Taiwanese Journal of Obstetrics & Gynecology 57 (2018) 608–610

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Research Letter

A 17-year-old boy with Klinefelter syndrome presenting Marfan syndrome-like clinical features of tall stature, scoliosis, arachnodactyly and subluxation of bilateral elbow joints

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ARTICLE INFO

Article history:
Accepted 8 May 2018

Dear Editor,

A 17-year-old boy who had been suspected to have Marfan syndrome since childhood was referred for molecular genetic analysis of the mutation of Marfan syndrome-related genes. He was the second child of a 35-year-old father and a 31-year-old mother at his birth at term with a birth weight of 3500 g. There was no family history of tall stature and congenital malformations. The parents did not have tall stature. At referral, he had a body weight of 50 Kg, body height of 190 cm (>97th centile), an arm span of 191 cm and a head circumference of 90 cm. He manifested a long and narrow face, tall stature, scoliosis, arachnodactyly, subluxation of bilateral elbow joints, mild intellectual disability, wry neck, strabismus, esotropia, myopia, equivocal wrist and thumb signs, a small penis and scrotums but no pectus deformity and no congenital heart defects (Fig. 1). Sequence analysis revealed no mutation in the genes of *FBN1* and *TGFBR2*. Simultaneous cytogenetic analysis of the peripheral blood revealed a karyotype of 47,XXY (Fig. 2).

Jo et al. [1] previously reported Klinefelter syndrome in a 13-year-old boy with tall stature but no other physical abnormalities and normal biochemical and imaging studies, and suggested that when evaluating men with tall stature, Klinefelter syndrome should be ruled out. We additionally reported a boy with tall stature and a misdiagnosis of Marfan syndrome. Our presentation highlights the importance of genetic evaluation of tall stature.

Tall stature is usually defined as a height above 2 standard deviations (SD) above average for same sex and age [2,3]. Tall stature may result from normal variants or generalized overgrowth disorders. Differential diagnosis of the etiology of tall stature in children should include: (1) normal variants of constitutional advancement of growth and familial tall stature; (2) endocrine disorders of hyperthyroidism, obesity, pituitary gigantism (excessive growth hormone), precocious sex-steroids exposure, virilizing disorders, hypogonadism, aromatase deficiency and estrogen resistance due to *ESR1* mutation; (3) supernumerary sex chromosome aneuploidies of 47,XXY (Klinefelter syndrome) and 47,XXX (triple X syndrome); and (4) genetic disorders such as Beckwith-Wiedemann syndrome, homocystinuria, Marfan syndrome, fragile X syndrome, Sotos syndrome (cerebral gigantism), Weaver syndrome, *IGF1R* duplication, epiphyseal chondrodysplasia (Miura type), CATSHL syndrome, Bannayan-Riley-Ruvacaba syndrome, Simpson-Golabi-Behmel syndrome, Lujan-Fryns syndrome, congenital contractural arachnodactyly and sclerosteosis [2–5].

Other clinical features and familial history in association with tall stature are helpful in the differential diagnosis of the etiology of tall stature. For examples, (1) homocystinuria and sclerosteosis are

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https://doi.org/10.1016/j.tjog.2018.06.025

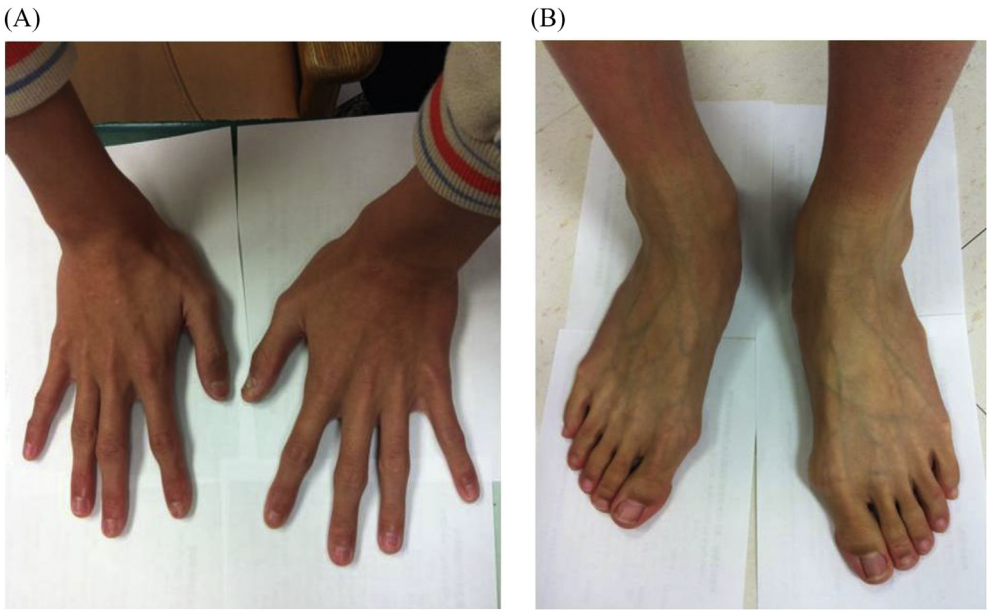

Fig. 1. Arachnodactyly of (A) the hands and (B) the feet.

autosomal recessive disorders associated with consanguinity; (2) familial tall stature, Marfan syndrome, epiphyseal chondrodysplasia (Miura type) are autosomal dominant inheritance associated with a family history; (3) homocystinuria, Sotos, CATSHL, fragile X, Bannayan-Riley-Ruvacaba, Weaver and Lujan-Fryns syndromes present developmental delay, intellectual disability and behavior problems; (4) overgrowth syndromes are associated with large for date at birth, obesity and facial dysmorphism; (5) macrocephaly is associated with Sotos, Bannayan-Riley-Ruvalcaba, Weaver, Lujan-Fryns, Simpson-Golabi-Behmel and fragile X syndromes; (6) microcephaly is associated with CATSHL syndrome; (7) thyrotoxicosis causes sleep difficulty, hyperactivity, poor school performance, palpitation, weight loss, exophthalmos, goiter and tachycardia; (8) precocious sex-steroids exposure causes presence of precocious secondary sexual characteristics; (9) Klinefelter syndrome manifests hypogonadism and body disproportion; (10) Marfanoid habitus of arm span larger than height, arachnodactyly and hyperlaxity appears in Marfan, Sotos and Lujan-Fryns syndromes, homocystinuria and epiphyseal chondrodysplasia (Miura type); (11) kyphoscoliosis appears in CATSHL syndrome and

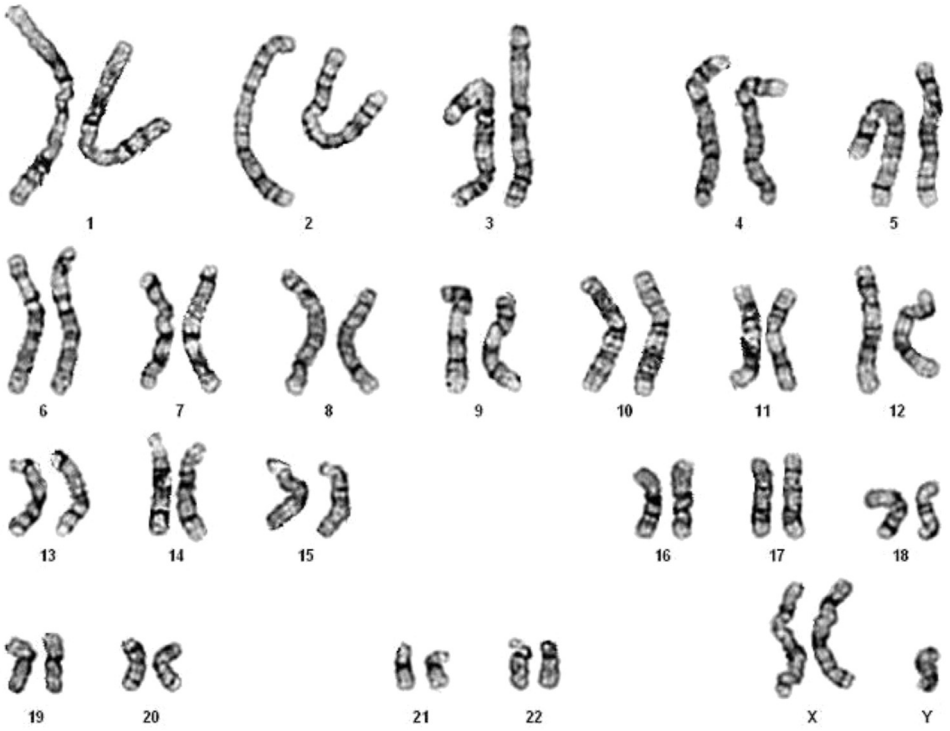

Fig. 2. A karyotype of 47,XXY.

epiphyseal chondrodysplasia (Miura type); and (12) campodactyly appears in CATSHL and Weaver syndromes [5].

Evaluation of tall stature should include the diagnostic tests of X-ray for bone age determination, blood tests to check IGF-1, TSH, free-T4, LH, FSH, testosterone/estradiol levels and homocysteine, karyotyping, ophthalmologic examination, echocardiography, mutational analysis of *FMR1* and *FBN1*, array comparative genomic hybridization analysis of microdeletions or microduplications, and target whole exome or gene panel sequence [5].

In summary, we present a case of Klinefelter syndrome presenting Marfan syndrome-like clinical features. We discuss the differential diagnosis of disorders associated with tall stature.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

Acknowledgements

This work was supported by research grants MOST-105-2314-B-195-012 from the Ministry of Science and Technology and MMH-E-106-04 from MacKay Memorial Hospital, Taipei, Taiwan.

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