

Trichothiodystrophy

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Abstract

Trichothiodystrophy (TTD) is a rare autosomal recessive genetic disorder characterized by abnormal synthesis of the sulphur containing keratins and consequently hair dysplasia, associated with numerous symptoms affecting mainly organs derived from the neuroectoderm. This phenotypic aspect is due to mutations in the DNA-dependent ATPase/helicase subunit of TFIIH, XPB and XPD. Abnormalities in excision repair of ultraviolet (UV)-damaged DNA are recognized in about half of the patients. The clinical appearance is characterized by brittle and fragile hair, congenital ichthyosis, nail and dental dysplasias, cataract, progeria-like face, growth and mental retardation. The abnormalities are usually obvious at birth, with variable clinical expression.

*The variants of TTD, depending on their different associations, are known by the initials **BIDS, IBIDS, PIBIDS, SIBIDS, ONMRS**, as well as the eponyms of the Pollit, Tay, Sabinas syndromes or Amish brittle hair. The exact prevalence of TTD is unknown, but appears to be rather uncommon. About 20 cases of PIBI(D)S have been reported in the literature. Up to 1991, clinical data of 15 cases with IBIDS were published. Prenatal diagnostic of TTD is available. There is no specific treatment.*

Keywords

Brittle hair, photosensitivity, ichthyosis, BIDS, IBIDS, PIBIDS, SIBIDS, ONMRS, Tay-syndrome

Definition

Trichothiodystrophy (TTD) is a group of rare autosomal recessive disorders with heterogenic clinical appearance characterized by brittle and fragile hair, congenital ichthyosis, progeria-like face, physical and mental retardation and remarkable signs of premature ageing.

It was first described in 1971 by Tay (1), while just in 1976 Baden (2) proposed the acronym **BIDS** for describing the association between **Brittle hair**, **Intellectual impairment**, **Decreased fertility** and **Short stature**.

In 1980 Price *et al* (3) related brittle hair to sulphur-deficient hair, which gives an abnormal hair pattern under polarizing microscopy (tiger

tail pattern). They named it Trichothiodystrophy, noticing also an increased **Photosensitivity** and **Ichthyosis** in these patients (**PIBIDS**). In 1984 Happle (4) added the presence of trichoschisis and in 1988 Chapman (5) described osteosclerotic anomalies too. The variants of TTD, depending on their different associations, are the syndromes known by the initials **BIDS, IBIDS, PIBIDS, SIBIDS, ONMRS**, as well as the eponyms of the Pollit, Tay, Sabinas syndromes or Amish brittle hair (6-11). The different clinical possibilities have been grouped in Table 1. Many acronyms and eponyms have been created to describe sulphur-deficient brittle hair associated with neuroectodermal abnormalities, leading to

confusion (see Table 2). However, the exact relationship between the molecular characteristics and the clinical spectrum of PIBI(D)S remains to be fully elucidated.

Table 1: Different clinical variants of TTD

Types of TTD	Clinical variants
Type A	Isolated congenital hair defect
Type B	Type A + nail dystrophy
Type C	Type B + neonatal retardation
Type D	Type C + growth retardation
Type D1	Type D + decreased fertility
Type E	Type D + ichthyosis
Type F	Type E + light sensitivity

Table 2: Clinical markers of TTD syndromes

Clinical markers of a mental and growth complex syndrome characterized by:	TTD retardation + nail dystrophy + lamellar ichthyosis + ocular dysplasia + dental caries + decreased fertility
BIDS Syndrome	Brittle hair + Impaired intelligence + Decreased fertility + Short stature
IBIDS Syndrome	Ichthyosis + BIDS
PIBIDS Syndrome	Photosensitivity + IBIDS
SIBIDS Syndrome	Osteosclerosis + IBIDS
ONMR	Onyco-tricho-dysplasia + Neutropenia + Mental Retardation

Epidemiology

The exact prevalence of TTD is unknown, but appear to be rather uncommon. About 20 cases of PIBI(D)S have been reported in the literature. Up to 1991, clinical data of 15 cases with IBIDS were published.

Etiology

The photosensitivity in patients with TTD may be related to a defective repair of DNA damage. PIBIDS appears to be linked to *XPD*, as revealed by defective DNA excision repair after UV exposure. Genetic evidence shows that the brittle phenotype is due to transcriptional defects in nucleotide excision repair (**NER**) pathway as a consequence of mutations in *XPD*, *XPB* or *TTDA*, three genes that are all related to TFIIH (transcription factor 2H), the multiprotein complex involved in NER and transcription (13). Mutations in some of the TFIIH components in humans may produce three hereditary disorders: [xeroderma pigmentosum](#) (XP), [Cockayne syndrome](#) (CS), and trichothiodystrophy (TTD)

(17,48,49). In addition, defects in TFIIH may have a role in the generation of cancer. UV-induced unscheduled DNA synthesis (UDS) can't be distinguished between the various diseases with an excision repair defect. In contrast to patients with XP, however, no increase of skin cancers in patients with TTD has been observed. TFIIH is a multisubunit protein complex involved in RNA polymerase II transcription and nucleotide excision repair, which removes a wide variety of DNA lesions, including UV-induced photoproducts (14). NER has broad substrate specificity and is capable of removing several classes of lesions to the DNA including those that accumulate upon exposure to UV radiation. Loosing this activity gives rise to characteristic sensitivities to UV that, in humans, is manifested as a greatly elevated sensitivity to exposure to the sun. It plays an important role in the removal of such diverse lesions as UV light induced photoproducts as well as chemically induced bulky adducts, cross-links and oxidized bases. It repairs many types of lesions that cause a distortion of the DNA helical structure, including pyrimidine dimers. It has also been reported that TFIIH may participate in base excision repair (BER), when DNA suffers oxidative damage. TFIIH is formed by the DNA helicases *XPB* and *XPD* (15).

Clinical description

Children have congenital ichthyosis and sparse, short, uneven, fragile and brittle scalp hair (Fig. 1), eyebrows and eyelashes, which is also associated with a characteristic facial aspect: receding chin, protruding ears, microdolichocephaly with a complacent or receptive attitude.



Fig.1 Child with congenital ichthyosis and sparse, short, uneven, fragile and brittle scalp hair

It's often associated with mental retardation, raspy voice, growth retardation, urological malformations, increased proneness to infections, hypogonadism, nail dystrophy and, occasionally, with photosensitivity and slightly aged appearance (21,24,31-40). The abnormalities are usually obvious at birth and the clinical expression is variable. Ocular abnormalities like strabismus and high myopia are common but most frequent are bilateral cataracts (41).

Photosensitivity

It can be extreme in patients affected by PIBIDS, in particular for UVB and UVA, because of the defective DNA excision-repair system. In fact, only a few minutes outdoors or behind a glass pane are able to induce a severe burn. Interestingly, the photosensitivity seems to diminish with age, and it does not affect patients with congenital ichthyosis, but only those with ichthyosis that develops later in infancy (12).

Ichthyosis

It has been frequently reported in patients with TTD, especially on the trunk, in lamellar type (8). Ultrastructural studies showed reduction and irregularly arranged bundles of tonofilaments related to a generalized anomaly in high sulphur proteins, reflecting abnormal synthesis of the sulphur containing keratins (16).

Skin

The follicular keratosis may be a sign of ichthyosis. Itching, eczema, freckles, telangiectasias, actinic cheilitis have also been found (17-19).

Brittle cystine-deficient hair

The cystine deficiency is the biochemical marker of TTD. Interestingly, hair show biochemical differences also among them as reported by Reborá and Crovato, who found different levels of amino acids, in particular in the phenylalanine content, that seems to vary depending on the photosensitivity (17).

Impaired intelligence

At first examination patients appear to be promptly and sociable and they smile and talk easily. A more detailed examination reveals that their intelligence is impaired. Some studies showed decreased IQ in patient with TTD and PIBI(D)S (17,19,20). Mental retardation and delayed or arrested physical maturation occur frequently in these patients (21). The patient with TTD can present central nervous system alterations such as dysarthria, spasticity, diplegia and quadriplegia, hemiparesis or tetraparesis,

cerebellar deficiency, ataxia, pyramidal signs, intention tremor, hyper-reflexia, impaired motor co-ordination, absence of deep tendon reflexes, peripheral neuropathy, diminished muscle tone, neurosensory hearing impairment, jerky eye movements, nystagmus and seizures which are among the reported neurological signs in these patients. In addition, lethargy, irritability and unusual sociable behaviour have been reported (21).

Decreased fertility

Decreased fertility and gonadal defects have been found in association with TTD (1,3,4,19,21,22).

It has been postulated that the sulphur deficiency and subsequent decreased disulphide bound formation that leads to brittle hair, account at least in part for impaired fertility, in that the normal structure of mature spermatozoa incorporates disulphide bonds into the nucleus and tail (3,21). Hypoplasia of the genitalia has been described in TTD and cryptorchidism may be associated (4,5,22-25).

Delayed menarche, absent breast tissue, and oligomenorrhoea in patients with childish external genitalia, has been described in females affected by TTD (22,26). Lucky et al (27) and Meynadier et al (20) described testicular failure in patients who had PIBIDS.

Later Przebdorski et al (22) reported an abnormal gonadotrophic response to luteinizing hormone-releasing hormone in a sibship with TTD; the boy had delayed puberty, whereas his two sisters had hypergonadotrophic hypogonadism with ovarian failure.

Jackson et al (28) described an Amish Kindred in northern Indiana in which infertility was associated with TTD, intellectual impairment and short stature. Brittle hair and relative infertility have also been reported in Sabina's syndrome in Mexico (29).

Osteosclerosis

Radiographs revealed often marked osteosclerosis of the vertebral column and cranium related to a younger skeletal age (30).

Short stature

Growth retardation and alteration in body proportions have been frequently found. In particular progeria, polythelia, microcephaly, thin beaked nose, ear malformations, hemiatrophia faciale, small mouth, macrochelia and cranial dysplasia have been described (22).

Diagnostic methods

The tiger-tail appearance of affected hair (Fig. 1), characterized by bright and dark bands along the hair shaft under polarized light microscopy

and low sulphur content, is a clinical marker for a neuroectodermal abnormality (42). In fact, the amino acid analysis (43) shows a low sulphur content in the hair, which corresponds to severe fractures of the cuticle and cortical part of the hair shaft and is associated with several disorders such as mental and physical retardation, follicular keratosis, neutropenia, erythroderma, hypohidrosis, ocular dysplasia, dental caries, congenital heart disease and cryptorchidism (1,3,10,21,41,44-47). This is a biochemical marker which shows the importance of high sulphur content protein for the normal functionality of the ectodermal derived organs. In children showing brittle and fragile hair and/or mental retardation the following examinations should be performed:

Light microscopy

Hair shafts show undulating contour and folding along their axis with typical trichoschisis with clean transverse fractures (59).

Polarized light

Alternation of bright and dark bands confirming the typical striped "tiger-tail pattern" (Fig. II), that changes when the filters are moved. The mechanism causing the tiger tail phenomenon in TTD (alternating light and dark banding of hair shafts when examined with polarized light) has yet to be explained with certainty.

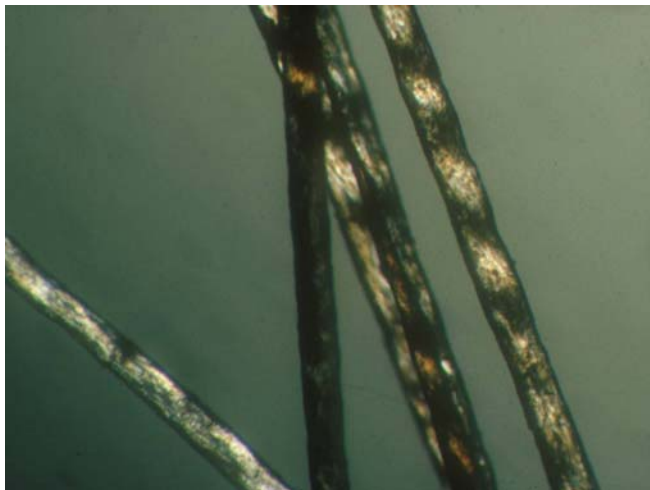


Fig.II Typical striped "tiger-tail pattern" in thiotrichodystrophy (in polarized light)

However, it was proposed a simple and easily tested hypothesis to explain its striking aspect. Although the hair shafts obtained from patients with TTD were fairly straight, the cortical hair fibers were not. These fibers undulate up and down (or back and forth), a feature that is easily observed because of melanin granules embedded in each fiber. Normal hair shafts do not exhibit the phenomenon because the hair

fibers are straight and parallel to the long axis of the hair. It is the regular undulation of fibers that changes the optical properties of the hair shafts and causes a predictable banding when the shafts are examined by polarized light (60,61).

Scanning electron microscopy

Completely flat hair with trichoschisis (Fig. III) Fractures and a surface furrowed by longitudinal crests all along the hair shaft, as well as cuticular weathering.

Severe cuticular and secondary cortical degeneration along almost the entire hair shaft, with reduced or absent cuticular pattern and abnormal ridging and fluting (62,63).

Fig.III Completely flat hair with trichoschisis (in scanning electron microscopy)

X-Ray microanalysis

Severe sulphur deficiency (64)



Chromatography of hair amino acids

Decreased amount of sulphur-containing amino acids such as cysteine and proline, threonine (64).

Hair characteristics are, in fact, key diagnostic factors in this genohypotrichosis.

Prenatal diagnosis

In patients affected by TTD, photosensitivity may be present and the molecular excision repair defect seems to be similar to [xeroderma pigmentosum](#) (XP) group D (XPD) (50-52). Patients without photosensitivity showed an excision repair of cultivated cells, ranging from normal to severely altered. Lehamann et al (53) revealed patients with a normal response, with a response similar to XPD and with a 50% excision repair defect. Such heterogeneity has not been described in PIBIDS. The biological diagnosis of an excision repair defect, with UV-induced UDS may be performed for PIBIDS detection in families where a PIBIDS index case

is viable and shows a clear defect after UV irradiation (54). The evaluation of the expression of the DNA excision repair mechanism in the chorionic villi is quite suitable for prenatal diagnosis of PIBI(D)S syndrome at the first trimester (55-56). Prenatal diagnosis can be also made by following UV-induced UDS on trophoblast biopsy cells around the 14th gestation week. This early detection allows possible confirmation of the result either by measurement of UDS in cells from amniotic fluid or by fetal hair biopsy for TTD (50). Quintero et al described a prenatal diagnosis in utero using endoscopically guided fetal eyebrow biopsy in the second trimester (57).

Brusco et al demonstrated that the tiger-tail pattern of the hair shaft in TTD may not be evident at birth, but can appear some months later. For this reason hair examination should be repeated more often in suspected patients (58).

Management

Specific treatment of TTD is not available. Management of children with TTD is symptomatic. Family psychological and social support is needed. Children should be educated to avoid sun-exposure and any trauma by aggressive combing or hair dressing because of the particularly weakness of hair shaft.

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Table III : Trichothiodystrophy hair aminoacid analysis

	N.V.	A	B	C	D	E	F	G	H	I	J
ASP	4.9	6.1	7.5	4.6	7.7	8.2	8.5	7.9	8.5	6.1	6.3
THR	6.8	8.5	5.4	6.7	5.3	5.5	3.5	5.3	4.4	4.5	6.6
SER	11.8	10.1	8.9	10.1	5.3	10.6	8.9	9.2	8.1	8.2	9.6
GLU	11.4	15.3	15.5	13.9	9.4	15.2	15	16.4	16.8	14.1	12.9
PRO	8.4	8.9	6	7.9	6.3	5.8	4.4	4	4.6	8.3	6.8
GLY	6.4	6.5	6.2	6.8	6.8	6.7	7	6.7	6.6	6.2	6.3
ALA	4.5	4.6	6.4	5.2	6.3	7	6.5	6.7	7.4	7.2	5.6
CYS	17.8	11.2	10.2	13.6	8.3	7.5	12.4	9.9	8.5	14.1	14.1
VAL	5.8	5.3	5.5	5	4.1	6.8	6.5	6.3	6.1	6.5	5.6
MET	0.6	0.3	0.5	0.2	0.7	0.5	-	-	0.1	-	0.3
ISO	2.6	2.4	3.6	2.4	3.5	1.6	3.3	3.4	3.6	3.5	3.3
LEU	5.8	6.5	8.6	6.8	8.5	8.6	8.7	9	9.1	8.3	7.6
TYR	2	1.6	2.1	1.6	2.8	0.9	0.9	0.6	1.6	0.5	2.2
PHE	1.6	1.8	2.3	1.8	2.4	2.9	2.6	2.4	2.6	1.8	2.2
HIS	0.9	0.9	1	1.1	1.1	1.2	0.9	1	1.1	1	1.1
LYS	2.7	2.6	4.1	6.5	4.2	2.7	4.4	3.8		6.1	6.3