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Ophthalmic Manifestations of Xeroderma Pigmentosum

A Perspective from the United Kingdom

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Purpose: To document the ocular manifestations of xeroderma pigmentosum (XP), presenting via the United Kingdom (UK) XP service, and to analyze the correlations between XP genotype and ophthalmic phenotype.

Design: Prospective observational case series.

Subjects: Eighty-nine patients seen by the UK Nationally Commissioned XP Service, from April 2010 to December 2014, with a genetically confirmed diagnosis of XP.

Methods: Patients underwent a full ophthalmic examination at each visit. Clinical features from both eyes were recorded on a standard proforma. The most recent assessments were analyzed. A 2-tailed Fisher exact test was used to assess for differences in ocular features between patients in XP subgroups with impaired transcription coupled nucleotide excision repair (TC-NER) (category 1: XP-A, B, D, F, and G) and preserved TC-NER (category 2: XP-C, E, and V).

Main Outcome Measures: Lid and periocular abnormalities, ocular surface pathologies, neuro-ophthalmologic abnormalities, lens and retinal abnormalities, and visual acuity (VA).

Results: Ninety-three percent of XP patients in our cohort had ocular involvement, with 65% describing photophobia. The most common abnormalities were in the periocular skin and ocular surface, including interpalpebral conjunctival melanosis (44%) and conjunctival injection (43%). Eleven percent of patients had required treatment for periocular cancers and 2% for ocular surface cancers. The most common neuro-ophthalmologic finding was minimal pupillary reaction to light (25%). Patients in category 2 had significantly more ocular surface abnormalities than patients in category 1, including a greater proportion of conjunctival injection ($P = 0.003$), conjunctival corkscrew vessels ($P < 0.001$), corneal scarring ($P = 0.01$) and pingueculae under the age of 50 ($P = 0.02$). Meanwhile, patients in category 1 had a higher proportion of poorly reactive pupils ($P < 0.001$) and abnormal ocular movements ($P = 0.03$) compared with those in category 2. Five patients (6%) presented to ophthalmologists with ocular surface signs related to XP, before any formal diagnosis of XP was made.

Conclusions: A large proportion of XP patients have ocular involvement. Regular examination by an ophthalmologist is essential, especially in screening for eyelid and ocular surface tumors. The ocular phenotype–genotype segregation within XP patients suggests that XP is a heterogeneous and complex disease. With further study, we hope to offer these patients more individualized patient care. *Ophthalmology 2017;■:1–10 © 2017 by the American Academy of Ophthalmology*

Xeroderma pigmentosum (XP) is a rare autosomal recessive DNA repair disorder with ophthalmic, dermatologic, and neurological manifestations.[1,2] Most patients present to dermatologists with abnormal freckling, extreme sunburn reactions, or premature and multiple skin cancers.[1,2] Progressive neurodegeneration occurs in 20% to 30% of cases, initially affecting cognition, hearing, and mobility, but which can also result in premature death.[1,2] Ophthalmic pathology has been described in 40% to 100% of XP patients and generally affects the sun-exposed periocular skin and the ocular surface.[3–6] Changes include ectropion, lagophthalmos, conjunctival injection, conjunctival melanosis, corneal scarring and keratopathy, pterygium, and cancers of both the ocular surface and eyelids.[3–6] Commonly reported ocular symptoms include photophobia and dry eyes.[5–7] There is also some early evidence that XP patients experience an accelerated rate of corneal endothelial cell loss.[8]

The estimated incidence of XP in the United States, Japan, and Western Europe is 1 in 250 000,[9] 1 in 22 000[10] and 1 in 500 000,[11] respectively. The clinical manifestations of XP are extremely varied and are influenced by the precise genetic mutation (and therefore XP complementation group), as well as environmental factors, such as cumulative sun exposure.[1,2]

There are 8 known XP complementation groups (XP-A to XP-G, and XP-V), which correspond to the 8 genes that are affected in this condition. The proteins encoded by the *XPA* to *XPG* genes are involved in nucleotide excision repair (NER), which identifies and repairs DNA damage

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primarily induced by ultraviolet radiation (UVR).[1,2,12] There are 2 subpathways within NER: transcription-coupled nucleotide excision repair (TC-NER), which repairs actively transcribed DNA, and global genome nucleotide excision repair (GG-NER), which repairs DNA not undergoing transcription at that time. XPC and XPE proteins only contribute to GG-NER, whereas XPA, XPB, XPD, XPF, and XPG proteins are required for both GG-NER and TC-NER (Fig 1). XPV is not directly involved in NER; it encodes a DNA polymerase (η) that is required for DNA replication past damage that has not been repaired by NER, in a process known as translesion synthesis.[13,14]

XP patients from complementation groups C, E, and V (where TC-NER is preserved) have normal sunburn reactions for skin type and do not develop manifest neurodegeneration.[15,16] However, they have an earlier age of onset of first skin cancer.[15] However, XP patients from complementation groups A, B, D, F, and G (where TC-NER is impaired) have severe and exaggerated sunburn reactions on minimal sun exposure and suffer neurodegeneration.[15,16]

There is currently no cure for XP. Educating patients about the importance of rigorous photoprotection, as well as regular screening for cancerous lesions, is paramount in the management of this condition.[17] Due to the difficulties many patients face in accessing the necessary range of hospital services for screening and advice, a nationally commissioned multidisciplinary XP service was set up in the United Kingdom (UK) in 2010, with input from dermatologists, neurologists, ophthalmologists, psychologists, and geneticists.[18] Patients are generally seen once or twice a year and undergo a comprehensive review by the multidisciplinary team in a single visit that usually spans the day. In this study, we specifically describe the ocular manifestations of our patients in the UK National XP Service and the correlations between genotype and ophthalmic phenotype that we have observed. We also highlight the crucial role that ophthalmologists play in the diagnosis and management of this condition.

Methods

We conducted a prospective observational case series of all patients seen by the UK National XP Service, from its establishment in April 2010 until December 2014, in whom a genetic diagnosis of XP had been confirmed. The study was approved by the Research Ethics Committee of Guy's and St Thomas' Hospital National Health Service (NHS) Trust, London (reference 12/LO/0325). Informed consent was obtained from all patients and the study adhered to the tenets of the Declaration of Helsinki.

At each clinic attendance, all patients were seen by a single consultant ophthalmologist, or occasionally by a senior ophthalmic colleague. A full ophthalmic examination was conducted at each visit, including Snellen visual acuity (VA), Ishihara color vision, Goldman tonometry for intraocular pressure (IOP), ocular motility, pupillary responses, lid position and function, and slit-lamp assessment of the ocular surface, anterior chamber, lens, and fundus. All patients were also asked whether they experienced photophobia. The findings were recorded on a standard proforma each time and the clinical features of both eyes from each patient's most recent assessment were used in the data analysis.

The laboratory methods of XP genotyping used, as well as amalgamated data on the dermatologic, neurological, and ophthalmologic findings of the cohort, has been described in a previous article from our group[19] and will not be repeated here. However, this study will discuss the ophthalmologic findings, including periocular and neuro-ophthalmic findings, in greater detail.

As mentioned in the introduction, various phenotypic differences have been reported between the 8 XP complementation groups. These differences are most marked when comparing those groups in which TC-NER is impaired (i.e., XP-A, B, D, F, and G) with those where TC-NER is preserved (i.e., XP-C, E, and V) (Fig 1). As such, we performed a statistical analysis on the ophthalmic features of our patients by subdividing them into these 2 categories, termed category 1 and category 2, respectively. Statistical analysis was computed using SPSS v24.0 (IBM Corp, Armonk, NY) and a 2-tailed Fisher exact test was always used unless otherwise specified.

Finally, we also used an overall quantitative score for ophthalmic pathology to look at the specific ophthalmic morbidity of individual complementation groups. This score was similar to that described in our group's previous article,[19] but here we have included neuro-ophthalmic, fundal, and periocular features as part of the scoring.

Results

A total of 89 patients with a genetically confirmed diagnosis of XP were assessed successively in the study period and all were included. The XP complementation groups of these patients were as follows: 18 XP-A, 2 XP-B, 28 XP-C, 14 XP-D, 4 XP-E, 3 XP-F, 8 XP-G, and 12 XP-V. There were 45 female patients and 44 male patients. The median age in December 2014 was 23 years (range, 4−80 years) (Table 1), with notably older ages for patients in complementation groups B, E, and V. The represented ethnicities, based on the Office for National Statistics' breakdown of ethnic categories for classification from the 2001 census, are shown in Table 2. XP-A and XP-C were largely composed of patients of Eastern origin, including Pakistani and Bangladeshi patients, whereas XP-D, XP-E, XP-F, and XP-V comprised mostly white patients.

Eighty-three of 89 (93%) XP patients in this study had at least 1 ophthalmic abnormality. For ease of analysis, ophthalmic features were categorized into 1 of the following 4 groups: (1) periocular/eyelid abnormalities; (2) ocular surface abnormalities; (3) neuro-ophthalmic abnormalities; (4) lens/retinal abnormalities. A summary of the above results is given in Tables 3 and 4.

As VA, color vision, and IOP could not be reliably assessed in all pediatric or neurologically impaired patients, results from these ophthalmic assessments are discussed separately. The best-corrected visual acuity (BCVA) of the better eye of each patient is also shown in Table 5.

Eyelid Abnormalities

Fifteen of 89 (17%) patients had either ectropion or lagophthalmos on gentle closure, but none had entropion. All ectropia were related to cicatricial skin changes, principally secondary to surgery for management of periocular skin cancers (Fig 2A), but also due to dry, tight skin. Lagophthalmos was caused by upper lid scarring from surgery (Fig 2B) or marked periocular fat atrophy resulting in enophthalmos and superior sulcus hollowing. No statistically significant difference was found in the prevalence of ectropion or lagophthalmos between categories 1 and 2.

At the time of our assessment 10 of 89 (11%) patients had been diagnosed with and treated for eyelid skin tumors; this included 2 squamous cell carcinomas (1 XP-C and 1 XP-V patient), 7 basal