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Case report

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Bloom's syndrome: 5 siblings living in a sunny area of Brazil

Abstract

Bloom's syndrome is an extremely rare inherited disorder. We present 5 cases of Bloom's syndrome in a Brazilian family living in a very sunny area. Patients were born from a consanguineous union of second-degree cousins and presented growth retardation, narrow facies with poikiloderma, café-au-lait macules and photosensitivity.

Keywords: Bloom's syndrome, genodermatosis, photosensitivity

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Introduction

Bloom's syndrome (BS) is a rare autosomal recessive disorder characterized by photosensitivity, facial telangiectasias, short stature, different degrees of immune disorders and a high predisposition to several malignancies, associated with underlying chromosomal instability.[1] It was first described in 1954 by David Bloom[2] and just over 250 cases have been documented. It can also be associated with other conditions such as diabetes mellitus, hypogonadism, infertility and ocular disorders.[3,4] To date, few cases have been reported in different countries, with one third of cases being found in Ashkenazi Jew population.[2] Sister chromatid exchange test is currently the standard method to confirm the BS diagnosis,[5] although the exclusion of differential diagnoses, in clinical basis, may also lead to the diagnosis, as we see in the family here portrayed. When in face of a patient with extreme photosensitivity and short stature, Rothmund-Thomson's syndrome, erythropoietic protoporphyria and Cockayne's syndrome should also be considered as possible diagnosis. Since BS has a poor prognosis, with high mortality secondary to malignant tumors, early diagnosis is fundamental. Patient management is usually symptomatic and with a multidisciplinary approach. Close follow-up is important for opportune detection of malignant tumors and infections.[1]

Case reports

Patient 1

23-year old female patient, born from consanguineous parents. She was referred to a dermatologist due to her photosensitivity. Physical examination revealed an appearance of a much younger person, short stature (129cm; - 5,15standard deviations [SD] from the mean) and low weight (25.2kg-3.5SD from mean). She had narrow and elongated facies, short forehead, prominent nose and high-pitched voice. Dermatological examination showed multiple café-au-lait oval-shaped maculae, of 5-30mm in diameter, on the anterior and posterior face of the trunk, and poikiloderma on the malar region and nasal bridge. Computed tomography (CT) scan of thorax showed several bronchiectasis in the lingula, medium lobe and both inferior lobes and also partial atelectasis of lingula and middle lobe. CT scan of head showed inflammatory sinusopathy at left maxillary sinus (Figure 1a).

Patient 2

17-year old male patient born from consanguineous parents (first degree cousins). Throughout his life, has suffered from various health problems, specially related to the urinary tract (recurrent urinary tract infection), that lead to a Mitrofanoff procedure at age 14. At physical examination revealed younger-than-apparent age, short stature (147cm;<3.89 standard deviations [SD] from the mean) and low weight (37.4kg;< 2.56SD from mean). He exhibited narrow and elongated facies, short forehead, prominent nose and high-pitched voice. Dermatological examination showed multiple café-au-lait oval-shaped maculae, of 5-30mm in diameter, on the posterior and anterior face of the trunk, and poikiloderma on the malar region and nasal bridge. The patient has remained under regular surveillance for the development of any malignancy, with preventive measures, such as sunscreens and sunlight avoidance(Figure 1b).

Patient 3

24-year old male patient born from consanguineous parents (first degree cousins). He described a series of urinary tract and skin infections throughout life. At physical examination, revealed younger-than-apparent age, short stature (147cm;<3.88 standard deviations [SD] from the mean) and low weight (34.5kg;<2.82SD from mean). Heshows narrow and elongated facies, short forehead, prominent nose and high-pitched voice.Dermatological examination showed multiple café-au-lait oval-shaped maculae, of 5-30mm in diameter, on the posterior and anterior face of the trunk, and poikiloderma on the malar region and nasal bridge. This patient shows less visible clinical features than most of his siblings and is now married. The patient has remained under regular surveillance for the development of any malignancy, with preventive measures such as sunscreens and sunlight avoidance(Figure 1c).

Patient 4

12-year old male patient born from consanguineous parents (first degree cousins). Parents described a series of skin and pulmonary infections throughout life. At physical examination revealed younger-than-apparent age, short stature (125cm;<3.08 standard deviations

[SD] from the mean) and low weight (22.6kg;<1.91SD from mean). Heshows narrow and elongated facies, short forehead, prominent nose and high-pitched voice like his siblings, but is the one which typical phenotype is less evident. Dermatological examination showed light poikiloderma on the malar region and nasal bridge. The patient has remained under regular surveillance for the development of any malignancy, with preventive measures such as sunscreens and sunlight avoidance (Figure 1d).

Patient 5

14-year old male patient born from consanguineous parentes (first degree cousins). Parents describe a series of skin and pulmonary infections throughout life.At physical examination revealed younger-than-apparent age, short stature (141cm;<2.73 standard deviations [SD] from the mean) and low weight (27.4kg;<2.28SD from mean). He shows narrow and elongated facies, short forehead, prominent nose and high-pitched voice. Dermatological examination showed very prominent poikiloderma on the malar region and nasal bridge. The patient has remained under regular surveillance for the development of any malignancy, with preventive measures such as sunscreens and sunlight avoidance. Thorax CT scan revealed bronchiectasis at inferior lingula (Figure 1e).

Figure 1 Characteristic sun-sensitive facial rash (from left to right 1a-1e).

Discussion

In 1954, Dr. David Bloom, a dermatologist from New York, reported 3 children with telangiectatic erythema and short stature.[6] He suggested that this condition represented a unique human syndrome. Soon thereafter, working at the New York Blood Center, Dr. James German began to follow persons with BS and to maintain clinical information, as well as a repository of biological samples in the Bloom's Syndrome Registry, which he established in 1960. In 1965, he published his observations of increased chromosome breakage and an increased risk for cancer in persons with BS.[7] In 1994, the genetic locus for BS was mapped to chromosome sub band 15q26.1 through homozygosity mapping[8] and through linkage disequilibrium studies in affected and unaffected individuals. Subsequent investigations have confirmed the increased carrier frequency in the Ashkenazim through DNA analysis of the common Ashkenazi mutation (blmAsh) in anonymous samples of persons with no known history of BS.[9] We now recognize that the presence of blmAsh in over 95% of the BS chromosomes in Ashkenazi Jews results from identical by descent inheritance from a common founder. The BLM mutations so far identified have also suggested additional founder mutations. Among 64 different mutations that were reported in 2007, 19 were recurrent, including several from Portuguese/Brazilian, Japanese, Anglo-German, and Italian American persons.[10] A recurrent founder allele (c.1642C>T) of BLM has also been identified in Slavic populations of Eastern Europe.[11]

Clinically,BS is characterized by abnormal growth, feeding difficulties in infancy, skin changes, immune deficiency, insulin resistance, an increased risk for diabetes, and an increased risk to develop cancer at a young age.[12] With regard to facial features of patients with BS, they may be indistinguishable from their age-matched peers, although, more commonly, they present differences in appearance that include a long and narrow face, underdeveloped malar area, and retrognathia or micrognathia.[7] Most people with BS have a head circumference that is below the 3rd percentile.[13] In spite of this reduced head circumference, intelligence is commonly normal.[14] Concerning to growing, it can be below the normal both in prenatal and postnatal period. Further, length and weight are affected and, by young adulthood, stature and weight are clearly deficient.[13] Contradictorily, growth hormone production and secretion are normal, as are serum concentrations of IGF-1 and IGFBP-3.[13,15]

Persons with BS typically have normal skin at birth and during early infancy. As they age, most patients develop a rash that appears initially on the face and which is exacerbated by sun exposure. Over time, the rash often appears on the dorsum of hands and forearms in children and adults.[16] Other reported cutaneous manifestations include cheilitis, fissuring, blistering, alopecia areata, eyebrow and eyelash hair loss, café au lait macules and areas of skin hypopigmentation are common and may be larger and more numerous than typically seen in unaffected individuals.[17,18] Additionally, subcutaneous adipose tissue is usually remarkably sparse, which results in a wasted appearance that is most obvious in children.[15]

Cancer is the most frequent and serious medical complication seen in individuals with BS and is the most common cause of death. Individuals with BS have an increased risk to develop skin cancer and, among the 168 patients in the Bloom Syndrome Registry who developed a malignancy, 27 developed skin cancer at a mean age of 31.7 years.[19] The most common skin tumor is basal cell carcinoma. No one

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in the Bloom's Syndrome Registry has had melanoma. Alongside with skin cancer, leukemia, lymphoma and the solid tumors of digestive and respiratory tracts are the most frequently occurring cancer type in persons with BS.[20]

Beginning with some of the first-described patients with BS, investigators have noted a pattern of recurrent infection that has suggested deficient immune function.[7] These infections are usually upper respiratory and gastrointestinal infections, and no consistent organism or class of organisms has been identified. Chronic lung disease is a serious complication of BS and a significant cause of early mortality. Ultimately, individuals with BS are subject to endocrine disturbances, particularly abnormalities of carbohydrate metabolism and insulin resistance.[15] Impaired fertility is a known sequela of BS and male patients are invariably infertile and have been found to have azoospermia or severe oligospermia.[14]

Though there are no established diagnostic criteria, a suggestive pattern of growth and medical problems lead to suspicion and rule out differential diagnosis. In this way, when in face of a patient with extreme photosensitivity and short stature, Rothmund-Thomson's syndrome (RTS), erythropoietic protoporphyria (EP) and Cockayne's syndrome (CS) should also be considered as possible diagnosis. RTS is a rare autosomal recessive genodermatosis, characterized by wide clinical expressivity, primarily accounted by locus heterogeneity, but to be further deepened considering allele heterogeneity and genetic modifiers. Approximately 400RTS patients are reported in the literature and generally all present as a hallmark sign the cutaneous erythematosus rash appearing within the first two years of life at sun-exposed areas, mainly on the face, then evolving into post-inflammatory chronic poikiloderma, a permanent lesion characterized by skin atrophy with hypo- and hyper-pigmented areas and telangiectasia. Other common features manifested in early childhood are growth delay, hyperkeratosis and sparse and thin hair, eyelashes and eyebrows, while premature aging is observed in adult age.[21]

EPP is an inherited disorder of the heme metabolic pathway characterized by accumulation of protoporphyrin in blood, erythrocytes and tissues, and cutaneous manifestations of photosensitivity. EPP has been reported worldwide, with prevalence between 1:75,000 and 1:200,000. It usually manifests in early infancy upon the first sun exposures. EPP is characterized by cutaneous manifestations of acute painful photosensitivity with erythema and edema, sometimes with petechiae, together with stinging and burning sensations upon exposure to sunlight, without blisters. These episodes have a variable severity depending on the exposure duration and may result in chronic permanent lesions on exposed skin. As protoporphyrin is a lipophilic molecule that is excreted by the liver, EPP patients are at risk of cholelithiasis with obstructive episodes, and chronic liver disease that might evolve to rapid acute liver failure. In most patients, EPP results from a partial deficiency of the last enzyme of the heme biosynthetic pathway, ferrochelatase.[22]

At last, CS is a rare, autosomal-recessive disorder that was first described in 1936 by Edward Cockayne. Early descriptions of CS identified the cardinal clinical features of the disorder: microcephaly and growth failure. Other authors recognized features include hearing loss, cataracts, retinal dystrophy, and developmental delay. Dermal photosensitivity is often considered a key feature of the diagnosis, particularly after defects in transcription-coupled nucleotide excision repair (tc-NER) were identified in classically affected patients. However, the importance of this feature has long been questioned.[23]

All the above Brazilian patients are born from the same first cousin parents and live in a tiny village, in the countryside of Brazil, state of Maranhao. The family has limited access to health facilities and as a result of that, it took more than 20 years and 11 children (5 with the phenotypical characteristics related to Bloom's syndrome) to diagnosis to be suspected. All the patients have suffered from many health issues throughout life, but they were treated as single isolated cases. It was only when the 23-year-old female patient attended a consultation with a dermatologist, due to the skin problems generated by the syndrome, that it was suspected and the whole family was summed to a group meeting with a team of doctors. Over there, it got clear that the 5 patients had the same phenotype, whereas the other siblings had a very different appearance, and actually resembled a lot of their parents. Further investigations lead us to understand that the mother actually had 4 children that were born and died short after from natural causes not investigated at the time. This first day was crucial to understand who our patients were and what type of problem they had concerning the syndrome.We ran head, thorax and abdomen CT scans looking for any kind of abnormal anatomy not visible in physical examination, and also requested blood exams to screen any disturbances. We found a series of different abnormalities described above.

In order to better understand the conditions these patients were susceptible to, we visited their home (Figure 2). Access was very difficult, and conditions were very poor, it was a daub hut with no proper "sanitation". Despite all that, the condition that appeared to be most critic was the sun exposure. This is a region with high solar incidence with sunny days in most part of the year and all of them were constantly being exposed brutally to sunlight. It became clear that the first providence to be taken needed to be related to this issue. With that in mind, we were able to provide a big amount of sunscreen, while we run more tests and stay surveillant for any other preventable occurrences. Beside usual sunscreens (like avobenzone, methoxycinnamate, zinc oxide), we used melanoidins from green coffee bean. Since melanoidins from coffee are generated in a condition rich in chlorogenic acid, its spectrum of protection involves both UVA and UVB and may last 6 to 10 hours.[24]

Figure 2 Family's hut in a very sunny area.

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Finally, nowadays, these patients are under careful surveillance in order to steadily diagnose any of those most frequent neoplasms and other complications.

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Conflict of interest

We declare no conflict of interest.

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