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# Central osteosclerosis with trichothiodystrophy

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**Abstract** Trichothiodystrophy (TTD) is a rare, autosomal recessive, multisystem disorder associated with defects in nucleotide excision repair. We report a 7-year-old boy with TTD due to mutation in the *XPD* gene. The patient has classic features of this condition, including brittle, sulphur-deficient hair, ichthyosis, growth retardation and developmental delay. In addition, he has radiological evidence of progressive central osteosclerosis. Although similar radiological findings have previously been reported in a small number of patients, this association is not widely recognised. We review the radiological findings in this and other similar cases and discuss the natural history of these bony changes.

**Keywords** Skeleton · Trichothiodystrophy · Osteosclerosis · Osteoporosis · Children

## Introduction

Trichothiodystrophy (TTD), or sulphur–deficient brittle hair, is a rare, autosomal recessive, multisystem disorder [1]. Associated findings may include short stature, mental retardation, photosensitivity, ichthyosis, nail dystrophy, cataracts and immunodeficiency. A number of different diagnostic labels have been used for patients with TTD and other associated features, including Tay, BIDS, IBIDS and PIBIDS syndromes (OMIM 601675). Cases of TTD with photosensitivity are associated with defects in nucleotide excision repair (NER) owing to mutations in *XPD*, *XPB* or *TTDA*, three genes related to the repair/transcription factor TFIIH [2].

We report a child with TTD, ichthyosis, nail dystrophy, short stature, mental retardation and defective

DNA repair. In addition to these classic features, he also had radiographic evidence of progressive central osteosclerosis. Similar radiographic changes have been described in a small number of patients with TTD syndromes, often as an incidental finding [3–8], but this association has not been well documented and little is known about the natural history of the osteosclerosis. This further case provides clear evidence for the progressive nature of these bony changes.

## Case report

### Clinical findings

The patient is the second child of healthy, unrelated parents. He was born at 32 weeks' gestation with a birth weight of 1.48 kg (ninth centile). At birth he was noted to have tight, hard splitting skin, similar to that seen in a collodion baby. This gradually improved, but he developed ichthyosis. There is no history of sun sensitivity. From birth his hair was brittle and sparse. He fed poorly and failed to thrive. He also suffers from chronic diarrhoea and multiple food intolerance, related to eosinophilic colitis. Other problems include delayed primary dentition, frequent upper respiratory tract infections and recurrent otitis media. At 4 years he developed a dense right facial palsy in association with a right-sided ear infection. This has only partially resolved. Repeated audiograms have shown mild conductive, but no sensorineural, deafness. He has been treated by the ophthalmologists for a left convergent squint, but has no evidence of cataracts.

His early developmental milestones were significantly delayed. He smiled at 10 weeks, sat at 15 months and walked at 3 years. At 4.5 years, he had a vocabulary of around 15 words. Now, at the age of 7 years, he has moderate-to-severe developmental delay and attends a school for children with special needs.

On examination at 4.7 years, his height was 91.5 cm (−5.5 SD), weight 10.3 kg (−3.6 SD) and head circumference 46.5 cm (second and ninth centile). He had sparse scalp hair and eyebrows and brittle nails. Ichthyosis was most marked over his trunk. He had signs of a recovering right, lower-motor-neuron facial nerve palsy. In addition, his deep tendon reflexes were increased, but limb tone and plantar reflexes were normal. Between the ages of 6 and 7 years, asymmetrical pyramidal signs evolved in his lower limbs, associated with acute episodes of right hip pain, thought to be due to muscle spasm. He has also developed a mild kyphosis.

Scanning electron microscopy of his hair showed evidence of trichorrhexis nodosa and trichoschisis with ridging and fluting of the hair shaft and deficient cuticles. Hair amino-acid analysis was consistent with the diagnosis of TTD. There was marked deficiency in unscheduled DNA synthesis (excision repair) and RNA synthesis following UV exposure. Mutation analysis of the *XPD* gene showed that he is a compound heterozygote for the R722W and the del 716–730/L461V alleles. He also had haematological features of $\beta$-thalassaemia trait with a low MCH (25.4 pg) and MCV (78.8 fl) and a raised level of Hb $A_2$ (4.7%).

### Radiological findings

A chest radiograph obtained at the age of 3 months showed that his bones were of entirely normal density at this stage (Fig. 1a). However, a subsequent radiograph of the chest at 5 years showed increased density of the bones (Fig. 1b). A full skeletal survey at 7 years showed marked increase in density of the spine, ribs, scapulae, clavicles, skull vault and base, facial bones and proximal humeri (Figs. 1c, 2, 3, 4, 5, 6). In contrast to the central skeleton, bone density in the left hand was normal (Fig. 7). There was evidence of acro-osteolysis of several distal phalanges with pointing of the distal ends of the distal phalanges.

Brain MRI at 5 years of age demonstrated a leucoencephalopathy, diffusely affecting the cerebral white matter (Fig. 8). Repeat MRI of the brain and spinal cord at 7 years 10 months showed reduction in white matter bulk and volume of the corpus callosum in comparison to previous imaging. Nerve conduction studies were normal. MRI studies of the right hip showed no additional pathology.

## Discussion

Central osteosclerosis, as seen in our patient, has been reported a few times in association with TTD [3–8], sometimes also with peripheral osteoporosis. However, in the majority of these reports, the radiological findings are included as an incidental finding and this association remains poorly recognised as part of the spectrum of features associated with TTD.

In 1989, Civitelli et al. [4] reviewed nine patients with similar clinical features, including hair abnormalities, ichthyosis and osteosclerosis. In six of these patients, the osteosclerosis was clearly confined to the central skeleton (predominantly the skull, spine, ribs, clavicles, pelvis and proximal tubular bones). Of these, at least three also had peripheral osteoporosis. The authors proposed that these patients represented a separate clinical entity, best described as "central osteosclerosis with ectodermal dysplasia". With hindsight, however, it seems likely that many, if not all, of these patients would fall into the broad spectrum of TTD associated with NER defects.

More recently, central osteosclerosis in association with TTD was reported in three males [5]. Striking

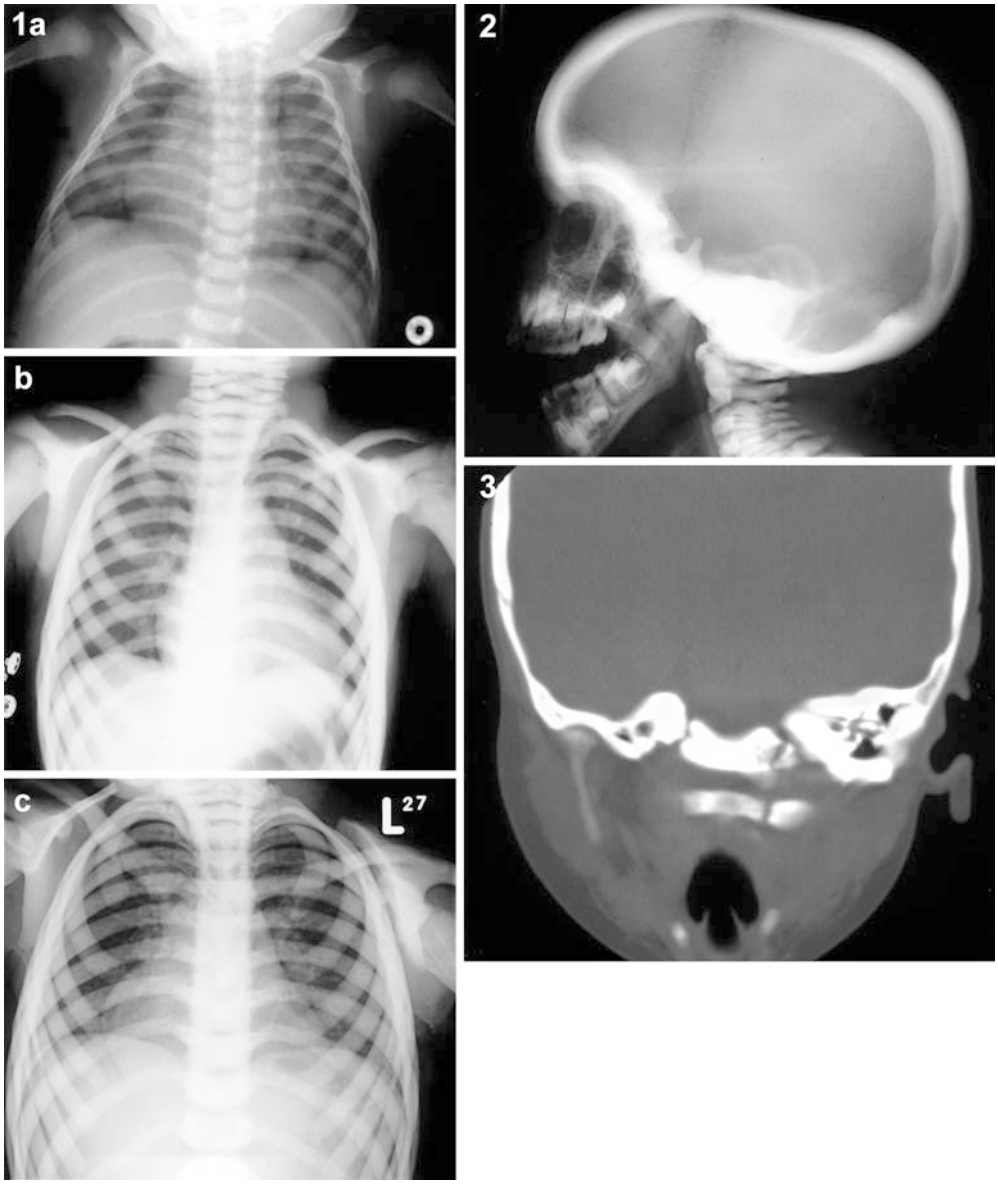


**Fig. 1a–c** AP radiographs of the chest at **a** 3 months, **b** 5 years and **c** 7 years of age. There is progressive increase in bone density and increasing width of the ribs

**Fig. 2** Lateral radiograph of the skull at age 7 years. The skull vault and base are thickened and sclerotic, and there is supra-orbital sclerosis. The mandible and cervical spine are also sclerotic. The maxillary antra and ethmoid sinuses are aerated, but there is absent pneumatisation of the sphenoid sinus and mastoid air cells. The angle of the mandible is wide

**Fig. 3** CT of the temporal bones on bone window settings demonstrates thickening of the bone and absent pneumatisation of the mastoid air cells

osteosclerosis was present in all three, involving the cranium, vertebral column and pelvis; the long bones were largely spared. As in our patient, significant peripheral osteoporosis was not seen. Two sisters with TTD were also described as having osteosclerosis in association with thoracic kyphosis [8]. Central osteosclerosis is alluded to in two further patients, though few clinical details are available [6, 7].

The presence of central osteosclerosis is highly distinctive and, in conjunction with other features of TTD, may help in excluding other differential diagnoses. Patchy alopecia, cataracts, ichthyosis and mental retardation can all be found in association with X-linked recessive and X-linked dominant forms of chondrodysplasia punctata. In both there is epiphyseal stippling but no osteosclerosis. Ichthyosis, other ectodermal problems and mental retardation are also found in other disorders, such as Sjögren-Larsson and Rud syndrome, but in these conditions skeletal problems are not present. Netherton syndrome consists of ichthyosis, eczema and alopecia with abnormal hair shafts. Although a couple

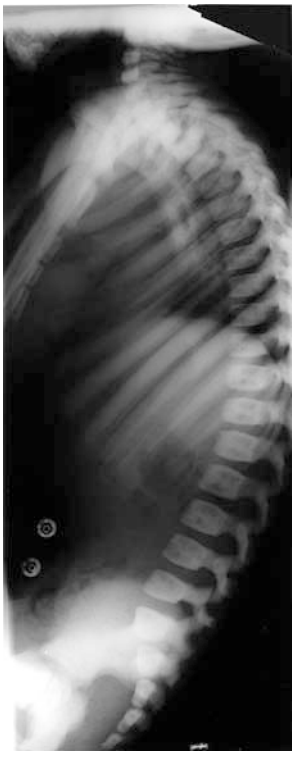

**Fig. 4** Lateral radiograph of the spine at the age of 7 years. Increased bone density affects the central parts of the vertebral bodies and the end plates

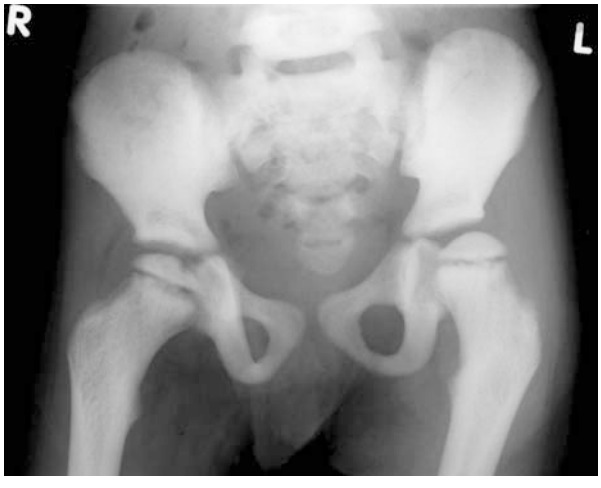


**Fig. 5** AP radiograph of the pelvis at the age of 7 years. There is generalised sclerosis with flattening of the femoral capital epiphyses and early fragmentation of that on the right. This is likely to represent early avascular necrosis

of patients have been described with central osteosclerosis [4], these patients had other features more typical of TTD and there may well be heterogeneity among published cases.

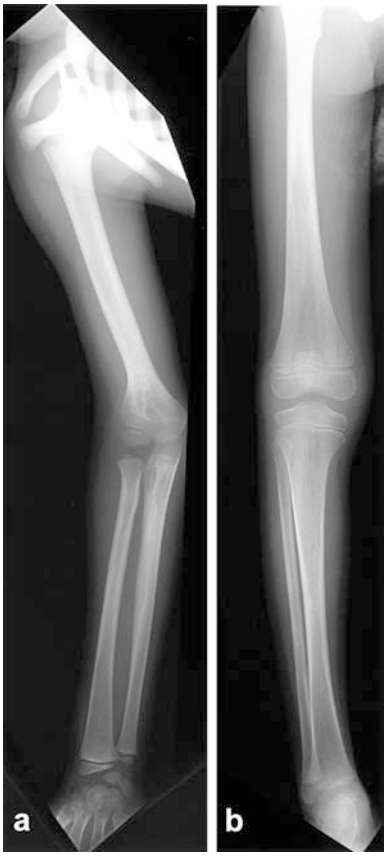


**Fig. 6a, b** AP radiographs of one upper and one lower limb at the age of 7 years. Sclerosis is only evident in the proximal humerus and proximal femur

All photosensitive TTD cases appear to have altered NER resulting from mutations in one of three genes: *XPD*/*ERCC*–2, *XPB*/*ERCC*–3, and *TTDA* [2]. All three of these genes are related to TFIIH, a multiprotein complex involved in both NER and initiation of transcription.

Xeroderma pigmentosum (XP) and a form of Cockayne syndrome (CS) with XP-like symptoms also result from mutations in *XPD*, and the three conditions overlap at both clinical and molecular levels. XP is characterised by photosensitivity, pigmentary abnormalities and (unlike TTD) a predisposition to skin cancer. The phenotype in CS includes photosensitivity, short stature and mental retardation. The wide clinical spectrum of disease associated with *XPD* mutations appears to be related to the fact that different mutations affect NER and transcriptional activities to varying degrees [9]. Mutations in *XPD* that affect DNA repair but not transcription give rise to XP. If transcription is also affected, TTD or CS result.

Neither XP nor CS has been reported in association with central osteosclerosis. However, skeletal changes have been noted in CS, including flattening of the

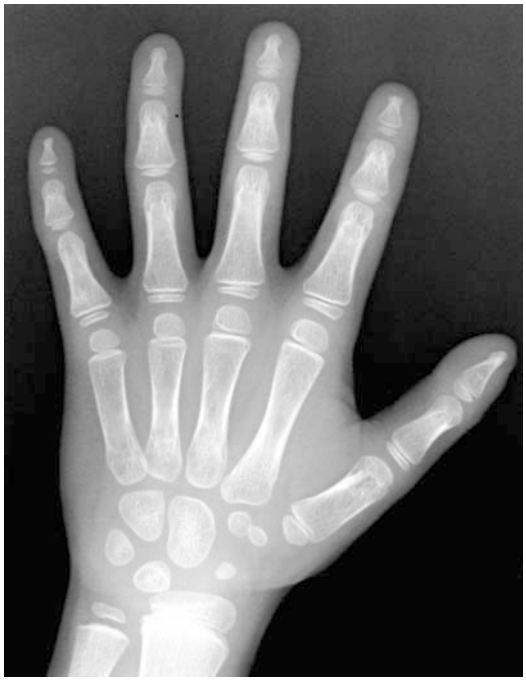

**Fig. 7** DP radiograph of the left hand at the age of 7 years. Bone density is entirely normal in contrast to the axial skeleton. There is some tapering of the distal phalanges and tuft erosion of the index and little fingers

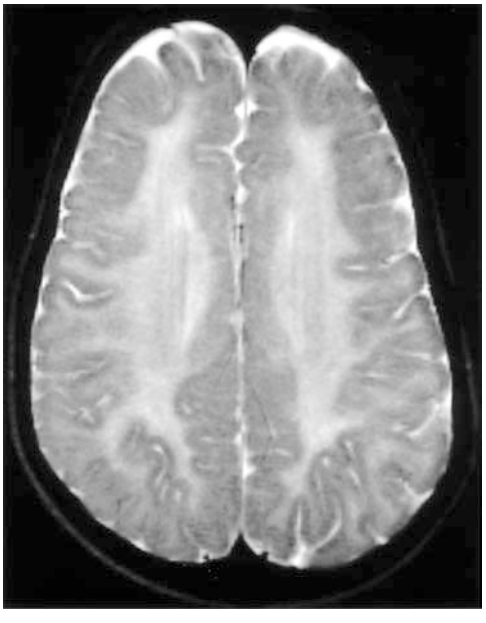

**Fig. 8** Axial MRI of the brain at the age of 5 years showing leucodystrophy

vertebral bodies, thickening of the cranial vault with intracranial calcifications, narrow diaphyses of the long bones with disproportionate widening of the metaphyses, pelvic abnormalities and sclerotic 'ivory' epiphyses [10]. Osteoporosis has also been noted in a few patients. It is interesting to note that many of these changes affect the central skeleton.

Our case is one of several TTD patients described with *XPD* mutations and the haematological phenotype of $\beta$-thalassaemia trait (patient TTD2LO [11]). This is associated with reduced levels of $\beta$-globin synthesis: the first evidence for reduced expression of a specific gene in TTD. The spectrum of different phenotypes seen in TTD may be related to the way in which distinct XPD mutations differentially affect the interaction of TFIIH with various transcriptional regulators [2]. Although genotype-phenotype correlations are emerging, no specific regions of the gene have yet been implicated in the bony changes described in TTD or CS.

A recent study looked at the phenotype of mice with R722W mutation in *XPD* (one of the mutations identified in our patient) [12]. These TTD mice were found to exhibit many signs of premature aging, including osteoporosis, osteosclerosis, early greying, cachexia, infertility and reduced life span. Although 2- to 4-month-old TTD mice showed no detectable skeletal abnormalities, by 14 months radiographs revealed prominent kyphosis and a generalised reduction in radiodensity of the skeleton, except for the skull. Thus the changes in this mouse model are similar to those seen in TTD patients. However, osteosclerosis is apparently less extensive in TTD mice, with reduced, rather than increased, mineral density in the vertebrae.

The radiological findings in this case were clearly progressive. Although minimal changes were present at 3 months, by the age of 5 years there was marked central osteosclerosis. This corresponds well with the findings of Civitelli et al. [4]. All the patients reviewed in this paper were diagnosed between the ages of 3 and 6 years. In one, the skull and spine were of normal density at 15 months but became sclerotic by 3.5 years [13]. However, very little is known about the longer–term consequences for TTD patients with osteosclerosis. The adult patient included in the review by Civitelli et al. [4] was atypical for TTD and had osteopetrosis rather than osteosclerosis [14]. Two other adult patients (aged 20 and 44 years) have been described: both had normal hearing and vision [5]. Central dysmyelination, as seen in our patient, has been reported in several cases of TTD [6, 8]. Sensorineural deafness has been described in some TTD patients, but may be due to underlying white matter changes rather than nerve entrapment [6]. The lower-motor-neuron facial palsy in our patient was probably secondary to inflammation of the facial nerve during an episode of acute suppurative otitis media. However, a compressive element related to osteosclerosis of the skull cannot be excluded. Overall, there are no clear reports of nerve entrapment associated with osteo-

sclerosis in TTD and it remains unclear whether this can arise.

It is difficult to assess the frequency of skeletal changes in TTD as a result of reporting bias in the published literature. However, it seems probable that they are more frequent than has been previously recognised. Radiographs do not currently form part of the routine diagnostic work-up for this condition and skeletal changes appear to cause few, if any, problems early in childhood. We believe that central osteosclerosis and peripheral osteoporosis are distinctive features of TTD, but may easily remain undetected. Since the skeletal changes are so characteristic, skeletal survey can be a useful investigation if the diagnosis of TTD is considered. It is hoped that, with greater recognition, the long-term significance of these skeletal changes will be better understood so that patients and parents can be given more accurate advice.

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