

## CASE REPORT

**CASE REPORT: CENTRAL PRECOCIOUS PUBERTY IN A CHILD WITH  
BLOCH-SULZBERGER SYNDROME.**

RELATO DE CASO: PUBERDADE PRECOCE CENTRAL EM UMA CRIANÇA COM  
SÍNDROME DE BLOCH-SULZBERGER.

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**ABSTRACT**

**Objective:** To describe a case of a child with Incontinentia Pigmenti associated with precocious puberty. **Case description:** a 1 year 7 months old female baby was taken by her parents to a medical appointment because of an aggravation of skin spots with a latté color disseminated throughout the body, which appeared when the child was five months old. The mother also referred premature thelarche and premature pubarche since the child was three months old.

**Comments:** Precocious puberty is defined as the development of secondary sexual characteristics before the age of eight in girls and nine in boys. The Bloch-Sulzberger syndrome, or Incontinentia Pigmenti, is a disorder linked to the X chromosome that affects the skin, eyes, teeth and may be associated with neurological deficits. As much as this specific syndrome involves multiple organs and systems, there was no association with an endocrine disorder.

**Key-words:** Precocious puberty, Bloch-Sulzberger syndrome, Incontinentia Pigmenti.

## RESUMO

Objetivo: Descrever o caso de uma criança com Incontinência pigmentar associada à puberdade precoce. Descrição do caso: uma criança do sexo feminino de 1 ano e 7 meses foi levada pelos seus pais a uma consulta médica devido ao agravamento de lesões cutâneas de coloração marrom, disseminadas por todo o corpo, que surgiram quando a criança possuía cinco meses de vida. A mãe também queixou de telarca e pubarca precoces, presentes desde os três meses de vida. Comentários: Puberdade precoce é definida como o desenvolvimento de características sexuais secundárias antes dos oito anos em meninas, ou antes dos nove anos de idade nos meninos. Já a Síndrome de Bloch-Sulzberger, ou Incontinência Pigmentar, é uma desordem ligada ao cromossomo X que afeta a pele, os olhos, os dentes e pode estar associada a déficits neurológicos. Por mais que essa síndrome específica envolva múltiplos órgãos e sistemas, não há associação com um distúrbio endócrino.

**Palavras-chave:** Puberdade precoce; Síndrome de Bloch-Sulzberger; Incontinência Pigmentar.

## INTRODUCTION

Puberty is the biological maturation process that, through hormonal changes, culminates in the appearance of secondary sexual characteristics, speeding up the growth rate and, finally, the acquisition of reproductive capacity of adult life<sup>1</sup>.

Precocious puberty (PP) is defined as the development of secondary sexual characteristics before the age of eight in girls and age nine in boys. It is classified as central PP, when the sexual characteristics develop by precocious activation of the hypothalamic-pituitary-gonadal axis (HPG) or peripheral PP, when the steroids secretion occurs independently of the secretion of gonadotropins LH (luteinizing hormone) and FSH (hormone follicle stimulating)<sup>2</sup>. It is a rare condition, with an estimated incidence of 1:5,000-1:10,000<sup>3</sup>, more common in girls, and in 80% of central PP cases, the etiology is idiopathic<sup>2</sup>.

The Bloch-Sulzberger Syndrome or, Incontinentia Pigmenti (IP), is a dominant ectodermal disorder linked to the X chromosome. It affects the skin, eyes,

teeth and may be associated with neurological deficits. It has an approximate incidence of 1: 50,000 and it is typically lethal in males<sup>4</sup>. In 50% of the cases, there is a family history. Recently, the IP's cause was attributed to a mutation that inactivates the NEMO gene located on the X chromosome (q28). The cutaneous presentation of IP regresses spontaneously by selective elimination of the cells presenting mutant X-chromosome, with gradual replacement by normal cells<sup>5</sup>. Usually, dermatological findings are the first sign observed<sup>4,5</sup>.

## CASE REPORT

C. P. M, female, 1 year 7 months old baby was taken by her parents to a medical appointment with an endocrine-pediatrician. The mother reported an aggravation of skin spots with a latte color, brindle aspect, disseminated throughout the body, which appeared when the child was five months old. The mother also referred premature thelarche and

premature pubarche since the child was three months old.

In the past obstetric history of the mother, there was an adequate prenatal care and no gestational pathologies. The child was the first one, born by natural vaginal delivery, at term, without complications, and with an appropriate weight and height at birth. The child had no associated diseases or past trauma, having only one ulnar fracture when she was nine months old. In addition, there was no evidence of medication use. The parents were healthy and the mother reported menarche at the age of 14. In anthropometry, the mother's height was 1.70 m high, the father height was 1.83 m high and the child target height was 1.70 m high, with a standard deviation of + or - 8 cm.

In clinical examination, it was seen diffuse light brown colored swirling hyperpigmentation in the child body (Figure 1). The child had a weight of 13.200 kg (p 75) and the height of 89 cm (above p 97.5). In relation to pubertal development, according to the Tanner stages, the child was M1 P2. The palpation

of the thyroid gland revealed no abnormalities.



Figure 1: 5 years old child. Light brown colored swirling hyperpigmentation typical of Incontinentia Pigmenti – third stage.

The mother had exams of when the child was eight months old, which were: 1) left hand and wrist X-ray, evaluated by the Greulich–Pyle methods, who revealed bone age of two years old; 2) a normal bone scan; 3) a normal cortrosyn stimulation test; 4) an abdominal ultrasound revealing an infantile uterus and ovaries; 5) LH = 0.43 mIU/ml; FSH: 6.58 mIU/mL (prepubertal values); and normal values of adrenal hormones.

Because of these results, we requested a GnRH stimulation test (75 mcg/m<sup>2</sup>) and a new left hand and wrist X-ray. A month and a half later the mother returned with the tests results, which showed a bone age of three years old (when chronologically the child was 1 year 8 months old); LH peak of 13.3 U/L and FSH peak of 55.2 U/L. In the new anthropometric examination, the results showed that the child had a height of 90,5 cm, demonstrating a growth velocity (GV) of 9 cm/year evaluated in the period of a month and a half. Estradiol (Chemiluminescence) was below 20, showing infantile ovaries. The child was diagnosed with precocious puberty and it was decided to start drug treatment due to the target height loss.

At the age of two, the child began treatment with Leuprolide acetate 3.75 mg IM every 28 days. It was also recommended a dermatology appointment for elucidation of skin lesions.

In appointment with the dermatologist, the child was diagnosed with Bloch-Sulzberger Syndrome

(Incontinentia Pigmenti), which was later confirmed by histopathological analysis of biopsied skin. It is a genetic syndrome, X-linked, whose available medical management is based purely on clinical follow-up. Therefore, it was recommended that a neurologist and an ophthalmologist should evaluate the child for diagnosis and monitoring of possible changes resulted from the syndrome itself. The first doctor requested a Magnetic Resonance Imaging (MRI) of the brain, which showed mild ectasia of the lateral ventricles and the fourth ventricle. Nevertheless, according to the evaluation of the doctor, the child showed no cognitive or neurological deficits. In relation to ocular changes, there was a refractive disorder (astigmatism) and keratitis, both were being treated by the responsible doctor.

After two years of treatment for precocious puberty, at the age of 3 years and 10 months old, the child was in good physical development, which was proved by the fact that she had achieved adequate weight and height for the age (Weight: 22.500 kg; Height: 112, 5 cm). There was a

bone age progression (bone age of 6 years old), however, with recovery of the target height. In this period, new laboratory tests showed suppressed dosages of FSH and LH. Currently, the child remains under care with endocrine-pediatrician.

## DISCUSSION

The Bloch-Sulzberger syndrome presents a nonspecific histological characteristic where there is a melanin incontinence on melanocytes of the basal layer in the superficial dermis<sup>5</sup>. In 90% of cases, in the first two weeks of life, the skin lesions appear and are characterized by four stages (4,5), which may occur concurrently or sequentially: 1) vesicular (blisters and vesicles located in the limbs, scalp and, sometimes, on trunk; 2) hyperkeratotic (linear hyperkeratotic plaques); 3) hyperpigmented (brownish pigmentation following the Blaschko's lines); 4) atrophic (skin atrophy zones)<sup>6-9</sup>. The child presented itself in the third stage, with light brown colored swirling hyperpigmentation skin lesions that followed the Blaschko's lines,

and that spread throughout the body (Figure 1).

In about 70-80% of cases, extracutaneous manifestations may occur. These include: dental abnormalities, that may be present in more than 80% of cases, as partial or total anodontia, conical teeth and tooth eruption delay; scarring alopecia in the scalp; nail dystrophy (7-40%) and ophthalmological manifestations (30%), which are the most serious and are usually associated with some neurological impairment<sup>6</sup>, including seizures, spastic paralysis, motor retardation and microcephalus<sup>5</sup>. Strabismus, nystagmus, cataract and optic nerve atrophy may occur. The retinal lesions are the result of vaso-occlusive events<sup>5</sup>. The child showed no such dental or ocular changes related to the syndrome, but the ectasia of the ventricles is an unusual sign resulted from the neurological involvement<sup>6</sup>. Both findings must be followed up by the appropriate specialties.

As much as this syndrome affects multiple organs and systems, the association with an endocrine disorder is

not common. The authors of this article searched in SciELO and Medline databases publications about this association, but no articles were found. This was again confirmed by a contact made with the Brazilian Society of Dermatology, which denied having scientific material that relates this syndrome to some endocrine disorder.

In the presented case, the child began to show clinical signs of precocious puberty at the age of three months, being observed by the mammary gland development, a fact that could be physiological, however, the bone age progression warned for the possibility of pathological PP. According to the literature, in girls, the development of the breast tissue and increased growth rate are the initial events of PP, under the influence of estradiol; while in boys, the increase in testicular volume > 4 ml or penis size > 2.5 cm are the first clinical manifestations of puberty<sup>2</sup>.

The diagnosis is confirmed by clinical findings, including the Tanner's stages and growth spurt, accelerated bone maturation, the GnRH

stimulation test results and, in girls, the evaluation of uterine and ovarian volume in the pelvic ultrasonography<sup>2</sup>. The child's classification M1 P2 at Tanner's stages confirmed the beginning of puberty. Besides, the discrepancy between bone age (BA) and chronological age (CA), analyzed by the left hand and wrist X-ray according to Greulich- Pyle's methods, showed an acceleration of the child's growth, and loss of target height in case the treatment wasn't promptly started.

Pelvic ultrasound in girls helps the evaluation of uterine and ovarian volumes, besides allowing the analysis of cysts and neoplasia as differential diagnosis of precocious puberty<sup>3</sup>. As this examination was normal in the children, as there was no history of use of external steroids, the possibility of precocious puberty of peripheral origin was dismissed. The central origin of the disease was again confirmed in the GnRH stimulation test. According to the most sensitive laboratory methods, basal LH value > 0.6 U/L (immunofluorometric method) or > 0.2 U/L (chemiluminescence method) in both genders is considered

pubertal<sup>3,10,11</sup>. As the child presented with LH peak of 13.3 U/L, it was possible to confirm the diagnosis of puberty.

Treatment with GnRH analogs (aGnRH) is indicated when the central PP is progressive. The goals of treatment are: to stop sexual development until the normal age of puberty onset; to slow growth and skeletal maturation; to avoid emotional problems in children; to delay the onset of sexual activity; to prevent pregnancy; to reduce the risk of sexual abuse and to reduce the risk of breast cancer associated with early menarche. Many GnRH are available as depot such as leuprolide acetate, goserelin and triptorelin, among others, intramuscular, subcutaneous or transdermal implants. The most used is the leuprolide acetate. The appropriate dose for satisfactory pubertal blocking varies around 3.75 to 7.5 mg every 28 days<sup>3</sup>. In this case, drug treatment with 3.75 mg of leuprolide acetate IM was enough to stop the child's growth. Ideal weight and height for age were reached, the target height was recovered and the bone age progression was stabilized.

Considering that precocious puberty and the Bloch-Sulzberger Syndrome are rare diseases, the description of a case in which both are associated makes this publication an interesting one, even more by the fact that no articles were found to relate this syndrome to any other endocrinopathy.

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#### CONFLICT OF INTEREST

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