CASE REPORT

PIBIDS syndrome in two Brazilian siblings

Kerstin Taniguchi Abagge,[1] Felipe Haupenthal,[1] Gabriella Yamashita Felber,[1] Salmo Raskin[2]

[1]Department of Pediatrics, Universidade Federal do Parana, Curitiba, Brazil
[2]Department of Genetics, Universidade Federal do Parana, Curitiba, Brazil

Correspondence to
Professor Kerstin Taniguchi Abagge, kerstinabagge@gmail.com

Accepted 28 November 2018

SUMMARY

Trichothiodystrophy is a rare condition associated with autosomal recessive or X-linked dominant variants in the ERCC2, ERCC3, GTF2H5, MPLKIP, RNF113A or GTF2E2 genes. The genes associated to photosensitive trichothiodystrophy encode subunits of transcription factor IIH, involved in the nucleotide excision repair pathway. The disease is characterised by cysteine-deficient brittle hair along with other neuroectodermal abnormalities. It has a variable clinical expression and some cases might be associated with photosensitivity, resulting in the acronym PIBIDS (*photosensitivity*, *ichthyosis*, *brittle hair*, *intellectual impairment*, *decreased fertility* and *short stature*). We report clinical findings of two siblings diagnosed with trichothiodystrophy associated with marked photosensitivity.

BACKGROUND

Trichothiodystrophy 1 is a rare genetic condition not yet fully understood and responsible for multisystem abnormalities, particularly in (but not limited to) dermatology. This clinical presentation is the first PIBIDS (*photosensitivity*, *ichthyosis*, *brittle hair*, *intellectual impairment*, *decreased fertility* and *short stature*) case reported in siblings in Brazil. It is necessary to stress the importance of photoprotection in those patients as the marked photosensitivity can lead to sunburns and eye damage, especially in tropical countries such as Brazil.

CASE PRESENTATION

Two siblings, patient 1 and patient 2, presented with fragile and brittle hair since birth associated with extreme sensitivity in sun-exposed areas (figure 1). Both of the kids were born from a third cousins' marriage, and they have a younger brother without the disease.

Patient 1, a 20-year-old girl, was born preterm at 32 weeks after a pregnancy complicated by pregnancy-induced hypertension, with a birth weight of 1720 g. At 1 year of age, on her first consultation, she presented dystrophic nails, koilonychia, brittle hair, teeth discolouration and skin dryness with an ichthyosiform pattern. She also showed a deep infantile hemangioma on her upper lip (figure 2). In the follow-up visits, it was evidenced extreme sun sensitivity, with many sunburn episodes and marked sun damage signs in photo-exposed areas such as the neck and face as well as marked pruritus and erythematous patches in the antecubital and popliteal skin folds with the diagnosis of atopic dermatitis. Her atopic dermatitis showed periods of severe exacerbation requiring the use of ciclosporin for approximately 6 months. Her hemangioma slowly decreased in size until complete disappearance at age 7.

Patient 2, a 19-year-old boy, was born preterm at 27 weeks after a pregnancy complicated by pregnancy-induced hypertension with a birth weight of 820 g. He also presented with brittle hair, koilonychia and dry skin, along with marked sun sensitivity, seen as sunburns episodes and chronic photodamage signs such as ephelides, actinic cheilitis and eye alterations.

Both patients had congenital cataract, keratitis, band-like keratopathy, pterygium, corneal scarring and neovascularisation (figure 3) more accentuated in patient 2.

On neurological examination, they showed an intellectual impairment with moderate to severe learning disability and, in patient 2, an outgoing behaviour associated with hyperactivity disorder. The siblings have short stature, hypogonadism and later developed muscle hypotrophy.

INVESTIGATIONS

The polarised light microscopic examination of the hair shafts showed alternating light and dark areas, corresponding to the tiger tail banding pattern, typical of trichothiodystrophy (figure 4). Polarising microscopy of the hair shafts also revealed nodules, characteristic of trichorrhexis nodosa–like abnormalities, and typical trichoschisis with clean transverse fractures.

Diagnosis of trichothiodystrophy 1 was confirmed by molecular genetic evaluation of patient 2, which showed a homozygous variant on the *ERCC2* gene, changing arginine to histidine (R112H).

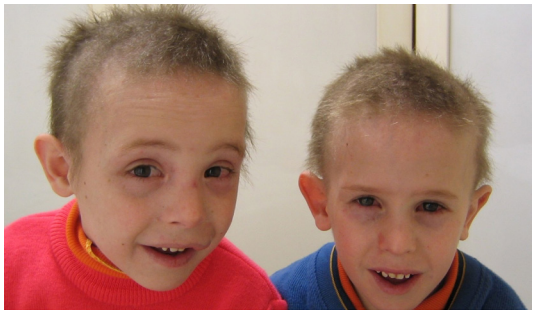

Figure 1 Clinical findings of the siblings when younger showing thick and brittle hair and eye cataract.

To cite: Abagge KT, Haupenthal F, Felber GY, *et al*. *BMJ Case Rep* 2018;**11**:e223744. doi:10.1136/bcr-2017-223744

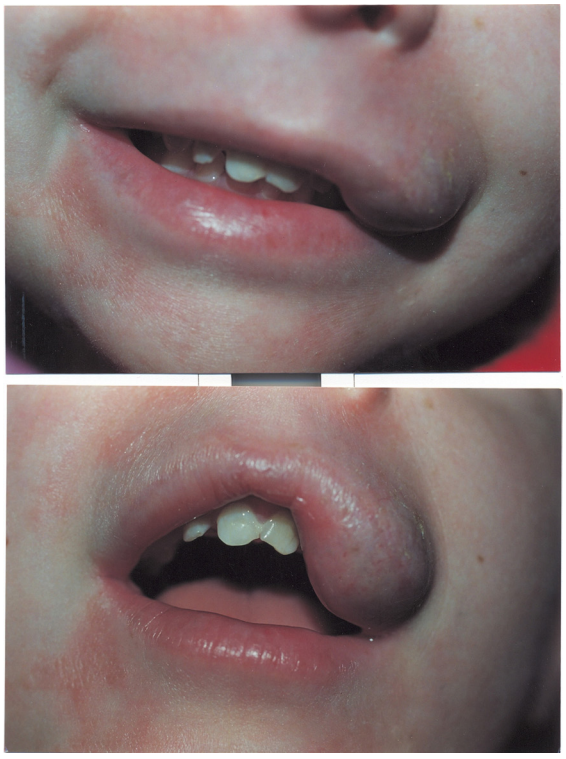

Figure 2 Presentation of the infantile hemangioma in patient 1.

DIFFERENTIAL DIAGNOSIS

Trichothiodystrophy (TTD) is a rare, autosomal recessive or X-linked dominant genetic disorder characterised by cysteine-deficient brittle hair, due to low sulfur content and lower stability of the disulfide linkages in the hair proteins.[1] It has a variable clinical expression comprising several subtypes. Brittle hair is associated with other neuroectodermal abnormalities, including intellectual impairment, decreased fertility, ichthyosis and short stature, distinguishing BI(D)S and IBI(D)S. About half of TTD clinical features may include photosensitivity, resulting in the acronym PIBIDS. The severity of the clinical phenotype varies from mild and moderate to very severe, influenced by the level of expression of the mutated allele.[2]

Among the six described gene locations associated to TTD, photosensitivity in patients with TTD is due to a variant in the *ERCC2* (TTD1), *ERCC3* (TTD2) or *GTF2H5* (TTD3) genes, distinguishing different phenotypes of the condition.[3] Those genes encode proteins of TFIIH, a complex composed of 10 subunits that participates in nucleotide excision repair (NER) pathway and has a role as a transcriptional factor.[4] The NER pathway is responsible for the removal of DNA lesions, including

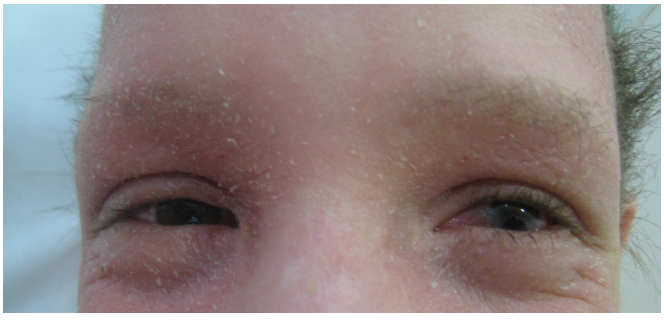

Figure 3 Pterygium and ocular redness in patient 1.

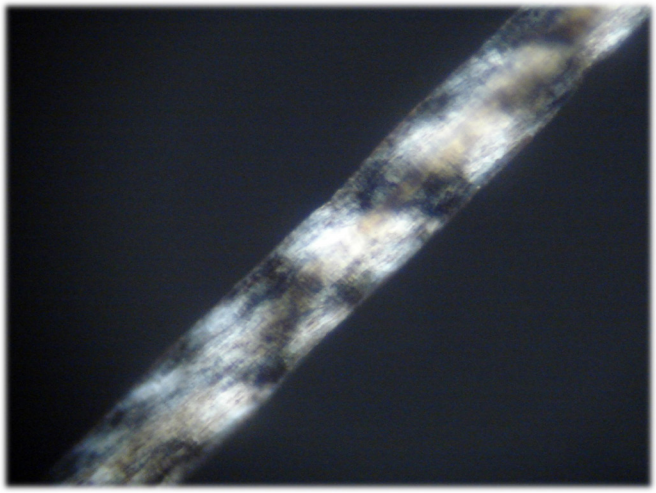

Figure 4 Polarised light microscopy of hair showing the tiger tail banding pattern.

damage induced by oxidative agents and UV light. DNA repair activity is compromised in several disorders, including xeroderma pigmentosum (XP) and Cockayne syndrome (CS). Therefore, different variants in the *ERCC2* gene may lead to one of several clinical disorders: XP, XP with neurological disease, TTD, the XP/CS complex or a severe form of CS known as cerebral–ocular–facial–skeletal syndrome (table 1).[5] The clinical phenotype is determined by the site of the mutation on the gene, which also determines the level of cell sensitivity to UV, by differentially interfering with the stability and conformation of the TFIIH complex.[5–7] Although TTD and XP share variants at the same gene, TTD is not related with an increase in skin cancer, one of the main features of XP.[8] Variants in TTD 1 are more frequent at three sites, all involving a single substitution of an arginine residue (Arg112, Arg658 and Arg722).[9]

TREATMENT

Since there is currently no effective disease therapy, the treatment involves a multidisciplinary approach, with the participation of neurology, ophthalmology, dermatology genetics and endocrinology teams. Intensive photoprotection (sunscreens), protective clothing and glasses as the main flares are always related to sun sensitivity. In order to reduce skin and hair damage, hydrating creams were prescribed along with orientations about mechanical and environmental stresses.

OUTCOME AND FOLLOW-UP

A multidisciplinary team is currently seeing our two patients, including a paediatric dermatologist, geneticist, neuropaediatrician, endocrinopaediatrician and ophthalmologist, as well as psychologist, occupational therapist, phonoaudiologist and music therapist. Patient 1 still shows flares of her atopic dermatitis and extreme photosensitivity.

DISCUSSION

In patients with TTD, the diagnostic hallmark is the presence of hair abnormalities along with several other neuroectodermal signs. The clinical presentation of our patients (brittle hair, intellectual impairment, ichthyosis, decreased fertility, short stature and photosensitivity) is characteristic of the PIBIDS variant of TTD.

Table 1 Clinical features of nucleotide excision repair syndromes

Clinical manifestations	TTD	XP	XP–ND	XP/CS	CS	COFS
Photosensitivity	+/–	++	++	++	+/–	+/–
Ichthyosis	+	–	–	–	–	–
Hair abnormalities	+	–	–	–	–	–
Progressive neurological degeneration	+	*	+	+	+	++
Growth defect	+	*	–	+	+	+
Hypogonadism	+	*	–	+	+	
Skeletal manifestations	+/–	–	–	+	+	+
Facial abnormalities	–	–	–	+	+	+
Skin cancer	–	+	+	+	–	–
Ocular manifestations	+	+	+	+	+	++

*Patients with XP with DeSanctis-Cacchione syndrome.
COFS, cerebral–ocular–facial–skeletal syndrome; CS, Cockayne syndrome; ND, neurological disease; TTD, trichothiodystrophy; XP, xeroderma pigmentosum; –, absent; +/–, may be present or absent; +, present; ++, marked.

The incidence of the photosensitive form of TTD has been recently estimated at 1.2 per million live births in Western Europe.[10] In Brazil, some cases of CS and XP have been previously described, in addition to two recently reported cases of patients with TTD associated with photosensitivity.[11–13] The two patients here reported are the first PIBIDS cases in siblings in this country.

The R112H substitution, present in one of the siblings, is associated with a severe defect in NER pathway, resulting in extreme UV sensitivity. A previous study with Italian patients with TTD, five of whom were homozygous for this variant, revealed that although homozygous patients have the most severe repair defect, they have a less compromised pathological phenotype.[2] Patients are able to live longer lives and to have social relations.

Ocular manifestations resulting from developmental impairment and extreme photosensitivity are well described in TTD and include cataract, nystagmus and microphthalmia.[14 15] As our patients show a variant shared by patients with XP, their ophthalmological findings are similar to those found in this syndrome, such as keratitis, band-like keratopathy, pterygium, corneal scarring, ulceration, neovascularisation and perforation, with the exception of carcinoma development.[16] Those ophthalmic findings, associated with premature ageing, might be due to the failure of TFIIH machinery in basal transcription, more accentuated in terminally differentiated tissues, including neural retina and corneal endothelium.[9]

In addition to the usual clinical features of TTD, it was noticed the presence of hemangioma on our patients. This finding has been previously reported in a male patient with TTD who presented an infantile hemangioma on his lip, which followed the usual sequence of enlargement followed by involution.[17] Although no apparent explanation was found, these consistent findings in two different patients with TTD may suggest an association between the disease and the development of hemangioma.

Learning points

- Trichothiodystrophy (TTD) is a rare genetic disease, characterised by brittle hair, intellectual impairment, decreased fertility, icthyosis and short stature.
- About a half of TTD clinical features may include photosensitivity, resulting in the acronym PIBIDS (*photosensitivity*, *ichthyosis, brittle hair*, *intellectual impairment*, *decreased fertility* and *short stature*).
- Diagnosis of TTD is confirmed by molecular genetic evaluation.
- The treatment involves intensive photoprotection.
- If correctly managed, patients are able to achieve a better quality of life.

Acknowledgements This publication is dedicated to the patients and family who have contributed to this study.

Contributors KTA: literature review and writing, revising text. FH: structure of text. GYF: literature review and update. SR: genetic evaluation and testing, review of final text.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Liang C, Morris A, Schlücker S, *et al*. Structural and molecular hair abnormalities in trichothiodystrophy. *J Invest Dermatol* 2006;126:2210–6.
2 Botta E, Nardo T, Broughton BC, *et al*. Analysis of mutations in the XPD gene in Italian patients with trichothiodystrophy: site of mutation correlates with repair deficiency, but gene dosage appears to determine clinical severity. *Am J Hum Genet* 1998;63:1036–48.
3 Online Mendelian Inheritance in Man, OMIM®. *Trichothiodystrophy 1, Photosensitive; TTD1. MIM Number: 601675*. Baltimore, MD: Johns Hopkins University, 2018.
4 Giglia-Mari G, Coin F, Ranish JA, *et al*. A new, tenth subunit of TFIIH is responsible for the DNA repair syndrome trichothiodystrophy group A. *Nat Genet* 2004;36:714–9.
5 Kraemer KH, Patronas NJ, Schiffmann R, *et al*. Xeroderma pigmentosum, trichothiodystrophy and Cockayne syndrome: a complex genotype–phenotype relationship. *Neuroscience* 2007;145:1388–96.
6 Hashimoto S, Egly JM. Trichothiodystrophy view from the molecular basis of DNA repair/transcription factor TFIIH. *Hum Mol Genet* 2009;18:R224–R230.
7 Lehmann AR. The xeroderma pigmentosum group D (XPD) gene: one gene, two functions, three diseases. *Genes Dev* 2001;15:15–23.
8 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;29:1194–208.
9 Stefanini M, Botta E, Lanzafame M, *et al*. Trichothiodystrophy: from basic mechanisms to clinical implications. *DNA Repair* 2010;9:2–10.
10 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;7:744–50.
11 Santiago KM, França de Nóbrega A, Rocha RM, *et al*. Xeroderma pigmentosum: low prevalence of germline XPA mutations in a Brazilian XP population. *Int J Mol Sci* 2015;16:8988–96.
12 Pereira LB, Valente NYS, Rocha VB. Do you know this syndrome? Ichthyosis associated with neurological condition and alteration of hairs. *An Bras Dermatol* 2018;93:135–7.
13 Silva DS, Almeida I, Netto CF, *et al*. Trichothiodystrophy: a case report of childhood glaucoma associated with non-acquired systemic disease. *Arq Bras Oftalmol* 2018;81.

14 Brooks BP, Thompson AH, Clayton JA, *et al*. Ocular manifestations of trichothiodystrophy. *Ophthalmology* 2011;118:2335–42.
15 Faghri S, Tamura D, Kraemer KH, *et al*. Trichothiodystrophy: a systematic review of 112 published cases characterises a wide spectrum of clinical manifestations. *J Med Genet* 2008;45:609–21.
16 Dollfus H, Porto F, Caussade P, *et al*. Ocular manifestations in the inherited DNA repair disorders. *Surv Ophthalmol* 2003;48:107–22.
17 Takayama K, Danks DM, Salazar EP, *et al*. DNA repair characteristics and mutations in the ERCC2 DNA repair and transcription gene in a trichothiodystrophy patient. *Hum Mutat* 1997;9:519–25.