CASE REPORT

PIBIDS syndrome in two Brazilian siblings

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SUMMARY
Trichothiodystrophy is a rare condition associated with autosomal recessive or X-linked dominant variants in the ERCC2, ERCC3, GTF2HS, MPLKIP, RNF113A or GF2E2 genes. The genes associated to photosensitive trichothiodystrophy encode subunits of transcription factor IIF, 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 discoloration 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). Polarisating 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).
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. 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. 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. 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. The NER pathway is responsible for the removal of DNA lesions, including 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). 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. 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. Variants in TTD 1 are more frequent at three sites, all involving a single substitution of an arginine residue (Arg112, Arg658 and Arg722).

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.

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.

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.

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. 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.

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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.
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, xanthoma 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.6

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.

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REFERENCES


Table 1 Clinical features of nucleotide excision repair syndromes

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*Patients with XP with DeSanscits-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.

Learning points

► Trichothiodystrophy (TTD) is a rare genetic disease, characterised by brittle hair, intellectual impairment, decreased fertility, ichthyosis 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.
Rare disease


