TWO SIBLINGS WITH BLOOM'S SYNDROME EXHIBIT DIFFERENT CLINICAL FEATURES: POSSIBLE EFFECT OF SEX*

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SUMMARY: Boduroğlu K, Tunçbilek E. (Clinical Genetics Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Two siblings with Bloom's syndrome exhibit different clinical features: possible effect of sex. Turk J Pediatr 1999; 41: 107-111.

Bloom's syndrome is a rare autosomal recessive disease. All patients with Bloom's syndrome have prenatally onset growth retardation and an increased tendency to develop various types of cancer. Features other than these are not constant and may not be present in some of the patients. Reason for the phenotypic heterogeneity is not clear. Different mutations in the same locus may explain the heterogeneous phenotypes in different ethnic groups. Here we present a seven-year-old boy and his four-year-old sister, both with Bloom's syndrome, who exhibit different clinical features with respect to sun-sensitive skin lesions. The sister has severe facial sun-sensitive skin lesions whereas her brother has none. It is expected that two siblings who are supposed to have the same mutation should also have similar clinical features. Possible role of environmental effects and sex are discussed. *Key words. Bloom's syndrome, sun-sensitive lesions, clinical heterogeneity, sex effect.*

Bloom's syndrome (BS) is a rare genetic disorder, with characteristic clinical features of proportionately small body size, unusual face, sun-sensitive skin lesions and predisposition to various types of cancer[1]. It was first described by a dermatologist in 1954[2]. The basic biochemical defect has not yet been identified.

Small body size and predisposition to cancer of all cell types and at all sites are constant features of Bloom's syndrome. Clinical features other than the growth failure and predisposition to cancer, such as hypersensitivity to sunlight, patchy areas of hypo and hyperpigmentation, diabetes mellitus and immunodeficiency, may or may not be present. If present, they may be in various degrees of severity[1, 3-5]. Variety in several clinical features in different ethnic groups is reported[5, 6]; However, complementation studies suggest that BS is due to a mutation at a single locus in all patients, even in different ethnic groups[7]. Bloom's syndrome gene (BLM) has recently been mapped to chromosome band 15q26.1[8]. Here we present two patients who have been added to the Bloom's Syndrome Registry. They exhibit different phenotypes with respect to sun-sensitive skin lesions.

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Case Reports

Case 1

This seven-year-old boy was the first child of second-degree consanguineous parents. His birth weight was 1200 g and he suffered feeding difficulties and vomiting during infancy. No history of serious infection was present. He had not experienced any sun-sensitive skin lesions until the time of his admission. Family had no complaint about his mental status.

On physical examination head circumference was 43.7 cm (< 5th percentile), height 96 cm (< 5th percentile) and weight 10.7 kg (< 5th percentile). There were numerous hyperpigmented and hypopigmented macular skin lesions in various dimension, disseminated over the body, but especially clustered over the back. Triangular face, malar hypoplasia, prominent nose and protuberant ears were the characteristic facial features (Fig. 1). Echocardiography showed normal cardiac structure. Chromosome analysis revealed an increased sister chromatid exchange (SCE) ratio, average 100 per metaphase.

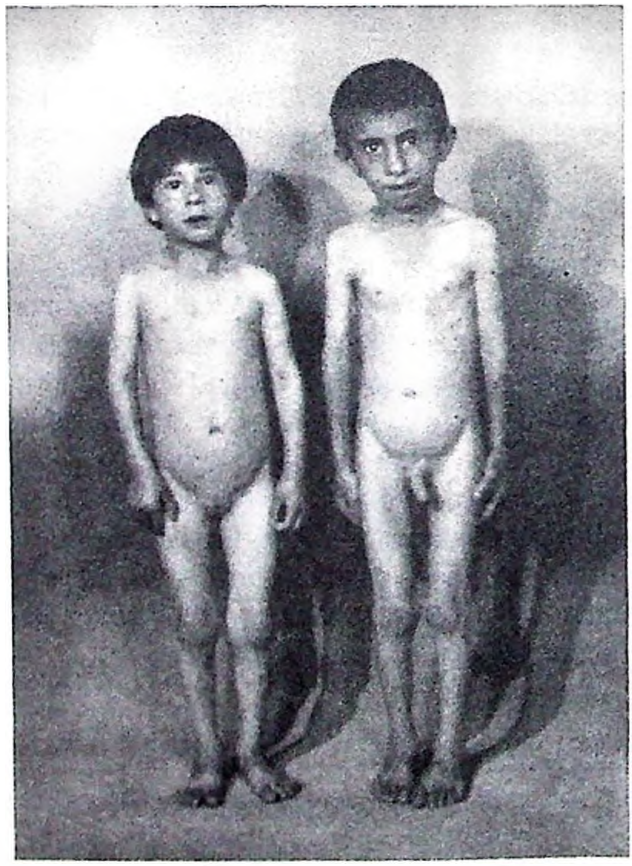

Fig. 1: General appearance of the two siblings with Bloom's syndrome.

Case 2

She is the four-year-old sister of Case 1, with a similar medical history except for having sunlight sensitivity since the age of one year. Her birth weight was 2000 g. She also was a poor sucker and failed to thrive. Prior to admission, she had experienced. three episodes of otitis media infections. At one year of age, after a significant exposure to sunlight, an erythema appeared on her face which continued with exacerbation in summers and remission in winters. Last year a dermatologist performed an incisional biopsy and it was reported as poikiloderma congenitale.

On physical examination head circumference was 42 cm (< 5th percentile), height 86 cm (< 5th percentile) and weight 9.8 kg (< 5th percentile). Telangiectases and erythema were present over the nose and cheeks. There were multiple hypo and hyperpigmented skin lesions over the trunk and proximal part of the lower extremities. Facial appearance was similar to her brother's (Fig. 1). Peripheral blood chromosome analysis revealed a mean of 98 SCE's per metaphase.

The third child of the family was normal except for a bifid thumb on the right hand. She had a normal growth pattern and never experienced a sun sensitive skin lesion. She had 9 SCEs per metaphase.

Discussion

Histological study of the sun-sensitive skin lesion has been undertaken in a few cases with Bloom's syndrome, but made no contribution to further understanding the pathogenesis[1]. Biopsy is not indicated for diagnostic purposes. Before receiving the definite diagnosis of Bloom's syndrome in Case 2, a dermatologist took a skin biopsy. We learned that the histopathological findings on light microscopy were consistent with poikiloderma congenitale. Our efforts to reevaluate the specimen failed because paraffin blocks were not found. Poikiloderma congenitale (Rothmund-Thomson syndrome) is an autosomal recessive disease, in which the characteristic features are erythema, dwarfism, hypogonadism and cataracts. Erythema begins on the face and subsequently extends to the dorsa of hands and feet, arms, legs and buttocks. Later, silght atrophy develops with telangiectases and mottled hyper and hypopigmentation. Exposure to sunlight aggravates the lesions. Histopathological examination shows hydropic degeneration of the basal layer leading to pigmentary incontinence, flattened epidermis, capillary dilatation and chronic inflammatory infiltration in the upper dermis. With the exception of pigmentary incontinence, all these findings are common for Bloom's syndrome and poikiloderma congenitale. Aside from these histopathological findings, Bloom's syndrome resembles poikiloderma by demonstrating telangiectatic erythema of the face starting in infancy, sensitivity to sunlight and growth retardation. It differs from poikiloderma congenitale by the lack of mottled hyper and hypopigmentation, absence of hypogonadism and

cataracts, high incidence of sister chromatid exchanges, and an increased risk for malignant disease. Differentiation is better made on clinical rather than histopathological grounds[9].

It is reported that physical features other than small body size and predisposition to cancer may present in varying degrees of severity in patients with Bloom's syndrome. Phenotype may differ due to ethnic origin. Complementation studies have confirmed that all patients have the same mutated locus. The phenotypic difference between different populations may be due to different mutations in the same locus[10, 13]. Although cells from all cases with Bloom's syndrome exhibit the diagnostic high SCE rate, in some, a minor population of low SCE lymphocytes exists in the blood[11, 12]. Because recombination events also occur within the BLM locus, these low SCE lymphocytes arise in patients who inherited paternally and maternally derived BLM alleles mutated at different sites[10]. But there is no evidence that these compound heterozygotes have a different phenotype. Even if there is evidence, it does not explain the difference in our patients. Since their parents are related they have to have the same mutation on both BLM alleles. These two sibs, however, exhibit different clinical features although they have the same mutation.

Environmental factors may affect the clinical presentation. Two sibs are different with respect to sun-sensitive skin lesions over the face. In this case, the environmental factor responsible for the difference may be exposure to sunlight. There are reports of sibships with multiple affected children, in which the rigorous protection from the sun of a later-born affected child is frequently associated with mild or absent skin lesions[1]. Our patients live in the same house and play together. Because they were diagnosed at the same time, the parents did not protect one of the children from sunlight, as with an experience of a previously diagnosed child. The amount of exposure to sunlight is same for these two patients or even longer in the case of the brother due to his older age.

The explanation for the difference between them, then, may be their sex. The sex ratio among all persons with Bloom's syndrome recognized to date is distorted: 94 males and 71 females. There is a male preponderance that is unexpected because of the autosomal recessive mode of transmission. Studies from different countries confirm the deficit in females. A possible explanation for the relatively low incidence in females is thought to be the high death rate among females during fetal or early postnatal life, before the pathognomonic skin lesion appears. Underdiagnosis is a second possible explanation for the low incidence Bloom's syndrome among females; their skin lesions are usually less severe than that of males. Observations have shown that one-fifth of all known affected females have had minimal skin lesions and only one-fifth had severe lesions. In contrast, among all known males only two had minimal lesions, and four-fifths were severely

affected[3, 4-6]. In this report the older male patient has no sun-sensitive skin lesions, whereas the younger female patient has severe facial lesions. This is in contrast to the previous information provided by various reports.

Bloom's syndrome gene (BLM) has recently been assigned to chromosomal locus 15q26.[18]. There are reports of various mutations in different ethnic groups. We think that effects of sex on the clinical presentation need further explanation. Mutation analyses of a greater number of BS patients may construct a phenotype/genotype correlation and the role of sex on phenotype.

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