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XERODERMA PIGMENTOSA: AN EXTREMELY RARE ILLNESS WITH NO CURE

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ABSTRACT

Extreme photosensitivity, including blistering after brief exposure to sunlight, early onset of freckling and lentiginous pigmentation, and other features of poikiloderma, as well as an increased risk of skin cancer, are hallmarks of Xeroderma pigmentosum (XP), a rare disorder of defective UV-radiation-induced damage repair. This concise overview compiles the most recent findings on the genetic, molecular, and clinical aspects of XP. Diseases with an X-linked recessive pattern are those that affect the systems in charge of repairing broken DNA. Many negative health effects have been associated with exposure to UV radiation and its metabolites. Diseases and tumours of the skin, eyes, nervous system, central nervous system, and other tissues are just some examples. Complications such as skin cancer and brain damage contribute to a reduced life expectancy for many people with XP compared to the general population, but taking measures to restrict their exposure to UV radiation can postpone the onset of disease and possibly add years to their lives. It is critical to understand the biological defences against photoaging and UV-induced malignancy.

INTRODUCTION:

In 1874, Hungarian dermatology professor Moritz Kohn Kaposi initially described Xeroderma pigmentosum (XP). Two people were found to have XP; their skin was thin, dry, tight, and checkered, and they were diagnosed with many cutaneous tumours at a young age. Kaposi coined the term "dry and pigmented skin" to describe this condition, which has been used ever since. XP is an autosomal recessive genodermatosis caused by mutations in genes responsible for repairing UV-induced DNA damage (UVR).Some of the symptoms of this illness include a sensitivity to light and an increased chance of developing skin cancer[1]. Mutations can cause XP symptoms to range from mild to severe. In order to lessen the severity of the effects of XP, a diagnosis should be made as soon as feasible following exposure to UVR.

Rare nucleotide excision repair mutations cause xeroderma pigmentosum, an autosomal recessive genodermatosis (XP). Extreme photosensitivity, changes in skin pigmentation, the appearance of malignant tumours, and even gradual neurologic deterioration are all symptoms of this condition. One in a million Americans may be affected by this disease, whereas in Japan that rate jumps to 45. Exposure to the sun's ultraviolet (UV) radiation increases the risk of developing skin cancer, tongue cancer, and eye cancer[2-3]. Although the cornea and iris are in closer contact with the sun, the lens shields the retina and vitreous humour, which are located deeper in the eye, from its harmful ultraviolet (UV) radiation. 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[4]. Sun protection is especially important for XP patients since they are less likely to get skin cancer by keeping their skin and other tissues protected.

Moriz Kaposi, a dermatologist, first described xeroderma pigmentosum in 1874. Dr. Kaposi detailed several cases of young people with extensive skin tumours, dry skin, and pigmentary abnormalities. Extreme photosensitivity has been shown to have a critical role in the pathogenesis of xeroderma pigmentosum, according to studies conducted over the past several decades[5-6]. 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[7]. These analyses shed light on the relationships between UVR exposure, DNA damage and repair, and tumour development.

Skin Reactions

Early onset is typical for these problems. Children with XP are more likely to get sunburned quickly, and the effects of a bad burn can last for weeks[8].According to NORD, the tip of the tongue is just as susceptible to infection as any other exposed place when it comes to XP. Usually, the eyelids will feel the effects first, followed by the eyeballs.

Acne-like skin lesions, known as lentigines, have been observed in XP patients. Usually, a parent will notice this in their child before the toddler years.

Not only are these symptoms conceivable, but so are others, such as:

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

Aetiopathogenesis

NER repairs cyclobutane pyrimidine dimers and 6-4 pyrimidone dimers. Photoproduct removal is unnecessary because NER repairs DNA. UV protection requires an optimal NER system. Most NERs are TC-NER and global genome NER (GG-NER). Unlike GG-NER, TC-NER targets transcribed DNA. Eight genes encode NER proteins (XPA, XPB, XPC, XPD, XPE, XPF, XPG, and XPV). After NER, XPV repairs DNA damage. Seven complementation groups and one variant result from the XP gene mutation (XPV)[9-10].NER cannot repair UVR-induced DNA damage and XP patients have poor photoproduct elimination. NER functions, although DNA Pol gene mutations can induce XPV (which is involved in translation). Pol helps trans-lesion synthesis, or transcription beyond UVR-damaged DNA that NER has not repaired. Sunlight reduces DNA replication in infected people. UVR-induced photoproducts and unrepaired DNA damage generate XP skin characteristics, development, and early cancer. DNA oxidation

causes neurodegeneration[11].

Implications for One's Eyesight

Eighty percent or more of XP patients experience visual impairment. One possible side effect is photophobia, or an intolerance of light. Consequently, the corneas, the generally transparent outer layers of protection for the eyes, can get clouded, resulting in red, irritated eyes. Keratitis, a persistent corneal irritation, has been linked to the onset of dry eye syndrome. In severe cases, keratitis might lead to total blindness[12]. Overexposure to the sun can cause eye problems like thinning eyelid skin and bald spots, as well as damage to the retina and other structures of the eye.

Differential Diagnosis

However, xeroderma pigmentosum isn't the only possible explanation; there are a number of syndromes and medical disorders that share similar symptoms. Together, XP and these two diseases have advanced our knowledge of the proteins and genes that facilitate nucleotide excision repair.

Mutations in the CSA or CSB genes disrupt nucleotide excision repair, leading to Cockayne syndrome. Features of Cockayne syndrome include microcephaly, retinal degeneration, deep-set eyes, large ears, sensorineural hearing loss, kyphoscoliosis, and gait difficulties[13-15]. The photosensitivity experienced by patients with Cockayne syndrome is similar to that of XP patients, but they do not have an elevated risk of skin cancer or pigmentary alterations.

Cockayne syndrome and xeroderma pigmentosum symptoms may overlap, resulting in a condition known as the Cockayne-XP overlap syndrome (CS-XP). Short height, sensitivity to light, joint contractures, and degenerative neurological symptoms are just some of the ways this disease can slowly deteriorate a person's health. All of the cutaneous symptoms of xeroderma pigmentosum are present in patients with CS-XP[16].

Management and Preventative Measure

Unfortunately, XP treatment and a cure remain unavailable. Symptom management and preventative care are common areas of focus for both medical professionals and those living with the disease.

Medical treatment may be provided by the following professionals with XP:

- Specialists in the domains of medicine, surgery, optometry, otology, otology, audiology, otology, and otology
- Patients with XP should see a dermatologist every 6-12 months for skin cancer screenings. It is also advisable to have frequent checkups of the eyes, ears, and neurological system.

Those with XP should take special precautions to avoid sun exposure. Since sun exposure is a major risk factor, it's important to take the following precautions whenever spending time in the open[17].UV-blocking accessories, including sunglasses, hats, and gloves, are used for safety.Protective eyewear throughout the daytime hours against the sun's rays.

Prognosis

Patients with xeroderma pigmentosum younger than two years of age often have severe photosensitivity. A small amount of time in the sun can cause erythema and bullae. Changes in skin pigmentation (melasma), telangiectasias, and actinic keratoses all emerge gradually over time as a result of sun damage[18-21]. The average age for a person to be diagnosed with non-melanoma skin cancer is 9. Non-melanoma skin cancer can cause dozens to hundreds of new cases per year in a single person. Those with xeroderma pigmentosum have a chance of acquiring non-melanoma skin cancer that is almost 10,000 times higher than the average person's. Typically, malignant melanoma strikes at the age of 22. The chance of acquiring malignant melanoma in people with XP is about 2,000 times higher than in the general population. In order to prevent precancerous lesions and skin cancers, it is important to get frequent full-body dermatological inspections and have any moles or growths that look worrisome removed right away[22].

Patients with xeroderma pigmentosum may have a shorter than average life expectancy because to their condition. The prognosis for patients with XP who are also suffering from neurodegeneration is not encouraging[23]. There is no known treatment for XP, however without neurodegeneration, the median lifespan for XP patients is 37 years. When compared to other forms of XP, neurodegenerative XP patients have a significantly lower median age of death (about 29). People with the XP variation subtype tend to fare better than those with other XP subtypes. Neurodegeneration is a major cause of death among XP patients, ranking third behind metastatic malignant melanoma and invasive squamous cell carcinoma.

Evaluation

Currently, xeroderma pigmentosum can only be identified using unscheduled DNA synthesis (UDS) or gene sequencing because there is no effective diagnostic imaging or conventional laboratory testing available.

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[24]. DNA synthesis that occurs in response to DNA damage, as opposed to the DNA synthesis that occurs on schedule during cell replication, is referred to as "unscheduled DNA synthesis." 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[25]. When a patient has a low level of UDS after being exposed to UV light, we can diagnose them with xeroderma pigmentosum.

Cultured fibroblasts from people with the XP variation are less photosensitive than those from people with the XP variation subtypes A through G. Caffeine is used as a pretreatment for sensitising fibroblasts from XPV patients grown in the lab to UV light. Caffeine-treated fibroblasts are cultured for a long time after UV exposure, and the cells are then compared to untreated normal fibroblasts for any impairment in UDS[26]. Common to this kind of xeroderma pigmentosum is heightened sensitivity to the sun's rays as a result of coffee use.

Treatment

The goals of treating people with xeroderma pigmentosum are to lessen the likelihood that malignant tumours will form, speed up detection and treatment of any tumours that do form, and boost patients' quality of life generally. By avoiding direct sunlight and using protective clothing, people with XP can reduce their risk of developing most malignancies. Patients and carers should be made aware of the various methods available for shielding themselves from the sun's potentially damaging ultraviolet radiation[27]. Staying inside all day is recommended because going outside throughout the day can exacerbate their conditions. Patients should liberally apply sunscreen all over their body, including the lips and ears, if they need to spend the day outside. Every two hours, apply and reapply a broad-spectrum sunscreen. In addition, people should use a lip balm with SPF in it. In order to prevent sunburn, the patient should dress in long-sleeved shirts and slacks. They should wear a hat and protective sunglasses. Applying UV-blocking film to all windows at home, in the car, and at school is highly suggested. Furthermore, patients should stay away from fluorescent, metal halide, and halogen lighting because of the UV radiation they produce[28].

Prognosis

Sixty percent of XP patients don't make it past the age of twenty. In

most cases, when one reaches the age of 32, one has already lived their entire lives. It has recently been discovered that metastatic skin cancer has surpassed neurological illnesses and internal tumours as the main cause of mortality around the world[29]. Malignancies have varying prognoses based on a number of circumstances, such as how quickly they were diagnosed and treated, how severe the disease was, whether or not mutations in the relevant gene were present, and how diligently sun avoidance and protection techniques were utilised. Infection with XPV is associated with a better prognosis than with other strains of the virus.

Enhancing Healthcare Team Outcomes

Xeroderma pigmentosum treatment requires the coordinated efforts of several medical professionals. Patients at a high risk of getting malignant tumours require the expertise and experience of multiple clinicians to achieve the optimum clinical outcome and quality of life during and after therapy. If paediatricians keep an eye out for the first signs of this condition, they can refer their young children to a dermatologist for prompt treatment. It is recommended that patients see a dermatologist on a regular basis for screening for precancerous or cancerous growths and subsequent treatment. A dermatologist might refer you to a general surgeon or plastic surgeon if the tumour is too big to be removed with a local anaesthetic[30]. Any time a person with XP experiences vision problems or for routine examinations, they should visit an ophthalmologist. Anyone with XP suffering neurological symptoms should visit a neurologist for a proper diagnosis and treatment plan. The pharmacist should discuss the benefits and risks of using retinoids for cancer prevention with the patient. Patients and their carers should be made aware of a xeroderma pigmentosum support group in addition to treatment choices[31]. It is essential that all members of the interdisciplinary team work closely together due to the significant mortality rate caused by XP.

Closing Remarks

Although there is presently no therapy for xeroderma pigmentosum, improving the quality of life for those who have it can be accomplished through increasing public awareness, facilitating early identification, and mandating severe sun avoidance and protection. However, while XP may not have a definitive cure, skin cancer and other complications can be prevented and managed. So, early XP diagnosis is critical for initiating preventative measures at a young age. Together with early cancer diagnosis and treatment, this can have a major impact on patients' health and longevity. However, further research is required before recommending widespread use of gene therapy to treat X-linked recessive disorders.

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