Molecular mechanism in a rare autosomal recessive case of xeroderma pigmentosum - a case report

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Abstract

Chromosomal instability syndromes are a special group of disorders of cytogenetic interest which comprises of several rare, autosomal recessive conditions. Following exposure to sunlight, excessive chromosomal instability, breakage, defective nucleotide excision repair in DNA, defective apoptosis and increased susceptibility to neoplasia occurs. Xeroderma pigmentosum (XP) is characterised by the presence of chromosomal breakages, associated with increased frequency of sister chromatid exchanges. This is a case report of a 6 year old, male child having XP with dermal and ocular manifestations. Chromosomal breaks in chromosomal spread are seen. If it occurs in families, consanguinous marriages should be avoided; appropriate genetic counselling suggested and simple sun guarding techniques with appropriate protection from UV exposure can reduce the morbidity in these patients.

Keywords: sister chromatid exchange, nucleotide excision repair, UV light, hyperpigmentation

Introduction

Xeroderma pigmentosum (XP) is a rare multigenic, autosomal recessive disease caracterised by defective repair of DNA damage caused by Ultraviolet ray (UV) exposure. It was described in 1874 by Hebra and Kaposi. Occurrence is favoured by consanguinity. It occurs at a frequency of 1:2,50,000 live births in United States, but with higher frequency in Japan and the Mediterranean. Heterozygotes are unaffected but homozygotes are characterised by xerosis (dry skin) and poikiloderm (patches of hypo and hyperpigmentation), atrophy, telengectasia and premature ageing.

Progressive degeneration of sun exposed regions such as skin and eyes, usually leads to cutaneous malignancy. Ocular abnormalities are limited to anterior UV exposed portion of eyes resulting in photophobia (often the first sign), keratitis, corneal opacification, vascularisation, entropion, ectropion, loss of lashes and sometimes lids. About 30% of affected individuals progress to neurologic degeneration with microcephaly, sensorineural hearing loss and impaired cognition, and diminished or absent deep tendon reflexes. In this article, we report a case of xeroderma pigmentosum with dermal and ocular features and also highlight the molecular mechanism, resulting in genetic instability.

Case report

A six year old male child, third born to consanguinously married parents presented with mucocutaneous hyper and hypopigmentation on sun exposed regions (face, neck and forearm) (Figure 1 and 2). He presented with ocular features of photophobia, lacrimation, corneal and conjunctival ulcers and cataract (Figure 3). He had normal hearing, mentation and stature. No history of drug intake. The parents are not affected and have two other female children who are healthy. No family history of similar manifestation upto last three generations (Figure 4). He is the only one male child with features suggestive of xeroderma pigmentosum. He has no signs of significant lymphadenopathy or organomegaly.

Histopathological examination of the skin lesion showed hyperplastic squamous epithelium with lymphocyte and macrophage infiltration into the dermis. Electromyograph (EMG) was normal and showed no axonal neuropathy. Audiometry was normal and had no high tone hearing loss. Computed tomography of brain...
Fig. 1: Photograph shows mucocutaneous pigmentation on sun exposed regions (face and neck), in the patient with Xeroderma pigmentosum.

Fig. 2: Photograph shows parched skin with hyperpigmented freckles and hypopigmented macules in xeroderma pigmentosum.

Fig. 3: Photograph shows conjunctival and corneal ulcerations.

Fig. 4: Pedigree chart shows that no member of the family are affected except the patient (indicated by arrow).

Fig. 5(a): Chromosomal spread showing site of DNA damage with breaks and Fig. 5(b) showing site of sister chromatid exchange.

was normal with no thinning of cortex or enlarged ventricles. The chromosomal spread study showed regions of breakage (indicated by arrow) in Figure 5a and areas where sister chromatid exchange (SCE) had taken place (bold arrows) in Figure 5b. Thus identifying the sites of DNA damage and defective nucleotide excision repair (NER).

Discussion

Xeroderma pigmentosum is a rare genetic disease with dermal, ocular and neurological manifestations. Minimal UV exposure causes acute sunburn resulting in freckle like hyperpigmented macules, whereas continuous exposure to sun, turns these areas dry and parched. Median age of onset of symptoms is between 1 and 2 years. The anterior parts of eyes (conjunctiva, cornea, eyelids) may be affected whereas the posterior part (retina) is usually shielded from UV radiation. In this patient conjunctival and corneal ulcerations were prominent with photophobia and lacrimation.

Neurological disturbances may manifest either early or later (2nd decade). About 30% of individuals with XP are affected with neurologic abnormalities. It may vary from mild hyporeflexia to severe spasticity, ataxia or seizures. Some may develop difficulty in swallowing or vocal cord paralysis. Few patients with neurological disorder may present with dwarfism and immature sexual development collectively termed as Desanctis Cacchione syndrome. Predominant neurologic abnormality is loss of neurons, primary axonal degeneration in peripheral nerves with demyelination.
Chromosome instability and breakage

Defective repair

Mutated XP gene

XP Cell

Fig. 6: Illustration comparing the molecular mechanism involved in normal and Xeroderma pigmentosum cells.

<table>
<thead>
<tr>
<th>Complementation group</th>
<th>Locus name</th>
<th>Gene</th>
<th>Chromosome number</th>
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<tr>
<td>A</td>
<td>XPA</td>
<td>XPA</td>
<td>9q22</td>
</tr>
<tr>
<td>B</td>
<td>XPB</td>
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<td>C</td>
<td>XPC</td>
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<td>3p25</td>
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<tr>
<td>VARIANT</td>
<td>POLH</td>
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</tbody>
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Table 1: Nine complementation groups of XP and genes involved (Modified from Kraemer KH and DiGiovanna JJ) \( ^{34} \).
and reduced nerve conduction. This patient did not exhibit any early neurological disturbances, however he needs to be followed-up to detect any neurological disturbances in future as he is only in his 1st decade of life.

Apart from the dermal, ocular and neurological disturbances, XP patients may be affected with various neoplasms. The median age of onset of neoplasms in these patients is eight years. Neoplasia in XP can affect any organ. Basal cell carcinoma, squamous cell carcinoma, melanoma, leukemia, gliomas of brain and spinal cord, cancer of lung, breast, pancreas, stomach, kidney and testicles have been reported in these patients. However, this patient did not show any carcinomatous changes.

The basic defect in XP is the instability of chromosomes which occurs following exposure to UV rays with frequency between 280-310 nm. The chromosomes become unstable and break. At these damaged sites (breaks), there is increased frequency of sister chromatid exchange (SCE) than seen in normal cell. The defect is in the nucleotide excision repair (NER) machinery in XP. The adjacent pyrimidine nucleotides form covalently linked ring structure called dimers. A normal cell, with the help of endonuclease will excise these ring dimers and replace it with short single stranded segments of newly synthesised DNA. If DNA repair does not occur, apoptosis ensues in the cell. However patients with XP, lack the endonuclease due to mutation of XP genes in the chromosomes and therefore the ring dimers persist. This results in premature ageing. This mechanism is illustrated in Figure 6. There are different loci of genes involved in producing nine genetic complementation groups of XP as enlisted in Table 1.

Prognosis of XP patients is not good as less than 40% of patients survive beyond the age of 20 years. The prevention of XP is important and this can be achieved by avoidance of consanguinous marriages. However in case of consanguinous marriages, prenatal prediction of XP by way of amniocentesis and chorionic villus sampling should be carried out. Genetic counselling should be given to affected families. The parents of xeroderma pigmentosum patients are obligate carriers of one of the nine genes associated with xeroderma pigmentosum. Heterozygotes are asymptomatic. The siblings of an affected individual have 25% chance of being affected, 50% chance of being asymptomatic carrier and 25% chance of being unaffected and not a carrier.

Detection of XP after birth can be carried out by skin biopsy and fibroblast culture. Affected persons should be educated on solar protection using clothing, sunglasses, topical sunscreen. They should avoid carcinogens and regular surveillance for cancer and prompt detection and treatment for neoplasms with agents such as 5-fluorouracil and oral retinoid should be carried out. Protein and gene therapy are under trial. In protein therapy, dimeric T-123C T-lotus introduces the missing protein directly into the cell and in gene therapy the DNA repair enzyme T4 endonuclease V is applied to the skin which repairs the dimers formed due to DNA damage.

The diagnosis is based clinically on skin, eye and neurologic manifestations. A detailed family history and indications of consanguinity may aid in diagnosis. Functional tests on living cells can be used to identify abnormalities in DNA repair following UV exposure. The chromosomal spread study of this patient indicates sites of DNA breakage and sister chromatid exchange.

Conclusion

The case presented here shows cutaneous and ocular manifestations of XP. He is born to consanguinously married parents. Parents may be heterozygotes and carriers. They do not manifest the disease. The chromosomal spread, highlights the breakage of chromosomes and subsequent sister chromatid exchange, which favours the diagnosis of XP. The inability of DNA repair mechanism to excise the resulting dimer as a result
of lack ofendonuclease following exposure to sunlight is the cause for progerial symptoms. The line of management includes genetic counseling, guarding from sun exposure and other carcinogens (like smoking). This case has been reported as it is a rare autosomal recessive disease with DNA breakages in chromosomal spread suggestive of inability in NER mechanism.

References
Xeroderma pigmentosum - Vijaya & Anand


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