Research Inventy: International Journal of Engineering And Science
Vol.14, Issue 8 (August 2024), PP 01-05
Issn (e): 2278-4721, Issn (p):2319-6483, www.researchinventy.com

Detail review on Bloom Syndrome

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Abstract
Bloom syndrome or Bloom syndrome is a scarce human autosomal recessive disorder belongs to a group of "chromosomal breakage syndromes". Bloom syndrome (BS) is defined by the marked instability of genes along with higher exchange of sister chromatids which leads to the greatly increased predisposition of cancer usually affecting the common population. The persistent clinical features of BS are mainly cancer predisposition and pre and postnatal growth retardation. Another clinical feature includes gastrointestinal disorders, facial sun sensitive telangiectactic erythema, patchy areas of hypo and hyper pigmentation of skin and acute to modest immunodeficiency. The only one criterion for diagnosis of BS is a 10folds increase in exchange of sister chromatids of BS cells and compare them with normal cells. Clinical diagnosis is verified cytogenetically through demonstrating characteristic instability of chromosomes. BS occurs through mutation in both the copies of BLM gene which encodes a 3'-5' DNA helicase, which is a member of RecQ helicase family. As function of BLM protein is remaining unclear some evidences support a role of BLM protein in maintaining genomic stability. BS frequency is unclear because it is very rare occurring disorder in general population. There is no specific treatment for BS but physician should follow BS patient carefully in order to achieve early diagnosis of cancer.

Keywords
Bloom stroke, RecQ helicase, Sister Chromatids, BLM gene, Predisposition of cancer

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Date of Submission: 01-08-2024 Date of acceptance: 10-08-2024

I. Introduction

Bloom's syndrome is aninfrequent autosomal recessive disease characterized by three "cardinal features" [1] lupuslike, erythematous telangiectasias of the face, sun sensitivity, and stunted growth.Normally, neurologic or metabolic abnormalities are absent [2]. Bloom syndrome is caused by mutations in the BLM gene which is member of the RecQ DNA helicase family. More broadly, Bloom syndrome is member of class of clinical entities that are characterized by chromosomal instability, genomic instability or both and by cancer.

II. Etiology

Bloom syndrome is happened due to mutation in BLM gene which is located on chromosome 15. The BLM genes provide instructions for making a member of protein family RecQ helicase. Helicase are the enzymes which bind to the DNA and separate the two strands of DNA. This separation process is essential for cell division and damaged DNA repair. During cell division, sister chromatids sometimes exchange small part of DNA which is named as exchange of sister chromatids. Research says that sister chromatid exchange is response to DNA damage during DNA copying process. BLM protein avoids excess sister chromatid exchange and maintain genetic stability. BLM gene mutation occurs in absence of BLM protein. An excess 10 fold increase in sister chromatid exchange than average leads to bloom syndrome. Also, chromosome breakage occurs more frequently in BS patient. All of the changes are related with gap and damage in genetic material that affects normal cell activities. In absence of BLM protein cell is less able to repair damage caused by UV light which leads to sun sensitivity. Genetic variations also lead to uncontrolled cell division which leads to the cancer [3].

III. Epidemiology

Bloom syndrome is very an uncommon disease and its frequency in the general population in unknown. Bloom syndrome is more frequent in askenazic jewish population reaching of approximately 1 in 48000 [4]. The time it was first recognized in 1954, Bloom's Syndrome Registry lists 265 individual cases reported as suffering from this rare disorder (as of 2009) [5].

IV. Clinical Description

In the program of surveillance referred as Bloom syndrome registry has been established in 1960 in which 168 Bloom syndrome patients has been reported till 1991 [6]. Bloom Syndrome is an autosomal recessive multisystem condition which characterized by abnormal growth, feeding difficulties in infancy, insulin resistance, skin changes, immune deficiency, high risk for diabetes, and an increased risk to develop cancer in an earlier age.

4.1 Facial Appearance

The facial features of people with BS are different and may be indistinguishable from their age-matched peers. Commonly, there are differences in appearance that include a long and narrow face, underdeveloped malar area, and retrognathia or micrognathia [2]. People with BS have a 3rd percentile below head circumference and their head shape is long and narrow [7].

4.2 Growth

People who affected with BS have prenatal and postnatal growth deficiency. Both weight and length affected. Children are usually born small for gestational age, with an average birth weight of 1,890 gm in males and 1,868 gm in females and the average birth length is 43.4 cm in males and 43.8 cm in females [7].Bone maturation is usually a bit delayed [8]. Also, hold up cellular generation time has been shown in tissue culture of some Bloom's syndrome patients [9] [10].

4.3 Skin lesions

The skin is normal at birth and during early and sun exposure during the first and second year of life, a red sun sensitive skin lesion seems on the butterfly area of the face and sometimes on the dorsa od hands and forearms. Also, originally reported as “congenital”, only single case has neem identified as such [11]and in one report the facial rash did not appear until 8 years of life [12].

4.4 Immunological abnormalities

The immune function of Bloom's syndrome patients is an unusual. Lymphocytes from these patients have shown a decreased phytohemagglutinin and pokeweed mitogen stimulation, mixed lymphocyte reaction, and immunoglobulin production when contrasted with lymphocytes from normal individuals [13] [14].
Since 1967, numerous reports of immunoglobulin deficiencies of at least one class, IgG, IgM, or IgA, have been reported [15] [8].These patients have persistent histories of respiratory and gastrointestinal infections with both gram-negative and gram-positive bacteria. The infections decreased with age, and susceptibility to viral infections is not evident [2].

4.5 Neoplasia

Neoplasia in bloom’s syndrome affects multiple tissue to contrast to other recessively transmitted neoplastic disorders. Dissimilar xeroderma pigmentosum, Bloom's syndrome cells do not exhibit a defect in DNA repair. [16] [17].Viable mechanisms for carcinogenesis in Bloom's syndrome include:
(1) chromosome structural change that would pass an oncogene to an "active" location,
(2) unequal crossing over that would lead to amplification of an oncogene,
(3) expression of a recessive oncogene allows deletion or segregation,
(4) immunodeficiency facilitating malignant transformation.[18][19]

4.6 Chromosomal aberrations

Bloom's syndrome is one of the chromosomal-breakage disorders. Cultured lymphocytes from patients with these disorders demonstrate a notable increase in spontaneous chromosome breakage [20]. In Bloom's syndrome chromosomal aberrations observed include sister chromatid reunions, chromatid and isochromatid gaps, polycentric chromosomes, and chromatid interchange configurations [2] [21].

4.7 Fertility

Women with Bloom's syndrome, even though sometimes fertile, enter menopause prematurely. The men who have Bloom's syndrome appropriately examined have been azoospermic. Five women with Bloom's syndrome followed in the Registry have given birth to nine normal and healthy babies.

V. Differential diagnosis

Bloom syndrome is associated with a group of “chromosomal breakage syndrome”. It is a genetic disorder which is transmitted in autosomal genetic disorder. Increased frequency of breaks and interchanges occurs randomly is a characterization of cells from affected individuals. Patient affected with Bloom syndrome have increased predisposition of cancer. The commonly accepted chromosome syndromes are Fanconi anemia,

ataxia telangiectasia, Xeroderma pigmentosum and Bloom stroke. Though approximately 10 fold increase in the rate of sister chromatid exchanges (SCE) as compared to normal cells is characteristic feature of Bloom syndrome [22]. The intent criteria of Bloom syndrome diagnosis are the increased level of SCE's. In about 20% of Bloom syndrome patients, normal levels of SCE are observed in a subpopulation of B and T lymphocytes [23,24]. Another characteristic of bloom syndrome is Quadriradial configuration of chromosomes. Other conditions may imitate the characteristic Bloom's syndrome facial rash or stature. Ataxia-telangiectasia is also an autosomal recessive disorder having similar characteristics of Bloom's syndrome along with ataxia, dysarthria, hypotonia by the age of 2 years [25].

Poikiloderma congenitale or also called as Rothmund-Thomson syndrome is also an autosomal recessive disorder with similar photosensitive rashes as bloom'syndrome. Along with these patients also diagnosed with telangiectactic rash on thighs and front of legs as well as the sparse facial hair and hypogonadism [26].

VI. Diagnostic Methods

6.1 Clinical Diagnosis

Bloom syndrome should be considered in the following [27]:

- An individual with unexplained, severe intrauterine growth retardation that continue into infancy and childhood.
- Any unusual small, well-proportioned individual with sun-sensitivity erythematous skin lesions in a "butterfly distribution" on the face.
- An individual with unusually developed cancer.

If suspected clinically, the diagnosis of Bloom syndrome is confirmed by cytogenic analysis showing increased number of sister chromatid exchanges or quadriradial configurations in lymphocytes or fibroblasts. The targeted mutational analysis can be used for diagnosis of bloom syndrome. Genetic and prenatal testing is recommended for high risks carrier population.

6.2 Cytogenetic Testing: Clinical methods

Chromosomal analysis: The diagnosis of Bloom's syndrome can be done by chromosome analysis of any celltype that can be cultured. The most commonly used cells are B lymphocytes, but aminocytes and cultures of skin fibroblasts can be studied. The cytogenetic characters of Bloom syndrome cells in mitosis are increased numbers of chromatid breaks and gaps and numbers of quadriradial configurations [28].

6.3 Sister Chromatid Exchange (SCE)

A great increased in the frequency (e.g. greater than 50 per metaphase) of SCE's in demonstrable in Bloom syndrome cells exposed to bromodeoxyuridine. Bloom syndrome is the only disorder in which such evidence of hyper-recombination is known to occur.

6.4 Molecular Genetic Testing-

6.4.1 Clinical Uses:

There are some clinical uses of molecular genetic testing which are as follows [29]:

- Diagnostic testing
- Confirmatory diagnostic testing
- Carrier detection in families with bloom's syndrome
- Population screening
- Prenatal diagnosis
- Preimplantation genetic diagnosis

6.4.2 Clinical Method:

- Targeted mutation analysis:

A germline genetic testing method is aimed to detect a specific mutation or variant or a panel of variant. This type of testing is different from complete gene sequencing or mutation scanning method. The method is designed to detect the most of the mutation or variants in the region being tested. Targeted mutation analysis is applied to any genetic test [30].

6.4.3 Research:

- Sequence Analysis/ mutation scanning:

In research laboratories, Bloom syndrome causes mutation in the BLM gene in non-Ashkenai Jewish families have been characterized by:

Mutation scanning and DNA sequencing amplified by reverse transcriptase polymerase chain reaction on mRNA which is isolated from untransformed fibroblast and cell lines of lymphoblastoid.
Mutation scanning (D-HPLC) and exon containing DNA fragment sequencing amplified by polymerase chain reaction of genomic DNA isolated from various sources and Southern blot analysis of selected genomic DNA's. All abnormalities are detected by mutation scanning which is characterized by DNA sequence analysis and confirmed by analysis of DNA fragment sequencing from the parents of the person with the Bloom syndrome gene [31].

VII. Genetic counselling

Genetic counselling is the process of providing individuals and families with information on the nature, inheritance, and implication of genetic disorder to help them make informed medical and personal decisions.
7.1 Mode of inheritance
Bloom's syndrome is inherited in an autosomal recessive manner.
7.2 Risk of Family Member
7.2.1 Parents of a proband

- Both parents of an affected person are assumed to carry a mutation in BLM, the Bloom's syndrome gene. However, one example of uniparental disomy has been reported
- Heterozygous are normally developed and healthy

7.2.2 Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affectedand a 25% chance of being unaffected and not a carrier, a 50% chance of being an asymptomatic carrier.
- At-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.

7.2.3 Offspring of a proband

- Men with Bloom's syndrome are infertile.
- Children born to a woman with Bloom's syndrome are assumed to be heterozygous for a BLM mutation.

Due to the autosomal recessive transmission mode of Bloom's syndrome, sibs of two heterozygous carriers are at 25% risk of having BS and 50% risk of being a carrier. It should be noted that among the ashkenzi jewish population, the heterozygous carrier frequency of this mutation is approximately 1 % [32].

VIII. Management and treatment:

Preventive medicine plays an important role in the management of Bloom's syndrome patients. Maximum protection sunscreens should be used, as well as protective clothing. If initiated early, these measures can alleviate the psychologic impact the rash may have on a child, also prevent future scarring and pigmentary alterations. These patients should be carefully observed for early signs of infection and appropriate measures should be taken Judicious use of antibiotics aids in the prevention of chronic respiratory problems.

Presently, the most life-threatening feature of this syndrome is the increased risk of neoplasia. Patients should be educated as to know the early warning signs of cancer. Bone marrow storage is an excellent idea since these patients are particularly prone to hematologic neoplasms, and chemotherapy may necessitate marrow replacement. Unfortunately, aside from proper nutrition to ensure optimal growth, there is no method of improving the stature of Bloom's syndrome patients [33]

IX. CONCLUSION:

Although it has been about 65 years since the original patients with Bloom syndrome were described, much work remains to understand the pathogenesis of some of its prime features such as growth retardation, pulmonary complications, insulin resistance and immune deficiency. Early diagnosis and management of cancer continue to be the most important health concerns for persons affected with Bloom stroke. Newer treatments that restore *BLM* function or that block the excessive homologous recombination hold the promise of improving effect, but there are continuing challenges to the development of such treatments and the delivery of these treatments to the specific target tissues.

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