CASE REPORT

Microcephalic osteodysplastic primordial dwarfism type II and Klinefelter syndrome: report of two competing growth syndromes

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ABSTRACT

Background: Microcephalic osteodysplastic primordial dwarfism (MOPD) is a wide spectrum of monogenic disorders with several subtypes and numerous genes have been identified. It is characterized by the significant pre- and post-natal growth retardation, severe short stature (dwarfism), and microcephaly. MOPD type II (MIM# 210720) is a recessive disease, which is the first mapped MOPD caused by mutations in *PCNT* (605925) gene encoding pericentrin protein, in chromosome 21q22. In contrast, Klinefelter syndrome (KS; XXY syndrome) is a known numerical chromosomal disorder that is considered the most frequent sex chromosomal with no or minimal physical features before puberty. Affected children may have tall stature and subtle intellectual disabilities, speech delay, and evolving psychosocial dysfunctions.

Case Presentation: We present a 3-year-old dwarf child with the facial and physical finding of MOPD. Interestingly, his karyotype revealed 47;XXY abnormality. While searching for the main cause for his dwarf phenotype, gene testing for *PCNT* gene showed pathogenic homozygous mutation with both parents proved to be heterozygous for the same mutation.

Conclusion: While the karyotype proved the 47;XXY syndrome, the clinical phenotype of MOPD caused by *PCNT* leads his physical array and dominated the patient's facial profile. Early diagnosis for both syndromes is essential in order to offer early treatment for the complications or to provide an appropriate counseling and intervention if needed.

Keywords: Intrauterine growth retardation, IUGR, primordial dwarfism, MOPD, *PCNT*, Klinefelter syndrome, developmental delay, 47,XXY.

Introduction

Intrauterine growth retardation (IUGR) is a common childhood problem caused by diverse maternal and fetal mechanisms. It is classified to symmetrical and asymmetrical categories (1). Genetic and maternal infections and/or diseases may contribute to the vast majority of causes. However, genetic disorders are being increasingly responsible for many causes of severe syndromic and non-syndromic growth dysfunctions.

Primordial dwarfisms or microcephalic osteodysplastic primordial dwarfism (MOPD) is genetic and might be a potential etiology for IUGR. It is classified into two subtypes; type I (MOPD; OMIM 210710) and type II. Both are monogenic recessive disorders which are characterized by severe physical growth retardation, prominent facial dysmorphia (Seckel face), microcephaly and progressive disproportion short stature secondary to shortening of the distal and middle segments of the limbs, and variable bony abnormalities (2). It is the first MOPD to be mapped that is caused by mutations in the pericentrin (*PCNT*) gene on chromosome 21q22.3 (3).

The 47;XXY; Klinefelter syndrome (KS) is a sex chromosomal syndrome first described by Klinefelter in 1942 (4) that approximately affects 1 in 660 newborn boys with only 10% being diagnosed before puberty (5,6).

Patients with KS show phenotypic variability but they are generally tall and present with perpetual primary

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testicular failure with reduced testicular volume and hypergonadotropic hypogonadism. In addition, developmental, psychosocial, behavioral, and learning impairments are frequent (7).

We are reporting two opposing growth syndromes in one boy who has typical Seckel features but with Klinefelter syndrome. The phenotype of primordial dwarfism dominates over the features of Klinefelter features. The 47;XXY child harbor a homozygous PCNT pathogenic mutation.

Case Presentation

The index is 3-year-old boy referred by endocrinology department because of short stature and developmental delay. He was born at 26-week gestation via vaginal delivery with a birth weight of 600 g, height 27 cm, and head circumference 19.4 cm. All below the 3rd centile for his matched gestational age. He stayed 3 months in intensive care for prematurity and required mechanical ventilation for 1 month. He was diagnosed with congenital hypothyroidism and maintained on L-thyroxin since birth. No family history of similar condition. The mother is 38 year and the father is 46 years of age.

He was failing to grow and has an odd and smallish face. Assessment at the age of 14 months showed severe retarded weight (3 kg), dwarf with length 49 cm, and microcephaly (OFC 35.5 cm). All were severely below the 3rd centile. He sat and crawled at 20 months and obtained 2–3 words at 3 years. The speech showed a high-pitched voice which was confirmed receptive and expressive dysfunctions.

Examination at 3 years showed prominent microcephaly (37 cm < 3rd centile), retarded weight (4.87 kg < 3rd centile), and height (62.5 cm < 3rd centile). He has micrognathia, deep-seated eyes, prominent and large nose, small mouth (Figure 1), spindle-shaped fingers, bilateral clinodactyly, small hands and feet, small and hypoplastic nails. The male genitalia showed micropenis with undescended testis. Audiology and ophthalmology assessments were normal. Skeletal survey showed generalized osteopenia and thin bone cortex and mild kyphoscoliosis.

Thyroid function test showed low free T4 (11.23; reference 12–22 pmol/l) with high TSH (29.34; reference 0.3–3.04 mlU/l). The serum insulin-like growth factor-1 and IGFBP-3 were normal. The routine karyotype analysis revealed 47 chromosomes with extra X chromosome (47;XXY). Chromosomal microarray (Agilent 180,000 probe platform) showed the presence of Y chromosome with duplication of X chromosome; thus, confirming Klinefelter syndrome. Parental karyotype and chromosomal microarray were normal. Looking for the cause of dwarfism, a research-based whole exome sequence performed and the result showed a nonsense pathogenic homozygous mutation in the *PCNT* gene (NM_006031.5:c.2374C>T: p.Arg792Ter).

Discussion

We describe herein a patient with a unique combination of proven microcephalic osteodysplastic primordial dwarfism and KS. The phenotype of MOPD ((MIM# 210720) dominates over the KF, demonstrating severe microcephaly, short stature, cognitive and speech delay with facial characteristics of primordial dwarfism.

In addition, the patient had bilateral cryptorchidism and micropenis; an earliest clinical presentation of KS during this age (7). The presence of severe growth failure as a major indication of karyotype led us to diagnose KS. However, short stature also contradicts the diagnosis of KS and a dual diagnosis was the likely key to explain his phenotype. The whole exome sequence solved this mystery and showed a nonsense pathogenic mutation in the *PCNT* gene; a gene that is highly linked to primordial dwarfism and the first one to be linked to PD (3).

The combined consequences of both syndromes, especially on patient's stature needed regular follow-up and favor the *PCNT* pathogenic effect and masked the KS phenotype.

PCNT gene encodes pericentrin protein (also called kendrin) and is responsible for MOPD type II ((MIM# 210720) and Seckel syndrome, both are now considered one homogenous spectrum of MOPD. There have been more than 50 cases published; however, up to our

Figure 1. *Showed typical Seckel-like face.*

knowledge, the MOPD is never been reported in patients with KS.

Few KS patients demonstrated short stature mainly associated with clear growth hormone deficiency (8–11); however, none has had coexisting detailed molecular testing as in our patient.

The phenotypes of primordial dwarfism caused by *PCNT* gene dominated over the features of Klinefelter feature. With its major impact in bipolar spindle formation and chromosome assembly in early meiosis, PCNT might play stronger and powerful effect on somatic growth as compared to even gross chromosomal aneuploidy.

Conclusion

We described a patient with both MOPD type II and Klinefelter syndrome. He has the typical phenotype of MOPD II than KS. Early diagnosis for both syndromes is essential in order to offer early treatment for the complications or to provide an appropriate counseling and intervention if needed.

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Consent for publication
Written consent was obtained from the parents.

Ethical approval
Ethical approval is not required at our institute to publish an anonymous case report.

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Declaration of conflicting interests
The authors declare that there is no conflict of interests.

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