ORIGINAL ARTICLE

Macular and Retinal Nerve Fibre Layer Thinning in Xeroderma Pigmentosum: A Cross-sectional Study

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ABSTRACT

The purpose of this study was to evaluate retinal thickness in different Xeroderma Pigmentosum (XP) complementation groups using spectral-domain optical coherence tomography (SD-OCT).

This was a cross-sectional pilot study of 40 patients with XP. All patients had healthy-looking retinæ and optic nerves on slit lamp biomicroscopy, and subtle or no neurological deficits. Patients were divided into two groups based on the known tendency for neurodegeneration associated with certain XP complementation groups. A third control group was obtained from a normative database. Using SD-OCT, we compared peripapillary retinal nerve fibre layer (pRNFL) and macular thickness between the groups.

XP patients with a known tendency for neurodegeneration were found to have a statistically significant reduction in both pRNFL ($p < 0.01$) and macular thickness ($p < 0.001$) compared with healthy controls. In contrast, there was no statistically significant difference between pRNFL and macular thickness in XP patients not expected to develop neurodegeneration compared to the same control group. When both XP groups were compared, a statistically significant reduction in total pRNFL ($p = 0.02$) and macular thickness ($p = 0.002$) was found in XP patients predisposed to neurodegeneration.

Our results suggest that pRNFL and macular thickness are reduced in XP patients with a known tendency for neurodegeneration, even before any marked neurological deficits become manifest. These findings demonstrate the potential role of retinal thickness as an anatomic biomarker and prognostic indicator for XP neurodegeneration.

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Introduction

Xeroderma pigmentosum (XP) is a rare autosomal-recessive disease characterised by defective or absent DNA repair in response to ultraviolet (UV) radiation damage.^{1,2} It was first described as “parchment skin” in 1874 by Moritz Kaposi and Ferdinand Ritter von Hebra.³ In Northern Europe the frequency of XP is estimated to be 1: 450 000, affecting males and females equally.^{4–6} The incidence of XP is higher in Japan, North Africa and the Middle East (1: 50 000), especially in communities where consanguinity is high.^{6,7}

Mutations in eight different genes give rise to seven complementation groups (XP-A through to XP-G) and a so-called variant type (XP-V).⁸ All patients with XP, with the exception of XP-V, have defects in genes coding for proteins involved in nucleotide

excision repair (NER).^{9,10} The XP-C and XP-E proteins are solely implicated in global genome NER, whereas the other XP proteins (XP-A, XP-B, XP-D, XP-F, and XP-G) are involved in the global and also the transcription-coupled repair pathway. Patients with the variant type (XP-V) have defects in DNA polymerase η and therefore have normal NER but are defective in translesion synthesis.

XP presents with cutaneous, ophthalmic and neurological manifestations. Patients develop drying and freckling of the skin when exposed to the sun, and carry a 10,000-fold increased risk of non-melanoma skin cancer with the median age of first cancer being nine.¹¹ The risk of melanoma under the age of 20 is increased 2000-fold.¹¹ While these, and other clinical features, are shared by all XP patients, other features vary considerably between the different XP complementation groups.¹²

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Patients with XP-A, XP-B, XP-D, XP-F, and XP-G suffer from exaggerated sunburn and blistering after minimal sun exposure, whereas patients with XP-C, XP-E, and XP-V have a normal sunburn response,¹³ reflecting the different repair pathways affected.

Ocular disease in XP is almost exclusively limited to the anterior, UV-exposed structures of the eye: the lids, conjunctiva, and cornea.^{14,15} Patients frequently experience photophobia, dry eye, conjunctivitis, pingueculae and other UV-related ocular surface disease such as pterygia and tumours of the eyelid or ocular surface itself.¹⁵ Except for two case reports that showed subclinical retinal changes in a patient with XP-A and XP-D on postmortem histopathology, retinal abnormalities have not been observed in XP.¹⁶ This is in stark contrast to Cockayne Syndrome, another DNA repair disorder, in which retinal dystrophy is a major feature.¹⁷ Similarly, optic atrophy is not a known hallmark of XP, and has only ever been described in one case,¹⁶ where it may have been a coincidental finding.

Twenty to thirty percent of XP patients also develop severe progressive neurodegeneration.^{18,19} This appears selectively to affect complementation groups XP-A, XP-B, XP-D, XP-F, and XP-G; that is, those with defective transcription-coupled repair who also are prone to exaggerated sunburn.^{8,13} In contrast, patients with XP-C, XP-E, and XP-V appear to be spared from clinically apparent neurodegeneration. Children in groups with progressive neurodegeneration can show cognitive impairment before they start school and may display microcephaly. Cerebellar symptoms can occur from early childhood and include dysarthria, ataxia and abnormal eye movements.^{18,20} In more severe cases, corticospinal involvement follows in early adulthood and may progress to spastic tetraplegia before patients succumb to their disease.¹⁸ The majority of patients with XP neurological degeneration also develop progressive sensorineural hearing loss,²¹ sensory neuropathy, absent or diminished deep-tendon reflexes and pupils that respond poorly to light.¹⁵

The aetiology of neurological disease in patients with XP remains poorly understood, but oxidative stress and excitatory amino acid toxicity in the brain have been suggested as potential causes.^{20,22,23} Not all patients with the excessive sunburn phenotype go on to develop neurodegeneration, and the rate of decline

varies markedly, even for the same complementation groups. Predicting those who are at risk of doing so would help patients and their families anticipate future morbidity and mortality. However, the lack of a reliable prognostic indicator has made this, as yet, impossible.

Optical coherence tomography (OCT) is a fast, non-invasive imaging technique that uses near infra-red light to create high-resolution cross-sectional images of the retina and optic nerve head *in vivo*, with highly quantifiable and reproducible results.^{24–27} Spectral-domain (SD) OCT is routinely employed in ophthalmology clinics as an adjunctive investigation for the diagnosis and management of age-related macular degeneration (AMD) and glaucoma. More recently, OCT imaging has been used to evaluate retinal nerve fibre layer (RNFL) and macular thickness, in several neurological diseases, such as Parkinson's disease,^{28–33} multiple sclerosis,^{34–42} Alzheimer's disease,^{43,44} schizophrenia,⁴⁵ spinocerebellar ataxia,^{46,47} Friedreich's ataxia,⁴⁸ and Central Nervous System (CNS) lupus erythematosus.⁴⁹

It is possible that changes in RNFL and macular thickness may be one of the earliest and most readily quantifiable signs of neurological decline in certain general neurodegenerative conditions. Consequently, OCT measures of the retina may serve as biomarkers for the future development or rate of progression of clinically relevant neurological disease. It could also provide a quantifiable assessment of patient response to potential treatments. We hypothesised that pRNFL and macular thickness in patients with XP was reduced, especially in those predisposed to neurodegeneration. Our study was therefore designed to evaluate the retinal thickness in XP patients from different complementation groups using SD-OCT, and to compare the pRNFL, macular thickness and macular volume between these groups and normal controls.

Methods

Guy's and St Thomas' NHS Foundation Trust is the only designated national service for children and adults with XP in the United Kingdom. The multidisciplinary XP clinic at St Thomas' is funded by the National Commissioning Group and includes specialists in photodermatology, dermatological surgery, neurology (adult and paediatric), genetics,

ophthalmology, and psychology. The diagnosis of XP is made clinically and confirmed by next-generation DNA sequencing of blood samples at Guy's Hospital. Prior to this being available, the diagnosis was confirmed by DNA repair assays followed by complementation group analysis conducted at the Genome Damage and Stability Centre, University of Sussex in Brighton. Informed consent was obtained from all patients (or their guardians), and this study was performed in accordance with protocols approved by the Research Ethics Committee of Guy's and St Thomas' Hospitals NHS Foundation Trust, London (reference 12/LO/0325), and the Declaration of Helsinki.

Study subjects

We conducted a cross-sectional pilot study of 43 patients with XP examined at St Thomas' Hospital, between 2012 and 2015, for whom data from the same OCT machine were available. All patients included in this study underwent detailed dermatological, neurological and ophthalmic evaluation at the time of their OCT examination. Best-corrected visual acuity (BCVA) in each eye was measured with a Snellen chart. Slit-lamp biomicroscopy of the anterior and posterior segments of the eye was performed, together with intraocular pressure (IOP) measurements by applanation tonometry. Patients with ophthalmic conditions that might affect the RNFL, such as AMD or glaucoma, were excluded from further analysis. Finally, patients were divided into two comparison groups (Table 1), based on their complementation group and its association with neurodegenerative

changes: Group 1 contained patients with XP-A, XP-B, XP-D, XP-F and XP-G, and Group 2 contained those with XP-C, XP-E, and XP-V.

Controls were derived from the OCT normative database provided by Topcon (Topcon Medical Systems, Inc., Oakland, NJ, USA) that comprises 189 normal healthy individuals (Table 1).

OCT

Measurements of peripapillary RNFL (pRNFL), together with macular thickness and volume, were taken for both eyes using a Topcon 3D OCT-2000. All spectral-domain OCT (SD-OCT) scans were obtained by the same experienced operator. As pupil size does not influence RNFL measurements,^{50,51} the majority of our patients were scanned without mydriasis to prevent exacerbation of photophobia. The Topcon OCT rates image quality from 0 to 100, with a good quality scan usually having an image quality of greater than 50; therefore, only scans fulfilling this criterion were selected for this study.

For the pRNFL measurements, three-dimensional cube OCT data were obtained using the "Disc: 3D scan" protocol, that performs 128 horizontal scan lines consisting of 512 A-scans in a 6 × 6 mm square centred on the optic nerve head (Figure 1). After creating a RNFL thickness map from this data set, the OCT software automatically extracts a circumpapillary circle (3.4 mm in diameter) from the cube data set for RNFL thickness measurement. The RNFL parameters generated include the total RNFL average (in micrometres), RNFL thickness in four 90-degree quadrants (superior [S], temporal [T], inferior [I] and

Table 1. Demographic characteristics of XP patients and controls.

Characteristic	Group 1	Group 2	Group 3 (Controls)
Eyes, <i>n</i>	23	17	189
Age, <i>y</i>			
Mean ± SD (range)	32.0 ± 16.6 (14–80)	32.7 ± 17.6 (10–70)	42.6 ± 15.9 (19–84)
Sex, <i>n</i> (%)			
Male	12(52)	12(71)	67(35.4)
Female	11(48)	5(29)	122(64.6)
Ethnicity, <i>n</i> (%)			116(≥61.4)
White	13(57)	10(59)	38(≥20.1)
Black	2(9)	0	28(≥14.8)
Hispanic	N/A ^a	N/A ^a	28(≥14.8)
Indian/Pakistani	6(26)	7(41)	U ^b
Chinese	1(4)	0	U ^b
Mixed	1(4)	0	U ^b

^aNot applicable

^bUnknown

Figure 1. Optic nerve scan report of a patient from Group 2.

An example of a disc (optic nerve) scan report from a patient with XP-V obtained with SD-OCT. The subject's left peripapillary RNFL thickness is shown as a graph and table above disc topography parameters on the left-hand side of the report. The average RNFL thickness for each 90 degree quadrant and each clock hour is further illustrated using pie charts on the right-hand side of the report. The quadrants are labelled as follows: superior (S), temporal (T), inferior (I), and nasal (N).

nasal [N]) and 12 clock hour positions. The optic disc and cup are outlined further by the OCT's viewing software that calculates topographic parameters such as disc, cup and rim areas (in square millimetres) and cup-disc ratios, all of which are of particular relevance for the assessment of glaucoma and not analysed further in this paper.

The macular region was evaluated using the "Macula: 3D scan" protocol that performs 128 horizontal scan lines consisting of 512 A-scans in a 6 × 6 mm square, centred on the fovea (Figure 2). The software provides retinal thickness values from the inner limiting membrane (ILM) to the retinal pigment epithelium (RPE) in micrometres for nine areas that correspond to the Early Treatment Diabetic Retinopathy Study (ETDRS) grid.⁵² This grid includes

a central 1 mm diameter circle (Centre) representing the fovea, and 3 mm and 6 mm inner and outer rings, respectively. The latter are divided into superior, nasal, inferior and temporal quadrants, giving rise to eight separate areas (Inner T, Inner S, Inner N, Inner I, Outer T, Outer S, Outer N, and Outer T). Average macular thickness and total volume are also calculated as part of the standard analysis, but OCT segmentation data were not available with the machine used.

Statistical analyses

The Z-test was performed to compare pRNFL thickness and macular thickness in Group 1 and Group 2 with healthy controls from the Topcon normative database (Table 2). The Shapiro-Wilk test was used

Figure 2. Macular scan report of a patient from Group 2. An example of a macular scan report from a patient with XP-C obtained with SD-OCT. The subject's right macular thickness is given for the nine areas of the ETDRS grid in the center of the report. We labelled the segments as follows: Centre, Inner T, Inner S, Inner N, Inner I, Outer T, Outer S, Outer N, and Outer I. Average and central thickness, together with total volume, are tabulated below the ETDRS grid.

to verify the normality of the data set. The differences in pRNFL and macular thickness, as well as macular volume, between Group 1 and Group 2 were analysed with the independent *t*-test. The Mann–Whitney U test was performed in case the data were not normally distributed.

Results

Of 76 patients with XP seen by the XP service during the defined time period, 43 (57%)

underwent OCT imaging. This included 39 adults (91%) and an additional four children under 16 who were willing to do so (9%). Adult patients did not have an OCT scan if they were too neurologically impaired to undertake one, if they did not wish to have one performed, or if OCT scanning was unavailable on the day of the ophthalmic examination. Due to co-existent AMD, glaucoma and insufficient image quality, three patients were excluded from further analysis. Of the 40 remaining patients, 23 (58%) had both macular and disc OCT

Table 2. Comparison of pRNFL and macular thickness between Group 1, Group 2, and healthy controls.

	Group	Mean	SD	<i>p</i> -value ^a
Peripapillary RNFL, μm				
Superior	Group 1	98	20	<0.001
	Group 2	114	14	0.45
	Control	116	13	
Inferior	Group 1	110	19	<0.001
	Group 2	118	18	0.05
	Control	124	13	
Nasal	Group 1	73	16	0.012
	Group 2	78	12	0.33
	Control	81	13	
Temporal	Group 1	63	14	0.001
	Group 2	70	15	0.96
	Control	71	10	
Macular thickness, μm				
Macular central thickness	Group 1	207	20	<0.001
	Group 2	236	13	0.63
	Control	234	20	
Macular inner ring thickness				
Inner S	Group 1	252	30	<0.001
	Group 2	294	11	0.07
	Control	302	16	
Inner I	Group 1	252	29	<0.001
	Group 2	289	17	0.03
	Control	298	15	
Inner N	Group 1	260	27	<0.001
	Group 2	299	10	0.23
	Control	304	15	
Inner T	Group 1	246	28	<0.001
	Group 2	280	12	0.02
	Control	290	15	
Macular outer ring thickness				
Outer S	Group 1	222	31	<0.001
	Group 2	250	14	0.09
	Control	257	14	
Outer I	Group 1	230	27	<0.001
	Group 2	247	13	0.90
	Control	247	15	
Outer N	Group 1	239	31	<0.001
	Group 2	272	11	0.52
	Control	275	17	
Outer T	Group 1	208	29	<0.001
	Group 2	238	11	0.53
	Control	240	13	

^aBased on Z-test

scans, whilst 17 (42%) had only one or the other. All patients had a BCVA of 6/9 or better in each eye. Group 1 included 23 (57.5%) patients (nine XP-A, two XP-B, eight XP-D, two XP-F, and two XP-G) and Group 2 included 17 (42.5%) patients (ten XP-C, two XP-E, and five XP-V). Of the children included in the study, one was XP-A, another was XP-D and two children were XP-C. They were aged 15, 14, 10, and 15, respectively. Demographic data were comparable in both groups (Table 1). One scanned eye was included per patient. If both eyes had been scanned successfully, the scan with the higher image quality was selected.

The Z-test showed that the mean pRNFL thickness in the principal four quadrants was similar between Group 2 (i.e., XP-C, XP-E and XP-V) and healthy controls: $p(S) = 0.45$, $p(T) = 0.96$, $p(N) = 0.33$, and $p(I) = 0.05$. However, the corresponding values differed markedly between Group 1 and the normative database: $p(S) < 0.001$, $p(T) = 0.001$, $p(I) < 0.001$, $p(N) = 0.012$, as shown graphically in Figure 3.

Analysis of the macular scans showed that the mean retinal thickness in the central and four outer areas of the ETDRS grid were similar between Group 2 and healthy controls from the normative database:

Figure 3. Distribution of pRNFL thickness (superior quadrant) in Group 1, Group 2 and healthy controls.

Distribution of pRNFL in other quadrants was similar. Average total pRNFL was not supplied by the normative database and is therefore not displayed here.

$p(\text{Centre}) = 0.63$, $p(\text{Outer T}) = 0.53$, $p(\text{Outer S}) = 0.09$, $p(\text{Outer N}) = 0.52$, and $p(\text{Outer I}) = 0.90$. This is illustrated graphically for central retinal thickness in Figure 4. There was a borderline significant difference between Group 2 and the controls for two of the four inner areas, the Inner T ($p = 0.02$) and Inner I ($p = 0.03$) sectors, but not the Inner S ($p = 0.07$) and Inner N ($p = 0.23$) areas. However, when comparing macular thickness between Group 1 and the normative database, the difference was statistically significant throughout the ETDRS grid, with p values < 0.001 in all nine sectors. Macular volume data were not provided by the Topcon normative database and, therefore, comparisons could not be carried out against controls for this.

The Shapiro–Wilk test confirmed that the vast majority of data were normally distributed. However, as normality was not observed throughout, both the independent t -test and Mann–Whitney U test were employed to compare pRNFL, macular thickness and macular volume between Group 1 and Group 2.

The results of the independent t -test (T) and Mann–Whitney U test (MWU) were similar. Although the difference in the total average pRNFL thickness between Group 1 and Group 2 was statistically significant ($p = 0.024$ [T], $p = 0.032$ [MWU]), the difference in pRNFL thickness in individual areas varied and was not statistically significant for the temporal ($p = 0.15$ [T], $p = 0.25$ [MWU]), nasal ($p = 0.38$ [T], $p = 0.42$ [MWU]), and inferior ($p = 0.27$ [T], $p = 0.52$ [MWU]) quadrants.

However, macular thickness and volume in Group 1 were both significantly reduced compared to Group 2 in all areas assessed except in the Outer I area, where statistical significance could not be proven: average macular thickness ($p = 0.002$ [T], $p = 0.01$ [MWU]), macular volume ($p = 0.002$ [T], $p = 0.01$ [MWU]), Centre ($p < 0.001$ [T], $p = 0.001$ [MWU]), Inner T ($p = 0.001$ [T], $p = 0.003$ [MWU]), Inner S ($p < 0.001$ [T], $p < 0.001$ [MWU]), Inner N ($p < 0.001$ [T], $p = 0.002$ [MWU]), Inner I ($p = 0.001$ [T], $p = 0.005$ [MWU]), Outer T ($p = 0.004$ [T], $p = 0.011$ [MWU]), Outer S ($p = 0.01$ [T], $p = 0.02$

Figure 4. Distribution of central macular thickness in Group 1, Group 2 and healthy controls.

[MWU]), Outer N ($p = 0.004$ [T], $p = 0.01$ [MWU]) and Outer I ($p = 0.06$ [T], $p = 0.06$ [MWU]).

Discussion

Our study suggests that retinal thinning, detectable and quantifiable by OCT scanning, occurs in XP patients from complementation groups predisposed to neurodegeneration (i.e. XP-A, XP-B, XP-D, XP-F, and XP-G). These patients showed a statistically significant reduction in pRNFL ($p < 0.01$) and macular thickness ($p < 0.001$) compared with controls. In contrast, there was no statistically significant difference between pRNFL or macular thickness (except for two out of nine sectors) between patients from XP complementation groups that do not classically develop neurodegeneration (i.e. XP-C, XP-E, and XP-V) and the same control group. When Group 1 (i.e. XP-A, XP-B, XP-D, XP-F, and XP-G) and Group 2 (i.e. XP-C, XP-E, and XP-V) were compared, a statistically significant reduction in macular volume and macular thickness was found for Group 1.

This outcome is interesting as it is the first time a potential link has been demonstrated between retinal thinning and neurodegeneration in XP. Such an association is not unexpected and similar relationships have been documented between retinal thickness and other neurodegenerative conditions such as Parkinson's disease,³² Alzheimer's disease,⁴⁴ schizophrenia,⁴⁵ and Friedreich's ataxia.⁴⁸ In subsequent studies it may be helpful to correlate such XP retinal changes with deeper neurological phenotyping, for example SARA scores, although the need to perform a meaningful OCT means that patients involved in such studies would need to have a reasonably high level of neurological function, as was the case here.

The exact mechanisms for these retinal changes in our XP patients remain unclear, but our study suggests that they are highly likely to relate to those causing XP-associated neurodegeneration. As discussed in the introduction, patients with XP, except XP-V, have defective NER, and those with associated clinical neurodegeneration (Group 2 in our study) have a defective transcription-coupled NER pathway. Accurate transcription of DNA is essential for the effective functioning of

all metabolically active cells, and cumulative errors in this will lead to abnormal gene expression and RNA transcripts, eventually resulting in cell death. The DNA damage induced by UV light (cyclobutane pyrimidine dimers or CPDs) can only be repaired by NER, hence its devastating effect on patients with XP. The wavelengths of UV light responsible for CPDs cannot penetrate into the human brain and, likewise, would not be expected to reach the retina.^{53–55} However, some forms of endogenous oxidative DNA damage have been identified which are also exclusively repaired by NER and which may contribute to XP-associated neurodegeneration, including the retinal changes that we have identified. Of these, the most convincing candidates are the 8,5'-cyclopurine-2'-deoxynucleosides (cyPudNs) that result from hydroxyl radical attack on 2'-deoxyadenosine (dA) and 2'-deoxyguanosine (dG) within DNA.²² It has been shown that cyPudNs are not substrates for any other DNA repair pathway in mammalian cells, augmenting their significance in patients with defective NER such as in XP.^{56,57} Furthermore, they are strong blockers of gene expression in XP cells and have been found to stimulate the production of mutant RNA transcripts in human cells.^{56,58} Lastly, cyPudNs are stable, endogenous DNA adducts and will therefore accumulate over time within a cell in the absence of NER.^{59,60} Slow accumulation of these products, created endogenously in cells from metabolic oxidative damage, could potentially result in progressively defective gene expression and transcription and cause slow neuronal damage and loss. Whilst all cells in the body would be affected by these products, the lack of neuronal cell turnover, the high neuronal metabolism and the longevity of neuronal cells make them particularly vulnerable to such degeneration.

It is interesting that the changes we observed between the two XP groups and controls were more pronounced in the macular regions than the pRNFL. This may have been due to confounding factors such as a higher baseline RNFL variability between subjects or may relate to factors associated with the mechanism of the retinal neurodegeneration itself. In future studies, new OCT software, such as that available in the latest Spectralis OCT device (Heidelberg Engineering,

Heidelberg, Germany) will not only allow us to look at overall macular thickness but to distinguish individual neuroretinal layers.⁶¹ This may allow us to pinpoint exactly which layers are affected by XP, which, in turn, may give us further insight into the pathophysiology of XP neurodegeneration.

In more affluent countries, great advances have been made in minimising the exposure of XP patients to UV and thus reducing the burden of UV-related morbidity. However, the development, progression and management of associated neurodegeneration remains a major concern for patients with XP here. It would be useful for practitioners to be able to predict which patients within the XP cohort are more likely to develop neurodegeneration and, more importantly, the likely rate of such decline. In addition, if more neuroprotective treatments were to become available, it would be extremely helpful to have a quantitative and sensitive means of measuring their effect on the rate of neurological disease progression. Our pilot study constitutes the first to suggest that retinal, and, in particular, macular thickness and volume measurements, offer a powerful prognostic tool in the management and understanding of this rare disease.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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