

CASE REPORT

McCune-Albright syndrome case report

Síndrome de Mc Cune-Albright presentación de un caso

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ABSTRACT

**Introduction:** McCune Albright syndrome (SMA) is considered a rare genetic disease, characterized by bone dysplasia, endocrine disorders and hyperpigmentary skin lesions. In SMA, postzygotic somatic mutations occur in the Gs protein gene (GNAS1) and an increase in CAMP, modifying the formation of osteoblasts and increasing bone resorption by osteoclasts, denying the hereditary nature of this disease and the possibility of rapid bone consolidation.

**Objective:** to point out the need to deepen the knowledge of the disease for early detection and multidisciplinary care in order to avoid the consequences.

**Method:** retrospective observational study of the clinical history of a patient treated in the orthopedic service of the San Isidro General Hospital in Tocoa, Honduras.

**Results:** a 13-year-old patient was admitted to the orthopedic service due to a pathological fracture of the right humerus, in which lytic lesions were observed in the humerus, radius, femur and tibia on the same side, as well as varus deformity of the right hip; café-au-lait spots on the chest and abdomen that did not respect the midline; Tanner 4 breast and pubic bone, vaginal bleeding at 3 months of age, hyperthyroidism and microprolactinoma; pathological fractures of the neck of the femur and right tibia on two occasions at 3 years of age and surgery at 6 years of age. It is interesting to note that the patient's mother had café-au-lait spots on the dorsal region. Plaster treatment of the humerus fracture was performed, achieving bone consolidation at 10 weeks.

**Conclusions:** the asymmetric appearance of the spots in the patient and the rapid bone consolidation are rare clinical aspects of the syndrome. The irregular treatment of her illness and its complications generated sequelae in the patient, which limited her quality of life, highlighting the need for early detection of the disease and multidisciplinary care.

**Keywords:** Mccune Albright Syndrome; Bone Fibrous Dysplasia; Café Au Lait Spot; Endocrine Disorders.

RESUMEN

**Introducción:** el síndrome de Mc Cune Albright (SMA) está considerada una enfermedad genética rara, caracterizada por displasia ósea, trastornos endocrinos y lesiones hiperpigmentarias de la piel. En el SMA se producen mutaciones somáticas poscigóticas en el gen de la proteína Gs (GNAS1) y un aumento del AMPc modificando la formación de los osteoblastos y aumentando la reabsorción ósea por los osteoclastos, negándose, el carácter hereditario de esta enfermedad y la posibilidad de una rápida consolidación ósea.

**Objetivo:** señalar la necesidad de profundizar en el conocimiento de la enfermedad para una detección temprana de la misma y atención multidisciplinaria a fin de evitar las secuelas.

**Método:** estudio observacional retrospectivo de la historia clínica de una paciente atendida en el servicio de ortopedia del Hospital General San Isidro de Tocoa Honduras.

**Resultados:** se presenta una paciente de 13 años de edad que es internada en el servicio de ortopedia por presentar fractura patológica supracondilia de húmero derecho, en la que se observan lesiones líticas en húmero, radio, fémur y tibia del mismo lado, así como deformidad en varo de la cadera derecha; manchas café con leche en tórax y abdomen que no respetaban la línea media; Tanner 4 mamario y pubiano, sangrado vaginal a los 3 meses de edad, Hipertiroidismo y Microprolactinoma; fracturas patológicas de cuello de fémur y tibia derecha en dos ocasiones a los 3 años y operada a los 6 años. Es de interés señalar que la madre de la paciente presentaba mancha café con leche en región dorsal. Se realizó tratamiento con yeso de la fractura de húmero lográndose consolidación ósea a las 10 semanas.

**Conclusiones:** la aparición asimétrica de las manchas en la paciente y la rápida consolidación ósea, resultan aspectos clínicos poco frecuentes del síndrome. El tratamiento irregular de su enfermedad y sus complicaciones generaron secuelas en la paciente, que limitaron su calidad de vida, evidenciándose la necesidad de una detección temprana de la enfermedad y atención multidisciplinaria.

**Palabras claves:** Síndrome de McCune Albright; Displasia Fibrosa Ósea; Mancha Café con Leche; Trastornos Endocrinos.

## INTRODUCTION

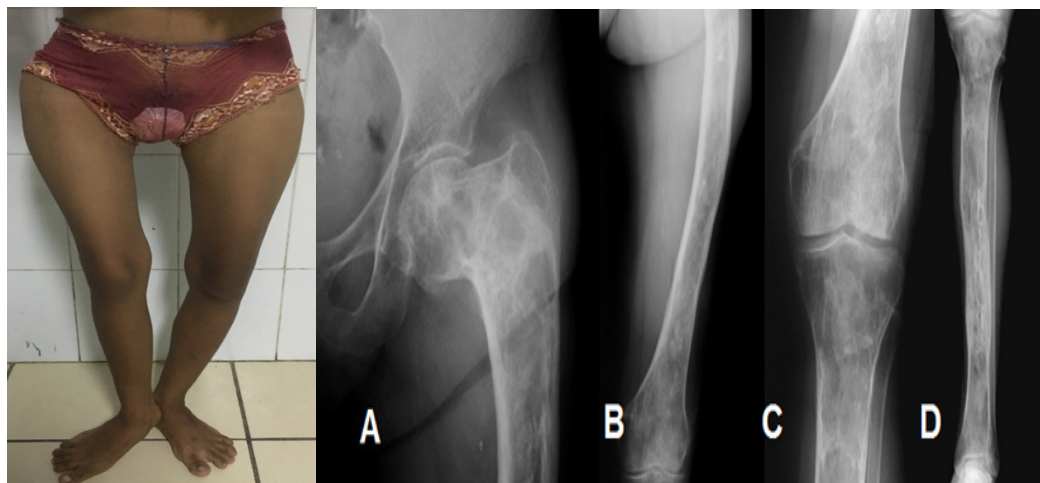
McCune Albright Syndrome is a non-hereditary congenital disease characterized by a triad of clinical signs, fibrous bone dysplasia, the presence of café-au-lait skin lesions and endocrine disorders, considered a rare disease with an estimated prevalence between 1/100000 and 1/1000000.<sup>(1,2)</sup> Genetic studies of G proteins have identified that alterations occur on the long arm of chromosome 20 (20q13.2) in the GNAS1 gene, in which postzygotic somatic mutations of the mosaicism type occur in different tissues, giving rise to the clinical manifestations.<sup>(3,4)</sup> Fibrous bone dysplasia includes one or several bone segments of the skeleton, generally unilateral, progressive during childhood or adolescence, and static in its evolution during adulthood; clinically, it presents as pathological fractures or deformities of the skull, facial, scoliosis, deafness or loss of vision, it is estimated that only 1 % of these lesions evolve to malignancy.<sup>(4,5)</sup>

In the different forms of dysplasia, there is a progressive substitution of bone tissue by fibrous tissue as a result of mutations in the subunits of the Gs protein that produce an increase in cAMP, altering the differentiation of osteoblasts associated with an increase in bone resorption by osteoclasts, so that the conditions for bone consolidation are very limited in these patients.<sup>(6)</sup> This syndrome is more common in the female sex. One of the most common manifestations is precocious puberty, due to a heterozygous activating mutation of the gene coding for the alpha subunits of the G protein, resulting in continuous stimulation of endocrine functions leading to precocious puberty, hyperthyroidism, Cushing's disease, gigantism, hyperprolactinemia, acromegaly, hyperparathyroidism, hypercorticism, etc.<sup>(7,8)</sup> Café-au-lait spots are typically the first clinical manifestations of the syndrome and are due to the activating function of G-protein on melanocytes; they retain the characteristic of being irregular borders and do not cross the midline; the trunk and face are most commonly affected.<sup>(9,10)</sup> The treatment of these patients has undergone significant progress, such as the use of peripheral blood leukocytes for the detection of Gs protein mutations (R201H and R201C) in an easily accessible tissue such as blood, the use of drugs aimed at regulating precocious puberty, such as inhibitors of synthesis of G-protein synthesis in melanocytes, the use of drugs aimed at regulating precocious puberty, and the use of drugs aimed at regulating precocious puberty, such as inhibitors of sex steroid synthesis as well as other drugs in the control of thyroid metabolism, bisphosphonates to improve bone quality and modern devices in the osteosynthesis of fractures and their complications.<sup>(11,12,13)</sup> The above clinical variations in the patient highlight the diversity of the syndrome in which bone, skin, and endocrine symptoms can change in their onset forms. The presence of sequelae affected the patient's quality of life, which is why this study aims to point out the need for early detection and multidisciplinary care of the disease, achieving a better incorporation of these patients into social life.<sup>(14)</sup>

## CASE REPORT

13-year-old female patient was admitted to the orthopedic service of the General Hospital San Isidro in Tocoa, Honduras, in February 2018, for presenting with pathological fracture supracondylar right elbow after a fall from her feet, with a personal history of: pathological fracture of right femur and tibia on two occasions at 3 and 6 years of age, operated on right hip (bone graft) at 6 years of age and with the diagnosis of Hyperthyroidism and Microprolactinoma during infancy, as well as vaginal bleeding at 3 months of age. Healthy mother G: 3 A: 1 P: 2 prenatal controls: 7, with the presence of café-au-lait spots in the dorsal region of the thorax. Father healthy. The patient was born of normal birth, walks at 2 years old, and has normal cognitive development. Physical examination: standard fascia, discrete exophthalmos, Tanner 4 mammary and pubic, deformity and increase of volume in the elbow and varus of the right hip, dorso-lumbar scoliosis, shortening of 3 centimeters of the right

lower limb (figure 1); brown spots with irregular edges in the thorax that do not respect the midline (figure 2).



**Figure 1.** Coxa vara and shortening of the right lower limb; images of bone dysplasia in the right hip femur and tibia



**Figure 2.** Coffee-with-milk spots crossing the midline in the dorsal region and neck; use of cast immobilisation

The results of the blood tests performed were:

- Hb: 9,7g/dl, Hto: 30,22 %, Plt: 493,000/ 10,9 /L
- GB: 12,600, Glicemia: 92 mg/dl, Creatinina: 0.5 mg/ dl
- FSH: 0,1mUI/ml, LH: 0,02mUI/ml, Prolactina: 13,5 ng/ml
- T3: 1,32 ng/dl, T4:0,9 ng/dl, TSH: 1,32mUI /L

In plain radiographs, osteolytic images were observed taking the suprachondrial region of the right humerus and extending to the diaphysis and thinning of the cortices, also taking the radius, femur and tibia on that side (figure 3).



**Figure 3.** Pathological suprachondrial fracture of the right humerus, note images of bone dysplasia at the fracture site, humerus, ulna and radius

For orthopedic treatment, the patient underwent closed fracture reduction and immobilization with a plaster splint, with healing achieved in 10 weeks (figure 4).



Figure 4. Bone consolidation after 10 weeks of treatment, persistence of humeral bone dysplasia lesions

## DISCUSIÓN

It is of great interest to reach the diagnosis of this syndrome (SMA) if we consider that due to its low prevalence, it appears among the rare congenital diseases coded according to ORPHA: 562. The clinical triad that characterizes it, precocious puberty, fibrous bone dysplasia, and café au lait skin spots, have been present in the patient we present. The mutation and activation of the alpha subunit of the G protein are responsible for the congenital anomalies that give rise to the syndrome.<sup>(1,2)</sup>

The phenotype of SMA is caused by the activation of a postzygotic somatic mutation of the GNSA1 gene mosaicism type with different clinical manifestations depending on the tissue affected by the mutation in the gene so that the manifestations will be sporadic and diverse; in our patient, the large number of cell lines involved by the mutation is evident. The criterion of the non-hereditary origin of the syndrome is unanimous, so it is a curiosity to have found the café au lait spots on the back of the patient's mother.<sup>(3,4)</sup>

The cases reported in the literature show a great diversity of atypical forms of presentation of the syndrome, in which fibrous dysplasia and some other signs have always been present.<sup>(16,17)</sup>

The first manifestation of the syndrome in the patient presented here was the appearance of café-au-lait spots at birth, with no change in intensity during growth or variation in position, with irregular borders, atypically crossing the midline, a clinical sign that does not correspond to that described in the literature in which it is almost unanimously stated that 'these lesions respect the midline'; Some studies have considered that the skin lesions are not related to the most severe clinical forms of the syndrome and in some patients they were seen between 6 months and 6 years after the onset of precocious puberty.<sup>(1,2,18)</sup>

The early appearance of these lesions, which crossed the midline and did not involute during growth, shows the severity of the mutations in the patient's melanocytes.<sup>(3,4,13)</sup>

The appearance of vaginal bleeding at 3 months of age is the second clinical manifestation of the syndrome. The early appearance of the mammary bud and pubic hair, Tanner 4 mammary and pubic hair, shows that precocious puberty was the most important endocrine hyperfunction due to ovarian hypersecretion derived from ovarian function independent of hypothalamic-pituitary control, as evidenced in the patient, who had a cyst in the right ovary.

The diagnosed hyperthyroidism remained with subclinical manifestations of the disease, and the finding of a micro prolactinoma at 10 years of age was another endocrine manifestation of the syndrome for which she did not receive treatment due to her socioeconomic conditions. The patient's skeletal maturation remained advanced during growth even though the height achieved was to her genetic potential. This aspect coincides with the results of other studies, which is explained by the fluctuating nature of ovarian activity in the control of bone maturation.<sup>(1,18,29,20)</sup>

The first sign of bone dysplasia appeared when the patient suffered a pathological fracture of the right femur at the age of 3 years, and other lesions were also observed scattered throughout the right femur, for which she underwent surgery at the age of 6 years, as well as two fractures of the tibia on the same side. The polyostotic form of the dysplasia in the patient confirms the presence of the syndrome, who also suffered a



supracondylar fracture of the right humerus, and other lesions were observed in the humerus and radius on the same side.

These lesions have marked a stage of crisis of the disease between the ages of 3 and 6 years in which the most critical fractures and deformities occur with a period of pause of the metabolic disorder. Only at 13 years of age does another ipsilateral fracture occur; the diversity and intermittency in the appearance of the symptoms coincide with the results of other studies.<sup>(21,22)</sup> The favorable evolution of the patient with the conservative treatment of the supracondylar fracture of the humerus and its rapid consolidation represents another of the curiosities of the case we present because, as has been pointed out, the deformed state of the osteoblasts and the high bone resorption generated by the osteoclasts, do not allow rapid bone consolidation in this syndrome, according to the reports of other studies the estimated consolidation for this patient should be between 12 and 15 weeks.<sup>(11,23)</sup>

In the literature reviewed, we observed that there could be a broad clinical spectrum for the same molecular defect, so the atypicality noted in the patient is part of the heterogeneity of the syndrome.<sup>(24,25)</sup> The serious sequelae of this patient demonstrate the importance of knowledge of the disease to achieve an early diagnosis and avoid the complications that complicate its treatment; the advances achieved justify the creation of national societies for the care of these so-called rare diseases, and the development of new drugs and means that, from a multidisciplinary point of view, provide a solution to such a complex disease.<sup>(26,27)</sup>

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The authors declare that there is no conflict of interest.

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