First case of Bohring-Opitz syndrome inherited from the father

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INTRODUCTION

Bohring-Opitz Syndrome (BOS) is a rare congenital genetic disorder characterized by significant craniofacial dysmorphism, feeding difficulties, developmental delay and intellectual disability. Patients usually have characteristic body positioning known as BOS posture which is characterized by flexion of elbows with ulnar deviation, flexion of the wrists and metacarpophalangeal joints. More than 50 cases have been reported worldwide to date. In about 50% of them have different de novo heterozygous nonsense or frameshift mutations in ASXL1. Loss-of-function mutations ASXL1 are the major cause of this syndrome. Therefore the syndrome is considered as an autosomal dominant (AD) condition resulting from usually de novo mutations. However, individuals with BOS inherit the altered gene from their unaffected mother very rarely.

OBJECTIVES

Herein we present the first case of BOS inherited from the father in literature.

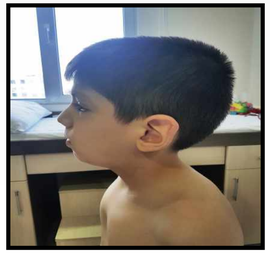

Figure 1. Frontal bossing and low set ear

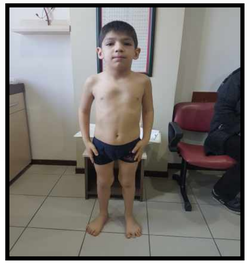

Figure 2. Slouching shoulders, bent elbows

CASE

A 7-year-old boy presented with a complaint of gait disturbance. The patient had been diagnosed with hereditary sensorimotor neuropathy in another clinic and genetic analysis including karyotype, PMP22, and MFN2 (mitofusin) gene mutation were all normal. The patient's motor skills and development were appropriate for his age. He is the second child of healthy non-consanguineous parents. He was born after an uncomplicated pregnancy and an uneventful delivery weighing 3500 grams, measuring 50 cm and a head circumference of 35 cm. Physical examination revealed hypertelorism, hyperlaxity, frontal bossing, and low set ear (figure 1). He had characteristic body position as slouching shoulders, bent elbows and wrists with ulnar deviation (figure 2, video 1). Brain and spinal MRI, electroencephalography, electroneuromyography, echocardiography and WISC-R test were all normal. Whole exome analysis revealed pathogenic heterozygous ASXL1 gene c.3908A>G(p.K1303R) mutation which was also detected in his father. Since difference in missing penetrans and expressivity is a feature of AD disorder and dysmorphic features consistent with BOS, he was diagnosed as BOS.

DISCUSSION

Bohring-Opitz syndrome is characterized by multisystem abnormalities, significant craniofacial dysmorphism, feeding difficulties, severe developmental delay, profound intellectual disability, and recognizable BOS posture. One of the characteristic findings of the syndrome is “BOS posture”, which consists of the external rotation and/or adduction of shoulders, with flexion at the elbows and wrists and ulnar deviation of the wrists and/or fingers at the level of the metacarpophalangeal (MCP) joint (video 1). Gait disturbances may be seen in patients due to this posture disorder and developmental delay as in our patient. Craniofacial dysmorphism is another cardinal finding of the syndrome including microcephaly, trigonocephaly, palatal abnormalities, prominent eyes, and hypoplastic supraorbital ridges, upslanting palpebral fissures, depressed nasal bridge, and anteverted nares, facial nevus flammeus, low-set, posteriorly angulated ears. Although our patient did not have microcephaly, he had hypertelorism, hyperlaxity, frontal bossing and low set ear. Some patients with BOS may have congenital anomalies such as structural brain abnormalities, cardiac genital and renal abnormalities. Our case did not have any other congenital anomalies.

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DISCUSSION

Bohring-Opitz syndrome is caused by mutations in the ASXL1 gene which is located on chromosome 20q11. The ASXL1 gene regulates the expression of HOX which play important roles in development before birth. Although BOS is considered an autosomal dominant condition resulting from usually de novo mutations. Very rarely, individuals with BOS inherit the altered gene from their unaffected mother, who has the mutation only in some cells, including egg cells, but not in others. On the other hand, there is no case in the literature with healthy maternal or paternal transmission as AD inheritance, which is explained by the variable expressivity and clinical presentation in AD diseases. We report for the first time a case of BOS inherited from an unaffected father as AD inheritance.

CONCLUSIONS

Children with BOS can be presented with gait disturbances due to BOS postüre similar to our patient. To the best of our knowledge, this case is the first case of BOS inherited from an unaffected father in literature.

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