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XERODERMA PIGMENTOSUM: A LITERATURE REVIEW

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Abstract: Objectives: This review aimed to group studies related to xeroderma pigmentosum, presenting their means of diagnosis and current therapeutic strategies. **Methods:** A search was carried out in the PubMed and Virtual Health Library (BVSALUD) databases using the descriptors: "XERODERMA PIGMENTOSUM", "XERODERMA PIGMENTOSO", "DNA REPAIR", "SKIN CANCER", "PHOTOSENSITIVITY", "CUTANEOUS NEOPLASMS" and "PHOTOSENSITIVITY" in the last 10 years, analyzing and applying the inclusion and exclusion criteria. In the end, 8 articles were selected. **Discussion:** Xeroderma Pigmentosum is an autosomal recessive disease, being of hereditary character and that increases the prevalence of cutaneous neoplasms and is subdivided into 7 groups in which the error is in the NER protein (Nucleotide Excision Repair) and 1 group with defect in the DNA polymerase. Based on the intensity and type of UV light and on the mutation presented, the clinical picture may vary, being milder or more aggressive, and may affect only the skin, nervous system or more than one system, also causing internal tumors. The diagnosis is clinical, but molecular tests to evaluate DNA synthesis in cells exposed to the sun and complementary analyzes can be performed to better define the alteration. When it comes to therapeutic strategies, currently the most used is sunlight deprivation since childhood, while other forms of management are still being studied. **Conclusions:** It is concluded that Xeroderma Pigmentosum is a disease of difficult control, diagnosis and management, requiring further studies on the subject and universal access to early diagnostic methods, enabling adequate prophylaxis in order to avoid future complications from the disease.

Keywords: Xeroderma pigmentosum, Xeroderma pigmentosum, DNA repair, Skin cancer, Photosensitivity, Skin neoplasms, photosensitivity.

INTRODUCTION

This review aimed to group studies related to Xeroderma Pigmentosum, presenting its means of diagnosis and current therapeutic strategies.

It is an autosomal recessive disease, of hereditary character, being more common in populations with consanguinity and that is manifested by greater sensitivity to ultraviolet radiation due to error in DNA repair, increasing the incidence of cutaneous neoplasms, but also with manifestations in several organs and systems.

For context, currently 3 intensities of UV radiation are known: UVA is the least harmful and that most crosses the ozone layer (95%), with a spectrum of 320-400 nm and leading to the production of reactive oxygen species and oxidation of nitrogenous bases of the DNA; UVB is of intermediate intensity, crossing the ozone layer by only 5% and causing damage by producing CPDs, 6-4PPs and Dewar isomers, with a spectrum of 290-320 nm; UVC is the most harmful, but it is completely blocked by the ozone layer.

This disease has 8 subtypes, A-G and V (based on the mutation site), being differentiated by the clinical picture and the type of genetic mutation involved, presenting different severities. Men and women have similar incidences, but the black population is slightly less affected.

The diagnosis is clinical, but for greater specificity of the mutation in question, DNA tests can be performed.

The most indicated treatment is severe restriction of UV radiation since childhood, but some drug therapies are being studied.

METHODOLOGY

A search was carried out in PubMed and

Virtual Health Library (BVSALUD) databases using the descriptors: "XERODERMA PIGMENTOSUM", "XERODERMA PIGMENTOSO", "DNA REPAIR", "SKIN CANCER", "PHOTOSENSITIVITY", "CUTANEOUS NEOPLASMS" of "PHOTOSENSITIVITY" in the last 10 years, being analyzed and selected with the inclusion criteria: articles in Portuguese/English, human sample, case series, reviews, cohort and cross-sectional studies; and exclusion criteria: articles that did not include the theme, animal sample, articles without an English version, case reports and studies prior to 2011. In the end, 8 articles were obtained to be studied.

RESULTS

Table below.

DISCUSSION

Xeroderma Pigmentosum is an autosomal recessive disease, being hereditary and which increases the prevalence of skin neoplasms and is subdivided into 7 groups whose error is in the NER protein (Nucleotide Excision Repair), known as XPA-XPG, and 1 group with defect. in DNA polymerase or XPV, involving an inherent photosensitization due to a failure to repair the effects caused by UV rays on DNA (1).

NER is divided into 2 groups: GG-NER (global genome nucleotide excision repair), capable of globally repairing lesions in the genome, and TC-NER (transcription-coupled nucleotide excision repair), which repairs only lesions in actively transcribed genes (2). Based on the intensity and type of UV light and the mutation presented, the clinical picture may vary, being milder or more aggressive.

When it affects only the skin, it is manifested by acute sensitivity to the sun, progressive dyschromatosis, poikiloderma, age-disproportionate photoaging and increased risk of cutaneous neoplasms (more common in XP-D, XP-E, XP-F and XP-C subtypes), nervous system with profound decrease in reflexes, cognitive impairment and hearing loss (more common in XP-A and XP-D subtypes) or more than one system, also causing internal tumors in the brain, colon, lung and blood – leukemias. In addition, they also have alterations in the ocular tissues exposed to the sun's rays, among them we can mention conjunctivitis, corneal neovascularization, ectropion, conjunctival pigmentation and cataract (3).

It is also known clinical picture whose skin changes are accompanied by Cockayne Syndrome where there is reduced growth, observed since intrauterine life, microcephaly, neurological abnormalities (from birth), sensorineural hearing loss, cataract (appearance in the first 3 years), structural anomalies eye defects, retinopathy pigmentosa, cutaneous photosensitivity, dental caries and a half-life of 12-13 years (up to 20 years), which is extremely rare (1,2).

Regarding the greater chance of malignant and premalignant lesions, a Chinese study that analyzed the clinical-molecular epidemiology of XP identified, in patients with type XP-A, 4 basal cell carcinomas at 11 years of age, melanoma at 24 years and SCC at age 21 (4).

The diagnosis is clinical, but molecular tests, such as HCR ("host cell reactivation"), in which exons and introns are amplified through the Sanger method in blood cells and fibroblasts (5), evaluate DNA synthesis in cells exposed to the sun. and complementary analyzes can be performed to better define the alteration (6). There must be a multidisciplinary approach to specialties such as dermatology, ophthalmology and neurology (5).

It is extremely important to focus on the identification of XP mutations, since it allows establishing the most accurate correlations between genotype and phenotype, leading

Title	Year and study design	Sample	Objectives	Results	Conclusion
Xeroderma Pigmentosum: Diagnostic procedure, interdisciplinary, patient care and novel therapeutic approaches	2014 Review				
Xeroderma pigmentosum clinical practiceguidelines	2017 Cross-sectional study	To establish clinical practice guidelines.	They were divided into 3 groups: XP with skin changes (45% -	XP involves an inherent photosensitization that occurs because of a deficiency in repairing the effects caused by UV rays on DNA. Skin changes involve progressive freckles and dyschromatosis, in addition to malignant skin tumors when patients do not protect themselves from the sun. In Japanese patients, most of them have central and peripheral neurological changes, such as psychomotor retardation. 90% are XP-D, XP-E, XP-F, XP-C and 75% XP-G and XP-V), XP with neurological alterations (55% - XP-A and XP-D and some XP -G) and XP/CS complex that has skin changes along with Cockayne syndrome (they are extremely rare, with only 3 patients being found, 2 with XP-D and 1 with XP-G)	
Novel therapeutic	2019 Review			XXP presents different phenotypes, closely linked to its molecular biology, but also under the influence of several factors such as the type of mutation and remaining function of proteins, among others. Currently, the main management strategy is aimed at preventing skin cancers by protecting the skin with the use of sunscreen, long sleeves and UV filters on windows, as well as frequent consultations with a dermatologist and ophthalmologist. Research into new therapies has focused on 4 strategies: alleviating the DNA repair defect with topical enzymes or gene transfer, stopping codon reading when a stop codon mutation is present, antioxidants for relieving oxidative stress, and oral, topical, and injectable agents for treat non-melanoma and melanoma skin cancers. Possible new strategies are: acetohexamide or glimepiride (sulfonylureas), nicotinamide and calorie restriction.	

approaches to xeroderma pigmentosum				
Clinical and molecular epidemiological study of xeroderma pigmentosum in China: A case	2017 Study performed	Patients were selected from the Departm ent of	Patients in groups A, D, F and G had sunburn reactions with persistent erythema with or without intense	The freckles identified in XP patients are darker, irregular and diffuse. patients with XP-A, XP-D,
series of 19patients.	Dermatol ogy Peking Univertit y First Hospital, from the following neurological (neurological abnormalities, microcephaly) and dermatological symptoms, from type XP-A to XP-G and XP-V, clinical history, dermatological evaluation, laboratory tests of blood or amniotic fluid (in two pregnant women) for genome evaluation using TIANamp blood DNA minikit.	sun exposure, unlike types C and V who had an abnormal pigmentation, similar to freckles in places that were exposed to the sun. Freckles developed in all patients, eventually (if using sunscreen, they had it later than if not), with onset of pigmentation averaging 13.5-/+20.2 months. Type XP-A patients had cutaneous reactions (in addition to those mentioned, 4 patients with basal cell carcinoma at 11 years, melanoma at 25 and SCC at 21) and neurological (profound decrease in the tendon reflex, microcephaly, abnormal gait, cognitive impairment, sensorineural hearing loss) similar despite having different XPA mutations.	XP-Fand XP-G had more acute sunburn reactions than patients with XP-C and XP-V, in agreement with the other published studies. This is due to the fact that XP-C and XP-E cells are defective in repairing the global genome. However, in XP-A, XP-B, XP-D, XP-F and XP-G they are also not working to protect against the action of ultraviolet radiation. Groups A, B, D, F and G are associated with neurological symptoms. XP-C patients are more common in China and the United States, whereas in Japan, there are more XP-A patients, due to the greater number of people carrying the mutation (1% of the population).	

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	They were separated into 6 groups: XP-A (9 patients), XP-C (4 patients), XP-D (1 patient), XP-F (1 patient), XP-G (2 patients), XP -V (2 patient s)				
Xeroderma pigmentosum -facts and perspective	2018 Review	XP patients are 10,000x more likely to have basal cell carcinoma and SCC and 2,000x more likely to have melanoma, in addition to being more common to find conjunctivitis, cataracts and pterygium. A mutation of this gene generates manifestations of different types of phenotypes. These mutations were diagnosed and confirmed through DNA testing (takes blood cells or skin biopsy and then irradiates it with UV rays after it is compared with the	The diagnosis is made through some DNA repair analysis tests, in which it helps to prevent malignant skin tumors early when starting treatment and protection against UV rays. The HCR (host cell reactivation) is used, in which it is possible to identify which protein has the mutation, since all eeons and introns are amplified, through the Sanger method, and for this, blood cells and fibroblasts are used. In conclusion, cells from patients with		

normal cells of the patient), and must be done as early as possible to start protection against UV rays.

XP normally has a normal karyotype without a major chromosomal defect. There is no such effective treatment, so an early diagnosis is necessary for protection against UV rays and regular examinations with dermatologists to check for pre-malignant lesions. It is possible to use isotretinoin to reduce the number of cancer cells, but it has many side effects (hyperlipidemia, teratogenicity, calcification of the tendons) and must only be used in patients with a certain amount of cancer cells. In addition, there are creams with repair enzymes that are proving effective.as a prophylactic for malignant lesions. Showing that inhibitory checkpoint therapy is becoming showing effective against all types of cancers.

Understanding photodermatoses associated with defective DNA repair: Syndromes with cancer predisposition	2016 Many cases	XP is a hereditary and recessive disease, with a higher incidence in populations with a high degree of consanguineous relationships, presenting 8 known groups A-G and V, with different mutation sites. Men and women have similar incidences, with the Black population being slightly less affected. The classic clinical picture includes skin and eye abnormalities, usually in areas exposed to the sun, with variations according to the variant. The frequency of neurological findings varies with the subgroups, being more common in D and with different severities. Other Changes Include mucous membranes, oral tumors, melanoma skin cancers and non-melanoma, internal tumors.		(brain, colon, lungs and blood - leukemia). The diagnosis is clinical, but molecular tests to evaluate DNA synthesis in cells exposed to the sun and complementary analyzes can be performed to better define the alteration. Current management is through severe restriction of UV rays from childhood - some therapeutic techniques have shown benefit: topical T4 endonuclease V, oral isotretinoin with or without chemotherapy and radiation.
The key role of UVA-light induced oxidative stressin human Xeroderma Pigmentosum Variant cells	2019	1 Patient	XP-V cells are more sensitive to UVA light than cells with normal levels of DNA polymerase, have slower DNA injury repair, and UVA-induced DNA damage results in replication arrest.	This work showed the deleterious effects of UVA light on XP- V. UVA-induced DNA damage is related to oxidative stress in these cells.
Characteristics of Xeroderma Pigmentosum in Japan:	2019 Review		The frequency of XP- a is the highest, basal cell carcinoma is the	

Lessons FromTwo Clinical Surveys and Measures forPatient Care	most frequent, followed by squamous cell and melanoma, the frequency of skin CA has decreased in the last 20 years and the age of onset of CA development has increased. The incidence of melanoma is similar to SCC in XP-V while in XP-A SCC is higher. Regarding neurological symptoms XP-A has < DNA repair capacity, manifests the most severe symptoms such as developmental delay, hearing loss, atrophy of the brain, brainstem and cerebellum and die around 20 years, however the life expectancy currently it's bigger. The mechanisms are not fully understood, but studies indicate that mitophagy impairment is the cause of the neurological manifestations. May have ocular manifestations such as conjunctivitis, wound healing	Lessons FromTwo Clinical Surveys and Measures forPatient Care	most frequent, followed by squamous cell and melanoma, the frequency of skin CA has decreased in the last 20 years and the age of onset of CA development has increased. The incidence of melanoma is similar to SCC in XP-V while in XP-A SCC is higher. Regarding neurological symptoms XP-A has < DNA repair capacity, manifests the most severe symptoms such as developmental delay, hearing loss, atrophy of the brain, brainstem and cerebellum and die around 20 years, however the life expectancy currently it's bigger. The mechanisms are not fully understood, but studies indicate that mitophagy impairment is the cause of the neurological manifestations. May have ocular manifestations such as conjunctivitis, wound healing	Lessons FromTwo Clinical Surveys and Measures forPatient Care	most frequent, followed by squamous cell and melanoma, the frequency of skin CA has decreased in the last 20 years and the age of onset of CA development has increased. The incidence of melanoma is similar to SCC in XP-V while in XP-A SCC is higher. Regarding neurological symptoms XP-A has < DNA repair capacity, manifests the most severe symptoms such as developmental delay, hearing loss, atrophy of the brain, brainstem and cerebellum and die around 20 years, however the life expectancy currently it's bigger. The mechanisms are not fully understood, but studies indicate that mitophagy impairment is the cause of the neurological manifestations. May have ocular manifestations such as conjunctivitis, wound healing

to a better assessment of the prognosis and course of the disease (7).

Regarding the differential diagnoses, we can highlight freckles, however, there are no more serious symptoms of photosensitivity, and hereditary symmetric dyschromatosis, which differs from XP by the presence of dyschromatosis on both the back of the hands and the back of the feet and also by erythropoietic protoporphyria, in which the definitive diagnosis is made through the gene responsible for the disease (1).

When it comes to therapeutic strategies, currently the most used is severe deprivation of sunlight since childhood, through the use of clothes, sunscreen, hats and sunglasses, as well as window protectors, in addition to regular consultations with dermatologists to checking for pre-malignant lesions and treating them when necessary (2,6) and with ophthalmologists to prevent eye damage (2). Therefore, early diagnosis is necessary, avoiding the complications of this disease (5), in which it was found that when using sun protection, skin lesions develop later (4).

However, other forms of management are still being studied, and benefits have been observed with the use of topical T4 endonuclease V (a reduction in BCC and actinic keratosis was observed in patients using this drug via liposomal medication), oral isotretinoin associated or not chemotherapy (shown to be beneficial in patients with unresectable SCC and as a protector against skin cancers), radiotherapy (for the treatment of SCC, but 1 study in a 7-year-old individual showed a lower occurrence of cancers in the irradiated region), acetoexamidhe or glimepiride (sulfonylureas that increase resistance to UV rays, reducing damage in the XPA subtype, increasing CPD clearance through the degradation of MUTYH – DNA glycosylase involved in the repair of nitrogenous bases) (2,6).

An animal model study demonstrated that 30% calorie restriction tripled their life expectancy and the mechanism attributed to this has not yet been delineated, but is believed to be related to increased resistance to stress induced by DNA damage (2).

The analysis of DNA damage caused by UVA rays and the consequences for XP-V cells was performed in a study, showing that the use of antioxidants is protective against the effects of this exposure (8).

In addition, as XP is a hereditary disease, genetic counseling is necessary for all patients (1), and exact knowledge about the mutation in question may be relevant in the future, enabling the search for an individualized therapy for each case (7).

CONCLUSION:

It is concluded that Xeroderma Pigmentosum is a disease of difficult control, diagnosis and management, requiring further studies on the subject and universal access to diagnostic methods.

Early, enabling adequate prophylaxis in order to avoid future complications from the disease.

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