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Review Article

# Xeroderma Pigmentosa: An Extremely Rare Illness with No Cure

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ABSTRACT

Xeroderma pigmentosum (XP) is a rare disorder characterized by extreme sensitivity to sunlight, which can lead to blistering after brief exposure, early onset of freckling and pigmentation, and other symptoms of poikiloderma. Additionally, individuals with XP have an increased risk of developing skin cancer. This condition is caused by a defect in the body's ability to repair damage caused by UV radiation. This overview summarizes the latest research on XP's genetic, molecular, and clinical aspects. Diseases that have an X-linked recessive inheritance pattern, which affect the DNA repair systems, are frequently associated with negative health outcomes resulting from exposure to UV radiation and its byproducts. Skin, eye, nervous system, and other tissues may develop diseases and tumors as a result of exposure to UV radiation. Due to complications such as skin cancer and brain damage, individuals with XP have a shorter life expectancy than the general population. However, restricting exposure to UV radiation can delay the onset of the disease and potentially add years to their lives. Understanding the biological mechanisms that protect against photoaging and UV-induced malignancy is critical.



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## INTRODUCTION

Xeroderma pigmentosum (XP) was first described by Hungarian dermatology professor Moritz Kohn Kaposi in 1874. He observed two people with thin, dry, tight, and checkered skin who were diagnosed with many cutaneous tumours at a young age[1]. Kaposi coined the term "dry and pigmented skin" to describe this condition, which is still used today. XP is an autosomal recessive genodermatosis that results from mutations in genes responsible for repairing UV-induced DNA damage (UVR). Symptoms of XP include extreme sensitivity to light and an increased risk of developing skin cancer. The severity of XP symptoms can range from mild to severe depending on the mutations. An early diagnosis following exposure to UVR can help reduce the severity of XP effects[2-3].

XP is a rare condition caused by nucleotide excision repair mutations, which are autosomal recessive. Symptoms of this condition include extreme photosensitivity, changes in skin pigmentation, the appearance of malignant tumours, and even gradual neurologic deterioration. The prevalence of XP is 1 in a million in America, whereas in Japan, it jumps to 45. Exposure to the sun's UV radiation can increase the risk of developing skin cancer, tongue cancer, and eye cancer[4]. The lips and tongue are more vulnerable to cancer because they are more directly exposed to UV light than the more protected mucous membranes of the rest of the mouth and throat. Therefore, sun protection is crucial for XP patients to prevent skin cancer.

Over the past several decades, studies have shown that extreme photosensitivity plays a critical role in the pathogenesis of xeroderma pigmentosum[6-9]. In the 1960s, Dr. James Cleaver discovered that xeroderma pigmentosum fibroblasts cultivated in the lab demonstrated defective DNA repair after being exposed to UV light. People with xeroderma pigmentosum who also show neurologic symptoms have considerably reduced DNA repair following UV exposure compared to patients with XP who do not have neurologic characteristics. These analyses provide insight into the relationships between UVR exposure, DNA damage and repair, and tumour development[10].

### Skin Reactions

Xeroderma pigmentosum (XP) is a condition that typically manifests at an early age. Children with XP are particularly vulnerable to sunburn and can suffer from the effects of a bad burn for weeks. According to the National Organization for Rare Disorders (NORD), the tip of the tongue is just as susceptible to infection as any other exposed area when it comes to XP. In most cases, the eyelids are the first to feel the effects of sun exposure, followed by the eyeballs[11].

XP patients may also develop acne-like skin lesions called lentigines, which are typically noticed by parents before the toddler years. In addition, the following symptoms may occur:

- Dry skin (xerosis) and skin discoloration and thinning
- Telangiectasia, in which the skin's tiny blood veins enlarge unnaturally and take on a threadlike appearance.

It is important to recognize these symptoms as early as possible so that appropriate measures can be taken to reduce the severity of the disease's effects[12-13]. Protecting the skin from sunlight is particularly important for XP patients to minimize the risk of skin damage and skin cancer.

### Aetiopathogenesis

NER, or nucleotide excision repair, is a vital process that repairs DNA damage caused by UV radiation. Specifically, NER repairs two types of photoproducts: cyclobutane pyrimidine dimers and 6-4 pyrimidone dimers. Photoproduct removal is unnecessary because NER repairs the DNA. For optimal UV protection, a functional NER system is essential[14].

There are two main types of NER: transcription-coupled NER (TC-NER) and global genome NER (GG-NER). Unlike GG-NER, which repairs DNA throughout the genome, TC-NER targets transcribed DNA. Eight genes encode NER proteins (XPA, XPB, XPC, XPD, XPE, XPF, XPG, and XPV). After NER, XPV repairs any remaining DNA damage. Mutations in the XPV gene result in seven complementation groups and one variant (XPV)[15].

It is important to note that NER cannot repair UVR-induced DNA damage, and XP patients

often have poor photoproduct elimination. While NER functions well, mutations in DNA Pol genes can induce XPV, which is involved in translation. DNA Pol helps with trans-lesion synthesis, or transcription beyond UVR-damaged DNA that NER has not repaired.

Sunlight can reduce DNA replication in infected individuals, and UVR-induced photoproducts and unrepaired DNA damage can lead to XP skin characteristics, early cancer development, and neurodegeneration due to DNA oxidation[16].

*Table :1 Xeroderma Pigmentosum surveillance recommendations*

| System/Concern | Evaluation | Frequency |
|---|---|---|
| Skin | Exam by physician | Every 3-12 mos depending on severity of skin disease |
| | Exam by affected person or caregivers to look for abnormal pigmented lesions or appearance of basal cell or squamous cell carcinoma (requires instruction in recognition of cutaneous neoplasms) | Whenever caregivers have opportunity to view affected child's skin; at least 1x/wk |
| Eyes | Exam for signs of UV exposure & damage | At least every 6 mos depending on severity of ocular UV exposure & damage |
| Neurologic | Routine neurologic exam for progressive neurologic abnormalities that are present in minority of persons w/XP & may not be detected in young children | Every 12 mos for symptomatic patients unless there is new onset of neurologic abnormalities |
| Hearing | Audiograms | Every 6-12 mos |
| Female reproductive system | Laboratory assessment for premature ovarian insufficiency 1 | Every 12 mos beginning at age 18 yrs |

**Implications for One's Eyesight**

XP patients commonly experience visual impairment, with more than 80% being affected. One of the potential side effects is photophobia, which is the intolerance of light. This can lead to the clouding of the corneas, which are the transparent outer layers that protect the eyes, resulting in redness and irritation. Dry eye syndrome has been linked to keratitis, which is persistent corneal irritation. In severe cases, keratitis can cause total blindness[17]. Moreover, overexposure to the sun can cause eye problems such as thinning eyelid skin, bald spots, and damage to the retina and other eye structures.

**Differential Diagnosis**

As it turns out, xeroderma pigmentosum is not the only possible cause for the symptoms that patients with this condition experience. There are several syndromes and medical disorders that have similar symptoms, and together, these diseases have helped us to learn more about the proteins and genes involved in nucleotide excision repair.

Mutations in the CSA or CSB genes, for instance, can disrupt nucleotide excision repair, leading to the development of Cockayne syndrome. This disorder is characterized by several features, such as microcephaly, retinal degeneration, deep-set eyes, large ears, sensorineural hearing loss, kyphoscoliosis, and gait difficulties. Like XP patients, individuals with Cockayne syndrome also experience photosensitivity, but they are not at an increased risk of skin cancer or pigmentary alterations[18-21].

There are instances where symptoms of Cockayne syndrome and xeroderma pigmentosum overlap, giving rise to a condition called the Cockayne-XP overlap syndrome

(CS-XP). This disease can slowly deteriorate a person's health, causing short height, sensitivity to light, joint contractures, and degenerative neurological symptoms. All of the cutaneous symptoms of xeroderma pigmentosum are also present in patients with CS-XP.

**Management and Preventative Measure**

Xeroderma pigmentosum (XP) is a disease for which there is currently no known cure or specific treatment. As a result, managing symptoms and taking preventive measures are key areas of focus for both healthcare professionals and individuals affected by the disease.

Medical care for XP patients may involve a team of specialists, including dermatologists, surgeons, optometrists, audiologists, and neurologists. Routine check-ups are highly recommended to monitor the skin, eyes, ears, and neurological system for any signs of abnormalities or complications[22].

Since sun exposure is a major risk factor for XP patients, it's crucial to take precautions to avoid harmful UV radiation. Wearing protective gear such as UV-blocking sunglasses, hats, and gloves can provide an additional layer of safety. It's also important to protect the eyes from sun damage with appropriate eyewear during the daytime hours. By taking these preventive measures, XP patients can minimize the harmful effects of sun exposure and improve their overall quality of life.

**Prognosis**

Patients with xeroderma pigmentosum who are younger than two years old often experience severe photosensitivity, with even minimal exposure to the sun leading to erythema and bullae. Gradually, changes in skin pigmentation, telangiectasias, and actinic keratoses appear due to sun damage. Non-melanoma skin cancer is diagnosed in patients with XP at an average age of 9 years old, and they have a nearly 10,000 times higher risk of developing it than the general population. Malignant melanoma usually occurs at the age of 22, with XP patients having a 2,000 times higher chance of acquiring it[23]. To prevent precancerous lesions and skin cancers, it is essential for XP patients to receive frequent full-body dermatological inspections and have any suspicious growths or moles removed immediately.

XP patients may have a shorter life expectancy than the average person, and their prognosis is even poorer if they also suffer from neurodegeneration. Unfortunately, there is no known cure for XP. However, without neurodegeneration, the median lifespan for XP patients is 37 years. Neurodegenerative XP patients have a significantly lower median age of death, at around 29 years old, making it the third leading cause of death among XP patients after metastatic malignant melanoma and invasive squamous cell carcinoma. Patients with the XP subtype variation tend to have a better prognosis than those with other XP subtypes.

**Evaluation**

At present, there are no effective diagnostic imaging or conventional laboratory tests available to diagnose xeroderma pigmentosum (XP). Instead, medical professionals use unscheduled DNA synthesis (UDS) or gene sequencing to identify the disease[24]. One method involves testing a patient's fibroblasts in culture by exposing them to UV radiation to trigger unscheduled DNA synthesis and then assessing the cells' capacity to repair the damage. Unscheduled DNA synthesis is the DNA synthesis that occurs in response to DNA damage, as opposed to the DNA synthesis that occurs on schedule during cell replication. UDS can be measured in part by counting how many more nucleotides are present in DNA following irradiation. Fluorescence testing, autoradiography, and liquid scintillation counting are only some of the methods available for determining how many nucleotides were incorporated into DNA. If a patient has a low level of UDS after being exposed to UV light, we can diagnose them with xeroderma pigmentosum.

Patients with the XP variation subtype tend to be less photosensitive than those with subtypes A through G. Caffeine is used as a pretreatment to sensitize fibroblasts from XPV patients grown in the lab to UV light. After UV exposure, the caffeine-treated fibroblasts are cultured for an extended period, and the cells are then compared to untreated normal fibroblasts for any impairment in UDS. Heightened sensitivity to the sun's rays is common to this kind of xeroderma pigmentosum as a result of caffeine use.

**Treatment**

Treating people with xeroderma pigmentosum involves three main objectives: reducing the risk of malignant tumour formation, early detection and treatment of any tumours that do form, and improving patients' overall quality of

life. To reduce the risk of developing most malignancies, patients with XP are advised to avoid direct sunlight and wear protective clothing[25-26]. Patients and caregivers should be informed about various ways to shield themselves from the sun's harmful ultraviolet radiation[27]. Since going outside during the day can worsen their condition, patients should stay indoors as much as possible. If patients need to spend time outside, they should apply sunscreen liberally all over their body, including their lips and ears. Broad-spectrum sunscreen should be reapplied every two hours. Patients should also use lip balm with SPF and wear long-sleeved shirts and pants to avoid sunburn. Additionally, wearing a hat and protective sunglasses is recommended. It is highly suggested to apply UV-blocking film to windows at home, in the car, and at school. Patients should avoid fluorescent, metal halide, and halogen lighting as they emit UV radiation[28].

**Prognosis**

Xeroderma pigmentosum is a severe condition that can significantly affect a patient's life expectancy. Sadly, 60% of patients with XP don't survive beyond their twenties, and the majority don't live past the age of 32. While neurological illnesses and internal tumours were once the primary cause of mortality, metastatic skin cancer has now surpassed them. The prognosis for malignancies in XP patients varies depending on factors such as the speed of diagnosis and treatment, the severity of the disease, the presence of gene mutations, and how well patients adhere to sun avoidance and protection techniques. It's worth noting that the prognosis is generally better for those infected with XPV than for those with other strains of the virus[29].

**Enhancing Healthcare Team Outcomes**

The treatment of xeroderma pigmentosum necessitates the collaborative efforts of several healthcare professionals. To achieve the best clinical outcome and quality of life during and after therapy, patients at high risk of developing malignant tumours require the expertise and experience of multiple clinicians. Pediatricians can refer young children with the first signs of this condition to a dermatologist for prompt treatment. It is recommended that patients undergo regular screenings for precancerous or cancerous growths and subsequent treatment by a dermatologist[30]. If the tumour is too large to be removed with a local anaesthetic, a dermatologist may refer the patient to a general surgeon or plastic surgeon. Any vision problems or routine examinations for a person with XP should be evaluated by an ophthalmologist. If a person with XP experiences neurological symptoms, they should consult with a neurologist for a proper diagnosis and treatment plan[31]. The patient's pharmacist should discuss the benefits and risks of using retinoids for cancer prevention. In addition to treatment options, patients and their carers should be made aware of a support group for xeroderma pigmentosum. Due to the significant mortality rate caused by XP, it is crucial for all members of the interdisciplinary team to work closely together.

**Closing Remarks**

Although a cure for xeroderma pigmentosum is currently unavailable, steps can be taken to improve the quality of life for those affected by the disease. Public awareness campaigns can increase knowledge and understanding of XP, leading to earlier detection and diagnosis. Severe sun avoidance and protection are also necessary to prevent skin cancer and other complications associated with XP. Early diagnosis is crucial to initiate preventive measures at a young age and to detect and treat cancer in its early stages. These measures can have a significant impact on patients' health and life expectancy. However, more research is needed before gene therapy can be widely recommended for treating X-linked recessive disorders.

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