Ocular Manifestations of Trichothiodystrophy

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Objective: Trichothiodystrophy (TTD) is a rare, autosomal recessive disorder characterized by sulfur-deficient brittle hair and multisystem abnormalities. Many TTD patients have a defect in known DNA repair genes. This report systematically evaluates the ocular manifestations of the largest-to-date cohort of TTD patients and xeroderma pigmentosum (XP)/TTD patients.

Design: Case series.

Participants: Thirty-two participants, ages 1 to 30 years, referred to the National Eye Institute for examination from 2001 to 2010; 25 had TTD and 7 had XP/TTD.

Methods: Complete, age- and developmental stage-appropriate ophthalmic examination.

Main Outcome Measures: Visual acuity (VA), best-corrected VA, ocular motility, state of the ocular surface and corneal endothelial cell density, corneal diameter, and lens assessment.

Results: Developmental abnormalities included microcornea (44% TTD), microphthalmia (8% TTD, 14% XP/TTD), nystagmus (40% TTD), and infantile cataracts (56% TTD, 86% XP/TTD). Corrective lenses were required by 65% of the participants, and decreased best-corrected VA was present in 28% of TTD patients and 71% of XP/TTD patients. Degenerative changes included dry eye (32% TTD, 57% XP/TTD) and ocular surface disease identified by ocular surface staining with fluorescein (32% TTD) that usually are exhibited by much older patients in the general population. The 2 oldest TTD patients exhibited clinical signs of retinal/macular degeneration. Four XP/TTD patients presented with corneal neovascularization.

Conclusions: These TTD and XP/TTD study participants had a wide variety of ocular findings including refractive error, infantile cataracts, microcornea, nystagmus, and dry eye/ocular surface disease. Although many of these can be ascribed to abnormal development—likely owing to abnormalities in basal transcription of critical genes—patients may also have a degenerative course.

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Trichothiodystrophy (TTD; Online Mendelian Inheritance in Man-OMIM #601675, photosensitive and #234050, non-photosensitive), previously referred to as BIDS (Brittle hair, Intellectual impairment, Decreased fertility and Short stature), PBIDS (+ Photosensitivity), IBIDS (+ Ichthyosis), Pollitt syndrome or Tay syndrome, is a rare, autosomal recessive, multisystem disorder. Trichothiodystrophy, xeroderma pigmentosum (XP), and Cockayne syndrome (CS) are related DNA repair/transcription syndromes.[1]

Trichothiodystrophy has been estimated to occur in 1.2 per million live births in a western European population,[2] and presents clinically as brittle, sulfur-deficient hair with a wide spectrum of systemic involvement (Fig 1A–D). When viewed under polarizing light microscopy, TTD hair shows an alternating light and dark pattern called "tiger-tail banding"[3,4] (Fig 1E). Disease severity can range from abnormal hair alone to multisystem involvement, including severe mental and physical impairment, short stature, decreased fertility, and serious infections, as well as signs of premature aging, and extreme sensitivity to sunlight.[5–7] Magnetic resonance imaging frequently shows hypomyelination of cerebral white matter.[1] Although patients with the related disorder XP have greatly elevated risk of skin cancer,[8–11] TTD patients do not.[1,12]

Patients have been described with defects in the DNA repair/transcription genes *XPD*, *XPB*, and *p8/TTDA* genes whose proteins contribute to the transcription factor IIH complex[13–16] or with defects in the *C7orf22/TTDN1* gene,[14] whose function is currently unknown. Rarely, patients have also been identified with features of both XP and TTD (XP/TTD, OMIM #278730) including an increased risk of skin cancer as in XP.[11,17]

In this article, we report the ocular characteristics of all TTD and XP/TTD patients examined at the National Eye Institute (NEI) from 2001 to 2010, including visual acuity (VA), best-corrected VA, ocular motility, state of the ocular surface, and corneal endothelial cell density (ECD), corneal diameter, and lens assessment.

Materials and Methods

The patients were evaluated under a protocol (99-C-0099) approved by the National Cancer Institute Institutional Review Board and the research adhered to the tenets of the Declaration of

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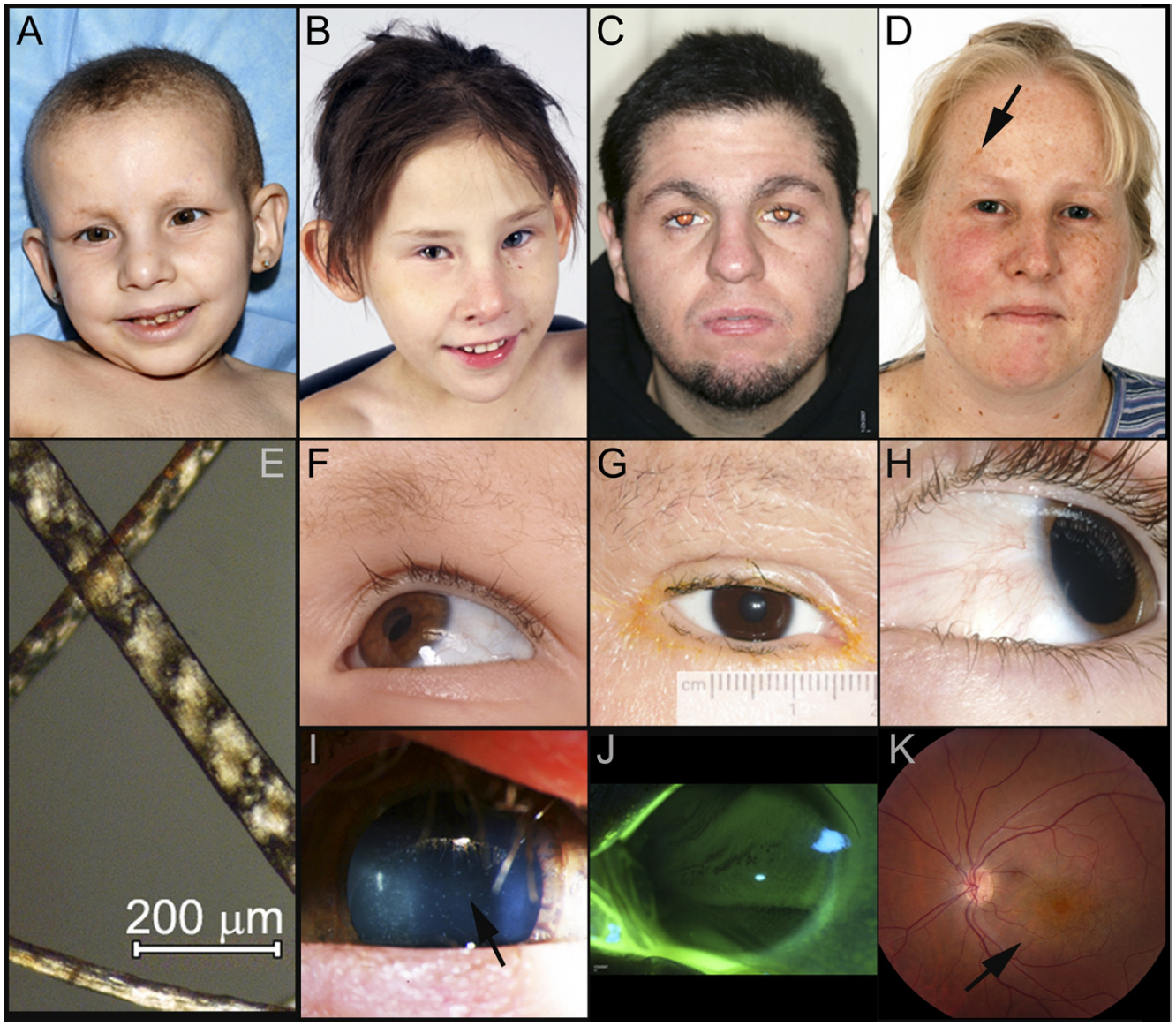

Figure 1. Distinctive features of trichothiodystrophy (TTD) and xeroderma pigmentosum (XP)/TTD-affected patients. TTD patients present with widely varying degrees of facial dysmorphia, hair abnormalities, and ocular characteristics. **A,** Case 1, 7-year-old patient TTD354BE who exhibits facial dysmorphia, ichthyosis, and extremely short, brittle hair. **B,** Case 2, 6-year-old patient TTD383BE with microphthalmia, microcornea, large ears, and dysmorphic facial features but long hair. **C,** Case 3, 26-year-old patient TTD331BE who has unremarkable facial features and relatively long hair. **D,** Case 4, 30-year-old patient XPTTD64BE, who has very long hair, facial lentigines (arrow), and freckling, normal-appearing eyebrows and lashes, and corneal neovascularization OS. Note that all TTD and XP/TTD patients, including those with normal-appearing hair, still exhibited tiger-tail banding under polarizing light microscopy. **E,** Banding seen in the magnified hair of Case 1. **F,** The combination of extremely brittle or sparse eyebrows, and long, thick upper lashes common in most of the TTD patients, shown here in Case 1. **G,** Microcornea and extremely brittle or sparse eyebrows and eyelashes in 19-year-old patient TTD403BE. **H,** Long eyelashes and early pterygium in 5-year-old patient XPTTD392BE. **I,** Visually insignificant punctate corneal opacities (arrow) in Case 2, photographed at 3 years old. **J,** Slit lamp photograph of the cornea (OS) of Case 3 using fluorescein staining. Damaged/degenerated epithelial cells are stained bright green, Oxford scale grade 6. **K,** Fundus photograph also from Case 3 (age 26 at time of photo) showing focal primary retinal degeneration (arrow).

Helsinki. The work is compliant with the Health Insurance Portability and Accountability Act, and informed consent from patients (including consent for use of patient photographs) was obtained. This clinical trial is registered under trial identifier NCT00004044 in the public database http:www.clinicaltrials.gov (last accessed 2/25/2011). This natural history diagnostic protocol studies clinical and genetic features of patients with XP, TTD, or CS.

All patients were evaluated by National Cancer Institute dermatologists (J.J.D. and K.H.K.) and found to have diagnostic features of TTD, including tiger-tail banding of the hair under polarizing microscopy.[3] All patients with TTD who had an ophthalmic examination between July 1, 2001 and October 1, 2010 at the National Institutes of Health Clinical Center were included in this report.

The complete ophthalmic examinations included (when possible) best-corrected Snellen VA measurement, slit-lamp biomicroscopy, and corneal ECD by specular microscopy (Konan NONCON ROBO Pachy Specular Microscope with the KC-3009 Konan

Fully Automatic Cell Analysis System; Konan Medical, Irvine, CA), and dilated fundus examination with an indirect ophthalmoscope. Corneal fluorescein staining,[18] Schirmer test with anesthesia,[19] corneal topography and thickness (Orbscan, Bausch & Lomb, Model DP-3002, Bausch & Lomb, Rochester, NY), and axial length measurements were performed as the patients were able, according to their age and developmental stage. Schirmer values >10 mm/5 minutes indicate normal baseline tear production, values from 6 to 10 mm/5 minutes are considered borderline dry eye, and ≤5 mm/5 minutes confirms the clinical diagnosis of dry eye syndrome.[20] Ocular surface staining was graded according to the Oxford scale.[18] Using standardized frontal photographs taken with a ruler placed on the patients' forehead, we were also able to measure the horizontal corneal diameter. Charts, consult letters, and data in the patients' medical records were reviewed and the data abstracted for this report.

Complementation group status was assigned as previously described using peripheral blood lymphocytes or cultured fibroblasts or lymphoblastoid cells.[3,17,21,22] Patient identification numbers used in this study were preceded by a code for the diagnosis, either TTD or XPTTD (XP/TTD) and followed by a location code "BE" indicating Bethesda, Maryland, as used in previous manuscripts.[3,4,21–24]

The majority of patient data reported are from each patient's single NEI evaluation at ages 1 to 30. Seven patients (TTD405BE, TTD355BE, TTD354BE, TTD351BE, TTD403BE, TTD331BE, and TTD332BE) were examined at the NEI at least twice and had a median longitudinal duration of follow-up of 28 months (range, 13–68). One patient (TTD401BE) underwent 1 NEI examination at age 7 and prior records from other treatment facilities were used in assessing the progression of ocular symptoms.

Results

A total of 32 patients with TTD or XP/TTD underwent ophthalmic examination by ≥1 of the authors of this paper (BPB, JC, or WZ) during the 9-year study period. Table 1 (available online at http://aaojournal.org) is a "clinical array" detailing ophthalmic and relevant nonophthalmic features of the patients in this study. All of the TTD and some of the XP/TTD patients were intellectually impaired and/or developmentally delayed; many had immune deficiencies and ichthyosis (data not shown). Eleven of the TTD patients and all of the XP/TTD patients experienced acute sunburn upon minimal sun exposure. The median age of the 25 TTD patients (16 males and 9 females) at last visit was 9 years (range, 1–29). There were 3 sets of siblings among the TTD patients Table 1, available online at http://aaojournal.org). Two of the TTD patients in this study are deceased, both owing to infection.

There were 7 XP/TTD patients (2 males and 5 females; median age, 17 years; range, 5–30), all in complementation group XP-D. Four of the XP/TTD patients were siblings. Patient XPTTD384BE, last examined at age 28, died of metastatic melanoma at age 31.

Morphology and Ocular Metrics

Figure 1A–D uses 4 cases to show the wide variations of facial, hair, and ocular characteristics in TTD patients. Case 1 (TTD354BE) is a 7-year-old girl with ichthyosis and extremely short, brittle hair (Fig 1A). She died of methicillin-resistant *Staphylococcus aureus* infection at the age of 10. Case 2 (TTD383BE) is a 6-year-old girl with dysmorphic facial features and long hair (Fig 1B). She also had coloboma in the right eye, but not in the left eye (Fig 1B). It is difficult to determine whether this was a manifestation of TTD or her prenatal alcohol exposure. She died of infection (*Clostridium difficile,* age 7) as well. Case 3 (TTD331BE) is a 26-year-old man who has unremarkable facial features and relatively long hair that seems normal on casual observation (Fig 1C). He has primary retinal degeneration, which we discuss in more detail below. Case 4, a 30-year-old female XP/TTD patient, has very long hair, facial lentigines (arrow), normal-appearing eyebrows and lashes, and corneal neovascularization left eye (Fig 1D). She had a basal cell carcinoma removed from the skin of her cheek at age 27. The hair of all of the patients showed characteristic "tiger tail" banding under polarized microscopy (Fig 1E), even when appearing normal on casual observation.

Photographs of patients taken during their examinations were used to assess the normalcy of eyebrows and eyelashes (Table 1; available online at http://aaojournal.org). None of the XP/TTD patients had abnormal eyebrows or eyelashes. Abnormal eyebrows with short stubble, most marked at the lateral third of the eyebrow, as seen in Fig 1F,G, were present in twenty-three (92%) of the TTD patients (Table 1; available online at http://aaojournal.org). Most of the TTD patients had long, thick upper eyelashes even if their lower lashes were not completely normal (Fig 1H). However, extremely brittle or sparse upper and lower eyelashes (Fig 1G), were present in 8 (32%) TTD patients (Table 1; available online at http://aaojournal.org).

Five of the 17 patients assessed had normal corneal diameters ≥11.0 mm in both eyes, including 1 XP/TTD patient. Four TTD patients had borderline diameters of 10.5 mm in both eyes and 7 TTD patients had diameters ≤10.0 mm in 1 or both eyes (Table 1; available online at http://aaojournal.org). The right eye of patient TTD403BE shows microcornea with a corneal diameter of 9.5 mm in both eyes (Fig 1G).

Axial length was assessed in 9 of the 32 patients. Four were normal (TTD404BE, TTD125BE, TTD328BE, and TTD403BE), and 3 had simple microphthalmia, defined as axial lengths that were ≥2 standard deviations smaller than the age-adjusted norms. These patients were TTD383BE (case 2, 6 years), TTD401BE (7

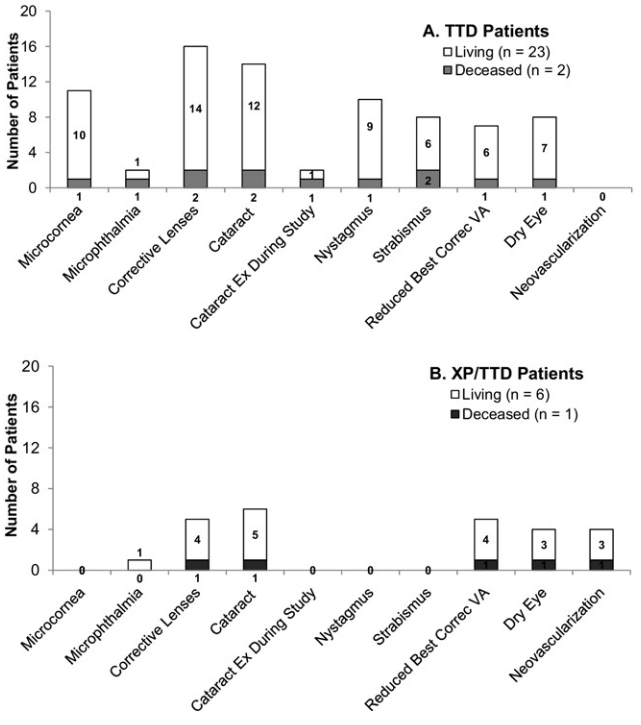

Figure 2. Visual abnormalities in trichothiodystrophy and xeroderma pigmentosum/trichothiodystrophy patients. EX = extracted; TTD = trichothiodystrophy; VA = visual acuity; XP = xeroderma pigmentosum.

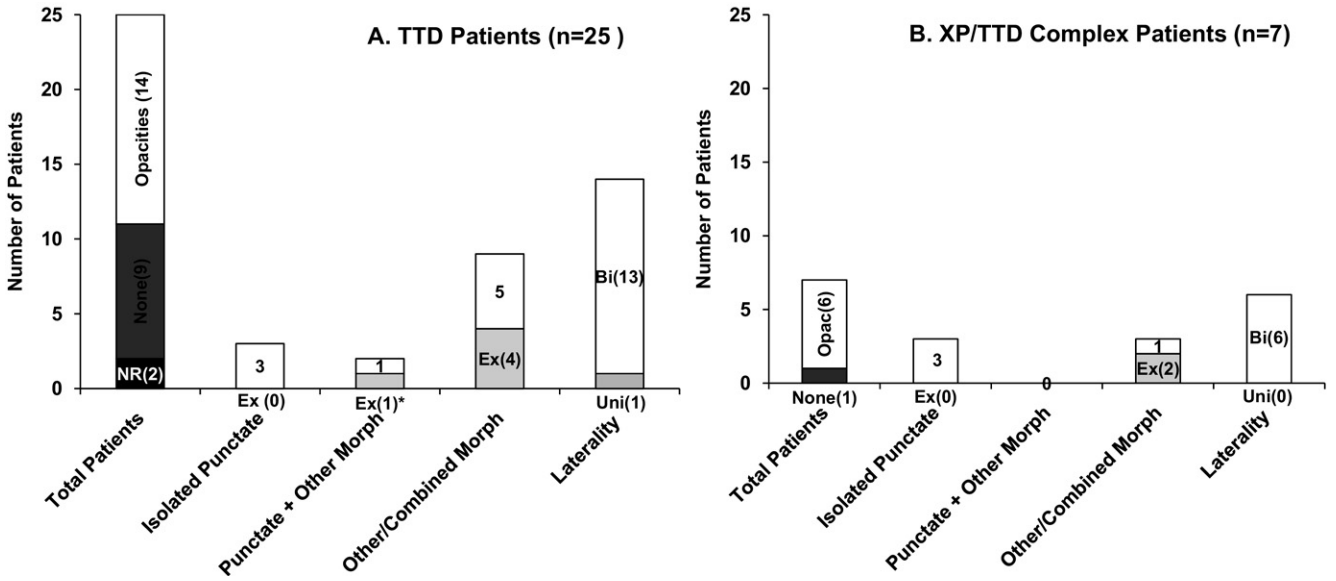

Figure 3. Lens opacities and opacity morphology in trichothiodystrophy (**A**) and xeroderma pigmentosum/trichothiodystrophy (**B**) patients. Bi = bilateral; EX = extracted; NR = not recorded; TTD = trichothiodystrophy; Uni = unilateral; XP = xeroderma pigmentosum.

years), and XPTTD438BE (11 years). In contrast, patients TTD331BE (case 3, 26 years) and TTD332BE (29 years) both had longer axial lengths (25.7 mm right eye, 25.3 mm left eye and 26.5 mm right eye and 27.1 mm left eye, respectively) than the norm of 23.6 ± 0.7 mm for their age.[25]

Basic Ocular Characteristics

Table 1 (available online at http://aaojournal.org) and Fig 2 show the prevalence of visual abnormalities in the TTD (Fig 2A) and XP/TTD (Fig 2B) patients. The most common visual abnormality overall was refractive error severe enough to require corrective lenses (16 TTD and 5 XP/TTD patients (Fig 2). Visual acuity in individual patients is reported in Table 1 (available online at http://aaojournal.org). We found that VA worsened over time, requiring attention to be sure that corrective lenses were up to date (data not shown).

Cataract was the second most common visual abnormality. Fourteen (56%) TTD patients and 6 (85%) XP/TTD patients either presented with lens opacities or a history of cataract excision (Table 1, available online at http://aaojournal.org; Fig 2); all opacities were bilateral (Fig 3) with the exception of 3-year-old patient TTD445BE, who had visually insignificant fetal nuclear cataracts left eye (Table 1, available online at http://aaojournal.org; Fig 3).

The type and severity of the cataracts in each group is shown in more detail in Fig 3. Four TTD and 2 XP/TTD patients had cataracts excised before the beginning of this study. Of the 14 patients with opacities at the time of the study, 6 (43%) patients—TTD405BE, TTD403BE, TTD332BE, XPTTD387BE, XPTTD385BE, and XPTTD384BE—presented with isolated punctate lens opacities. These opacities were mild and either congenital or presumed congenital, and visually insignificant. None of the patients with isolated punctate opacities had a history of cataract excision or required excision during the study period. Cataract progression was only observed in 2 TTD patients. At age 10, patient TTD351BE presented with cortical spoke-like opacities in addition to the punctate opacities observed at age 8. These opacities were still judged visually insignificant at the time of last visit, and did not require extraction. Patient TTD354BE (case 1, Fig 1) also had visually insignificant punctate opacities at age 3 (Fig 1F). By age 6, however, she had developed punctate and lamellar opacities with a decrease in functional VA and extraction was performed.

Some degree of nystagmus was exhibited by 8 of the TTD patients, and one patient had a history of nystagmus which resolved before her first study visit (Table 1, available online at http://aaojournal.org; Fig 2). None of the XP/TTD patients had either current nystagmus or a history of nystagmus (Table 1, available online at http://aaojournal.org; Fig 2). Of the patients who were seen multiple times at the NEI or had detailed ophthalmic records in their charts from other institutions only patient TTD405BE had a change of status from no clinical nystagmus to nystagmus. This patient was treated using corrective lenses at age 3 months through 18 months, her nystagmus subsequently resolved, and there was no clinically apparent nystagmus at age 3. On her return visit to the NEI at the age of 4, after a hospitalization for pneumonia, her nystagmus had returned. In general, neurologic symptoms of the patients tend to worsen when they have infections and gradually return to their preinfection status when they recover. VA tended to be lower overall in patients with nystagmus compared with patients without nystagmus (Table 1, available online at http://aaojournal.org).

Strabismus was present in 8 of the TTD patients and none of the XP/TTD patients (Table 1, available online at http://aaojournal.org; Fig 2). Two TTD patients had esotropia and 3 had exotropia at the time of the study. Of the 3 additional TTD patients with a history of strabismus, only patient TTD383BE (case 2) required surgical intervention (Table 1, available online at http://aaojournal.org).

In addition to needing corrective lenses, 7 of the 25 TTD patients and 5 of the XP/TTD patients experienced decreased best-corrected VA (Fig 2). This decreased best-corrected VA ranged from mild (20/30, TTD404BE) to more serious (20/400 right eye, 20/300 left eye, TTD331BE/case 3). This decrease in an individual eye's best-corrected acuity was partially mitigated in some cases when the effects of latent nystagmus were limited by binocular evaluation. Patient TTD331BE/case 3, for instance, improved to 20/160 binocularly. All of the patients with reduced best-corrected VA also had lens opacities, although the most were

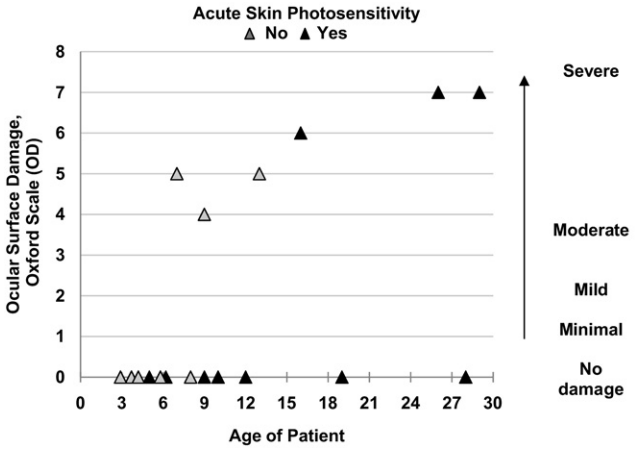

Figure 4. Quantification of ocular surface damage in trichothiodystrophy-affected patients via epithelial surface staining with fluorescein. OD = right eye; TTD = trichothiodystrophy.

visually insignificant. It also is possible that ocular surface disease or neurologic abnormalities contribute to this reduction; however, the cause of decreased best-corrected VA in these patients is unclear.

Four patients ranging in age from 8 to 29 experienced fluctuations in best-corrected VA occurred between visits, some worsening (TTD331BE/case 3 between ages 23 and 6; TTD403BE between ages 16 and 19); others had unexplained improvements (TTD351BE between ages 8 and 10; TD332BE between ages 26 and 29).

Dry eye was common in all age groups. Thirty-two percent of the TTD patients and 57% of the XP/TTD patients reported symptoms of dry eye and were being treated for the condition (Table 1, available online at http://aaojournal.org; Fig 2). All of the patients age ≥20 years had symptoms of dry eye (Table 1; available online at http://aaojournal.org). Tear meniscus height, tear breakup time, tear production, and tear lake size could not be accurately assessed in this patient population owing to poor cooperation. Among those younger patients able to undergo testing, only patient XPTTD387BE had normal tear production (age 12, 25 mm/5 minutes) by Schirmer testing. Patients TTD328BE (age 13) and TTD331BE/case 3 (age 26) had values that would be sufficient for a formal dry eye diagnosis, and patients XPTTD385BE, XPTTD384BE, TTD332BE, and XPTTD64BE had ≥1 eye with values <5 mm/5 minutes.

Twenty-one patients were able to undergo epithelial surface staining with fluorescein and lissamine green to assess the state of the corneal and conjunctival surface. Epithelial surface staining indicates some level of dead or degenerated epithelial cells. Two patients were qualitatively assessed and had very mild superficial staining (TTD426BE and TTD404BE). Semiquantitative assessment using the Oxford Scale[19] was possible in the remaining 19 patients (Fig 4). None of the XP/TTD patients showed ocular surface staining, whereas 8 of the 16 TTD patients tested were positive for some level of ocular surface disease. Corneal epithelial damage was present in these patients regardless of their complementation group or sun sensitivity phenotype. The highest Oxford values were 7 in the right eye and 6 in the left eye in a 26-year-old patient TTD331BE/case 3 (Fig 4). Figure 1J shows a photo of the right eye of this patient with extensive corneal and conjunctival staining. None of the patients with multiple visits to the NEI had epithelial surface evaluation using fluorescein on >1 visit.

Corneal neovascularization, a feature of XP, was seen in 4 of the XP/TTD but none of the TTD patients (Table 1, available online at http://aaojournal.org; Fig 2). An example of an early pterygium lesion in 5-year-old patient XPTTD392BE is shown in Figure 1H. It is advisable to closely monitor pterygium, because squamous cell carcinoma of the conjunctiva can have a similar appearance.

In view of the high rates of corneal size abnormalities and ocular surface disease in TTD patients, we evaluated ECD and morphology using specular microscopy. At birth[26] ECDs are between 3500 and 6000 cells/μm^2 and decrease very gradually through early adulthood, where values stabilize between 2500 and 3000 cells/μm^2 for the remaining lifespan.[27] Normally, the percentage of hexagonal cells in patients of this age range would be between 60% and 75%.[26,28,29] Two of the 6 patients assessed had normal ECDs (XPTTD385BE and TTD403BE, both age 19). One patient (XPTTD64BE, age 30) had borderline low ECDs of 2475 cells/μm^2 in the right eye and 2445 cells/μm^2 in the left eye. Low ECDs were seen in 3 patients, 9-, 12-, and 13-year old patients TTD125BE (1764 ± 163 cells/μm^2 right eye with 44% hexagonal cells and 1739 cells/μm^2 left eye), and TTD124BE (1825±175 cells/μm^2 right eye and 1795±208 cells/μm^2 left eye), and XPTTD387BE (1764±163 cells/μm^2 right eye, 1739 cells/μm^2 left eye). Patient TTD124BE also had a low percentage of hexagonal cells (45% right eye and 35% left eye).

Central corneal thickness was evaluated in 5 patients and found to be in the normal range[30,31] in 4 patients (TTD124BE, XPTTD387BE, XPTTD385BE, XPTTD64BE/case 4). Thinner than normal central corneal thickness (457 right eye, 446 left eye) was present in 28-year-old patient XPTTD384BE.

Signs of retinal/macular degeneration were present in 2 adult TTD patients, 26- and 29-year-old brothers TTD331BE/case 3 and TTD332BE. The older patient is shown as case 3 in Fig 1. His fundus photograph in Figure 1K shows a focal area of macular degeneration with pigment mottling within or beneath the retinal pigment epithelium. Scotopic ERG responses in this patient were delayed and of borderline amplitude. Both the "a" and "b" waves of the maximum combined responses were delayed and reduced in amplitude. Both photopic flash and flicker responses were extinguished. These results, taken together with the maculopathy present on fundus examination, are indicative of cone–rod degeneration.

Complementation Groups

Twenty-four of the patients were complementation group XP-D (17 TTD and all 7 XP/TTD patients), 2 were complementation group TTD-N1, 2 were complementation group TTD-A, and 4 were not classifiable into any of the currently known complementation groups. All had ocular abnormalities (Table 1, available online at http://aaojournal.org).

Discussion

Our study reports the ocular status of the largest group of TTD or XP/TTD patients systematically examined at 1 facility. Of the 32 patients, 94% presented with some degree of visual abnormality. In a previous systematic literature review of reports of 112 TTD cases through 2005,[5] ocular abnormalities were reported in 51% of patients and included cataracts (32 pts), nystagmus (16 patients), strabismus (11 patients), myopia (7 patients), astigmatism (6 patients), photophobia (5 patients), conjunctivitis (4 patients), ectropion (4 patients), dry eye (1 patient), and retinal pigmentation (1 patient). Because developmental delay is a prominent fea-

ture of TTD, our examinations were sometimes limited by the child's ability to cooperate.

In general, these patients' ophthalmic findings can be broadly grouped into (1) developmental phenotypes and (2) premature aging or degeneration. Our patients experienced a high frequency of the developmental phenotypes microcornea (44% TTD) and microphthalmia (8% TTD, 14% XP/TTD), infantile cataracts (56% TTD and 86% XP/TTD) and nystagmus (38%, TTD only; Table 1, available online at http://aaojournal.org; Figs 1 and 2). Because of this high frequency of microcornea and microphthalmia in these young patients, routine refraction and treatment of amblyopia is important.

Estimates of the frequency of congenital/infantile cataracts in the United States range from 2.03 to 13.6 per 10 000 births[32] or infants,[33] respectively. However, >60% (20/32) of the patients in our study had cataract (Table 1, available online at http://aaojournal.org; Figs 1, 2, and 3). Many were incidental findings that were not visually significant and were presumed developmental. Cataracts in 2 patients, however, progressed from minimal punctate opacities to opacities with a combination of morphologies that were more visually significant, and 1 patient required operative extraction.

The frequency of nystagmus in the general population is not well studied. However, a recent study from the United Kingdom estimated the prevalence as 24 per 10 000,[34] which is much lower than the 28% (9/32) of TTD patients observed in this study (Table 1, available online at http://aaojournal.org; Fig 2). Overall, patients with nystagmus tended to have decreased VA compared with patients without nystagmus (Table 1, available online at http://aaojournal.org). This is not a surprising finding, given that nystagmus reduces foveation time and can be caused by many conditions that are more likely to occur in TTD patients, such as decreased best-corrected VA, uncorrected bilateral cataracts (although this does not seem to be the cause in these patients), possible retinal degeneration, as well as developmental abnormalities. Although the direct mechanism leading to these manifestations of the disease are unknown, TTD patients usually have central nervous system dysmyelination.[35–38] Although we do not have enough radiologic data to make a clear connection, this dysmyelination may be related to the high prevalence of nystagmus in TTD. We do not know whether the clinical improvement in nystagmus observed in some patients was related to central nervous system myelination.

The XP-D complementation group patients predominated in the study (as they do in the general TTD patient population).[5,39] The XP-D, TTD-N1, and unknown group patients had a similar ocular phenotype to the rest of the patients. The 2 TTD-A patients were the brothers (TTD331BE/case 3 and TTD332BE) who had longer than normal axial length, strabismus, nystagmus, reduced best-corrected VA, and signs of retinal degeneration. We do not know if this is related to the specific genetic defect or to their relatively older age. The *XPD* and *TTDA* genes code for proteins that participate in both DNA repair and in transcription as subunits of the transcription factor IIH complex.[13,14,40–42] The *XPD* mutations lead to reduced expression of several hormone-dependent transcription factor nuclear receptors such as the vitamin D receptor, thyroid receptor, retinoic acid receptor, and peroxisome proliferator activated receptor that are essential for normal development.[43,44] The most apparent clinical symptoms of TTD such as brittle, sulphur-deficient hair, ichthyosis, and dysmyelination of the brain, are seen in terminally differentiated tissues. In these tissues, de novo synthesis is in decline and the concentration of available transcription factor IIH is therefore thought to be limiting.[45]

Often, TTD is considered as primarily a disease of development, as opposed to one of premature aging so clearly manifested in the closely related syndromes of XP and CS.[1] This systematic study, however, shows that some of these TTD patients exhibit characteristics reminiscent of premature aging as well, including ocular surface disease, possible retinal degeneration, and possible early corneal endothelial cell loss. Perhaps postmitotic tissues in the accessory lacrimal glands, the neural retina, and the corneal endothelium require a basal level of transcription that TTD patients are unable to maintain or changes in basal transcription of survival genes affect these tissues. In addition, TTD patients have been reported to exhibit signs of segmental progeria such as osteosclerosis.[38] The XPD^{R722W} TTD mouse model supports a role for the XPD gene in the aging process: Affected mice show osteoporosis, early graying, cachexia, infertility, and reduced lifespan.[45,46]

Both the TTD and XP/TTD patients had ocular characteristics of a much older population with a high prevalence of dry eye symptoms or disease for a pediatric/young adult population. The prevalence of dry eye in the general population has been reported to range from 11% to 22%, with older people and women most often affected.[47] In a large study of an older Chinese population, 33.7% of patients over age 64 reported ≥1 dry eye symptoms either "often" or "all the time."[48] In the present study, 38% (12/32) of the TTD patients presented with dry eye, even though none were over 30 years old (Table 1, available online at http://aaojournal.org; Fig 2). Because chronic dry eye disease can lead to pathologic changes of the ocular surface, early use of artificial tears and lubricating ointments, and careful use of contact lenses, may minimize irritation and the risk of corneal ulceration. Making this diagnosis may be particularly important in children with TTD or XP/TTD, because dry eye evaluation is often not a part of the standard pediatric eye examination.

Abnormal corneal ECD was also present in some patients. Two TTD patients (ages 9 and 10) and 2 XP/TTD patients (ages 12 and 30) presented with low ECD. We cannot determine whether these patients experience a premature decrease in ECD or begin life with a lower baseline number of endothelial cells. Further observation will be necessary to determine whether these low ECD in childhood/young adulthood are indicative of future corneal complications.

Retinal/macular degeneration, as seen in the 2 oldest TTD patients (Fig 1, Case 3), is not recognized as characteristic of TTD, although it is characteristic of the related DNA repair disorder, CS.[49,50] This raises the question of whether photoreceptor dysfunction is a late manifestation of TTD. It is possible that, because TTD patients have longer life spans, new manifestations of the disease will be recog-

nized. The fundus of the third-oldest TTD patient in the study, 19-year-old TTD403BE, also exhibits a few small drusen, which can be an early (but not definitive) sign of age-related macular degeneration.

With the exception of bilateral cataract, XP/TTD patients do not seem to have the developmental features, like nystagmus and strabismus, that many TTD patients exhibit. Cataracts in the majority of the XP/TTD patients were visually insignificant. The XP/TTD patients did have, however, a high rate of ocular surface disease and exhibited more degenerative symptoms, including neovascularization in over half the patients—a symptom that was completely absent in the TTD patients. This finding, not present in any of the patients with pure TTD, should raise the clinical suspicion of the overlap diagnosis of XP/TTD. These phenotypes, however, should be considered preliminary owing to the small number of XP/TTD patients as well as the family relationship of 4 of the 7 XP/TTD patients.

This study brings a number of issues concerning the ocular manifestations of TTD into focus. First, although developmental abnormalities such as dysmorphic facial appearance and brittle hair and eyelashes are apparent in many cases, patients can present with a normal appearance as well. Diligence regarding cataracts, best-corrected VA, ocular motility, and maintaining correct refractive lenses is required. Photoreceptor degeneration may be a late-appearing TTD ocular phenotype, and retinal/macular status should be monitored. Early monitoring of corneal endothelial cell densities may be warranted. These XP/TTD patients should be closely monitored for degenerative/inflammatory symptoms because, unlike TTD patients, XP/TTD patients are at increased risk for cancer. Extra diligence is needed to screen for and treat dry eye and ocular surface disease, even among pediatric patients, with a goal of preventing serious complications in both TTD and XP/TTD individuals.

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Footnotes and Financial Disclosures

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