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REVIEW

Xeroderma pigmentosum: an updated review

Alexander KC Leung[1,2], Benjamin Barankin[3], Joseph M Lam[4,5], Kin Fon Leong[6], Kam Lun Hon[7,8]

[1]Department of Pediatrics, The University of Calgary, Calgary, Alberta, Canada; [2]The Alberta Children's Hospital, Calgary, Alberta, Canada; [3]Toronto Dermatology Centre, Toronto, Ontario, Canada; [4]Department of Pediatrics and Department of Dermatology and Skin Sciences, University of British Columbia, Vancouver, British Columbia, Canada; [5]BC Children's Hospital, Vancouver, British Columbia, Canada; [6]Pediatric Institute, Kuala Lumpur General Hospital, Kuala Lumpur, Malaysia; [7]Department of Paediatrics, Hong Kong Institute of Integrative Medicine, The Chinese University of Hong Kong, Hong Kong; [8]Jockey Club School of Public Health and Primary Care, The Chinese University Hong Kong, Hong Kong

Abstract

Background: Early recognition of xeroderma pigmentosum is important to minimize the complications arising from the harmful effects of exposure to ultraviolet radiation. This narrative review aims to familiarize physicians with the clinical features, diagnosis and management of xeroderma pigmentosum.

Methods: A search was conducted in December 2021 in PubMed Clinical Queries using the key term "xeroderma pigmentosum". The search strategy included all clinical trials, observational studies and reviews published within the past 10 years. The information retrieved from the search was used in the compilation of this article.

Results: Xeroderma pigmentosum is a condition of abnormal DNA repair of ultraviolet radiation-induced and oxidative DNA damage, which leads to increased skin cancer susceptibility. Approximately 50% of patients with xeroderma pigmentosum have increased photosensitivity and certain types of xeroderma pigmentosum are more prone to ocular disease and progressive neurodegeneration depending on the causative mutation. The diagnosis should be suspected in patients with increased photosensitivity and characteristic cutaneous, ophthalmological and neurological findings. A definite diagnosis can be made by the identification of biallelic mutation in one of the causative genes. Strict and consistent sun avoidance and protection and early detection and treatment of premalignant and malignant skin lesions are the mainstays of management. Treatment options for actinic keratosis include cryotherapy, topical imiquimod, topical 5-fluorouracil, chemical peeling, excision, CO_2 laser resurfacing, fractional/pulsed laser therapy, and photodynamic therapy. Cutaneous malignancy can be treated by photodynamic therapy, curettage and electrodesiccation, or surgical excision. Oral isotretinoin, oral niacinamide, topical imiquimod and topical fluorouracil can be used for the prevention of skin malignancy. Treatment options for poikiloderma include chemical peeling, dermabrasion and laser resurfacing. Methylcellulose eyedrops and soft ultraviolet-protective contact lenses may be used to keep the cornea moist and protect against the harmful effects of keratitis sicca. Investigational therapies include the use of T4 endonuclease-V liposome lotion and oral nicotinamide to reduce the rate of actinic keratoses and non-melanoma skin cancers and gene therapy for radical cure of this condition.

Conclusion: Although currently there is no cure for xeroderma pigmentosum, increased awareness and early diagnosis of the condition, followed by rigorous sun avoidance and protection and optimal management, can dramatically improve the quality of life and life expectancy.

Keywords: conjunctival injection, conjunctival neovascularization, neurodegeneration, photophobia, poikiloderma, skin cancers, xeroderma pigmentosum.

Citation

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Introduction

Xeroderma pigmentosum (XP) was first described in 1874 by Moritz Kohn Kaposi, a Hungarian professor of dermatology, who reported two patients with thin, dry skin, skin contraction, checkered pigmentation, dilatation of cutaneous blood vessels, and development of multiple cutaneous tumours at a young age.[1] Kaposi coined the term 'xeroderma pigmentosum' to denote the characteristic 'dry and pigmented skin'. XP is an autosomal recessive inherited genodermatosis due to mutations in genes involved in the DNA repair machinery, leading to deficient repair of DNA damaged by ultraviolet radiation (UVR).[2,3] The condition can manifest as photosensitivity and increased skin cancer susceptibility. Certain types of XP are more prone to ocular disease and progressive neurodegeneration, dependent on the causative mutation.[4,5] Early recognition of XP is important so that avoidance and protection from UVR can be initiated early to minimize the complications arising from the harmful effects of UVR.

Methods

A search was conducted in December 2021 in PubMed Clinical Queries using the key term "xeroderma pigmentosum". The search strategy included all clinical trials (including open trials, non-randomized controlled trials, and randomized controlled trials), observational studies and reviews (including narrative reviews and meta-analyses) published within the past 10 years. Only papers published in the English literature were included in this review. The information retrieved from the search was used in the compilation of this article.

Review

Aetiopathogenesis

When DNA is exposed to UVR, nucleic acid-based photoproducts (e.g. pyrimidine 6–4 pyrimidone dimers and cyclobutane pyrimidine dimers) result, which are amendable to DNA repair via the nucleotide excision repair (NER) process.[6–10] NER is capable of removing these nucleic acid-based photoproducts and replacing damaged DNA with new DNA.[11,12] NER is a central pathway safeguarding cells and genomes damaged by UVR.[9] Two types of NER are recognized: the transcription-coupled (TC)-NER and the global genome (GG)-NER.[6] TC-NER repairs actively transcribed DNA whilst GG-NER repairs DNA not undergoing transcription at that time.[13,14] Eight NER proteins (XPA, XPB, XPC, XPD, XPE, XPF, XPG and XPV) and their genes have been identified.[2] XPA–XPG are involved in different steps of the NER in the presence of DNA damage whereas XPV is involved in the postreplication repair of damaged DNA.[2] Based on the mutation of the specific gene, XP can be divided into seven complementation groups (XPA, XPB, XPC, XPD, XPE, XPF and XPG) and an XP variant (XPV).[5,11,15] Generally, patients with XP are unable to clear the UVR-induced photoproducts or employ NER to mend UVR damage to the DNA.[6] Those with XPV have normal NER but have mutations in the translational DNA *Pol η* gene.[16] *Pol η* is involved in DNA synthesis and allows transcription past UVR-damaged DNA that has not been repaired by NER, in a process known as trans-lesion synthesis.[5,6,14,16] As such, the ability to replicate DNA after UVR damage is impaired in individuals with XPV.[17,18] The cutaneous features of XP, their progression and patients' propensity to early cancer result from an accumulation of UVR-induced photoproducts and unrepaired DNA damage.[2] Oxidative stress and the cumulative oxidative DNA damage in neurons are responsible for neurodegeneration.[2]

XP is inherited as an autosomal recessive trait with 100% penetrance.[4,19] As such, absence of a family history of XP does not preclude the diagnosis.

Incidence

XP affects all races with a worldwide incidence of 1 in 250,000 live births.[20,21] The incidence of XP is estimated to be 1, 2.3, 17.5 and 45 per million live births in the United States, Western Europe, Middle East and Japan, respectively.[4,6,11,22,23] The incidence is increased in areas where consanguinity is common.[24] The sex ratio is approximately equal.[5] Worldwide, the subtypes XPA, XPC and XPV account for approximately 75% of all cases of XP whilst XPV alone accounts for approximately 30% of cases.[11] XPC is the most common subtype in the United States, Europe and Africa whilst XPA is the most common subtype in China and Japan.[6,11,24–26]

Histopathology

Histological findings include increased melanin and melanocytes in the basal cell layer, hyperkeratosis, lymphocytic infiltrate in the upper dermis, atrophic and/or elastotic dermis, thinning of the stratum malpighii with atrophy and/or elongation of the rete, telangiectasia and keratinocyte atypia.[5,27,28]

Clinical manifestations

XP is characterized by increased photosensitivity, early-onset UVR-induced skin pigmentary changes, UVR-induced damage to the eyes, an increased risk of cutaneous tumour development and, in some cases, progressive neurological degeneration.[29,30] Many risk factors can exacerbate the cutaneous manifestations, including chronic exposure to UVR, sunny weather, poor protection from sunlight and fair skin.[28] Clinical manifestations vary and are influenced by the precise gene mutation and environmental factors such as cumulative exposure to UVR.[14,31,32]

The appearance of the skin of patients with XP is usually normal at birth.[11,33] However, the skin has an extreme sensitivity to UVR and is soon damaged with minimal exposure to UVR.[20] This may manifest as severe or exaggerated sun tanning,

burning, or blistering upon minimal sun exposure.[11] Erythema may persist for weeks in about 60% of cases.[34] XP subtypes XPA, XPB, XPD, XPF and XPG are associated with severe and exaggerated sunburning after minimal sun exposure.[4,6,35,36] On the other hand, patients with subtypes XPC, XPE and XPV have less severe sunburning and can even tan after minimal sun exposure; yet, affected patients still develop abnormal skin pigmentation, including freckles and lentigos.[4,6,35] Marked freckling-like skin changes typically present before the age of 2 years on sun-exposed areas.[4,6,11] Over time, the skin undergoes premature aging, with progressive xerosis, atrophy, wrinkling, telangiectasia, early-onset lentigos which increase in size, number and colour, and poikiloderma (Figures 1–7).[4,6,31,37,38] The hypopigmented areas may represent mutated melanocytes that have lost their ability to produce melanin.[20] Actinic keratoses are observed at an early age, and actinic cheilitis is not uncommon.[11,23,39]

The anterior parts of the eye (conjunctiva, lens, cornea and eyelids) are particularly susceptible to damaging effects of UVR in patients with XP.[6,40] The posterior parts of the eye are protected by the lens which acts as a barrier to UVR.[13] Approximately 90% of patients with XP have ocular involvement.[14,39] Common ophthalmological manifestations include photophobia, conjunctival xerosis, blepharospasm, prominent conjunctival injection, conjunctival

Figure 1. Multiple pigmented freckles, papules, and dryness on the face characteristic of xeroderma pigmentosum.

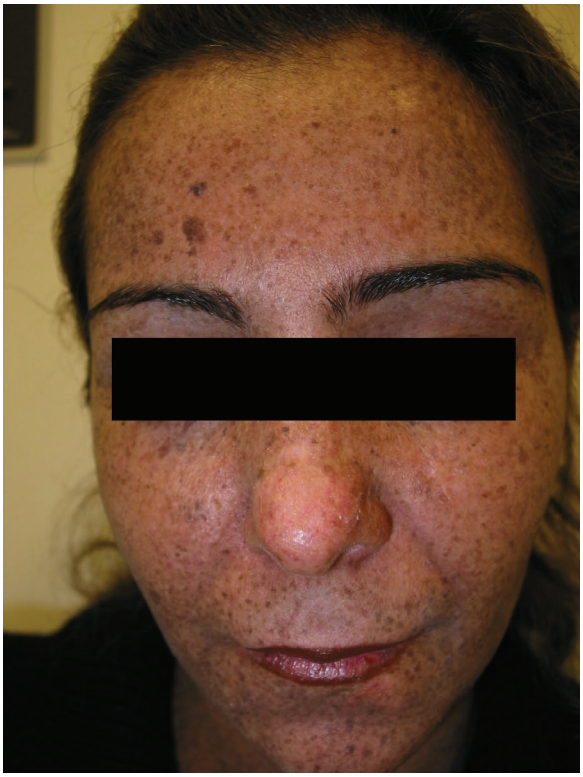


Figure 2. Xeroderma pigmentosum presenting with dry, warty papules and mottled hyperpigmented and hypopigmented macules on the face.

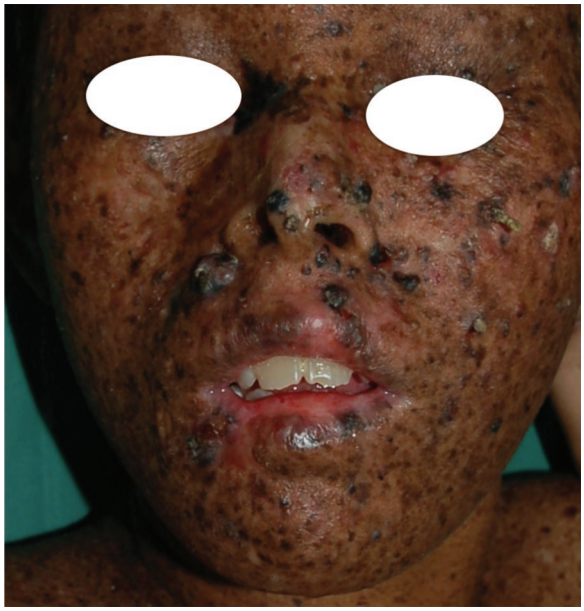


Figure 3. Multiple dry, scaly, mottled hyperpigmented and hypopigmented macules giving rise to the characteristic 'salt and pepper appearance' on the neck and upper back.

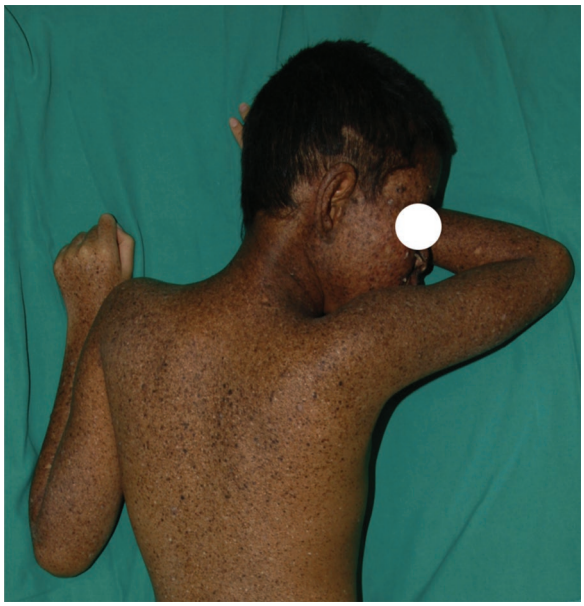


Figure 4. Excessive freckling and hypopigmented macules on the forearm.

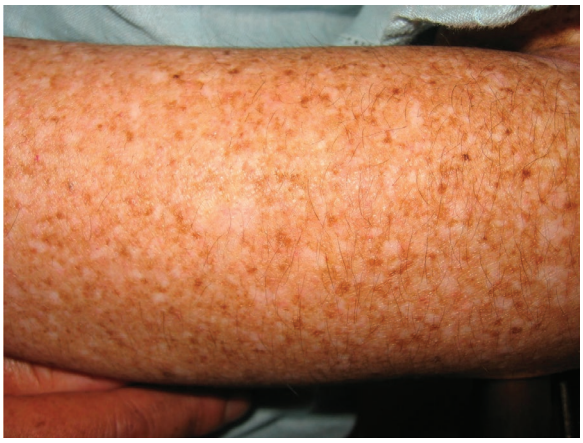
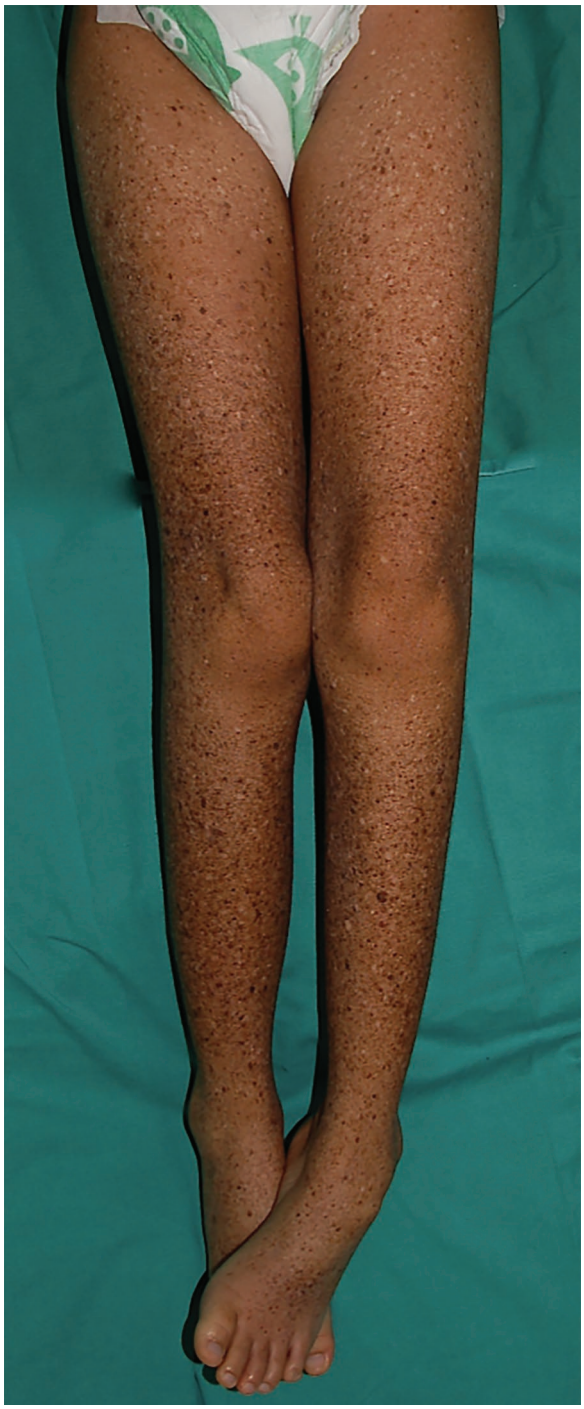


Figure 5. Multiple, dry, scaly, mottled hyperpigmented and hypopigmented macules on the lower limbs.



neovascularization (Figure 8) and conjunctival melanosis; findings are usually obvious in the first decade of life.[6,14,22,41] Other ophthalmological manifestations include irregularities in eyelid border, increased pigmentation of the eyelids with loss of eyelashes, trichiasis, blepharitis, ectropion, entropion, lagophthalmos, symblepharon, lacrimal point stenosis, blepharitis, keratitis, punctate keratopathy, band keratopathy, keratoconjunctivitis, corneal opacification (Figure 8), corneal ulceration and corneal scarring, pinguecula, pterygium, fibrovascular pannus of the cornea, iritis, ciliary body hamartoma, cataracts, macular oedema, chorioretinal adhesion, retinal degeneration with pigment migration and optic nerve atrophy.[11,14,27,34,41–43] Neuro-ophthalmic abnormalities in the form of minimal pupillary constriction to light, strabismus and abnormal extraocular movements have been reported in 25%, 8% and 7% of patients with XP, respectively.[14] Interesting, patients with subtypes XPC, XPE and XPV who have preserved TC-NER have significantly more ophthalmological abnormalities than those with subtypes XPA, XPB, XPD, XPF and XPG who have impaired TC-NER, presumably due to lack of aggressive and early initiation of sun-protective measures in patients with preserved TC-NER.[4,14]

The accumulation of 6–4 pyrimidine–pyrimidine dimers and cyclobutene–pyrimidine dimers from UVR exposure is crucial in cutaneous carcinogenesis.[12,44,45] Patients with XP develop numerous precancerous actinic keratoses early in life.[46,47] Affected patients are at risk for skin and mucous membrane cancers in sun-exposed areas.[47,48] The most prevalent skin cancers are squamous cell carcinoma followed by basal cell carcinoma and malignant melanoma.[49–53] Patients with XP have a 10,000-fold and 2000-fold increased risk over their lives of developing non-melanoma skin cancers (notably squamous cell carcinoma and basal cell carcinoma) and malignant melanoma, respectively.[34,54] The mean age for the first appearance of non-melanoma skin cancer and melanoma is 9 and 22 years, respectively, in patients with XP.[6,11,55] In contrast, the mean age of onset of UVR-induced non-melanoma skin cancer and melanoma is about 67 and 55 years, respectively, in the general population.[31,35,56] Multiple cutaneous malignancies are commonly found on sun-exposed areas in patients with XP.[28,57,58] Affected patients with no or minimal protection against UVR may develop hundreds of skin cancers on sun-

Figure 6. Premature aging of the skin with xerosis, atrophy, lentigines, and intermixed hyperpigmented and hypopigmented areas characteristic of xeroderma pigmentosum.

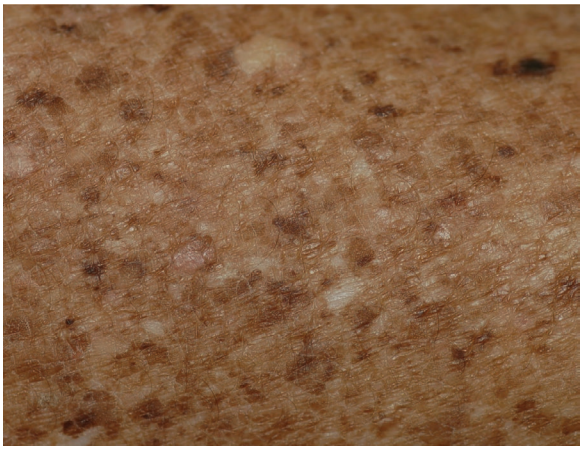


Figure 7. Severe poikiloderma with skin atrophy, xerosis, telangiectasias, cutaneous horns, disfiguring scars, lentigines, and intermixed hyperpigmented and hypopigmented areas.

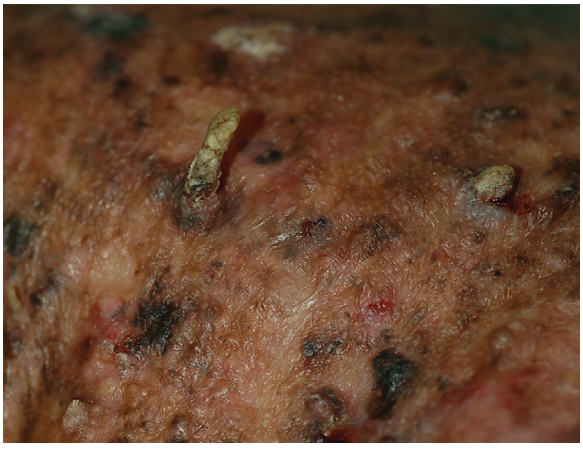
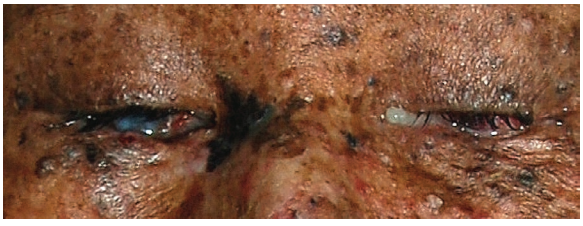


Figure 8. Excessive neovascularization and corneal opacification in a child with xeroderma pigmentosum.



exposed areas.[35] The incidence of intraoral cancers (notably squamous cell carcinoma of the tip of the tongue) is 3000–10,000 higher than in the general population.[4,59] Squamous cell carcinoma of the lower lip is also common.[60] XP is associated with various ocular surface malignancies, notably squamous cell carcinoma, basal cell carcinoma and melanoma.[14,61] The risk of ocular malignancies is increased about 2000-fold.[37] Ocular malignancies usually occur in the areas that are exposed to UVR such as the eyelids, conjunctiva and cornea.[21] Other skin cancers that occur with increased frequency in patients with XP include keratoacanthoma, epithelioma, sebaceous cell carcinoma, fibrosarcoma and angiosarcoma.[27,62,63] Surprisingly, patients without severe sunburn response tend to develop skin cancer earlier than those who have a severe sunburn response, presumably due to less strict sun-protective measures in the former.[35,36,64]

Progressive neurodegeneration occurs in approximately 25% of patients with XP.[6,34,36,65,66] The most common subtypes associated with neurodegeneration are XPA and XPD, followed by XPB, XPG and XPF.[2] Neurodegeneration is rarely seen in patients with XPC and XPE.[4] Patients with XPV tend to be spared the neurodegeneration seen in other subtypes.[67] Neurological manifestations include acquired microcephaly, progressive cognitive impairment, deterioration of neurological status, progressive sensorineural hearing loss, speech delay, dysarthria, ataxia, diminished or absent deep tendon stretch reflexes, loss of ability to walk, spasticity, dyskinesia, chorea, dysphagia, neurogenic bladder, dysuria, supranuclear ophthalmoplegia and seizures.[68–75] These manifestations are progressive and irreversible and may be attributed to loss of neurons in the cerebrum and cerebellum, primary axonal degeneration in the peripheral nerves and, occasionally, secondary demyelination.[76,77] Oxidative stress may play an important role in damaging the DNA of affected neurons.[78]

Diagnosis

The diagnosis should be suspected in patients with increased photosensitivity and characteristic cutaneous, ophthalmological and neurological findings (vide supra). A family history of XP or the finding of cutaneous malignancy within the first decade of life further supports the diagnosis. A definite diagnosis can be made by the identification of biallelic pathogenic variants in one of the causative genes.[34,79] Molecular testing may include the use of serial single-gene testing, multigene panel and more comprehensive genomic testing.[34] In families with a known history of XP, prenatal diagnosis can be made through DNA testing on chorionic villus-derived cells or on amniotic fluid cells from the pregnant mother in the course of an amniocentesis.[80]

Dermoscopy is a useful non-invasive diagnostic tool to discriminate between benign and malignant lesions in XP.[81,82] The presence of an asymmetrical blotch or irregular globules and dots are common dermoscopic features of malignant lesions.[82] Malignant melanoma can be differentiated from

benign melanocytic nevi by the presence of variegated colours, asymmetry, prominent pigment network, blue-grey areas, blotches, atypical dots/globules, perifollicular pigmentation and follicular obliteration.[81,82]

Differential diagnosis

The differential diagnosis includes Cockayne syndrome, XP/Cockayne syndrome complex, trichothiodystrophy, XP/trichothiodystrophy complex, Cockayne syndrome/trichothiodystrophy complex, cerebro-oculo-facio-skeletal (COFS) syndrome, UV-sensitive syndrome, Bloom syndrome (also known as Bloom–Torre–Machacek syndrome or congenital telangiectatic erythema), Rothmund–Thomson syndrome, Hartnup disease, Carney complex, De Sanctis–Cacchione syndrome, erythropoietic protoporphyria, cutaneous lupus erythematosus and LEOPARD syndrome (also known as Noonan syndrome with multiple lentigines).[83–96] The distinctive features of many of these conditions help to differentiate them from XP.

Complications

Dry parchment-like prematurely aged skin, poikiloderma (constellation of hyperpigmentation, hypopigmentation, atrophy, telangiectasia and keratotic skin lesions) and cutaneous premalignant and malignant lesions in visible areas have been reported by patients as disfiguring and embarrassing.[97,98] Affected children are more likely to experience loneliness, sadness, discrimination, shame, ridicule, harassment, teasing, bullying, rejection and abuse.[99] The psychological impact can be profound especially those individuals with malignancy and has an adverse effect on the quality of life.[45]

Patients with XP under 20 years of age have a 50-fold increased risk of developing tumours in the central nervous system, including glioblastoma, medulloblastoma, spinal cord astrocytoma, schwannoma and neurilemoma.[6,13,100–102] These malignancies are not UVR-related.[13] Haematological malignancies, such as acute lymphoblastic leukaemia, acute myeloid leukaemia, lymphoma and myelodysplastic syndrome, occur with increased frequency in patients with XP.[103–106] Patients with XP have a 12-fold increased risk for internal malignancy, such as nasopharyngeal carcinoma, squamous cell carcinoma of the oesophagus, carcinoma of the thyroid, adenocarcinoma of the lung, carcinoma of the breast, carcinoma of the pancreas, leiomyosarcoma of the kidney, cancer of the ovary and cancer of the prostate, suggesting that UVR might not be the only culprit causing malignancy in patients with XP.[107–116] Patients with XP are at higher risk of developing smoking-induced cancers.[13]

Women with XP are at risk for premature menopause.[117] In one study of 45 women aged 18 years or older with XP, 14 (31%) had premature menopause (before 40 years of age); the median age of menopause was 49.5 years.[117]

Patients with subtype XPC are at risk of developing pyogenic granuloma and multinodular thyroid.[118]

Prognosis

Approximately 60% of patients with XP die before the age of 20 years.[12] The median age of death is 32 years.[13] Metastatic skin cancer is the leading cause of death, followed by neurodegeneration and internal cancer.[34,63,119,120] In one study, the mean age of death in patients with XP with and without neurodegeneration was 29 and 37 years, respectively.[65] In general, the prognosis depends on how early sun avoidance and protection are initiated, how appropriate treatment is provided to slow down the progress of disease and its complications, how early malignancy is detected and treated, how severe the disease is, and the mutation of the specific gene. In this regard, patients with XPV typically fare better than patients with other subtypes.[11]

Management

At present, there is no cure for XP. Therefore, prevention of complications is crucial for this disfiguring and potentially lethal disease. Strict and consistent sun avoidance and protection and early detection and treatment of premalignant and malignant skin lesions are the mainstays of management. These and other treatment options are summarized in Box 1. Regular paediatric, dermatological, ophthalmological and neurological follow-up is essential.

Sun avoidance and sun protection

If possible, outdoor activities should be restricted to either before sunrise or after sunset. If exposure to the sun is inevitable, patients should wear protective wide-brimmed hats, long-sleeved clothing, UV-resistant face masks and UV-absorbing/blocking sunglasses with side shields, regularly use (preferably every 2 hours) broad-spectrum sunscreens with a sun protection factor of 30 or preferably greater to all exposed skin and lip balms to lips and use UV-resistant films on windows in cars and buildings.[11,35,121] Patients with XP should also be protected from unfiltered fluorescent light, metal halide lamps and halogen lights that can emit UVR;[31,121] such light sources should be shielded.

Sunscreens can be physical or chemical. Physical sunscreens containing microfine particles of zinc oxide, titanium dioxide and red ferric oxide help to reflect and block UVR.[5] Chemical sunscreens containing benzophenones mainly block UV-A whilst those containing avobenzone, cinnamates, salicylates and para-amino benzoic acid mainly block UV-B and absorb both UV-A and UV-B.[5] Broad-spectrum chemical sunscreens contain a combination of ingredients effective to block both UV-A and UV-B and absorb both UV-A and UV-B that have not been blocked.

Unfortunately, adherence to photoprotection varies widely and is a significant issue.[122,123] Indeed, it is difficult to achieve

Box 1. Treatment options for xeroderma pigmentosum.

A. Sun avoidance and sun protection
   1. Sun avoidance
   2. Sun protection (regular use of broad-spectrum sunscreens)

B. Chemoprevention of skin cancers
   1. Oral isotretinoin
   2. Topical imiquimod
   3. Topical fluorouracil

C. Treatment of poikiloderma
   1. Chemical peeling
   2. Dermabrasion
   3. Carbon dioxide (CO_2) or erbium-YAG laser resurfacing

D. Treatment of actinic keratosis
   1. Cryotherapy
   2. Topical imiquimod
   3. Topical 5-fluorouracil
   4. Chemical peeling
   5. Excision
   6. CO_2 or erbium-YAG laser resurfacing
   7. Fractional/pulsed laser therapy
   8. Photodynamic therapy

E. Treatment of skin cancers
   1. Photodynamic therapy
   2. Curettage with electrodessication
   3. Aggressive cryosurgery
   4. Surgical excision
   5. Oral vismodegib, pembrolizumab, nivolumab and cemiplimab

F. Ocular management
   1. Methylcellulose eyedrops
   2. Soft UV-protective contact lens
   3. For ocular surface squamous neoplasia
      a. Surgical resection and intraoperative cryotherapy
      b. Subconjunctival injection of IFNα2b with topical cycles of mitomycin C eyedrops

G. Neurological management
   1. May need hearing aids, speech therapy, physical therapy and occupational therapy
   2. No effective treatment for neurodegeneration

H. Investigational therapies
   1. Topical T4 endonuclease-V
   2. Oral vismodegib
   3. Oral nicotinamide
   4. Oral *Polypodium leucotomos* extract
   5. Oral coenzyme Q_{10}
   6. Gene therapy

I. Genetic counselling

J. Psychological counselling

full photoprotection throughout one's lifetime. For example, the use of broad-spectrum sunscreens on all sun-exposed skin every 2 hours, as some investigators have advised, can be quite expensive. In a cross-sectional survey of patients (n=156) with XP in the United States, United Kingdom, France and Germany, one-third of patients did not achieve optimal face photoprotection.[123]

As UVR, in particular UV-B radiation, is needed for the production of vitamin D in the skin from 7-dehydrocholesterol, individuals under strict sun protection may have vitamin D deficiency.[124,125] Affected patients should be encouraged to consume foods (e.g. eggs, fish and fortified foods) rich in vitamin D.[11] Vitamin D supplementation is recommended for individuals with low serum concentration of vitamin D.[4,34]

Failure to provide vitamin D supplements in patients with XP may result in rickets.[126,127]

Chemoprevention of skin cancers

High-dose (2 mg/kg/day) oral isotretinoin (13-cis-retinoic acid) can be used to reduce the number of skin tumours.[33,128] Adverse events associated with the use of oral isotretinoin include photosensitivity, myalgias, arthralgias, xerostomia, xerophthalmia, palmoplantar desquamation, alopecia, corneal opacities, delayed wound healing, pseudotumour cerebri, bone marrow suppression, hepatotoxicity, hyperlipidaemia, periostitis, hyperostosis and teratogenicity.[129] As such, high-dose oral isotretinoin should only be used in severely affected patients with a particularly high number of newly developed skin tumours.[31] Some affected patients, however, may respond to an intermediate dose (1 mg/kg/day) or lower dose (0.5 mg/kg/day) of oral isotretinoin with less adverse events.[34] Historically, some physicians have used acitretin for chemoprevention. The disadvantage of using acitretin for chemoprevention is its long half-life if esterified to etretinate and is therefore suboptimal for women of childbearing age.

Topical imiquimod and/or fluorouracil have been used with success for the prevention of skin malignancy in patients with XP.[128,130] The medications should be used prophylactically at the earliest onset of symptoms such as xerosis, dyspigmentation, actinic keratoses, or at the very early sign of skin malignancy.[4] The most common adverse events associated with the use of these two medications are erythema and pain at the site of application.

Treatment of poikiloderma

Treatment options for poikiloderma in patients with XP include chemical peeling (exfoliation), dermabrasion and carbon dioxide (CO_2) or erbium-YAG laser resurfacing.[128,131] Chemical peeling is preferred to dermabrasion. Topical application of trichloroacetic acid induces superficial coagulation of the proteins in the skin with consequent degradation of the epidermis and upper dermis, leading to activation of regenerative processes that trigger the renewal of damaged skin.[5] Nowadays, trichloroacetic acid is the gold standard of chemical peeling.[5] The use of a camouflage cream/make up may also be considered for cosmetic purposes.[132]

Treatment of premalignant skin lesions and skin cancers

Patients with XP should be screened regularly (every 3–6 months) for early detection and treatment of a wide range of cutaneous and ocular surface malignancies.[130] In this regard, colour photographs documentation of the entire skin surface and close-up photographs (including a ruler) of individuals lesions are important in early detection and follow-up of cutaneous malignancy. Computerized mole mapping (e.g. Fotofinder) ± artificial intelligence should also be considered.

Premalignant lesions, such as actinic keratosis, should be treated as early as possible to prevent the progression to squamous cell carcinoma. Treatment options for actinic keratosis include cryotherapy using liquid nitrogen, topical imiquimod, topical 5-fluorouracil, chemical peeling (e.g. trichloroacetic acid, phenol-based peeping solution), excision, CO_2 or erbium-YAG laser resurfacing, fractional/pulsed laser therapy and photodynamic therapy (e.g. methyl aminolevulinate or 5-aminolevulinic acid as a photosensitizer).[22,133,134]

Cutaneous malignancy can be treated by photodynamic therapy, curettage with electrodessication, aggressive cryosurgery or surgical excision depending on the type of skin cancer; the latter is the treatment of choice.[133,135] Cutaneous malignancies that are recurrent or in places with a high risk of recurrence, such as on the face, are best treated with Mohs micrographic surgery.[34,55] Historically IFNα provided modest benefit in the treatment of metastatic melanoma but newer therapies (e.g. kinase inhibitors and immunotherapeutic antibodies) are far more beneficial now.[22] Radiation therapy should be avoided in patients with XP. More recently, oral vismodegib (hedgehog pathway inhibitor), pembrolizumab (PD-1 inhibitor), nivolumab (PD-1 inhibitor) and cemiplimab (PD-1 inhibitor) have also been used to treat non-melanoma skin cancers and melanomas and the preliminary results are encouraging.[119,120,136–143] Electrochemotherapy may be considered for the treatment of advanced skin cancer.[128]

Ocular management

Methylcellulose eyedrops and soft UV-protective contact lens may be used to keep the cornea moist and protect against the harmful effects of keratitis sicca.[4] In addition, soft UV-protective contact lens may protect against mechanical trauma in patients with deformed eyelids.[34] Follow-up by ophthalmologists every 3–6 months is recommended for patients with XP.[22] Corneal transplantation can be used to restore vision in patients with severe keratitis with corneal opacity.[4,34]

Surgical resection and intraoperative cryotherapy are the traditional treatments for ocular surface squamous neoplasia.[144] Adverse events associated with surgical resection include conjunctival scarring, stem cell deficiency and recurrence due to inadequate resection of the neoplasm.[144,145] Recent studies have shown the successful use of subconjunctival injection of IFNα2b at the site of lesions with topical cycles of mitomycin C eyedrops for the primary or adjuvant treatment of ocular surface squamous neoplasia.[144,145] Both topical IFNα2b eyedrops and topical 5-fluorouracil eyedrops have also been used with success for the treatment of ocular surface squamous neoplasia with comparable results.[145–147] It is hoped that the previous findings can be confirmed by future studies, thereby circumventing the need for surgical intervention.

Neurological management

Affected patients with neurodegeneration may need hearing aids, speech therapy, physical therapy and

occupational therapy. Regular follow-up by neurology and otorhinolaryngology is recommended.

To date, there is no effective treatment for neurodegeneration. In a study of progeroid mice deficient in the DNA NER gene *Ercc1*, a 30% dietary caloric restriction tripled the lifespan of these mice and delayed numerous aspects of premature aging, including attenuation of neuron loss.[148] The authors speculated that caloric restriction might increase the resistance to stress-induced damage to the DNA, raise antioxidant defences and alter metabolic signalling to induce a shift from the production of pro-inflammatory cytokines to anti-inflammatory cytokines.[120,148] At present, the relevance of this finding in humans is not known.

Investigational therapies

T4 endonuclease-V, a bacterial prokaryotic DNA repair enzyme, in a topical liposome-containing preparation has been shown to repair cyclobutene–pyrimidine dimers resulting from UVR-induced DNA damage.[4,37] The formulation is able to penetrate the stratum corneum to reach the dermis. T4 endonuclease-V is highly efficient in providing temporary ratification of the underlying DNA repair defect in the skin of patients with XP and clinical trials have produced promising results.[128] In a multicentre, double-blind study, Yarosh et al. randomly assigned patients (n=20) to receive daily application of topical T4 endonuclease-V liposome lotion or a placebo liposome lotion (n=10) for 1 year.[149] At the end of the study period, the annualized rate of new actinic keratoses was 8.2% and 25.9% amongst patients assigned T4 endonuclease-V liposome lotion and a placebo liposome lotion, respectively (95% CI 11.8–26.5; p=0.004). The annualized rate of new basal cell carcinoma was 3.8% and 5.4% amongst patients assigned T4 endonuclease-V liposome lotion and a placebo liposome lotion, respectively. A 2019 phase II clinical trial confirmed the efficacy of T4 endonuclease-V liposome lotion in reducing the rate of actinic keratoses and basal cell carcinoma onset in sun-damaged skin.[5,134] Thus, T4 endonuclease-V liposome lotion can be an effective treatment for patients with XP without significant adverse events.[5]

Oral vismodegib, a hedgehog pathway inhibitor, has been approved by the FDA for the treatment of locally advanced basal cell carcinoma or metastatic basal cell carcinoma.[150] The medication can also be used for the treatment of basal cell carcinoma in individuals who are not suitable candidates for topical or surgical treatment.[148] The recommended dose of oral vismodegib is 150 mg/day. Adverse effects include alopecia, muscle spasm, arthralgia, dysgeusia, ageusia, fatigue, decreased appetite, weight loss and electrolyte disturbances.[150] As vismodegib is a teratogen, its use during pregnancy is contraindicated.[4,150] Thus far, there are no published studies on the use and efficacy of oral vismodegib in patients with XP.

Several studies have shown that nicotinamide (vitamin B3) 500 mg twice a day given orally can enhance the repair of UVR-induced DNA damage in human keratinocytes and therefore may have a role in the prevention of actinic keratoses and non-melanoma skin cancers.[151–155] Nicotinamide enhances the two pathways of DNA repair, namely, TC-NER and GG-NER.[154] It has been shown that patients on oral nicotinamide have a reduced number of actinic keratoses on sun-damaged skin.[155,156] Chen et al. randomized 386 immunocompetent patients who had at least two non-melanoma skin cancers in the previous 5 years to receive either 500 mg of nicotinamide or placebo twice per day. At 12-month follow-up, the rate of new non-melanoma skin cancers was lower by 23% in the nicotinamide group than in the placebo group (95% CI 4–38; p=0.02).[151] The number of actinic keratoses was 11%, 14% and 20% lower in the nicotinamide group than in the placebo group at 3 months (p=0.01), 6 months (p<0.001) and 9 months (p<0.001), respectively.[151] There were no significant adverse effects amongst treated patients. The authors concluded that oral nicotinamide was safe and effective in reducing the rates of new non-melanoma skin cancers and actinic keratoses in patients at high risk.

Studies have shown that oral *Polypodium leucotomos* extract, derived from a tropical fern of the Polypodiaceae family, has photoprotective properties through its chemoprotective, antioxidative, anti-inflammatory and immunomodulatory effects.[157–159] As such, *Polypodium leucotomos* extract has the potential to be used as an adjunctive treatment to lessen the phototoxic effects of UVR to reduce UVR-induced skin damage and skin cancers. So far, no studies on the use of oral nicotinamide or *Polypodium leucotomos* extract have been conducted on patients with XP presumably because of the difficulty in recruiting enough numbers of patients for the study.

It has been shown that patients with XP have lower serum concentrations of coenzyme Q_{10} (COQ_{10}) and the concentrations of COQ_{10} tend to decrease with age.[2,160] In a non-randomized study, daily administration of 0.9–1.5 mg/kg of COQ_{10} improved the daily activity of a subset of patients with XP.[160] It is hoped that future, well-designed, randomized, double-blind, placebo-controlled trials will provide more information on the efficacy and safety profile of COQ_{10} in patients with XP.

Gene therapy has opened a large opportunity for the treatment of XP. One approach is to use a retroviral or adenoviral vector to transfer functional DNA genes into both keratinocytes and skin fibroblasts of patients with XP to restore their capacity for NER.[4,20,130] Another approach for target therapy is based on non-viral carriers such as engineered site-specific nucleases (meganuclease, zinc finger nuclease, transcription activator-like effector-nuclease) or CRISPR–Cas9 to correct skin stem cells.[161–163] Although promising, gene therapy has to undergo significant further development and technical implementations before it can be tested clinically for the treatment of patients with XP.

Genetic counselling

Genetic counselling is indicated for all patients with XP. This is especially important in a family with an affected child and

if parents are considering more children. The risk of having another affected child and normal child is each 25% whilst 50% of children are asymptomatic carriers. Genetic testing of at-risk siblings allows early diagnosis and sun avoidance/protection from an early age.[34]

Psychological counselling

Psychosocial issues such as social isolation, peer rejection, discrimination and limited career prospects need to be addressed. Psychological counselling and support should be offered as appropriate.

Conclusion

Although currently there is no radical cure for XP, numerous options are available for the prevention and treatment of skin problems, including malignancies. As such, the diagnosis of XP should be made as early as possible so as to initiate protective measures at an early age. Together with early resection of malignant lesions, this can improve quality of life and increase life expectancy. Further research is necessary to determine the optimal management of XP, in particular the role and implementation of gene therapy for the treatment of this condition.

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Correspondence: Alexander KC Leung, The University of Calgary, The Alberta Children's Hospital, #200, 233 – 16th Avenue NW, Calgary, Alberta, Canada T2M 0H5. Email: aleung@ucalgary.ca

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