A Chinese girl with Turner syndrome and Duchenne muscular dystrophy: diagnosis and management of this "dual diagnosis"

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To the Editor: The coincidence of Turner syndrome (TS) and Duchenne muscular dystrophy (DMD) is extremely rare, although each is familiar as a sex chromosome aneuploidy and neuromuscular disorders. We report a Chinese girl with TS and DMD with a review of seven cases reported in the literature.

A 9-year-old girl from Hebei province was referred for short stature, muscle weakness and waddling gait. She tired easily, was unable to jump, had difficulty arising up from the squatting position and climbing stairs. She was born with healthy non-consanguineous parents. Her mother was 150 cm and maternal grandmother 149 cm of height. Short stature was present since the age of 3 years, which was thought to be "familial short stature" at the age of 4.75 years with the height of 91.8 cm (–4.21 standard deviation [SD]).

She presented with features commonly seen in TS patients including short stature with height of 111 cm (–3.98 SD), low posterior hairline, large and misshapen ears, multiple pigmented nevi on face and trunk, short and mildly webbed neck, shield chest, wide-spaced and inverted nipples, lordosis, cubitus valgus, nail dysplasia and hypoplasia, lymphedema of hands and feet. She also exhibited features uncommon among TS individuals such as up-slanting palpebral fissures, strabismus and relatively small mouth. Her proximal musculature of the upper and lower extremities showed mild hypotonia, weakness. She had a positive Gowers' sign and calf hypertrophy as well as exaggerated lumbar lordosis [Figure 1A–C].

Laboratory investigations showed increased serum creatine kinase (CK) 6566 IU/L (normal 25–200 IU/L), aspartate aminotransferase (AST) 110.4 U/L, alanine aminotransferase (ALT) 140 U/L. Electromyographies (EMGs) of the upper and lower limb muscles were consistent with myogenic lesions. The Wechsler nonverbal scale of intellectual ability evaluation revealed a score of 66, indicating borderline to mildly impaired intellectual ability. There was no evidence of cardiovascular malformation, and the renal ultrasound and pituitary magnetic resonance imaging (MRI) were normal. Karyotype analysis showed non-mosaic 45, X (50 cells counted). Single nucleotide polymorphism (SNP) array showed missing of the whole second sex chromosome. Molecular genetic analysis showed a frame-shift variant c.10273delT (p. S3425Pfs*20) in the exon 72 of DMD gene in the patient and her mother, but not in maternal grandmother. Her mother had no symptoms and had a normal CK level (136.4 U/L).

The girl was diagnosed as having both TS and DMD. Starting at age 9.5 years, she received growth hormone therapy (polyethylene glycol [PEG] with recombinant human growth hormone [rhGH; PEG-GH] 0.2 $mg \cdot kg^{-1} \cdot w^{-1}$), oral coenzyme Q10 and physical rehabilitation involving regular stretching of the ankle and knee. One year later, her height was 115.8 cm (–3.86 SD), with a bone age of 10 years. The serum levels were 112 U/L for AST, 174.9 U/L for ALT, 6478 U/L for CK, 810 U/L for lactate dehydrogenase (LDH). Insulin-like growth factors-1 (IGF-1) increased from 240 μg/L to 403 μg/L (88–452 μg/L), Insulin-like growth factors binding protein 3 (IGF-BP3), electrocardiography (ECG) and echocardiography (UCG) were normal.

TS is a familiar sex chromosome abnormality in phenotypic females and occurs in approximately 1 in 2000 female live births. DMD, a well-known X-linked recessive condition that affects approximately 1/4560 male live births every year in China.[1] The coincidence of TS and DMD is extremely rare. Since 1965, 7 cases of DMD in TS patients including 3 with 45, X, 2 with 45, X/46, XX, and 2 with 46,

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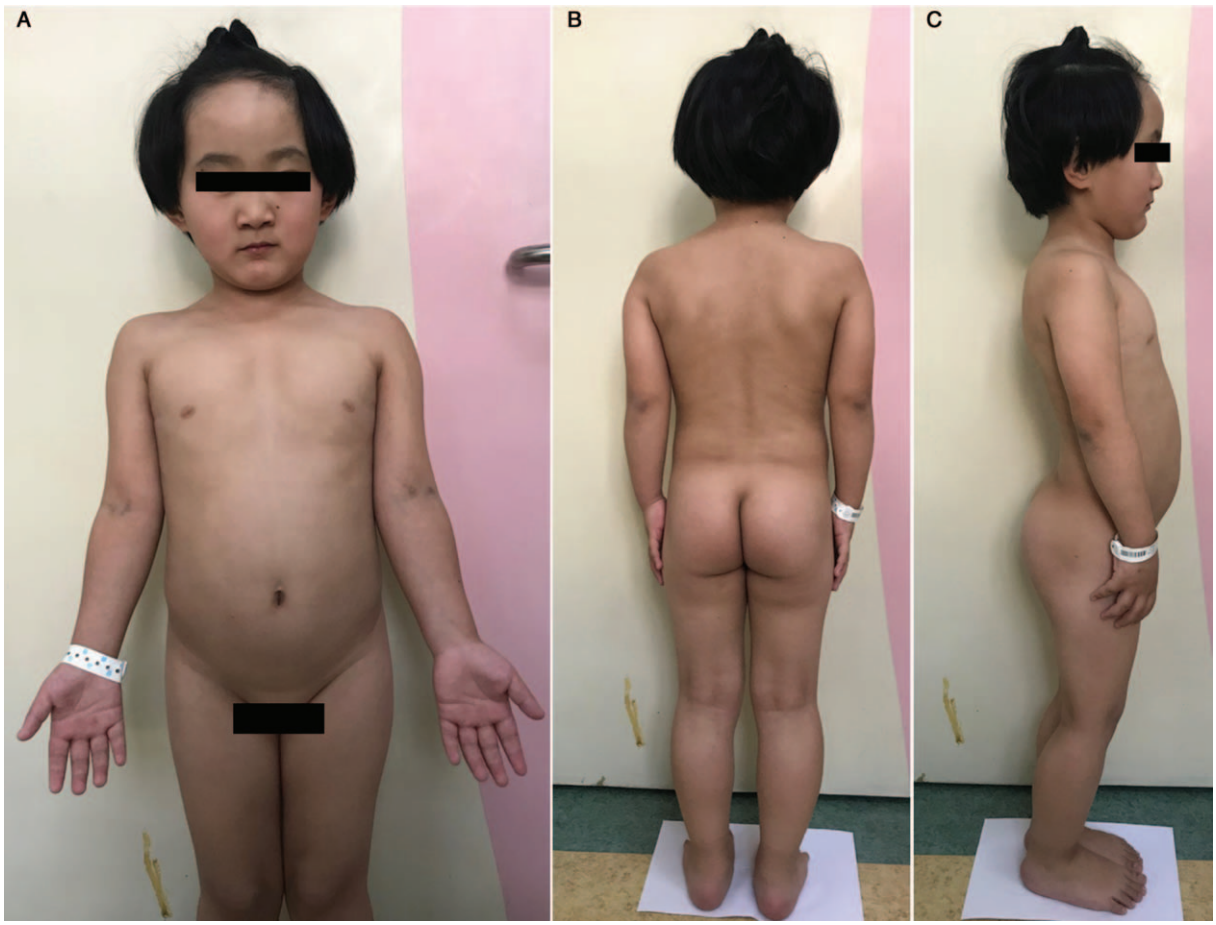

Figure 1: Full length photo of the patient at the age of 9 years, frontal plane (A), back plane (B), and lateral plane (C).

X,i(X)(q10), have been reported [Supplementary Table 1, http://links.lww.com/CM9/A361]. This case was confirmed as a dual diagnosis of TS and DMD at the same age based on the typical clinical manifestations of the two diseases and pathogenic novel (from her mother) frame-shift variant of DMD gene in the monosomy X.

The management of a patient with co-existing of TS and DMD is challenging. There is currently no cure for TS or DMD. To improve the quality of life, both of them need multidisciplinary assessment and care in all areas of life and support at all stages. Only one case report[2] mentioned growth hormone therapy (dosage and duration were not mentioned) and oral corticosteroids. That patient had progressive muscle weakness, inability to ambulate independently, and a 10-degree left lumbar curve on the lumbosacral spine X-rays at the age of 9. No follow-up information was mentioned. We treated our patient with growth hormone (PEG-GH 0.2 $mg \cdot kg^{-1} \cdot w^{-1}$). She gained 4.8 cm in the following year. We also treated our patient with coenzyme Q10 and physical rehabilitation directed by a neurologist for 1 year and no changes of DMD-related phenotypes after one year. For TS, GH early treatment (around 4–6 years of age, and preferably before 12–13 years of age) is recommended,[3] however, the efficacy and safety of GH in DMD patients are unknown due to very limited data.[4] Her parents are understandably very anxious about the future. The prognosis of the disease and reproductive counseling for the patients are still challenges.

Historically, multisystemic clinical manifestations were explained by one syndrome or another disorder. However, some deviations from Mendelian expectations have led to the discovery of more complicated genetic causes of conditions, such as a classic X-linked recessive disorder occurring in female patients.[5] Some atypical features which had been interpreted as an extension of the TS phenotype or as coincidental, have been confirmed as a second genetic disorder. With the improved diagnostic technologies, it is increasingly recognized that some patients may carry more than one pathogenic genetic locus with more than one clinical diagnosis.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms in which the family members of this patient provided their consent for the clinical information to be reported in the journal. They understand that the patient's name and initial will not be published and efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

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Conflicts of interest

None.

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