Trichothiodystrophy: a systematic review of 112 published cases characterises a wide spectrum of clinical manifestations

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ABSTRACT
Trichothiodystrophy (TTD) is a rare, autosomal recessive disease, characterised by brittle, sulphur deficient hair and multisystem abnormalities. A systematic literature review identified 112 patients ranging from 12 weeks to 47 years of age [median 6 years]. In addition to hair abnormalities, common features reported were developmental delay/intellectual impairment (86%), short stature (73%), ichthyosis (65%), abnormal characteristics at birth (55%), ocular abnormalities (51%), infections (46%), photosensitivity (42%), maternal pregnancy complications (28%) and defective DNA repair (37%). There was high mortality, with 19 deaths under the age of 10 years (13 infection related), which is 20-fold higher compared to the US population. The spectrum of clinical features varied from mild disease with only hair involvement to severe disease with profound developmental defects, recurrent infections and a high mortality at a young age. Abnormal characteristics at birth and pregnancy complications, unrecognised but common features of TTD, suggest a role for DNA repair genes in normal fetal development.

METHODS
We developed a standard Excel spreadsheet listing more than 200 clinical and laboratory characteristics. The search was restricted to published information in reports, and no effort was made to obtain unpublished data on the reported patients. This approach results in underreporting of characteristics not noted at the time of publication. However, when reported patients were identifiable as being the same individual in a subsequently reported paper, the data were consolidated. We searched PubMed/medline, web of science, and the references cited in retrieved articles. Search terms were trichothiodystrophy, TTD, Tay syndrome, Pollitt syndrome, PIBIDS, IBIDS, and BIDS.

The most definitive clinical criteria include microscopic examination of hair shafts for tiger tail banding and structural abnormalities and the analysis of hair shaft sulfur content. However, diagnostic criteria for TTD have evolved over the decades since these reports have been published. As a result, some reports included patients with convincing clinical features of TTD and a confirmed DNA repair abnormality, but the clinical workup did not include hair analysis. In order to standardise selection of patients, we chose criteria, which determined whether or not a case report was included. Inclusion criteria were based on having at least two of the four following clinical or laboratory abnormalities: (1) presence of brittle hair and/or hair shaft abnormalities; (2) tiger tail banding with polarised microscopy; (3) decreased sulfur or cystine content of hair; and (4) DNA repair abnormality. While any one of these features is highly suggestive of TTD, we required a minimum of two features to confirm the diagnosis. We chose criteria which we reasoned would allow us to capture reports of most patients with TTD and which were important in forming the basis for the various subtypes which have led to our current understanding of the disease. These criteria were developed in order to provide a uniform approach to inclusion of case reports with varied amounts of information and published over more than...
40 years and not to be used as criteria for clinical diagnosis of new patients.\(^3,4\)

In the case of reported siblings with similar clinical features, if one sibling qualified according to the above criteria, then both siblings were included. Patients described collectively as a group were not included when the clinical features could not be traced to individual patients. We did not include cases reported only in meeting proceedings, where the report was not indexed.

We considered intrauterine growth restriction (IUGR) as fetuses specified to have intrauterine growth retardation or intrauterine growth restriction in the report. If this was not stated we used the standard of <10th centile for gestational age at the time of birth based on the criteria specified in Lubchenco.\(^5\) Low birth weight was stated in the report or was defined as infants or who were <2500 g at birth.

**RESULTS**

**History of trichothiodystrophy**

Vera Price first proposed the name “trichothiodystrophy” in 1979 in the book Haar und Haarkrankheiten.\(^12\) In 1980, Price\(^1\) reported two patients with a wide range of clinical features, and associated the low sulfur (cystine) content of the hair with the alternating bright and dark banding with polarised microscopy, now known as tiger tailed banding. This work established specific hair findings as the unifying marker for this neurocutaneous symptom complex, which we now know as TTD.

Before the name TTD was coined in 1979, several papers were published describing cases that are today considered to be the earliest reports of TTD. Some of these papers, however, did not have sufficient hair analysis to meet the inclusion criteria that we chose for this paper.\(^6,7\) The earliest paper that we included in this study is from Pollitt\(^2\) in 1968, which described two severely affected siblings with brittle, sulphur deficient hair, as well as intellectual and growth retardation. This report led to the name Pollitt syndrome. In 1970, Brown\(^8\) described alternating birefringence in the hair viewed under polarised microscopy in a 4-year-old girl with brittle hair and normal intelligence. Tay,\(^9\) in 1971, reported three siblings in Singapore with brittle hair, mental deficiency and growth retardation, who also had non-bullous congenital ichthyosiform erythroderma. Tay suggested an autosomal recessive pattern of inheritance. Tay’s 1971 report did not, however, include sufficient hair analysis to meet the inclusion criteria for this analysis. In 1974, Jackson\(^10\) described decreased fertility and autosomal recessive inheritance in an Amish kindred with brittle hair, intellectual impairment and short stature. Two index cases were sufficiently described to be included in this analysis.

Jackson’s report led to the name “Amish brittle hair brain syndrome”. As a result of these similar clinical descriptions, the acronym BIDS (Brittle hair, Intellectual impairment, Decreased fertility and Short stature) was suggested in 1976.\(^15\)

Subsequently, the additional presence of ichthyosis led to the acronym IBIDS.\(^14,15\) Unlike some later cases of TTD with ichthyosis, it has been suggested that Tay syndrome specifically refers to the presence of congenital ichthyosis in addition to BIDS.\(^16\)

Two siblings from Sabinas, Mexico were reported in 1976 as having brittle hair, developmental delay, and normal stature. This report, in conjunction with a report\(^28\) of a group of 11 additional TTD cases from Sabinas, led to the name Sabinas syndrome in 1981, which refers to the presence of hair and nail abnormalities in association with mental retardation. The 1981 report\(^26\) was not included in this review because the patients were described as a general group and not individually.

The addition of photosensitivity to the acronym IBIDS (resulting in PIBIDS) was recommended in 1983 by Crovato.\(^17\) There was also some debate as to whether TTD was in fact a single entity, due to the various presentations of this neurocutaneous disorder.\(^18\) In 1988, Chapmann reported a patient and recommended the addition of skeletal abnormalities instead of photosensitivity to the acronym, resulting in SIBIDS.\(^19\) The patient described in this report did not meet our inclusion criteria for this analysis.

In 1985, Van Neste\(^20\) reported defective DNA excision repair in ultraviolet (UV) exposed lymphocytes from a TTD patient. The first such gene mutation was identified the next year,\(^21\) when cells from four patients with TTD were found to have cellular UV hypersensitivity, very low levels of unscheduled DNA synthesis, and characteristics of the XP-D complementation group. Despite some patients having the same gene defects seen in xeroderma pigmentosum (XPB and XPD), patients with TTD do not have an increased incidence of skin cancers.\(^2,3,11\) In 1993, patient TTD1BR was reported to have a new DNA repair complementation group, called TTD-A.\(^22\) A second patient with TTD-A has since been reported.\(^23\) The TTD-A gene (called GTF2H5) was identified in 2004.\(^35\) The recently discovered TTDN1 gene with unknown function was described in association with non-photosensitive patients.\(^7\)

To date, four genes have been identified as causing TTD: XPD, XPB, TTDA, and TTDN1.\(^7 32 33 36\) They contained data on 112 patients. The reported cases met at least two of the four entry criteria.\(^3 4 5\) The earliest paper that we included in this paper.\(^19–21\) The earliest paper that we included in this paper.\(^19–21\) The earliest paper that we included in this paper.\(^19–21\) The earliest paper that we included in this paper.\(^19–21\)
criteria, as follows: 96% (108 cases) had brittle hair or hair shaft abnormalities; there were 73% (82 cases) with tiger tail banding of the hair with polarised microscopy; 70% (78 cases) had decreased sulfur or cystine content of their hair; 37% (41 cases) had a DNA repair abnormality reported; four patients were included based on having brittle hair and a diagnosed sibling with TTD.85 90 98

Table 1 shows patient location and origin. As these data were only reported for 50 patients, the author’s location was used for the remaining 62 patients, assuming that the patients were from the same location as the author. Patients/authors were reported from 20 countries from all over the world, including Europe, North and South America, Africa, Asia and Australia. The greatest numbers of reports were from Italy (23%), the USA (16%), and the UK (16%).

Mode of inheritance, demographics, age, and survival
Gender was reported for 105 patients in this review, and consisted of 54 males (51%) and 51 females (49%). TTD is an autosomal recessive disease, and is therefore expected to have an equal distribution between males and females. There was one report65 suggesting the possibility of X-linked inheritance in a TTD patient with urea cycle dysfunction.

Age was reported for 110 of the 112 patients included in this study (fig 2). The age at last report ranged from 12 weeks to 47 years, with a median of 6 years. There was a median age of 6.5 years for males and 6 years for females. The ages ranged from 12 weeks to 44 years for males and 5 months to 47 years for females.

Twenty patients were reported as deceased, ranging in age from 12 weeks to 47 years (fig 2). All but one of these patients were under 10 years old and the median age at death was 5 years. The cause of death was pneumonia or other infection (especially sepsis) for 13 of these patients (fig 3).40 43 74 85 90 91 94 99 107 One additional patient died at 12 months after developing a fever, despite antibiotic use. The remaining patients died of drowning,62 cachexia and dehydration,63 respiratory failure,46 or a sudden or unexpected death.32 66 One patient who died suddenly had a history of frequent hospitalisations for respiratory and gastrointestinal illnesses, and thus may have also died from infectious complications. The oldest patient died at 47 years after presenting with generalised oedema and urinary retention, which progressed to coma. Cause of death was not reported for one patient.111

Kaplan–Meier analysis of the reported deaths indicated that at age 3 years there was 10.7% probability of reported death, and by age 9 years the probability had increased to 21.3%. This represents an approximately 20-fold higher mortality compared to the US general population. While we would expect that unusual and severe outcomes might be preferentially reported, this large number of deaths at a young age highlights the potential severity of TTD in the neonatal and early childhood period.

Recessively inherited disorders occur more commonly in populations where consanguinity is frequent. This literature review revealed 17% consanguinity, 49% non-consanguinity

Table 1 Distribution of patient location or origin for reported trichothiodystrophy patients (n = 112)

<table>
<thead>
<tr>
<th>Author location*</th>
<th>Patients No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Italy</td>
<td>27 (23)</td>
</tr>
<tr>
<td>USA</td>
<td>19 (16)</td>
</tr>
<tr>
<td>UK</td>
<td>18 (16)</td>
</tr>
<tr>
<td>France</td>
<td>12 (11)</td>
</tr>
<tr>
<td>Germany</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Canada</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Morocco</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Turkey</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Switzerland</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Other†</td>
<td>17 (15)</td>
</tr>
<tr>
<td>Total</td>
<td>112 (100)</td>
</tr>
</tbody>
</table>

*Author location used as surrogate for 62 patients whose location/origin was not reported.
†“Other” refers to one or two patients from each of the following countries: Australia, Belgium, Denmark, Mexico, Austria, India, Spain, Poland, Finland, Czechoslovakia, and the Netherlands.

Figure 2 Age at last report in trichothiodystrophy (TTD) patients (n = 110). The number in each bar indicates the number of patients reported in the indicated age group among the 90 reported living TTD patients. The shaded portion of the bar indicates the number of patients who died in the indicated age range among the 20 reported deceased TTD patients.

Figure 3 Infections reported (n = 51) in trichothiodystrophy patients. The number in each bar indicates the number of patients reported with the indicated type of infection among the 51 reported patients. A patient may have more than one reported infection. The shaded portion of the bar indicates the number of patients with the indicated type of infection as the cause of death among the 13 cases who died of infection. Aetiologies of infections included bacterial, fungal and viral. GI, gastrointestinal.

611

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and 36% unreported. None of the parents were reported to have TTD. Data were given on the presence or absence of siblings in 80 patients. Thirty-seven patients have a sibling who is also described as a patient in this review (represents 18 families for these 37 patients). The total number of siblings ranged from 0 to 9, with a median of 1.

Spectrum of clinical abnormalities reported in TTD patients

Figure 4 displays the common clinical features reported for each patient in the format of a clinical array. Each column represents one patient, with each clinical feature indicated as present, absent, or not mentioned in the report. The columns are grouped to facilitate identification of patients by gender with features of PIBI(D)S (28%), IBIDS (20%), BIDS (16%) and those that did not fit these categories (36%). Because decreased fertility (D) is age dependent and difficult to quantify from these reports, this feature was not included in this figure.

Skin findings

Seventy-nine per cent of the 112 reported TTD patients had skin abnormalities (table 2). Seven patients were reported to have normal skin and 16 reports did not include any skin descriptions. The most frequently reported skin finding was ichthyosis (65%) (table 2, fig 4). Of the 73 patients with ichthyosis, 27 had collodion membrane at birth. Ten patients were reported to have lamellar ichthyosis and six of these had collodion membrane at birth. Ichthyosis was seen in almost all age groups.
Six other patients with freckles were not reported to have skin XP (the XP/TTD complex), and one of them had a skin cancer. Although TTD is associated with the clinical finding of photosensitivity, there was not reported to have freckles. Other more rare skin findings include dry skin (21%), eczema (8%), and freckles (7%). Freckling is generally associated with XP and not TTD. Two of the TTD patients with freckles were reported to also have XP (the XP/TTD complex), and one of them had a skin cancer. Six other patients with freckles were not reported to have skin cancer. One additional TTD patient had a well differentiated, invasive squamous carcinoma on his nose, but was not reported to have freckles. Other more rare skin findings include two reports of haemangioma and three reports of cheilitis.

Nail abnormalities (table 4) were reported in 70 patients (63%). The most frequent nail abnormality reported was onychodystrophy in 41 patients (37%), which included dystrophy, dystrophic nails, thickening or yellow discoloration. Other common nail findings were brittle nails (14%), hypoplasia (13%), and koilonychia (12%).

Hair abnormalities were reported in all 112 patients (table 4, fig 4). They are a defining feature of TTD, and were part of the inclusion criteria. The most frequent hair findings were brittle hair or hair shaft abnormalities (96%), tiger tail banding (75%), and decreased sulfur or cystine (71%). Two patients with the XP/TTD complex were reported not to have brittle hair, but did have decreased sulfur, tiger tail banding with polarised microscopy, and XPD mutations. 8 Sparse hair (48%) and alopecia (39%) were also commonly reported. Eight patients had hair loss with fever or infection. Although TTD is usually associated with short hair (due to its brittle and easily breakable nature), there were also five reports of patients with long or normal length hair, including 1 XP/TTD patient.

Neurologic findings

Neurologic abnormalities were reported in 100 patients (table 5, fig 4). Developmental delay or intellectual impairment was reported in 86% of patients, and spanned all age groups. These usually presented as failing to achieve developmental milestones, such as sitting, walking, or talking, on time. Eleven of the 16 patients who were not reported to have developmental delay or intellectual impairment were <5 years old. Of the patients with developmental delay or intellectual impairment, 41 also had impaired motor control or psychomotor retardation. Seventeen of the patients with neurologic abnormalities were also described as having notably sociable or outgoing behaviour. This outgoing, sociable interaction is also a feature of patients with Cockayne syndrome (CS).

Intelligence quotient (IQ) was given for 21 patients. These tests included Terman–Merrill (three patients, IQ range 25–40), 59 Wechsler Intelligence Scale for Children (two patients, IQ range 45–89), 55–59 Stanford–Binet (three patients, IQ range 32–79) and not specified or other exam (such as Leiter scale and Ruth Griffiths test) (13 patients, IQ range 34–88). As a result, an average value could not be determined. Ichthyosis was closely linked to developmental delay since 67 (92%) of 73 patients reported with ichthyosis were also reported to have developmental delay.

Other abnormal neurologic findings described include microcephaly (50%), abnormal gait (26%), and increased deep tendon reflexes (13%). Audiologic examination was performed in 25 patients, and found normal hearing in 20 and sensorineural hearing loss in the other five. Nine patients were reported to have high pitched/rasp voice, and one patient had dysphonia. Six patients were reported to have attention deficit or hyperactivity, and three patients as autistic-like.

Neuroimaging abnormalities were given in 25% of patients. The most common findings were dysmyelination (14%), cerebellar atrophy (4%), and dilated ventricles (4%), which are similar to features found in CS. One patient had a progressive encephalopathy with ataxia and a gradual deterioration of previously acquired skills. In one patient, an attack of measles at age 4 years was reported to be followed by general disability, and according to his mother a regression of development, but subsequent to that had slow progress with no further degeneration. Another patient, however, did not change during a 50 year period. The electroencephalogram (EEG) findings were reported in 27 patients, of which 14 were normal and 13 were abnormal (four of these patients had seizures).
No gene defect was reported for these patients. The neurologic abnormalities seen in many TTD patients included delayed pubertal development. Additional genitourinary abnormalities included abnormal nails and one had dry skin, but none of these abnormalities in females included poor sexual maturation.

Table 4 Frequency of hair and nail features (n = 112) in reported trichothiodystrophy patients

<table>
<thead>
<tr>
<th>Patients</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hair feature</td>
<td>Brittle hair or hair shaft abnormality (63)</td>
</tr>
<tr>
<td>Brittle hair</td>
<td>112 (100)</td>
</tr>
<tr>
<td>Hair shaft abnormality</td>
<td>108 (96)</td>
</tr>
<tr>
<td>Tiger tail</td>
<td>98 (88)</td>
</tr>
<tr>
<td>Decreased sulfur or cystine</td>
<td>76 (68)</td>
</tr>
<tr>
<td>Sparse hair</td>
<td>79 (71)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>54 (48)</td>
</tr>
<tr>
<td>Nail feature</td>
<td>44 (39)</td>
</tr>
<tr>
<td>Hair loss with fever or infection</td>
<td>8 (7)</td>
</tr>
<tr>
<td>Dry hair</td>
<td>24 (21)</td>
</tr>
<tr>
<td>Fine hair</td>
<td>16 (14)</td>
</tr>
<tr>
<td>Slow growing hair</td>
<td>8 (7)</td>
</tr>
<tr>
<td>Long hair</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Normal nails; not reported</td>
<td>14 (13)</td>
</tr>
<tr>
<td>Total</td>
<td>112 (100)</td>
</tr>
</tbody>
</table>

*We collated reports of dysplasia, dystrophic nails, thickening and yellow discoloration as onychodystrophy.
†Slow growing nails (2 patients) and soft nails (1).

Five cases reported “mild TTD”, in which the patients had involvement of only hair, skin or nails. Two of these patients had abnormal nails and one had dry skin, but none had the neurologic abnormalities seen in many TTD patients. No gene defect was reported for these patients.

Facial dysmorphism was reported in 66% of patients (table 6). These included microcephaly (50%), large or protruding ears (30%), and micrognathia (29%). As in CS, there have been descriptions of TTD patients with aged (9%) or “bird-like” (30%) appearances (8%).

Growth abnormalities

Eighty-one per cent of patients were reported to have either low height and/or weight (which includes six patients described as having “growth retardation”) (fig 4). Sixty-one per cent of patients had both short stature and low weight or poor weight gain. An additional 13 patients had short stature with either normal or unreported weight. Six patients had normal height and weight.

Table 5 Frequency of neurologic features reported (n = 100) in trichothiodystrophy patients

<table>
<thead>
<tr>
<th>Patients</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developmental delay or intellectual impairment</td>
<td>96 (68)</td>
</tr>
<tr>
<td>Intellectual impairment</td>
<td>84 (57)</td>
</tr>
<tr>
<td>Developmental delay</td>
<td>76 (63)</td>
</tr>
<tr>
<td>Impaired motor control/psychomotor retardation</td>
<td>41 (37)</td>
</tr>
<tr>
<td>Sociable/outgoing behaviour</td>
<td>17 (15)</td>
</tr>
<tr>
<td>Clinical neurologic findings</td>
<td>84 (57)</td>
</tr>
<tr>
<td>Microcephaly</td>
<td>46 (50)</td>
</tr>
<tr>
<td>Abnormal gait/ataxia</td>
<td>29 (28)</td>
</tr>
<tr>
<td>Audiolingual exam performed: normal hearing; sensorineural hearing loss</td>
<td>20 (18); 5 (4)</td>
</tr>
<tr>
<td>Abnormal deep tendon reflex; increased; decreased</td>
<td>15 (13); 1 (1)</td>
</tr>
<tr>
<td>Electrophysiological evaluation: normal; abnormal</td>
<td>14 (13); 13 (12)</td>
</tr>
<tr>
<td>Abnormal muscle tone; increased; diminished</td>
<td>8 (7); 11 (10)</td>
</tr>
<tr>
<td>Nerve conduction velocity performed; normal; slow</td>
<td>9 (8); 3 (3)</td>
</tr>
<tr>
<td>Suggestive</td>
<td>11 (10)</td>
</tr>
<tr>
<td>Intention tremor</td>
<td>8 (7)</td>
</tr>
<tr>
<td>Seizure</td>
<td>7 (6)</td>
</tr>
<tr>
<td>Paresis/plegia</td>
<td>6 (5)</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Pyramidal signs</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Neuroimaging abnormality</td>
<td>26 (23)</td>
</tr>
<tr>
<td>Dysmyelination</td>
<td>16 (14)</td>
</tr>
<tr>
<td>Atrophy; cerebellar; cortical</td>
<td>5 (4); 3 (3)</td>
</tr>
<tr>
<td>Dilated ventricles</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Califications</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Other*</td>
<td>5 (4)</td>
</tr>
<tr>
<td>No abnormality reported</td>
<td>12 (11)</td>
</tr>
<tr>
<td>Total</td>
<td>112 (100)</td>
</tr>
</tbody>
</table>

*”Other” refers to partial agenesis of corpus callosum (1 patient), slight widening of subarachnoid spaces (1), thin corpus callosum (1), cerebral infarction (1), focal grey matter heterotopia and acute necrotising encephalopathy (1).

Gonadal dysgenesis

Sixteen patients (14%) had sexual/reproductive abnormalities reported (fig 4). Thirteen of these patients had hypogonadism of which two were females and nine had cryptorchidism. Two cases reported delayed pubertal development. Additional genitourinary abnormalities included poor sexual maturation and partial panhypopituitarism.

Pregnancy and birth characteristics

Thirty-four patients overall were reported to have parents in good health. When the TTD patients were born, the median reported maternal age was 25 years (based on 16 patients) and the median reported paternal age was 27 years (14 patients).

Two previously unrecognised findings not commonly associated with TTD are abnormal characteristics at birth (fig 5) and pregnancy complications (fig 6). Abnormal characteristics at birth were reported in 62 patients (55%) (fig 5). The most common finding was low birth weight (defined as birth weight <2500 g or specified as being low) which was reported in 41 patients (37%). In the USA for the year 2005 8.2% of infants were born with low birth weight (<2500 g). The actual birth weight was specified for 53 patients and ranged from 0.94–4 kg, with a median of 2.2 kg. This is much smaller than the median birth weight of 3.0–3.5 kg of infants born between 37–40 weeks gestation in the US general population. Five additional cases specified low birth weight without giving a value.

The length of gestation was reported in 58 patients and ranged from 25–42 weeks. The median gestational age for all reported cases was 37 weeks. Thirty-two of these patients (29%) were born prematurely (<37 weeks). Apgar scores were given for eight patients, two of which were at 5 min, indicating perinatal asphyxia. Twenty-nine of the infants (26%) had a colloidion membrane at birth. Twenty-seven of these also were reported to develop ichthyosis (six of which were lamellar ichthyosis). For the two patients with colloidion presentation not reported to have ichthyosis, one paper had very limited information about the patient and the other paper only reports that the patient later had dry scaly skin.

Thirteen patients had brittle or abnormal hair. There were 14 patients...
(13%) reported to have short birth length, and eight patients (7%) to have small birth head circumference. Values for birth length were given for 18 patients, ranging from 36–51 cm, with a median of 46 cm. Values for birth head circumference were given for 10 patients, ranging from 28–55 cm, with a median of 31 cm. Five additional patients were specified to have low birth head and birth circumference, but no value was given. Cryptorchidism was reported for nine (17%) of the boys. Congenital cataracts were reported for nine (17%) of the reported cases. This is also a feature of CS and is greatly elevated compared to the frequency identified in eight (7%) of the reported cases. This is also a feature of CS and is greatly elevated compared to the frequency identified in eight (7%) of the reported cases.

The course of pregnancy refers to the pregnancy of the patient’s mother, when she was pregnant with the reported TTD case (fig 6). There was no information reported for 52 (48%) of the pregnancies. This is not surprising since many of the reports were in the dermatologic literature. In 29 of the 112 cases (26%) the pregnancy was described as uncomplicated; however, eight of these neonates had abnormal characteristics at birth. Pregnancy complications were reported in 51 cases (28%) and the TTD neonates from these pregnancies all had abnormal characteristics at birth (fig 5). The reports contained information on gestational age at birth and birth weight of the newborns. Twenty-three patients (21%) had IUGR stated in the report or alternatively, which we determined as low weight for gestational age provided. 32 90 97–99

In addition to the patients described in this review, five additional patients were diagnosed with TTD in utero by prenatal diagnostic methods. Prenatal diagnosis was reported in families with a previous child diagnosed with TTD. None of the pregnancies with the affected fetuses went to term. Methods of prenatal diagnosis reported included fetal hair biopsy and DNA repair measurements. 90 98 100 104 118 One study measured UV induced unscheduled DNA synthesis (UDS) in cultivated amniotic fluid cells at 17 weeks gestation. After a therapeutic abortion, the diagnosis was confirmed by severe DNA excision repair defect in fetal skin fibroblasts. While UV induced UDS cannot differentiate among different DNA repair abnormalities, this family had a previous child with diagnosed TTD. During a later pregnancy in the same reported family, prenatal diagnosis was made by chorionic villus sampling at 9 weeks gestation and finding quantitatively normal DNA excision repair. 90

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Ocular abnormalities and infection

Ocular abnormalities were reported in 51% of patients (fig 7). Thirty-two of these patients had cataractas, of which 20 were specified as bilateral and eight as congenital (fig 5). The median
The age of reported patients with cataracts was 7.5 years, and all but one patient were \( < 25 \) years old. Three patients were reported to have surgery to correct their cataracts. Other ocular findings include nystagmus (14%) and strabismus (10%).

Infections were described in 51 patients (fig 3). Fourteen patients were described as having infections (especially respiratory infections) within the first year of life, including five in the neonatal period. Forty patients (36%) had recurrent infections. Reported infections were most commonly respiratory (29%), gastrointestinal (13%), and ear (11%). Recurrent urinary infections were reported in five patients, all starting younger than age 5 years. Aetiologies of infections included bacterial, fungal and viral. Two patients were reported to have hypogammaglobulinaemia, for which they both received intravenous immunoglobulin. One patient was reported to receive prophylactic trimethoprim–sulfamethoxazole, but was also the only patient reported to have combined immunodeficiency. Three patients with recurrent infections in childhood were reported in adolescence to no longer be prone to infections. In addition, patients were reported as having asthma or allergies (five patients) and hypergammaglobulinaemia (two patients). Thirteen patients died of infection, which mostly consisted of respiratory infection or sepsis. The immune system of one patient with combined immunodeficiency was studied in two papers. One found the patient to have defective dendritic cell maturation and the second found decreased T cell regulation repertoire complexity suggesting a possible T cell regulation abnormality.

**Skeletal and dental abnormalities**

Skeletal and dental findings are listed in table 7. All except one of these 46 patients also had neurologic abnormalities. Radiographic bone abnormalities were reported in 38% patients. The most common findings were osteosclerosis (14%), delayed bone age (13%), and osteopenia (9%). When specified, the osteosclerosis was usually axial, and the osteopenia distal.

**Table 7** Skeletal and dental abnormalities (n = 46) in reported trichothiodystrophy patients

| Patients No. (%) | Radiographic bone abnormality 43 (38) | Osteosclerosis* 16 (14) | Delayed bone age 14 (13) | Osteopenia 10 (9) | Kyphosis 7 (6) | Coxa valga 4 (4) | Other† 8 (7) | Joint abnormality 15 (13) | Contractures† 8 (7) | Joint dislocation 4 (4) | Other§ 7 (6) | Tooth abnormality 23 (21) | Caries 21 (19) | Enamel hypoplasia 4 (4) | Other* 4 (4) | Normal teeth 18 (16) | Normal or no skeletal or tooth abnormality reported 66 (59) | Total 112 (100) |

*4 patients had both osteosclerosis and osteopenia.
†Pectus excavatum (3 patients), scoliosis (2), halux valgus (2), bilateral hammer toe deformities (2).
‡Contractures of hips and knees (3), and hands (3).
§Clinodactyly of 5th finger, short limbs, tapering fingers, syndactyly, joint hypermobility.
* Dystrophic teeth (2) and hypoplastic teeth (enamel not specified) (2).
patients had both osteosclerosis and osteopenia.\textsuperscript{17} 51 63 106 Seven additional patients were reported as having normal bone age, and no radiographic bone abnormalities.

The most common joint abnormalities were contractures (7\%) and joint dislocation (4\%). Contractures were of hip and knees (three patients)\textsuperscript{66 71 105} and hands (three patients).\textsuperscript{56 71 105} Subluxation was of the hip (three patients)\textsuperscript{51 58 114} and toes (one patient).\textsuperscript{26} The most common tooth abnormality was caries (19\%). Eleven of these 21 patients had severe caries.\textsuperscript{13 17 22 47 57 58 69 72 76 77 99}

Cardiac and hepatic abnormalities

In addition, cardiac defects were noted in eight patients and included cardiomyopathy, pulmonic stenosis and ventricular septal defect.\textsuperscript{22 74 75 63 105} Three additional patients were reported to have a murmur, but no cardiac defect was identified.\textsuperscript{36 63 72}

Two patients\textsuperscript{85} were reported to have multiple liver haemangioendotheliomas.

Haematologic abnormalities

Haematologic abnormalities were reported in 24 patients (table 8). These findings consisted of anaemia (12\%), low mean corpuscular volume (MCV) (9\%), neutropenia (9\%), and elevated haemoglobin A2 (7\%). Two cases\textsuperscript{76 78} of anaemia were due to iron deficiency. Eight TTD patients\textsuperscript{111} with XPD mutations were reported as having “haematologic features of beta-thalassaemia trait, and reduced levels of beta-globin synthesis and beta-globin mRNA”. The cause of anaemia in the remaining three patients\textsuperscript{50 74 75} was Coombs positive haemolytic anaemia, sideroblastic anaemia, and unspecified. Twenty-one per cent of patients had either a normal complete blood cell count (CBC) or routine blood analysis.

DNA repair abnormalities and gene defects

DNA repair abnormalities or gene defects were reported in 41 patients. Thirty-two patients were reported as having mutations in XPD, two in XPB and two in TTDN1 (table 5, fig 4). Five patients,\textsuperscript{79 80 106 108} were reported to have cellular UV hypersensitivity, with no specific gene defect determined. Six additional patients\textsuperscript{2} were reported as having mutations in the newly discovered TTDN1 gene with unknown function. Eleven patients were reported to not have a DNA repair abnormality.\textsuperscript{57 58 67 72 75 75 96 107} Of the 32 patients with mutations in XPD, 27 were reported to have photosensitivity. While most of the cases with a DNA repair abnormality were from patients with photosensitivity, this might be due to ascertainment bias in that photosensitivity is a reason to suspect a DNA repair abnormality. Genotype–phenotype correlation is best studied on a group of patients who are studied in the same manner. It may not be valid to compare phenotypes from reports with different extents of clinical information provided.

**DISCUSSION**

Birth abnormalities, pregnancy complications and increased mortality in TTD

TTD has substantial morbidity and mortality in the neonatal and childhood years. There was an approximately 20-fold increase in the probability of death in reported TTD children \(<10\) years of age compared to the US general population. This increased mortality in TTD is neither widely recognised nor well understood. However, there may be bias in reporting more severe cases, thereby suggesting a worse prognosis for TTD.

This study documents the wide spectrum of severity within TTD. The high frequencies of reported abnormal characteristics at birth and pregnancy abnormalities suggest that childhood and neonatal morbidity can begin in the prenatal period. Fifty-three per cent of reported patients had abnormal characteristics at birth and 28\% of pregnancies were abnormal. The relatively young median parental ages (maternal: 25 years; paternal: 27 years) at birth of TTD patients indicates that advanced parental age was a not a factor in the frequency of pregnancy abnormalities or in the development of TTD. This surprisingly large number of reports of pregnancy abnormalities suggests that the pathophysiology of TTD involves a developmental abnormality directly affecting the pregnancy. This adds a complex dimension to understanding the clinical phenotype of TTD. Some of the clinical features may be due to the effect of TTD on the affected patient; in addition, some of the clinical disease may be secondary to compromise resulting from maternal pregnancy abnormality.

Different mutations in the XPD or XPB genes can lead to TTD, XP or a clinical overlap of both, the XP/TTD complex. Genes that are defective in TTD, XPB, XPD and TTDN1, are components of the basal transcription factor, TFIIH, as well as the nucleotide excision repair pathway.\textsuperscript{2 6 120 121} A current theory suggests that mutations in these genes in patients with XP predominantly impede DNA repair, while mutations in the same genes in TTD patients predominantly affect transcription.\textsuperscript{1 122} Thus, XP is a disease of progressive sunlight induced degeneration of the skin.\textsuperscript{2 121} In contrast to XP, TTD is primarily a disorder of development which may be the consequence of transcriptional anomalies resulting from different defects in the same DNA repair genes.\textsuperscript{11 120} Thus the finding of elevated haemoglobin A2 and low red blood cell MCV that mimic thalassaemia without a defect in a haemoglobin gene was interpreted as a transcription defect in TTD patients with mutations in the XPD gene.\textsuperscript{111} The other developmental features of TTD may represent abnormalities in transcription of genes that are essential for normal pregnancy and fetal development. The high frequency of reported fetal abnormalities and maternal pregnancy complications in mothers of TTD patients suggests a role of the DNA repair/transcription genes in normal pregnancy and fetal development. CS, another rare genetic disease with defective DNA repair, shares some of the same clinical features as TTD including photosensitivity, short stature, development delay, IUGR, dysmyelination of the brain, and an outgoing social personality.\textsuperscript{2 122} CS is caused by CSA and CSB genes, which have a role in repair of actively transcribing genes.

**Classification**

Trichothiodystrophy is a rare multisystem disorder with a wide spectrum of clinical involvement. We were able to identify only
112 patients reported in the world’s literature who fit our criteria for inclusion into this study of TTD reports. These criteria allowed us to capture a large number of TTD cases from the literature where limited information was available on each patient. These criteria were not intended to be used for diagnosis of new patients where more extensive evaluation should be possible. The goal of this study was to assess the frequency of clinical features in order to better understand the spectrum of manifestations of TTD. The most common clinical features were brittle hair or hair shaft abnormalities (96%), intellectual impairment or developmental delay (86%), short stature (75%) and ichthyosis (65%). While it is useful to look at the frequency of different features across the broad population of patients, it is also important to know how often a set of clinical features occurs together (fig 4). Sixty-four per cent of patients had the clinical features to fit into the category of either PIBI(D)S, IBI(D)S or BI(D)S; however, the others (36%) did not. Almost all of the patients who had clinical features sufficient to fit into these designations had additional clinical manifestations not specified by the acronyms. In addition, even the broadest acronym, PIBIDS, does not include several major clinical features found to be more common than photosensitivity (42%) and decreased fertility, including abnormal characteristics at birth (58%), ocular abnormalities (51%), and infections (46%), which should be considered major clinical features of TTD. So these acronyms are poor descriptors of TTD patients’ clinical manifestations.

Van Neste suggested a classification system in 1989 based on increasing severity beginning with only hair defects. While this schema takes into account additional features of TTD beyond PIBIDS, it intrinsically implies a sequential pattern to the progression of disease severity. As seen in fig 4, not all patients fit into a uniform sequence. For example, although the Van Neste classification lists photosensitivity as a more severe case of TTD, some patients may have photosensitivity without ichthyosis or short stature. Van Neste’s classification was later expanded to include more features, such as chronic neutropenia or immunoglobulin deficiency, severe IUGR and basal ganglia calcifications.

Multiple reported abnormalities in TTD
Surveys of reported clinical features have several weaknesses. These include ascertainment bias, leading to the reporting of patients who are more interesting and severe and the under-representation of more mildly affected patients. Reports vary with respect to thoroughness of clinical evaluation, leading to the probable underreporting of many features that may not have been evaluated. This suggests that the prevalence of many clinical features summarised here may under-represent their true frequencies. In addition, since we would expect milder phenotypes to be less likely to be reported, TTD may be much more common than the number of reported cases implies.

Neurologic abnormalities (86%) were frequently reported in TTD cases, manifesting most commonly as developmental delay, intellectual impairment, microcephaly, impaired motor control or psychomotor retardation. This high frequency may be an underestimate, since 11 of the 16 patients who were not reported to have developmental delay or intellectual impairment were <5 years old. In general, these findings were not found to be deteriorations in neurologic status, but rather were more suggestive of a chronic non-progressive condition. Two exceptions were reported. One patient had progressive encephalopathy and ataxia and a second patient had developmental regression after an episode of measles. This further supports an early developmental abnormality being a key factor leading to TTD neurologic involvement. In contrast, about 20% of XP patients, who have different mutations in many of the same genes as TTD patients, have neurological abnormalities which manifest as progressive degeneration. Recent studies have looked at the relationship between DNA repair defects and impaired neurologic development. The presence of ichthyosis may be a marker of a systemic developmental abnormality since more than 90% of the TTD patients reported to have ichthyosis also have developmental delay.

Infections were commonly (46%) reported and were often recurrent (56%). Sixty-five per cent of the 20 reported deaths were related to infections. This frequency and severity of infections suggests that the pathophysiology of TTD includes an immunologic abnormality. However, no consistent laboratory abnormality in the immune system has been identified in TTD patients.

TTD involves many medical specialties
Effective management of the multisystem abnormalities of TTD involves a multidisciplinary approach involving many medical specialties. Seventy-seven per cent of patients were <14 years old, and thus it is important for paediatricians to be aware of this disease. Sixty-three per cent of patients had abnormal characteristics at birth, signifying importance for the neonatologist. Twenty-three per cent were from abnormal pregnancies, which would bring these mothers to the attention of obstetricians. Twenty-nine per cent of patients had cataracts (median age 7.5 years), including eight with congenital cataracts, which, if undetected, can lead to vision impairment and interference with early childhood development and learning. The oldest TTD patient in the literature (47 years) was first seen by those researchers at age 17 with pruritis and urticaria. She also had symptoms in her first year of life, consisting of collodion baby, congenital hip subluxation, and psychomotor developmental delay.

These patients may present to specialists in obstetrics, neonatology, paediatrics, ophthalmology, neurology, orthopaedics, internal medicine, rehabilitation medicine, immunology, infectious disease, haematology, genetics, or radiology in addition to dermatology. If properly aware, any of these specialists can make the diagnosis. Since prenatal diagnosis is possible, establishment of a diagnosis can identify the risk to future pregnancies. It is surprising that a disorder with such a broad range of multisystem abnormalities can be unified by the simple finding of tiger tailed banding under polarised microscopy. This very simple and inexpensive test can reliably establish a diagnosis in both the healthy adult with learning disabilities and the severely ill, collodion baby in the neonatal intensive care unit. This review characterises the wide spectrum of TTD and reinforces the importance of this simple screening test for patients with these multisystem findings. Greater recognition among a broad range of specialists can facilitate early diagnosis and treatment and identification of risk to future pregnancies.

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REFERENCES


Review


124. **Faghri S, DiGiovanna JJ, Tamura D, Kraemer KH.** Trichothiodystrophy includes a broad spectrum of multisystem abnormalities and may have a high mortality at a young age. *J Invest Dermatol* April 2007;127(Suppl 1):S106.