From the Departments of Dermatology and Pediatrics, Mackay Memorial Hospital-Taipei
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Reprint requests: Pei-Lun Sun, M.D., Department of Dermatology, Mackay Memorial Hospital - No. 92, Sec. 2, Chung-Shan N Rd., 10499. Taipei, Taiwan, R.O.C. TEL: +886-2-2543-3535 ext. 2556 FAX: +886-2-2543-3642 E-mail: jlcvwm@giga.net.tw

Trichothiodystrophy
—A Case Report—

Pei-Lun Sun Yang-Chih Lin Hsin-Yi Su Shuan-Pei Lin¹

Introduction
Trichothiodystrophy (TTD) is a heterogeneous group of disorders characterized by short, brittle hair with low sulfur content and distinctive light and electron microscopic findings. It is inherited in an autosomal recessive pattern. Though cases with isolated TTD have been reported,¹,² it is usually associated with neuroectodermal abnormalities. We report a patient with TTD with physical development delay and briefly review the literature.
Case Report

A 2-year-2-month-old girl was admitted to our Pediatric Department with watery diarrhea, vomiting, and fever. She was born to a G5P2 mother via NSD at a gestational age of 36 weeks and was small for gestational age (birth weight: 1696 gm [<10th percentile], head circumference: 29cm [<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. There was no history of seizures, eye problems, intellectual impairment or skin photosensitivity. 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. Our Dermatology Department was consulted and found the hair to be thin, brittle, and sparse over the entire scalp (Fig.1). On light microscopy, trichorrhexis nodosa was noted on nearly every hair sampled (Fig.2A). No trichoschisis was seen. Polarized microscopy

Fig. 1
Sparse, brittle hair is noted all over the scalp of this 2-year-2-month-old girl.

Fig. 2
Trichorrhexis nodosa on light microscopy (A) and scanning electron microscopy (B). The absence of normal cuticular scales on the hair shaft can be noted.

Fig. 3
Alternating light and dark bands of the hair shaft on polarized microscopy.
revealed alternating light and dark bands of the hair (Fig. 3). The "tiger-tail" pattern was not clearly demonstrated. Scanning electron microscopy revealed the absence of normal cuticular scales on the hair shaft (Fig. 2B). The sulfur content of hair was decreased by more than 50% compared to a normal control specimen, using energy dispersive x-ray spectroscopy (Noran VANTAGE A4105). The plasma zinc was slightly elevated (1382 µg/L, reference range: 800-1200 µg/L), but copper was in the normal range. Plasma ammonia was normal. A chromosome study showed a normal female 46,XX karyotype. Urine organic acid analysis and plasma amino acid quantitative analysis were both normal. The complete blood count was grossly normal. 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). She had just learned to hop and to go upstairs with assistance, milestones of a 3-year-old child. No other neuroectodermal abnormalities were noted.

Discussion
The term 'trichothiodystrophy' (TTD) was first proposed by Price in 1980 to describe a disease complex characterized by brittle hair with a low sulfur content and neuroectodermal abnormalities. It is inherited as an autosomal recessive trait with a wide spectrum of clinical presentations. Patients with brittle nails, mental retardation, growth retardation, impaired sexual development, photosensitivity, ichthyosis, cataracts, recurrent infections, and ataxia have all been reported. Many eponyms and acronyms have been used to describe these subgroups of TTD (Table I). Our patient does not clearly fit any of the subgroups. Her disorder included only hair abnormality, growth retardation, and physical developmental delay.

Hair dysplasia is the most important and common feature of TTD. Examination usually

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<tr>
<th>Type</th>
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<tr>
<td>A</td>
<td>Hair +/-nails</td>
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<td>B</td>
<td>Hair +/-nails + mental retardation</td>
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<td>C</td>
<td>Hair +/-nails + mental retardation + folliculitis + retarded bone age +/-caries</td>
<td>Pollitt</td>
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<td>D</td>
<td>Brittle hair +/-nails + intellectual impairment + decreased fertility + short stature*</td>
<td>BIDS</td>
<td>234050</td>
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<td>E</td>
<td>Ichthyosis + BIDS. Hair +/-nails + mental retardation + short stature +/-decreased gonadal function +/-lenticular opacities/ cataracts + failure to thrive/&quot;progeria&quot; + microcephaly +/-ataxia +/-calcifications of the basal ganglia + erythroderma and scale</td>
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<td>F</td>
<td>Photosensitivity + IBIDS</td>
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<td>G</td>
<td>TTD with immune defects. Hair +/-mental retardation + chronic neutropenia or immunoglobulin deficiency</td>
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<td>H</td>
<td>Trichothiodystrophy with severe intrauterine growth retardation (IUGR). Hair +/-severe IUGR and failure to thrive + developmental delay + recurrent infections + cataracts + hepatic angioendotheliomas</td>
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*The original description "Brittle hair +/-nails + infertility + developmental delay + short stature" in the reference is corrected here according to OMIM.
reveals sparse, brittle hair, with or without involvement of the eyelashes and eyebrows. Trichoschisis and trichorrhexis nodosa can be seen with light microscopy. Under polarized microscopy, affected hair shows alternating light and dark bands resulting in a "tiger-tail" or "zigzag" pattern. Scanning electron microscopy shows damage or loss of cuticle scales and longitudinal grooving. Lack of the exocuticle and thinning of the cysteine-rich cuticular A layer can also be detected on a cross-section of the cuticle. Usually the sulfur or cysteine content of the hair is less than 50% of normal. However, urine and serum levels of these amino acid constituents are generally normal.

Normal hair is made up of two structural proteins: intermediate keratin filaments (low sulfur proteins), and matrix proteins, which includes cysteine-rich proteins (high-sulfur proteins) and glycine- and tyrosine-rich proteins. The reduction of high-sulfur proteins in late stage keratinocytes in TTD patients likely causes a decreased number of multiple covalent disulfide bonds between the intermediate keratin proteins. This results in the reported ultrastructural changes of the hair cuticle and cortex and clinically in sparse, brittle hair.

Alternating light and dark bands of the hair are a distinctive, though not diagnostic, feature of TTD. These can also be detected in patients with argininosuccinic aciduria, acrodermatitis enteropathica, methionine deficiency, and in normal infants. Argininosuccinic aciduria is an autosomal recessive metabolic disorder due to deficiency of argininosuccinate lyase. Hyperammonemia and markedly increased plasma argininosuccinic acid are noted. It is characterized clinically by mental retardation and dry, brittle hair, which in a few cases has alternating light and dark bands of the hair shaft. This condition can be reversed by reducing the protein load and giving arginine supplements. Acrodermatitis enteropathica is a disease due to zinc deficiency. Alternating light and dark bands can be detected occasionally. This condition can be reversed by zinc supplements. In 1996, Goerz et al. reported an 8-year-old girl with brittle and sparse hair in her early childhood. Alternating dark and bright bands of hair was noted on polarized microscopy. Hair amino acid analysis showed increased cysteine content and completely devoid of methionine. Hair growth improved at puberty and returned to normal during pregnancy. A "tiger-tail" pattern of the hair on polarized microscopic examination is also a relatively common finding in healthy infants. Sulfur amino acid analysis of the hair is the definitive test for TTD, which will distinguish it from these other disorders.

A low sulfur content in hair can be detected in other diseases such as kwashiorkor, ichthyosis and Clouston's syndrome (hidrotic ectodermal dysplasia). However, these disorders have characteristic clinical presentations and don't have the typical electron microscopic findings of TTD. Cold-wave lotions, depilatories, bleaching solutions, and synthetic-organic dyes also decrease the low sulfur content in hair.

For our patient, with congenital trichorrhexis nodosa, the differential diagnosis included argininosuccinic aciduria, citrullinemia, Menkes syndrome, and TTD. Normal arginine and citrulline levels excluded the two former disorders. Menkes syndrome is a disorder of defective copper metabolism with low plasma copper and ceruloplasmin. Our patient has normal plasma copper. Hair examination by light microscopy, polarized microscopy and electron microscopy all showed findings of TTD. We used energy dispersive x-ray spectroscopy to determine the sulfur content of the hair, a useful method for identifying specific elemental components of hair by their x-ray emission spectrum following electron bombardment.

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 syndromes. Mutations within the XPD, XPB or TTD-A gene (as yet unidentified) have been noted in affected persons.
Nucleotide excision repair is an important mechanism for repairing damaged DNA in order to reduce the chance of developing a malignancy. Surprisingly, TTD patients with nucleotide excision repair defects don't have an increased risk of malignancy as do patients with xeroderma pigmentosa. There may be several reasons for this, including hyperkeratosis of the epidermis which blocks UV light, preservation of cellular catalase activity, and different molecular characteristics of the mutation after UV irradiation. Recently, it has been suggested that TTD is a transcription disease with depressed RNA synthesis, which may account for the clinical features of growth retardation, neurologic abnormalities, and brittle hair and nails.

Currently, there is no known effective treatment for TTD. Food rich in cysteine is of little help because affected persons are not cysteine deficient; they can't utilize the cysteine they have due to a genetic error. The most important recommendation that can be made is to reduce physical stress (frequent washing, brushing, wearing of hats, and UV exposure) or chemical trauma to the hair.

In conclusion, trichothiodystrophy is a rare disease complex. When sparse, brittle hair is noted, direct hair sampling for light microscopic examination is of great help for diagnosis. Typical microscopic and electron microscopic findings and low sulfur content of the hair make the diagnosis. Thorough examination for other possible associated neuroectodermal abnormalities is also necessary.

Acknowledgement

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References
