Published in final edited form as:

Ophthalmology. 2011 December ; 118(12): 2335–2342. doi:10.1016/j.ophtha.2011.05.036.

Ocular Manifestations of Trichothiodystrophy

Brian P Brooks, MD, PhD^{a,*}, Amy H Thompson, PhD^a, Janine A Clayton, MD^a, Chi-Chao Chan, MD^b, Deborah Tamura, RN, MS^c, Wadih M Zein, MD^a, Delphine Blain, MS, MBA^{a,d}, Casey Hadsall, RN, BSN^a, John Rowan, COMT^a, Kristen E Bowles, OD, MS^a, Sikandar G. Khan, PhD^c, Takahiro Ueda, PhD^c, Jennifer Boyle, PhD^c, Kyu-Seon Oh, PhD^c, John J DiGiovanna, MD^c, and Kenneth H Kraemer, MD^c

^a National Eye Institute, National Institutes of Health, Bethesda, MD, USA

^b Immunopathology Section, Laboratory of Immunology, National Eye Institute, National Institutes of Health, Bethesda, MD, USA

^c Dermatology Branch, Center for Cancer Research, National Cancer Institute, Bethesda, MD, USA

^d MedStar Health Research Institute, Hyattsville, MD

Abstract

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: Twenty-five 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, lens assessment.

Results—Developmental abnormalities included microcornea (44% TTD), microphthalmia (8% TTD, 14% XP/TTD), nystagmus (40% TTD), and infantile cataracts (56% TTD and 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

© 2011 American Academy of Ophthalmology, Inc. Published by Elsevier Inc. All rights reserved.

*corresponding author: Brian P Brooks, National Eye Institute, National Institutes of Health, Building 10, Room 10B16, Bethesda, MD 20892; brooksb@mail.nih.gov.

Address for reprints: Brian P Brooks, National Eye Institute, National Institutes of Health, Building 10, Room 10B16, Bethesda, MD 20892

No conflicting relationship exists for any author.

This article contains online-only material. The following should appear online-only: Table 1

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

the general population. The two oldest TTD patients exhibited clinical signs of retinal/macular degeneration. Four XP/TTD patients presented with corneal neovascularization.

Conclusions—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. While many of these can be ascribed to abnormal development—likely due to abnormalities in basal transcription of critical genes—patients may also have a degenerative course.

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's Syndrome or Tay's Syndrome, is a rare autosomal recessive multisystem disorder. TTD, xeroderma pigmentosum (XP), and Cockayne syndrome (CS) are related DNA repair/transcription syndromes¹.

TTD has been estimated to occur in 1.2 per million live births in a western European population,² and presents clinically as brittle, sulphur-deficient hair with a wide spectrum of systemic involvement (Figure 1A–D). TTD hair, when viewed under polarizing light microscopy, shows an alternating light and dark pattern called “tiger-tail banding”^{3–4} (Figure 1E). Disease severity can range from abnormal hair alone to multi-system 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 (J Invest Derm 127:631, 2007).^{5–6} Magnetic resonance imaging frequently shows hypomyelination of cerebral white matter¹. Although patients with the related disorder XP have greatly elevated risk of skin cancer^{7–10}, TTD patients do not.^{1, 11}

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 IIIH (TFIIH) complex^{12–15} or with defects in the *C7orf22/TTDN1* gene¹³ whose function is currently unknown. Rare 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.^{10, 16}

In this paper, 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, corneal diameter, and lens assessment.

Materials and Methods

The patients were evaluated under a protocol (99-C-0099) approved by the National Cancer Institute (NCI) Institutional Review Board and the research adhered to the tenets of the Declaration of Helsinki. The work is HIPAA-compliant, 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 xeroderma pigmentosum, trichothiodystrophy or Cockayne syndrome..

All patients were evaluated by NCI dermatologists (JJD and KHK) 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 7/1/2001 and 10/1/2010 at the National Institutes of Health Clinical Center were included in this report.

The complete ophthalmic examinations included (when possible) best-corrected Snellen visual acuity (VA) measurement, slit-lamp biomicroscopy, and corneal endothelial cell density by specular microscopy (Konan NONCON ROBO Pachy Specular Microscope with the KC-3009 Konan Fully Automatic Cell Analysis System), and dilated fundus examination with an indirect ophthalmoscope. Corneal fluorescein staining,¹⁷ Schirmers test with anesthesia,¹⁸ corneal topography and thickness (Orbscan, Bausch & Lomb, Model DP-3002), and axial length measurements were performed as the patients were able, according to their age and developmental stage. Schirmer values > 10 mm/5 minutes (min) indicate normal baseline tear production, values from 6 mm/5 min to 10 mm/5 min is considered borderline dry eye, and ≤ 5 mm/5 min confirms the clinical diagnosis of dry eye syndrome.¹⁹ Ocular surface staining was graded according to the Oxford scale.¹⁷ 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 (J Invest Derm 119:93, 202).^{3, 16, 20} Patient identification numbers used in this study were preceded by a code for the diagnosis, either TTD or XP/TTD (XP/TTD) and followed by a location code —BE indicating Bethesda, MD as used in previous manuscripts (J Invest Derm 119:93, 202).^{3–4, 20–22}

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 to 68 months). One patient (TTD401BE) had one NEI examination at age 7 and prior records from other treatment facilities that were used in assessing the progression of ocular symptoms.

Results

A total of 32 patients with TTD or XP/TTD underwent ophthalmic examination by one or more of the authors of this paper (BPB, JC, or WZ) during the 9 year study period. Table 1 (available at <http://aaojournal.org>) is a "clinical array" detailing ophthalmic and relevant non-ophthalmic 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, with a range from 1 year to 29 years. There were three sets of siblings among the TTD patients (Table 1, available at <http://aaojournal.org>). Two of the TTD patients in this study are deceased; both due to infection.

There were 7 XP/TTD patients (2 males and 5 females) median age 17 years (range 5 to 30 years), 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 four 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 (Figure 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 (Figure 1B). She also had coloboma in the right eye (OD) but

not in the left eye (OS) (Figure 1B). It is difficult to determine if 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 appears normal upon casual observation (Figure 1C). He has primary retinal degeneration, which we will 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 OS (Figure 1D). She had a basal cell carcinoma removed from the skin of her cheek at age 27 years. The hair of all of the patients showed characteristic —tiger tail banding under polarized microscopy (Figure 1E), even when appearing normal upon casual observation.

Photographs of patients taken during their examinations were used to assess the normalcy of eyebrows and eyelashes (Table 1, available 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 Figure 1F and G, were present in twenty-three (92%) of the TTD patients (Table 1, available at <http://aaojournal.org>). Most of the TTD patients had long, thick upper eyelashes even if their lower lashes were not completely normal, as shown in Figure 1H. However, extremely brittle or sparse upper and lower eyelashes, as seen in Figure 1G, were present in 8 (32%) TTD patients (Table 1, available at <http://aaojournal.org>).

Five of the 17 patients assessed had normal corneal diameters ≥ 11.0 mm OU, including 1 XP/TTD patient. Four TTD patients had borderline diameters of 10.5 mm OU and 7 TTD patients had diameters ≤ 10.0 mm in one or both eyes (Table 1, available at <http://aaojournal.org>). The right eye of patient TTD403BE shows microcornea with a corneal diameter of 9.5 mm OU (Figure 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 at least two standard deviations smaller than the age-adjusted norms. These patients were TTD383BE (Case 2, 6 years), TTD401BE (7 years), and XP/TTD438BE (11 years). In contrast, patients TTD331BE (Case 3, 26 years) and TTD332BE (29 years) both had longer axial lengths (25.7 mm OD, 25.3 mm OS and 26.5 mm OD and 27.1 mm OS, respectively) than the norm of 23.6 ± 0.7 mm for their age.²³

Basic Ocular Characteristics

Table 1 (available at <http://aaojournal.org>) and Figure 2 show the prevalence of visual abnormalities in the TTD (Figure 2A) and XP/TTD (Figure 2B) patients. The most common visual abnormality overall was refractive error severe enough to require corrective lenses (16 TTD and 5 XP/TTD patients (Figure 2). Visual acuity in individual patients is reported in Table 1, available 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 at <http://aaojournal.org>; and Figure 2); all opacities were bilateral (Figure 3) with the exception of 3-year old patient TTD445BE, who had visually insignificant fetal nuclear cataracts OS (Table 1, available at <http://aaojournal.org>; and Figure 3).

The type and severity of the cataracts in each group is shown in more detail in Figure 3. Four TTD and 2 XP/TTD patients had cataracts excised prior to the beginning of this study. Of the 14 patients with opacities at the time of the study, 6 (43%) patients -TTD405BE,

TTD403BE, TTD332BE and XPTTD387BE, XPTTD385BE, 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 two 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, Figure 1) also had visually insignificant punctate opacities at age 3, shown in Figure 1F. By age 6, however, she had developed punctate and lamellar opacities with a decrease in functional visual acuity 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 prior to her first study visit (Table 1 [available at <http://aaojournal.org>] and Figure 2). None of the XP/TTD patients had either current nystagmus or a history of nystagmus (Table 1 [available at <http://aaojournal.org>], Figure 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, and 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, following a hospitalization for pneumonia, her nystagmus had returned. In general, neurological symptoms of the patients tend to worsen when they have infections and gradually return to their pre-infection status when they recover. VA tended to be lower overall in patients with nystagmus compared to patients without nystagmus (Table 1, available at <http://aaojournal.org>).

Strabismus was present in 8 of the TTD patients and none of the XP/TTD patients (Table 1 [available at <http://aaojournal.org>] and Figure 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 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 (Figure 2). This decreased best-corrected VA ranged from mild (20/30, TTD404BE) to more serious (20/400 OD, 20/300 OS, 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 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; TTD332BE 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 at <http://aaojournal.org>], Figure 2). All of the patients age 20 and older had symptoms of dry eye (Table 1, available at <http://aaojournal.org>). Tear meniscus height,

tear breakup time tear production, and tear lake size were largely un-assessable in this patient population due to poor cooperation. Among those younger patients able to undergo testing, only patient XPTTD387BE had normal tear production (age 12, 25 mm/5 min) by Schirmer's 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 at least one eye with values below 5 mm/5 min.

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). Semi-quantitative assessment using the Oxford Scale¹⁷ was possible in the remaining 19 patients, and results are shown in Figure 4. None of the XP/TTD patients showed ocular surface staining, while 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 OD, 6 OS in 26-year old patient TTD331BE/Case 3 (Figure 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 more than one visit.

Corneal neovascularization, a feature of XP, was seen in 4 of the XP/TTD but none of the TTD patients (Table 1 [available at <http://aaojournal.org>], Figure 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, as 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 endothelial cell density (ECD) and morphology using specular microscopy. At birth²⁴ ECDs are between 3,500-6,000 cells/ μm^2 and decrease very gradually through early adulthood, where values stabilize between 2,500–3,000 cells/ μm^2 for the remaining lifespan.²⁵ Normally, the percentage of hexagonal cells in patients of this age range would be between 60–75%.^{24, 26–27} 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 OD and 2445 cells/ μm^2 OS. Low ECDs were seen in three patients, 9-, 12- and 13- year old patients TTD125BE (1764 ± 163 cells/ μm^2 OD with 44% hexagonal cells and 1739 cells/ μm^2 OS), and TTD124BE (1825 ± 175 cells/ μm^2 OD and 1795 ± 208 cells/ μm^2 OS) and XPTTD387BE (1764 ± 163 cells/ μm^2 OD, 1739 cells/ μm^2 OS). Patient TTD124BE also had a low percentage of hexagonal cells (45% OD and 35% OS).

Central corneal thickness (CCT) was evaluated in 5 patients and found to be in the normal range^{28–29} in 4 patients (TTD124BE, XPTTD387BE, XPTTD385BE, XPTTD64BE/Case 4). Thinner than normal CCT (457 OD, 446 OS) was present in 28-year old patient XPTTD384BE.

Signs of retinal/macular degeneration were present in two adult TTD patients, 26- and 29-year old brothers TTD331BE/Case 3 and TTD332BE. The older patient is shown as Case 3 in Figure 1. His fundus photograph in panel 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 at <http://aaojournal.org>).

Discussion

Our study reports the ocular status of the largest group of TTD or XP/TTD patients systematically examined at one 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 pts), strabismus (11 pts), myopia (7 pts), astigmatism (6 pts), photophobia (5 pts), conjunctivitis (4 pts), ectropion (4 pts), dry eye (1 pts) and retinal pigmentation (1 pts). Because developmental delay is a prominent feature 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 a) developmental phenotypes and b) 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 at <http://aaojournal.org>] and Figures 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 US range from 2.03 to 13.6 per 10,000 births³⁰ or infants,³¹ respectively. However, more than 60% (20/32) of the patients in our study had cataract (Table 1 [available at <http://aaojournal.org>] and Figures 1, 2 and 3). Many were incidental findings that were not visually-significant and were presumed developmental. Cataracts in two patients, however, progressed from minimal punctate opacities to opacities with a combination of morphologies that were more visually significant, and one patient required surgical 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 10,000,³² which is much lower than the 28% (9/32) of TTD patients observed in this study (Table 1 [available at <http://aaojournal.org>] and Figure 2). Overall, patients with nystagmus tended to have decreased VA compared to patients without nystagmus (Table 1, available 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 appear to be the cause in these patients), possible retinal degeneration, as well as developmental abnormalities. While the direct mechanism leading to these manifestations of the disease are unknown, TTD patients usually have central nervous system dysmyelination.³³⁻³⁶ 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 if the clinical improvement in nystagmus observed in some patients was related to CNS myelination.

XP-D complementation group patients predominated in the study (as they do in the general TTD patient population).^{5, 37} The XP-D, TTD-N1, and unknown group patients had a

similar ocular phenotype to the rest of the patients. The two 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. *XPD* and *TTDA* genes code for proteins that participate in both DNA repair and in transcription as subunits of the transcription factor IIIH (TFIIH) complex.^{12-13, 38-40} *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 PPAR that are essential for normal development.⁴¹⁻⁴² 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 TFIIH is therefore thought to be limiting.⁴³

TTD is often 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 post-mitotic 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. TTD patients have been reported to exhibit signs of segmental progeria such as osteosclerosis.³⁶ 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.⁴³⁻⁴⁴

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.⁴⁵ In a large study of an older Chinese population, 33.7% of patients over age 64 reported 1 or more dry eye symptoms either “often” or “all the time.”⁴⁶ 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 at <http://aaajournal.org>] and Figure 2). Since 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, as dry eye evaluation is often not part of the standard pediatric eye examination.

Abnormal corneal endothelial cell density 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 endothelial cell densities. We cannot determine whether these patients experience a premature decrease in endothelial cell density or begin life with a lower baseline number of endothelial cells. Further observation will be necessary to determine if these low endothelial cell densities in childhood/young adulthood are indicative of future corneal complications.

Retinal/macular degeneration as seen in the two oldest TTD patients and shown in Figure 1, Case 3 is not recognized as characteristic of TTD, although it is characteristic of the related DNA repair disorder, Cockayne syndrome.⁴⁷⁻⁴⁸ This raises the question of whether photoreceptor dysfunction is a late manifestation of TTD. It is possible that as TTD patients have longer life spans, new manifestations of the disease will be recognized. 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 appear to have the developmental features like nystagmus and strabismus which 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 due to the small number of XP/TTD patients and also 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, while 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. XP/TTD patients should be closely monitored for degenerative/inflammatory symptoms since, unlike TTD patients, XP/TTD patients are at increased risk for cancer. Extra diligence is needed in order to screen for and treat dry eye and ocular surface disease, even in pediatric patients, with a goal of preventing serious complications in both TTD and XP/TTD individuals.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This study was supported by the Intramural Research Program of the National Institutes of Health, National Cancer Institute, Center for Cancer Research and the National Eye Institute.

The authors would like to thank Leslie Bilello, a summer student from Georgetown University School of Medicine, for her diligent work in assembling the non-ophthalmic clinical and laboratory data.

References

1. Kraemer KH, Patronas NJ, Schiffmann R, et al. Xeroderma pigmentosum, trichothiodystrophy and Cockayne syndrome: A complex genotype-phenotype relationship. *Neuroscience*. 2007; 145(4): 1388–96. [PubMed: 17276014]
2. Kleijer WJ, Laugel V, Berneburg M, et al. Incidence of DNA repair deficiency disorders in western Europe: Xeroderma pigmentosum, Cockayne syndrome and trichothiodystrophy. *DNA Repair*. 2008; 7(5):744–50. [PubMed: 18329345]
3. Liang C, Kraemer KH, Morris A, et al. Characterization of tiger tail banding and hair shaft abnormalities in trichothiodystrophy. *Journal of the American Academy of Dermatology*. 2005; 52(2):224–32. [PubMed: 15692466]
4. Liang C, Morris A, Schlucker S, et al. Structural and molecular hair abnormalities in trichothiodystrophy. *J Invest Dermatol*. 2006; 126(10):2210–6. [PubMed: 16728971]
5. Faghri S, Tamura D, Kraemer KH, Digiovanna JJ. Trichothiodystrophy: a systematic review of 112 published cases characterises a wide spectrum of clinical manifestations. *J Med Genet*. 2008; 45(10):609–21. [PubMed: 18603627]
6. Kraemer KH, Patronas NJ, Schiffmann R, et al. Xeroderma pigmentosum, trichothiodystrophy and Cockayne syndrome: a complex genotype-phenotype relationship. *Neuroscience*. 2007; 145(4): 1388–96. [PubMed: 17276014]
7. Kraemer KH, Lee MM, Scotto J. Xeroderma pigmentosum. Cutaneous, ocular, and neurologic abnormalities in 830 published cases. *Arch Dermatol*. 1987; 123(2):241–50. [PubMed: 3545087]

8. Kraemer KH, Lee MM, Scotto J. DNA repair protects against cutaneous and internal neoplasia: evidence from xeroderma pigmentosum. *Carcinogenesis*. 1984; 5(4):511–4. [PubMed: 6705149]
9. Kraemer KH. Sunlight and skin cancer: another link revealed. *Proc Natl Acad Sci U S A*. 1997; 94(1):11–4. [PubMed: 8990152]
10. Bradford PT, Goldstein AM, Tamura D, et al. Cancer and neurologic degeneration in xeroderma pigmentosum: long term follow-up characterises the role of DNA repair. *J Med Genet*. 2011; 48(3):168–76. [PubMed: 21097776]
11. Ruenger, T.; DiGiovanna, J.; Kraemer, K., editors. *Hereditary Diseases of genome instability and DNA repair*. 7. Vol. 2008. New York: McGraw Hill; 2008. p. 1311-25.
12. Weeda G, Eveno E, Donker I, et al. A mutation in the XPB/ERCC3 DNA repair transcription gene, associated with trichothiodystrophy. *Am J Hum Genet*. 1997; 60(2):320–9. [PubMed: 9012405]
13. Nakabayashi K, Amann D, Ren Y, et al. Identification of C7orf11 (TTDN1) gene mutations and genetic heterogeneity in nonphotosensitive trichothiodystrophy. *Am J Hum Genet*. 2005; 76(3):510–6. [PubMed: 15645389]
14. Stefanini M, Lagomarsini P, Arlett CF, et al. Xeroderma pigmentosum (complementation group D) mutation is present in patients affected by trichothiodystrophy with photosensitivity. *Hum Genet*. 1986; 74(2):107–12. [PubMed: 3770739]
15. Stefanini M, Vermeulen W, Weeda G, et al. A new nucleotide-excision-repair gene associated with the disorder trichothiodystrophy. *Am J Hum Genet*. 1993; 53(4):817–21. [PubMed: 8213812]
16. Broughton BC, Berneburg M, Fawcett H, et al. Two individuals with features of both xeroderma pigmentosum and trichothiodystrophy highlight the complexity of the clinical outcomes of mutations in the XPD gene. *Hum Mol Genet*. 2001; 10(22):2539–47. [PubMed: 11709541]
17. Bron AJ, Evans VE, Smith JA. Grading of corneal and conjunctival staining in the context of other dry eye tests. *Cornea*. 2003; 22(7):640–50. [PubMed: 14508260]
18. Jones LT. The lacrimal secretory system and its treatment. *Am J Ophthalmol*. 1966; 62(1):47–60. [PubMed: 5936526]
19. Tu, EY.; Rheinstrom, S.; Yanoff; Duker. *Ophthalmology*. 3. Edinburgh, England: Mosby/Elsevier; 2008. p. 326-7.
20. Boyle J, Ueda T, Oh KS, et al. Persistence of repair proteins at unrepaired DNA damage distinguishes diseases with ERCC2 (XPD) mutations: cancer-prone xeroderma pigmentosum vs. non-cancer-prone trichothiodystrophy. *Hum Mutat*. 2008; 29(10):1194–208. [PubMed: 18470933]
21. Moslehi R, Signore C, Tamura D, et al. Adverse effects of trichothiodystrophy DNA repair and transcription gene disorder on human fetal development. *Clin Genet*. 2009
22. Schlucker S, Liang C, Strehle KR, et al. Conformational differences in protein disulfide linkages between normal hair and hair from subjects with trichothiodystrophy: a quantitative analysis by Raman microspectroscopy. *Biopolymers*. 2006; 82(6):615–22. [PubMed: 16557500]
23. Gordon RA, Donzis PB. Refractive development of the human eye. *Arch Ophthalmol*. 1985; 103(6):785–9. [PubMed: 4004614]
24. Muller A, Doughty MJ, Wright L. Reassessment of the corneal endothelial cell organisation in children. *Br J Ophthalmol*. 2000; 84(7):692–6. [PubMed: 10873975]
25. Wilson RS, Roper-Hall MJ. Effect of age on the endothelial cell count in the normal eye. *Br J Ophthalmol*. 1982; 66(8):513–5. [PubMed: 7104267]
26. Carlson KH, Bourne WM, McLaren JW, Brubaker RF. Variations in human corneal endothelial cell morphology and permeability to fluorescein with age. *Exp Eye Res*. 1988; 47(1):27–41. [PubMed: 3409985]
27. Rao SKDO, Sen PRDOMS, Fogla RFRCS, et al. Corneal Endothelial Cell Density and Morphology in Normal Indian Eyes. *Cornea*. 2000; 19(6):820. [PubMed: 11095057]
28. Hussein MAW, Paysse EA, Bell NP, et al. Corneal thickness in children. *American Journal of Ophthalmology*. 2004; 138(5):744–8. [PubMed: 15531308]
29. Price FW Jr, Koller DL, Price MO. Central corneal pachymetry in patients undergoing laser in situ keratomileusis. *Ophthalmology*. 1999; 106(11):2216–20. [PubMed: 10571362]
30. Bhatti TR, Dott M, Yoon PW, et al. Descriptive epidemiology of infantile cataracts in metropolitan Atlanta, GA, 1968-1998. *Arch Pediatr Adolesc Med*. 2003; 157(4):341–7. [PubMed: 12695229]

31. SanGiovanni JP, Chew EY, Reed GF, et al. Infantile cataract in the collaborative perinatal project: prevalence and risk factors. *Arch Ophthalmol*. 2002; 120(11):1559–65. [PubMed: 12427072]
32. Sarvananthan N, Surendran M, Roberts EO, et al. The prevalence of nystagmus: the Leicestershire nystagmus survey. *Invest Ophthalmol Vis Sci*. 2009; 50(11):5201–6. [PubMed: 19458336]
33. Porto L, Weis R, Schulz C, et al. Tay's syndrome: MRI. *Neuroradiology*. 2000; 42(11):849–51. [PubMed: 11151695]
34. Itin PH, Sarasin A, Pittelkow MR. Trichothiodystrophy: update on the sulfur-deficient brittle hair syndromes. *J Am Acad Dermatol*. 2001; 44(6):891–920. quiz 1–4. [PubMed: 11369901]
35. Meyer-Puttlitz B, Junker E, Margolis RU, Margolis RK. Chondroitin sulfate proteoglycans in the developing central nervous system. II. Immunocytochemical localization of neurocan and phosphacan. *J Comp Neurol*. 1996; 366(1):44–54. [PubMed: 8866845]
36. Harreld JH, Smith EC, Prose NS, et al. Trichothiodystrophy with dysmyelination and central osteosclerosis. *AJNR Am J Neuroradiol*. 2010; 31(1):129–30. [PubMed: 20075106]
37. Stefanini M, Botta E, Lanzafame M, Orioli D. Trichothiodystrophy: From basic mechanisms to clinical implications. *DNA Repair*. 9(1):2–10. [PubMed: 19931493]
38. Cleaver JE, Thompson LH, Richardson AS, States JC. A summary of mutations in the UV-sensitive disorders: Xeroderma pigmentosum, Cockayne syndrome, and trichothiodystrophy. *Human Mutation*. 1999; 14(1):9–22. [PubMed: 10447254]
39. Cleaver JE. Splitting hairs--discovery of a new DNA repair and transcription factor for the human disease trichothiodystrophy. *DNA Repair (Amst)*. 2005; 4(2):285–7. [PubMed: 15590337]
40. Niedernhofer LJ. Nucleotide excision repair deficient mouse models and neurological disease. *DNA Repair (Amst)*. 2008; 7(7):1180–9. [PubMed: 18272436]
41. Dubaele S, De Santis LP, Bienstock RJ, et al. Basal Transcription Defect Discriminates between Xeroderma Pigmentosum and Trichothiodystrophy in XPD Patients. *Molecular Cell*. 2003; 11(6):1635–46. [PubMed: 12820975]
42. Ueda T, Compe E, Catez P, et al. Both XPD alleles contribute to the phenotype of compound heterozygote xeroderma pigmentosum patients. *J Exp Med*. 2009; 206(13):3031–46. [PubMed: 19934020]
43. de Boer J, de Wit J, van Steeg H, et al. A Mouse Model for the Basal Transcription/DNA Repair Syndrome Trichothiodystrophy. *Molecular Cell*. 1998; 1(7):981–90. [PubMed: 9651581]
44. de Boer J, Andressoo JO, de Wit J, et al. Premature aging in mice deficient in DNA repair and transcription. *Science*. 2002; 296(5571):1276–9. [PubMed: 11950998]
45. Brewitt H, Sistani F. Dry eye disease: the scale of the problem. *Surv Ophthalmol*. 2001; 45 (Suppl 2):S199–202. [PubMed: 11587143]
46. Lin P-Y, Tsai S-Y, Cheng C-Y, et al. Prevalence of dry eye among an elderly Chinese population in Taiwan: The Shihpai Eye Study. *Ophthalmology*. 2003; 110(6):1096–101. [PubMed: 12799232]
47. Dollfus H, Porto F, Caussade P, et al. Ocular manifestations in the inherited DNA repair disorders. *Surv Ophthalmol*. 2003; 48(1):107–22. [PubMed: 12559331]
48. Nance MA, Berry SA. Cockayne syndrome: review of 140 cases. *Am J Med Genet*. 1992; 42(1):68–84. [PubMed: 1308368]

Figure 1.

Figure 2.
 Visual abnormalities in TTD and XP/TTD patients.20

Figure 3.
Lens opacities and opacity morphology in TTD (Panel A) and XP/TTD (Panel B) patients.

Figure 4.
Quantification of ocular surface damage in TTD-affected patients via epithelial surface staining with fluorescein.