

Skinning the Surface of Bone Abnormalities in Trichothiodystrophy



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INTRODUCTION

Trichothiodystrophy (TTD) is a rare autosomal recessive disease characterized by multisystem abnormalities: low birth weight, short stature, developmental delay, microcephaly, absent myelin in the brain, ataxia and altered reflexes, congenital cataracts, photosensitivity, ichthyosis and sulfur-deficient, brittle hair (Figure 1).

Bone abnormalities, which include central osteosclerosis, peripheral osteopenia, and hip abnormalities, such as coxa valga (Figure 1), subluxation and avascular necrosis, significantly impact the quality of life of TTD patients.

Patients with TTD exhibit a diagnostic "tiger-tail" banding pattern in hairs examined utilizing polarized microscopy (Figure 2). The underlying cause of TTD involves mutations in the genes, *XPB, XPD, TTDA*, which collectively play a role in DNA repair and basal transcription (1). *TTDN1* gene, whose function is unknown, is also associated with TTD (1).

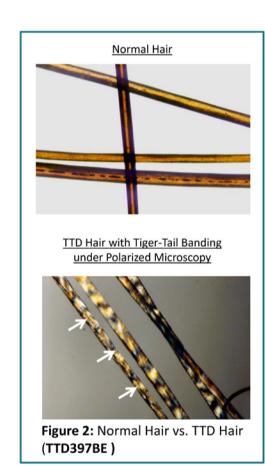


Figure 1: Female TTD Patient (TTD354BE, age 9) with short brittle hair, bilateral coxa valga, ichthyosis of scalp and torso and severe growth and developmental delay.

OBJECTIVES

- •Characterize the bone abnormalities and clinical manifestations present in TTD patients examined at NIH.
- •Identify TTD patients at risk for rapidly progressive bone abnormalities.

METHODS

- Reviewed clinical documents and imaging studies for the 32 TTD patients utilizing Clinical Research Information System (CRIS), as well as from clinical centers and hospitals around the world.
- •Evaluated 611 radiographic images (x-rays, CTs, MRIs) for changes in bone structure, hip orientation and trabecular architecture.
- •Assessed stage of avascular necrosis (AVN) as described in reference (2).
- •Measured the acetabular angle for the TTD patients exhibiting hip abnormalities (3, 4).

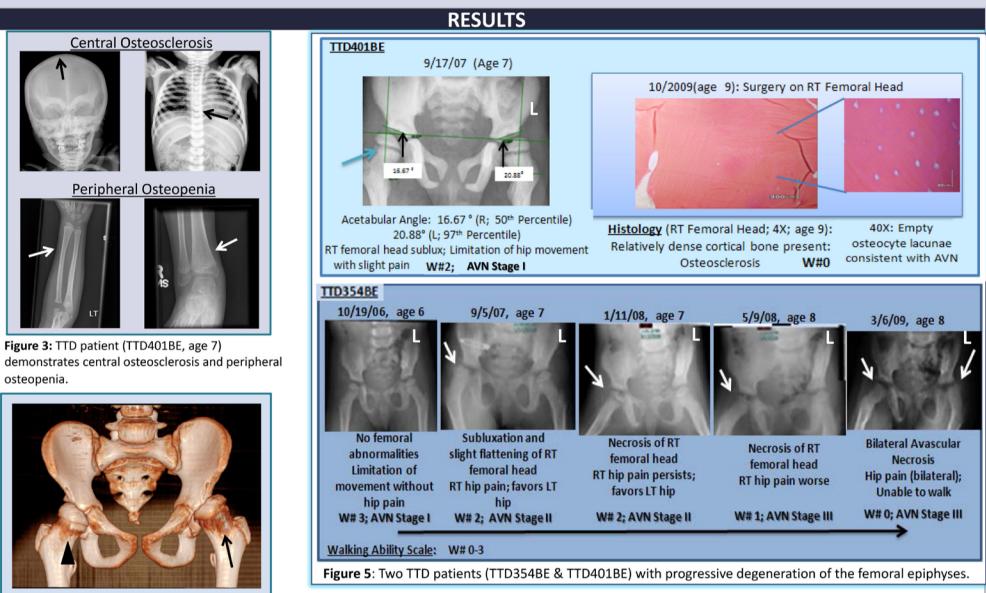
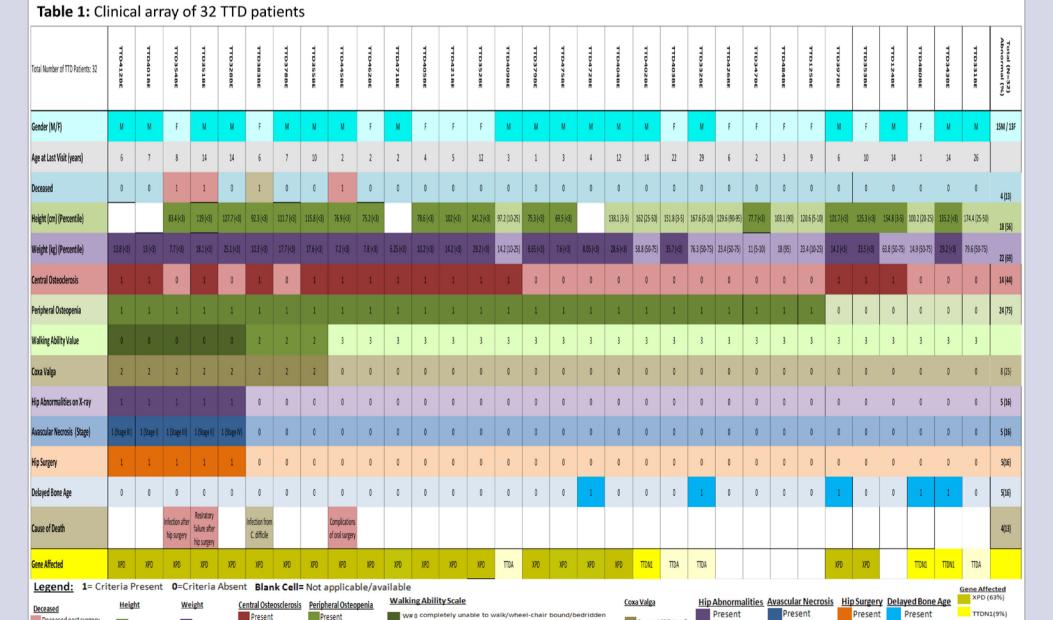
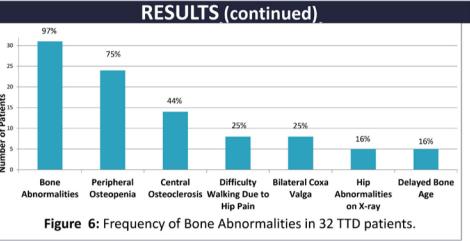
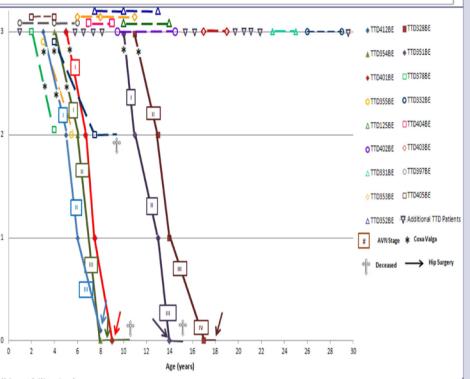


Figure 4: 3-D rendering of a hip CT from a male TTD patient (TTD328BE, age 14). Note presence of slight degradation of the right femoral neck (*arrowhead*), as well as, presence of necrosis of the left femoral neck (*arrow*). Pain when walking (L>R). W#2; AVN Stage II







Walking Ability Scale:

W# 3= No pain when at rest or walking / No problems with walking

W# 2= No pain at rest but some pain when walking / Favoring one leg

W# 1 = Some pain at rest and severe pain when walking / Refusing to walk or put weight on one or both legs **W# 0** = Unable to walk without assistance/ Wheel-chair bound / Bedridden

DASHED Line (Open Symbol) = No Hip Abnormality noted on x-ray

SOLID Line (Closed Symbol) = Hip Abnormality (subluxation and/or femoral head degeneration) noted on x-ray Avascular necrosis (AVN) Stage: 0, I, II, III, IV (based on clinical and radiographic findings)

Figure 7: Progression of walking and hip abnormalities on x-ray as a function of age in

SUMMARY & CONCLUSIONS

- Delayed bone age, central osteosclerosis, peripheral osteopenia, hip degeneration or coxa valga were present in 31 (97%) of 32 TTD patients. Thus bone abnormalities are a common clinical feature of TTD.
- Hip abnormalities (subluxation and/or femoral head degeneration) were present in 5 (16%) of 32 TTD patients. Acetabular angle measurements did not correlate with the clinical and radiological findings for 4 of these TTD patients.
- All patients with hip abnormalities exhibited difficulty walking, typically beginning at an early age ,followed by rapid worsening of ambulation over 4-6 years.
- Of the 5 TTD patients who received hip surgery, 2 died from post surgery complications and 2 remain bedridden following surgery. Thus, bone abnormalities, specifically hip degeneration, may significantly impact the TTD patient's quality of life.

FUTURE DIRECTIONS

 Further analyze the characteristics of hip degeneration in order to gain an understanding of the causative factors and events preceding the degeneration of the femoral head, with the goal of improving diagnosis and treatment for TTD patients.

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