other of the fingers, there were widened distal phalanges (Figure 5). In the same way, in the region of the feet, broad halluxes were identified with widened distal phalanges (Figure 6).

Diagnostic workshop

The patient was seen in a pediatric outpatient clinic at Enrique Garcés Hospital. After several visits, he was clinically diagnosed with Rubistein-Taybi Syndrome by applying the clinical criteria (Table 1). We intentionally searched for complementary ocular, auditory, dental, cardiac, respiratory, gastrointestinal, genitourinary, neurological, orthopedic, and dermatological clinical signs, which were negative. Genetic tests were not carried out in the present case.

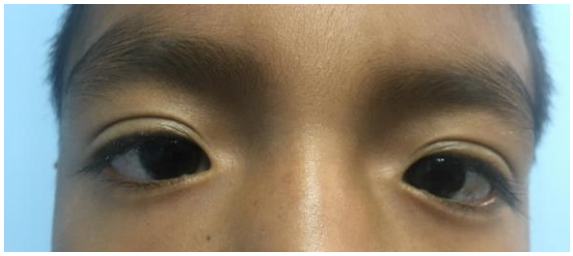

Fig. 1 Facial abnormalities: Thick and arched eyebrows, downward sloping lateral fissures and hypertelorism.

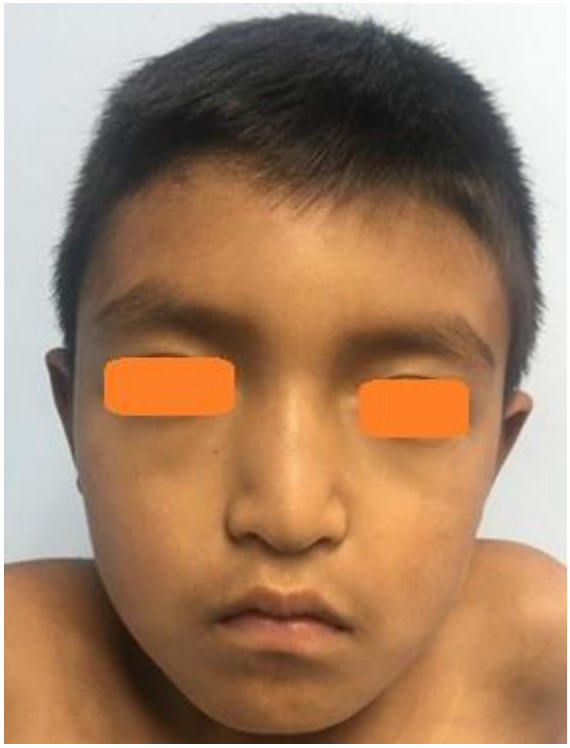

Fig. 2 Hirsutism in the frontal region and upper lip; wide nasal bridge and tip of the nose protrudes below the nasal wings.

Fig. 3 Stuffy nose.

Evolution

The patient is still under outpatient observation, and he was sent to speech, reading, and psychomotor therapy programs. He has not developed lung infections until the close of follow-up 6 months after diagnosis.

Discussion

Rubinstein-Taybi syndrome is a rare genetic disease. Due to this, there are no epidemiological data described in Ecuador [11]. It is caused by an alteration in the CREBBP gene or in the EP300 gene, but despite technological advances, in 30% of the cases, it is not possible to identify the alteration [3]. For this reason, different researchers have sought to correlate the clinical manifestations with the genotype of each patient and identify common clinical features.

In a literature review by Milani et al. [10], they reported that facial features (thick arched eyebrows, downward slant of palpebral fissures, pointed nose that protrudes below the wings of the nose, and an atypical smile), intellectual disability, delayed speech, and broad thumbs and halluxes present an incidence that varies between 90 and 100%. They did not report the genetic origin of each one. o Korzus et al. [3] carried out a review with the aim of comparing phenotypic manifestations based on their epigenetic origin. They identified that participants with positive CREBBP (n = 300) [11–13] present a higher incidence of intellectual disability that is severe, as well as anatomical manifestations, such as broad thumbs and a wide hallux compared to EP300-positive participants (n = 52) [7]. EP300-positive participants were characterized by mild intellectual disability and lower incidence of clinical manifestations.

The results for CREBBP are corroborated by Pérez-Grijalba [5], who added to these clinical expressions (high incidence of intellectual disability, wide thumbs and hallux, arched and thick eyebrows). That study identified a high prevalence of language delay. López [14] and Hamilton [15] did descriptive studies with participants who were positive for EP300. They.

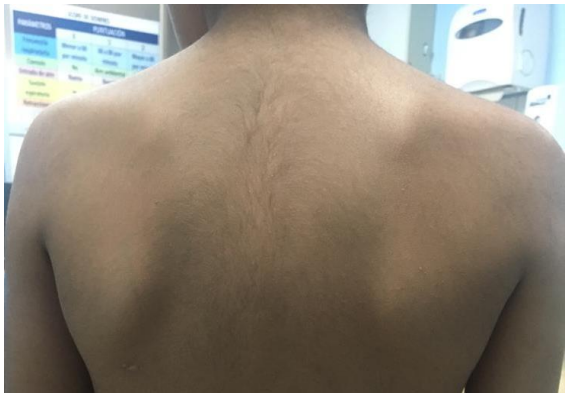

Fig. 4 Hirsutism in the cervical and interscapular region.

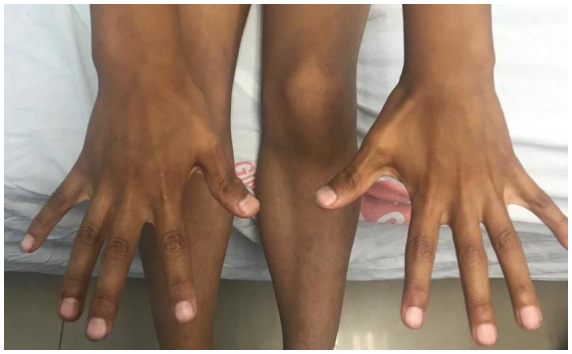

Fig. 5 Wide thumbs and widened distal phalanges (second to fourth fingers).

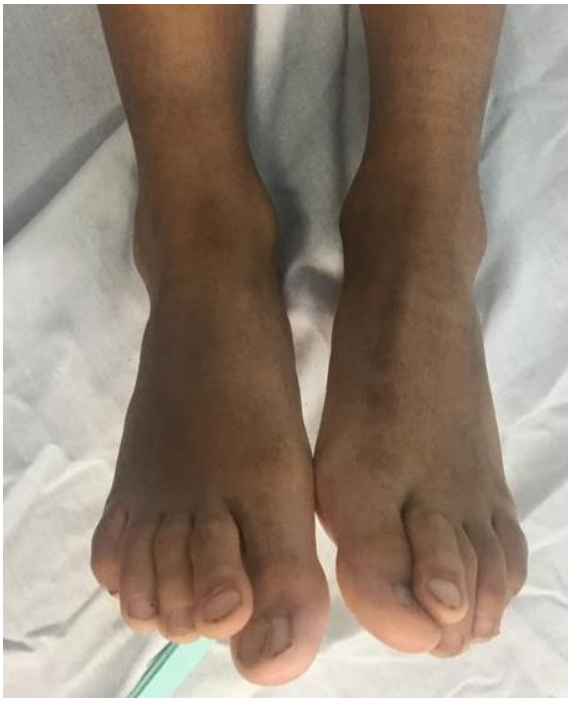

Fig. 6 Wide hallux and widened distal phalanges (from second to fifth toe) in supine position.

Table 2 Incidence of phenotypic characteristics based on epigenetic alteration

Characteristics	Korzus & col.[3]	Pérez-Grijalba & col. [5]	Fergelot y col. [7]	López & col. [14]	Hamilton & col. [15]	Clinical case
Gene altered	CREBBP	CREBBP	EP300	EP300	EP300	ND
Number of participants	308	39	52	84	9	---
Stunted growth	75%	65.7%	66%	ND	ND	No
Intellectual disability	99%	84.2%	94%	62.5%	100%	ND
- Severe	36%	ND	7%	12.5%	0%	
- Moderate	48%	ND	31%	50%	44%	
- Mild	14%	ND	62%	37.5%	56%	
Wide thumbs	96%	100%	69%	87.5%	89%	Yes
Wide Hallux	95%	100%	81%	50%	89%	Yes
Smile making faces	94%	ND	47%	50%	SD	No
Long eyelashes	89%	86.1%	90%	75%	SD	Yes
Tip of the nose below the nasal wings	88%	85.7%	92%	100%	78%	Yes
Arched and thick eyebrows	85%	91.4%	65%	50%	56%	Yes
Convex nasal bridge	81%	82.9%	44%	88%	ND	Yes
Downward sloping palpebral fissures	79%	86.8%	56%	83%	11%	Yes
Hirsutism	76%	78.1%	76%	38%	ND	Yes
Angled thumbs	49%	88.6%	2%	25%	ND	No
Language delay	ND	93.8%	ND	28.5%	100%	Yes
Psychomotor retardation	ND	88.6%	ND	28.5%	89%	Yes

ND.- No data.

reported a lower incidence of phenotypic manifestations, including delay in language, psychomotor development, and clinical anatomical features In this case study, the most frequent signs were identified according to the referenced literature: wide thumbs and halluxes, language delay, arched, and bushy eyebrows (Table 2). One of the difficulties in comparing these studies is the inclusion criteria since there are no clear and specific criteria for the clinical diagnosis of Rubinstein-Taybi syndrome, so it is difficult to maintain regularity in criteria. The few patients positive for EP300 do not allow for the identification of specific phenotypic characteristics.

Descriptive studies with a greater number of patients are needed, as well as systematic reviews to identify specific characteristics and generalize the clinical diagnosis of these patients. Patients with CREBBP-positive Rubinstein-Taybi syndrome present a higher incidence of intellectual disability, speech and growth retardation, with more marked morphological abnormalities than EP300-positive patients.

Conclusions

In this case report, we described the phenotypic alterations of the facial and limb characteristics of a child with Rubinstein-Taybi syndrome, which helped the clinical diagnosis.

Abbreviation

RSTS:. Rubinstein-Taybi syndrome.

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Authors' contributions

All authors contributed equally to this scientific article.
All authors read and approved the final version of the manuscript

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Availability of data and materials **The data sets generated and / or analyzed during the current study are not publicly available due to the confidentiality of the participants, but are available through the corresponding author upon reasonable academic request**.

Ethical statements

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

Data confidentiality The authors declare that they have followed the protocols of their work center on the publication of patient data without identification.

Publication consent Written informed consent was obtained from the patient's legal guardian for the publication of this case report and the accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal

Conflicts of interest The authors declare that they have no conflicts of interest.

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