REVIEW ARTICLE

Trichothiodystrophy (TTD): A rare disease of Dermatology

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ABSTRACT

Trichothiodystrophy (TTD) is a rare, inherited genetic disease with depressed RNA synthesis, which may be account for the clinical feature of growth retardation, neurological abnormalities and brittle hair and nail. The disorder is caused by a sulphur deficiency in tissues of neuroectodermal origin. The associated photosensitivity is the result of a defect in the Nucleotide Excision Repair (NER) system, which is responsible for repairing DNA. History of parental consanguineous marriage helps to make an initial proceed towards the diagnosis of rare autosomal recessive disorder. 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 in hair shaft, seen under polarised microscope. 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. Patients generally have complex health care needs and benefit from a multidisciplinary approach to their medical management. Proper psychological, hormonal, neurological and developmental assessment along with sufficient nutritional supplementation need to be maintained. Special health care provider should be involved in medical management depending on symptom (i.e. neurologist for seizures, dermatologist for skin symptoms, endocrinologist for growth tissue). Minimization of sun exposure, aggressive use of emollients, control of recurrent infections and regular screening for underlying malignancy should be emphasized. Greater recognition among a broad range of specialists can facilitate early diagnosis and treatment and identification of risk to future pregnancies.

KEY WORDS: Trichothiodystrophy, autosomal recessive, sulphur deficiency

INTRODUCTION

Trichothiodystrophy (TTD) is a rare, multisystem autosomal recessive disease, in which patients have brittle, sulphur deficient hair.[1,2] TTD results from mutations in one of several different DNA repair genes (XPB, XPD or TTDA)[3,4] and TTDN1, a gene of unknown function.[5] Although XPB and XPD mutations are also seen in xeroderma pigmentosum, a disease with a 1000-fold increase in skin cancer.[4,6–8] TTD patients have not been reported to have an increase of cancer. The recently discovered TTDN1 gene with unknown function was described in association with non-photosensitive patients.[9] In 1979, Price coined the term "trichothiodystrophy," which encompasses a wide spectrum of neurocutaneous findings, to describe the unifying features. The name reflects the brittle, sulfur deficient hair seen in all TTD patients (from Greek, tricho-meaning hair; thio-meaning sulfur; dys-meaning faulty; trophy-meaning nourishment). TTD patients display a wide variety of clinical features, including cutaneous, neurologi-

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cal, and growth abnormalities like photosensitivity, ichthyosis, brittle hair, intellectual impairment, decreased fertility and short stature.[10]

Hair dysplasia is the most important and common feature of TTD. Examination usually reveals sparse, brittle hair, with or without involvement of the eyelashes and eyebrows.[1] Normal hair is made up of two structural protein: intermediate keratin (low sulphur proteins) and matrix proteins, which includes cysteine-rich proteins (high sulphur proteins) and glycine-tyrosine rich proteins. The reduction of high-sulfur proteins in late stage keratinocytes in TTD patients likely causes a decreased number of multiple coavalent disulfide between the intermediate keratin proteins. This results in clinically sparse and brittle hairs. Photosensitivity is noted in nearly 50% of patients with TTD. This phenomenon is due to nucleotide excision DNA repair defects like those in the xeroderma pigmentosum or Cockayne syndrome.[11]

Neuroimaging findings have important role in the diagnosis of TTD. Being ectodermal derivatives, central nervous system and dermatologic abnormalities frequently occur. Generalized dysmyelination is the most common neuroimaging abnormality seen in TTD. Similar dysmyelination associated with Cockayne syndrome is more likely to demonstrate cerebral calcification, particularly in basal ganglia. 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. Sulfur amino acid analysis of the hair is the definitive test.[12-14] TTD is a rare disease complex. The presence of dysmyelination in a child with documented hair and skin abnormalities strongly suggests the diagnosis. Currently there is no known effective treatment for TTD.[15] Complications of trichothiodystrophy are mostly related to the high risk of acquiring severe and potentially life-threatening infections. During the neonatal and childhood period, there is substantial morbidity and mortality, with pneumonia and other infections (particularly sepsis) being the leading causes of death.

DISCUSSION

Vera Price first proposed the name "trichothiodystrophy" in 1979 in the book Haar und Haarkrankheiten.[10] In 1980, Price 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 visible with polarised microscopy, now known as tiger tailed banding.[16] This work established specific hair findings as the unifying marker for this neuroectodermal 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.[17-19] The earliest paper that we included in this study is from Pollitt in 1968, which described two severely affected siblings with brittle, sulphur deficient hair, as well as intellectual and growth retardation.[20] This report led to the name Pollitt syndrome. In 1970, Brown[21] described alternating birefringence in the hair viewed under polarised microscopy in a 4-year-old girl with brittle hair and normal intelligence. Tay, 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.[22] In 1974, Jackson described decreased fertility and autosomal recessive inheritance in an Amish kindred with brittle hair, intellectual impairment and

short stature.[23] 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.[24] Subsequently, the additional presence of ichthyosis led to the acronym IBIDS.[25] 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.[26]

Two siblings from Sabinas, Mexico were reported in 1976 as having brittle hair, developmental delay, and normal stature.[27] 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 addition of photosensitivity to the acronym IBIDS (resulting in PIBIDS) was recommended in 1983 by Crovato.[29] In 1988, Chapmann reported a patient and recommended the addition of skeletal abnormalities instead of photosensitivity to the acronym, resulting in SIBIDS.[30]

Jiménez-Puya et al presented the case of a 4-month-old preterm female infant with hair and nail defects and extremely dry, ichthyosiform skin since birth. On examination, she had progeria-like facies and very brittle hair and fish-like skin, with palmoplantar involvement. There was growth retardation, the child's weight, length, and head circumference were all below the third percentile, and the child's length–weight ratio was clearly abnormal. Mental development was normal. During the routine check-up visits, the mother reported that the child had photosensitivity problems and there were noticeable lentigines. Complementary examinations revealed microcytic hypochromic anemia, which classified as thalassemia trait due to the high number of red blood cells, the reduced mean corpuscular volume of the cells, and the family history. The trichogram revealed intermittent pili torti and trichoschisis due to trichorrhexis nodosa. The elemental analysis showed a slight sulfur deficiency in the hair in the frontoparietal region; the deficiency was more evident at the back of the head, where over 50% of the hairs were affected. In view of the clinical and other findings, they made an initial diagnosis of trichothiodystrophy and given the existence of ichthyosiform erythroderma, hair abnormalities, and growth retardation. The subsequent observation of photosensitivity and multiple lentigines on the face led them to suspect PIBIDS (photosensitivity,ichthyosis, brittle, sulfur-deficient hair, intellectual impairment, decreased fertility, and short stature).[31]

Pei-Lun Sun Yang et al reported a 2-year-2-month-old girl who was admitted to pediatric department with watery diarrhea, vomiting, and fever. She was born at a gestational age of 36 weeks and was small for gestational age (birth weight: 1696 gm [< 10th percentile], head circumference: 29 cm [< 10th percentile]). She had been admitted to hospital several times for intractable diarrhea. Developmental history revealed that she was incapable of scribbling, running, or hopping. Her parents reported that her hair had been dry and sparse since birth. Both parents and her elder sister were healthy. On physical examination, her height was 70.8 cm (< 3rd percentile) and weight 6214 gm (< 3rd percentile). Her face was otherwise normal. Her skin was dry but not ichthyotic. Dermatology department was consulted and they found the hair to be thin, brittle, and sparse over the entire scalp. On light microscopy, trichorrhexis nodosa

was noted in nearly every hair sampled. Polarized microscopy revealed alternating light and dark bands in the hair shaft. Scanning electron microscopy revealed the absence of normal cuticular scales on the hair shaft. The sulfur content of hair was decreased by more than 50% compared to a normal control specimen, using energy dispersive x - ray spectroscopy. The plasma zinc was slightly elevated (1382 µg/L, reference range: 800-1200 µg/L), but copper, plasma ammonia was normal. A chromosome study showed a normal female 46 XX karyotype. The diagnosis of trichothiodystrophy was made. The patient was seen again 1.5 years later, at which time the hair abnormality and developmental delay persisted, with primarily gross motor delay, as evaluated by the Denver Developmental Screening Tests (DDST).[32]

Asaduzzaman et al reported a 3-year-old boy, admitted to their dermatology department at Bangabandhu Sheikh Mujib Medical University, Bangladesh, with short stature, dry and ichthyosiform skin all over the body. He was the second issue of his consanguineous parents, whose first issue was healthy. Following maternal history of premature rupture of membrane, he was born with 2 kg body weight at 34 weeks of gestational age. At birth, an erythrodermic skin was noted. After 3 days, he developed multiple bullae over face, chest and upper back, which were short lived, spontaneously ruptured within 2 to 3 days. He could not open his eyes on broad day light. His development history was notable as he did sit for the first time at the age of 1.5 years and he did pull himself to stand at 2.5 years and at present at 3 he did not take a single step himself and uttered any word. On examination, his weight was 5 kg (below 3rd percentile), height was 72 cm (below 3rd percentile), and OFC was 41 cm (below 3rd percentile). He had progeria like facies, very brittle scalp hair, absence of eyelashes with scanty eyebrow and body hair. Skin was extremely dry and ichthyotic with generalised exfoliation more confined to palms and soles. He had multiple lentigenes distributed all over the body. Hair sample demonstrated Tiger Tail appearance under polarized light microscopy. Opthalmologic examination revealed patchy changes in both retina. Magnetic Resonance Imaging (MRI) of brain showed-diffuse high signal intensity T1W1 hypo, T2W1 and Flair hyper signal intensity in both periventricular deep white matter and centrum semionale region consistent with dysmyelination. There were partial empty sella and mild cerebeller atrophy. Complete hormonal evaluation was done and it suggested subclinical hypothyroidism. He was supplemented with adequate nutrients following paediatric nutritional assessment and was treated with thyroxine to correct subclinical hypothyroidism.[33]

Effective management of the multisystem abnormalities of TTD involves a multidisciplinary approach involving many medical specialties in addition to dermatology. If properly aware, any of medical specialties can make the diagnosis.

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