Rough skin, brittle hair, and photosensitivity: a mild phenotypic variant of trichothiodystrophy

EDITOR—The trichothiodystrophies (TTD) are named primarily for the hair sulphur deficiency which is their most specific feature and which leads to brittleness of the hair. Other ectodermal tissues may be affected and typically the skin is ichthyotic and the nails dystrophic. Additionally, there may be a distinctive facies and physical and developmental retardation of varying degree of severity. Inheritance is autosomal recessive and at least three loci exist, of which two are known, the excision repair/transcription factor genes XPD/ERCC-2 and XPB/ERCC-3. We describe an 8 year old girl in whom the diagnosis of a mild and in some respects atypical form of TTD was made on the synthesis of clinical, pathological, and biochemical data. The genotypic basis of this clinical phenotype has yet to be established.

The patient was the second child of a dizygous twin pregnancy born to unrelated, healthy, white parents by emergency caesarean section at 32 weeks because of pre-eclampsia. The family history was unremarkable and her male co-twin was healthy. Birth weight was 2100 g (90th centile for this gestation). Birth length and head circumference were 51.5 cm and 32.5 cm respectively. The skin was dry and flaky from birth (but never “collodion”), and in using a towel her mother had to pat her dry, rather than to rub. Thickening of the palms and soles developed in the first year of life. The nails were brittle from birth. Hair growth has always been slow and she has never had a proper haircut, only trims. Desquamated cells from the external auditory canal failed to clear and she has required periodic syringing.

She was referred to our service at 5 years of age because of concerns related to persistent dermatitis, dermal photosensitivity suggested by easy burning in the sun, mild developmental delay, and distinctive facial appearance. We noted the following features: hair that was “wiry” in texture, fragile, and easy to extract; abnormal scalp hair distribution with temporal recession; prominent forehead with sparse eyebrows (fig 1); a generalised dryness of the skin with areas of keratoderma; and brittle, spoon shaped fingernails and toenails. The keratoderma was particularly marked on the soles and palms (fig 2) and at the popliteal and antecubital flexures. Apart from congenital absence of the second premolars, the teeth were normal. Her weight was 27 kg (90th centile), height 128 cm (97th centile), and head circumference 54 cm (98th centile). These measurements are consonant with the parental heights and weights, which were in the 90th-97th centile range. She was attending a normal school and was in the appropriate class for

Figure 1 Patient aged 8 years. The hair is short (has only been trimmed) and stands up irregularly. There is temporal recession.

Figure 2 Palmar keratoderma.
We used this occasion in one allele (c1381C>G, c2146del45) and a causative mutation identified in that case, these being a null mutation XPD/ERCC2 heterozygote at the reported case of TTD (TTD183ME), who was a compound with reference to previously published values (table 1).

Table 1  Hair cysteine analysis results

<table>
<thead>
<tr>
<th>Sample</th>
<th>Mean cysteine content (µmol/g hair dry weight)</th>
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</thead>
<tbody>
<tr>
<td>Previously published controls</td>
<td>1407–1512</td>
</tr>
<tr>
<td>Control hair (age/sex matched)</td>
<td>1442.6</td>
</tr>
<tr>
<td>Patient’s hair</td>
<td>1172.8</td>
</tr>
</tbody>
</table>

age, but was receiving remedial help with reading and perceptual motor skills. Her co-twin did not display any of the above features on examination and was reported to be performing satisfactorily at school. On review at the age of 8½ years, her hair was becoming thicker but the growth rate remained very slow. The keratoderma continued to be a problem and was managed by a combination of skin creams. The skin photosensitivity was being dealt with by ultraviolet barrier cream and sun protection. Formal testing with monochromatic light across the ultraviolet A and B spectra did not produce usual erythema, indicating that the photosensitivity was of mild degree. Eye examination was difficult because of photophobia, but no abnormal retinal pigmentation was observed. She was having private tuition for reading and arithmetic.

Hair examination on polarised light microscopy showed no alternating dark and light band “tiger tail” pattern. On scanning electron microscopy, marked irregularity and flattening of hair shafts was observed. Some areas showed twisting and variation in shaft diameter. Transmission electron microscopy showed a defective A layer in the outermost cuticle cells (figure 3), a characteristic of TTD. The hair cysteine content of the patient and of an age and sex matched control was assessed on hair cuttings scoured as in Church et al2 and measured according to a modification of the method in Strydom and Cohen. All hair shafts showed decreased cysteine content compared to the control specimens and with reference to previously published values (table 1).

Since the patient came from the same city as a previously reported case of TTD (TTD183ME), who was a compound heterozygote at the XPD/ERCC2 locus, we first tested the mutations identified in that case, these being a null mutation in one allele (c1381C>G, c2146del45) and a causative mutation in the other (c2173G>C). We used this occasion to test the robustness of buccal smears for diagnostic purposes. We had previously used buccal smears successfully for the diagnosis of xeroderma pigmentosum complementation group A (XPA) patients (J E Cleaver, M McDowell, unpublished data), but we expected that the XPD gene, being larger than XPA and with more introns, might prove more difficult. Buccal smears were taken from the patient and her co-twin and sent by express mail from Melbourne to San Francisco. Samples were then solubilised in alkali extraction buffer and subjected to genomic amplification by PCR, using primers that flank those genomic regions in which mutations noted above had previously been identified. The PCR products were subcloned into a cloning vector and individual inserts sequenced. The unaffected co-twin had no causative mutations in the regions investigated, although there were two common neutral polymorphisms (c687G>A, c711C>T). The index case had neither of these polymorphisms and neither was the c1381C>G, c2146del45 null allele identified. We sequenced about 300 nucleotides around the region of the causative mutation (c2173G>C) and found only wild type sequences.

This child presents a mild phenotypic form of trichothiodystrophy (TTD). The scalp hair was abnormal in its texture, strength, and distribution, and the electron microscopic (but not light microscopic) picture was similar to that of the classical form of TTD. Hair cysteine content was reduced and the A layer of the cuticle cells defective, substantiating the diagnosis. Other clinical observations included keratoderma, nail dystrophy, and mild developmental delay. Linear growth was unaffected.

TTD can present with a notably wide clinical range. In its mildest form, the disorder may be confined clinically to an abnormality of the hair. The “tiger tail” hair sign is typical but not universal, as indeed our case exemplifies. A further grade of affection is illustrated in our patient, with mild to moderate involvement of the ectoderm and certain of its appendages, as well as (if indeed this is causally related) a minor cognitive component. At the other end of the spectrum, TTD is a seriously disabling disease, with a severe skin affliction and mental defect and growth retardation.

The TTDs comprise one of a group of related disorders resulting from abnormalities in components of the nucleotide excision repair (NER) system, these factors having a second role as subunits of the basal transcription factor TFIIH. Three TTD complementation groups exist, corresponding to the genes XPD/ERCC-2, and an uncloned gene TTDA. Xeroderma pigmentosum (XP) and a form of Cockayne syndrome (CS) with XP-like symptoms are also the result of defects
The first description of lethal pterygium syndrome with facial clefting (Bartsocas-Papas syndrome) in 1600

EDITOR—A recently reviewed 12 page pamphlet dated 1600, housed at the Bodleian Library, Oxford, contains a detailed account of a severely malformed infant born in Herefordshire in January 1600. The child, whose gender was uncertain to the observers, was born to first cousins. “A most strange, and true discourse, of the wonderfull judgement of God. Of a monstrous deformed infant, begotten by incestuous copulation, betwenee the brother’s sonne and the sister’s daughter, being both vmmarried persons”. Adhering closely to the language of the day the infant is described thus.

Head longer than ordinary children with no hair on the head or eyebrows.

Both eyes standing far out of the head, unequal to each other - right eye very small, like a black sloe sticked half out in the flat face - no eyelid or eyepit - “as it were a bullet in a plain wall”; the left eye was very big and eminently, sticking out like the other but with eyelids which were drawn the upper up and the lower down as if inside out.

Nose depressed flat to face - no nostrils - at lower end a round button of fleshy substance the size of a nut. On either side, higher than the nose the upper lip was slit or hare-thorne from which two slits thro’ the pallet or roof of the mouth there passed two hoolow trenches, almost two fingers deep - to the gullet, which seemed to be the passage of the nostrils - the lower part of the mouth on either side of the tongue like a deep trench.

Mouth smaller than usual - no gunns, jawbones or lips. Face more wrinkled than most - grim to behold.

No thumbs or any outward partition of fingers - fingers covered all with one skin, “as with a mitten”, but with joints.

Finger of left hand (digitus annularis/ring finger) had nail and was separated towards the end.