Xeroderma Pigmentosum

Xeroderma pigmentosum (XP) is a rare, autosomal recessive disorder. There is an impairment of the skin's ability to repair damage from ultraviolet (UV) light, leading to early skin changes, early sunburn, dry skin and a vastly increased tendency to develop skin tumours and eye damage from UV light.

Epidemiology[1]

XP is very rare but appears to be present throughout the world and in every ethnic group. There are currently approximately 100 diagnosed cases in the UK. The incidence in the USA is estimated as 1 in 1 million. Some areas such as Japan and the Middle East have higher rates of XP.[2]

Types of xeroderma pigmentosum[2]

Seven forms have been described, denoted by letters (XPA-XPG). There is an 8th type known as XP variant (XPV). Each has a different genetic characteristic. XPV was formerly known as pigmented xeroderma.

Previously, an individual with XP with any neurological abnormality was said to have the De Sanctis-Cacchione syndrome. Now that the spectrum of XP disease is better understood, this term is reserved for XP with severe neurological disease, dwarfism and immature sexual development (rare).

XP-Cockayne syndrome (XP-CS) includes facial freckling and early skin cancers typical of XP, with some features of Cockayne's syndrome.

Presentation[1, 2]

The main presenting features of XP are photosensitivity, skin changes and a high incidence of skin cancer at a very young age. Skin changes occur first over the areas most exposed to light, initially on the face.

Skin features

- Typically, there is marked freckling of sun-exposed areas in a child before the age of 2 years (rare in normal children).
- Photosensitivity - approximately 50% of XP patients show acute sun sensitivity, i.e. sunburn occurs after minimal sun exposure, often noticed in infancy.
- However, in some forms of XP (especially XPC), patients lack this acute sun sensitivity; they tan and freckle without burning. In these patients, the presence of skin cancers may be the first indication that the child has XP.[3]
- Xerosis (dry skin).
- Poikiloderma (comprising irregular patches of hyperpigmentation and hypopigmentation, telangiectasia and atrophy).
- Skin cancers develop early. The median age of onset of skin cancer is 8 years. [1] Reports in the literature range from 3 to 10 years (although this is prevented by good protection - see treatment under 'Management' section and 'Prognosis' section). These are solar keratoses (premalignant), squamous cell carcinoma (SCC), basal cell carcinoma (BCC) and malignant melanoma. BCC and SCC occur most frequently. They are more prevalent in areas exposed to sun. The anterior tongue is also vulnerable.

Eye features[4]

Eye features occur in the anterior, exposed part of the eye:

- Photophobia.
Conjunctival inflammation and keratitis. Severe keratitis can lead to corneal opacification and vascularisation.
Tumours of conjunctiva and eyelids - benign or malignant.
Eyelids may be pigmented, may lose lashes, or may atrophy - leading to ectropion or entropion.

**Neurological features**

30% of affected individuals have neurological manifestations, including acquired microcephaly, diminished or absent deep tendon stretch reflexes, progressive sensorineural hearing loss and progressive cognitive impairment.

- Neurological problems can be mild or severe.
- Possible features are hyporeflexia, sensorineural deafness, spasticity, poor co-ordination, seizures, acquired microcephaly or progressive intellectual impairment.
- These seem to be unrelated to UV exposure but tend to occur in those whose skin is most severely affected by UV.
- The De Sanctis-Cacchione syndrome is XP with severe neurological involvement, including dwarfism and delayed sexual development.

**Differential diagnosis**

- There are other causes of photosensitivity - eg, congenital erythropoietic porphyria.
- Other genetic conditions with photosensitivity due to defective DNA repair - eg, Cockayne's syndrome, the XP-CS complex, trichothiodystrophy (TTD), the XP-TTD complex, cerebro-oculo-facio-skeletal (COFS) syndrome and the UV-sensitive syndrome.

**Referral of suspected cases**

The initial diagnosis is clinical, based on skin, eye and neurologic manifestations. Note:

- Early diagnosis is important to prevent complications. Babies and children with photosensitivity should be referred to a dermatologist.
- Marked freckling of sun-exposed areas under age 2 years is unusual in normal children and should raise the suspicion of XP.
- Skin cancer in children is rare and merits investigation for an underlying cause.

**Investigations**

- The diagnosis is made by skin biopsy with fibroblast culture. Functional tests on living cells can be used to screen for abnormalities in DNA repair.
- Genetic testing is available for XPA and XPC types. Molecular genetic testing for other types is on a research basis only.
- Prenatal diagnosis is usually possible.

**Management**

Currently, there is no specific treatment for XP although research is ongoing. Management involves preventing damage and dealing with damaged tissues at an early stage.

**Specialist centres**

In the UK, Guy's and St Thomas' Hospital has been designated the national centre for treating children with XP, in collaboration with the photobiology unit at Ninewells Hospital, Dundee and the diagnostic laboratory service at the University of Sussex. Their aim is a department where specialists in dermatology, neurology, ophthalmology and other relevant fields work together to support XP patients and their doctors UK-wide.

**Avoidance of UV light**

Total protection from UV light greatly improves the prognosis and reduces skin changes and cancers. This is achieved by:
• Restricting outdoor activities to night time. If outdoors during the day, cover the skin completely.
• Clothing: long opaque clothes, sunhats, long hairstyles and UV protective sunglasses with side shields; custom-made face shields are also available.
• Protective film on windows (normal glass filters some but not all UV light).
• As some indoor lighting emits UV, light sources may need to be changed or protected. Standard incandescent light bulbs do not emit UV. Further information about suitable/unsuitable light bulbs is available on the XP Society's website.¹⁸
• Frequent application of high-factor sunscreen, even indoors.

### Surveillance

- Dermatologist reviews three-monthly for skin cancer surveillance. Photographs can be helpful in monitoring lesions.
- Relatives can be taught to do skin checks between appointments.
- Ophthalmology examinations annually.
- Early surgical removal of skin lesions.
- Regular neurological review and hearing tests.
- Monitoring of vitamin D levels was recommended in the past for patients undergoing strict UV protection but further research suggests this should be the routine for all XP patients. Research suggests that vitamin D levels may be normal, raised or decreased in such patients, irrespective of whether UV protection is used or not.⁹

### Drug treatments

- Vitamin D supplements may be needed, since sunlight (a major source of vitamin D) is excluded.¹¹
- Emollients for dry skin.
- Artificial tears for dry eyes.
- Oral isotretinoin may prevent new neoplasms. High doses were originally used but it has now been found that lower doses with less toxicity are equally effective.¹⁰
- Repair of UV photolesions in XP group C cells induced by translational readthrough is being investigated. Translational readthrough involves use of a special tRNA that recognizes the UAG and UGA codons (sequence of 3 DNA or RNA nucleotides) as modified amino acids, rather than as premature termination codons.¹¹

### Treatment of neoplasms and eye complications

- Premalignant lesions - eg, actinic keratoses: topical 5-fluorouracil or cryotherapy. Larger areas can be treated by dermabrasion or dermatome shaving.
- Skin and eye tumours are treated in the same way as for those without XP but with caution to conserve undamaged skin (because of the likely need for further procedures).
- Large areas with skin tumours can be grafted using unexposed skin.
- Corneal transplantation for severe keratitis.

### Other treatments

- Genetic counselling (see also section 'Genetic counselling and risk to relatives', below).
- Support and counselling for patients and families, because of the severe lifestyle restrictions involved.
- Avoidance of smoking, because cells from individuals with XP are also hypersensitive to environmental mutagens, such as benzo(a)pyrene found in cigarette smoke.

### Complications

- Skin and eye tumours, as above. The risk of these is approximately a thousand times normal.
- Vitamin D deficiency (and its complications) has been reported, although a small study from Germany found that some XP patients had normal or raised vitamin D levels.⁹
- Some patients with XP are hypersensitive to X-rays, so a small test dose is advised before therapeutic X-radiation. Most patients with XP have a normal response to therapeutic X-radiation.¹³
- There may be increased tobacco sensitivity. Lung cancer at a relatively young age has been reported in XP patients who smoke.
• Other cancers:
  • There seems to be an increased risk of buccal cancer (probably due to UV in the oral cavity).
  • There may be a higher rate of internal cancers, perhaps due to the underlying DNA repair defect combined with other toxins. Case reports suggest an increased susceptibility to lung cancer in smokers.

Genetic counselling and risk to relatives\(^1,2\)

• The inheritance is autosomal recessive.
• If parents are considering further pregnancies, prenatal diagnosis is often possible.
• Where XP is suspected, siblings should be protected from UV light until XP can be excluded.
• Recent investigations of heterozygotes with one of four XP genes (XPA, XPC, ERCC2, or ERCC5) have reported an increased risk of skin cancer, lung cancer, or altered response to certain chemotherapeutic agents.

Prognosis

The prognosis varies with the severity of the genetic disorder, the success in avoiding UV light and vigilance of screening. It also depends on the extent of any neurological involvement\(^14\).

Previously, the prognosis was a reduced life expectancy due to skin cancers or neurological complications. However, more recent information suggests that a normal lifespan is possible for patients without neurological problems who are fully protected from UV\(^1,6\).

History

XP was first described in 1870 by Hebra and Kaposi. The disease has a unique place in medical history: when Cleaver identified the basis of XP in 1969, it provided the first clear understanding of the central role played by DNA mutation in cancer\(^15\).

Further reading & references

- \(\text{Xeroderma Pigmentosum; Online Mendelian Inheritance in Man (OMIM)}\)
  2. Kraemer KH; Xeroderma Pigmentosum, Gene Reviews, Feb 2014
  3. XPC; Cancer Genetics Web, 2014
  6. XP Support Group UK
  7. Funding announced for national centre for rare childhood disease; Guy's and St Thomas' Biomedical Research Centre, 2009
  8. Know your light sources; Xeroderma Pigmentosum Society