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Presentation of Kleefstra syndrome: A case report

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ABSTRACT

Kleefstra syndrome is a genetic disorder that may involve different parts of the body, but its main characteristics are intellectual disability and childhood hypotonia. We report a 10-year-old mentally retarded male patient who presented with seizure. His medical history revealed recurrent upper respiratory infections, neurodevelopmental delay, and epilepsy. It was also found that he had had a hospitalization in the neonatal intensive care unit for five days due to tachypnea, low APGAR score, and meconium aspiration syndrome. His brain MRI had shown some degree of distension of the lateral cerebral ventricles with the basal cistern. The electromyography and the nerve conduction velocity were however normal. He was diagnosed with Kleefstra syndrome by the loss of the EHMT1 gene. He is now under treatment by piracetam and work-therapy. This is the second case report of this syndrome in Iran. This case presentation aims to improve the diagnosis of Kleefstra syndrome patients, as a rare syndrome with non-characteristic manifestations.

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Introduction

Childhood hypotonia and corresponding particular facial dysmorphisms along with intellectual disability are the main characteristics of Kleefstra syndrome. In 75% of the cases, a heterozygous microdeletion at chromosome 9q34.3, which overlaps the euchromatin histone methyltransferase 1 (EHMT1) gene, is responsible, and in the rest of the cases, a heterozygous intragenic pathogenic variation in the EHMT1 gene is known as the cause (1). A mental retardation syndrome has been reported, linked to submicroscopic subtelomeric deletions of chromosome 9q (2). Epileptic seizures, severe mental retardation without speech development, brachycephaly and microcephaly, distinct facial characteristics, heart defects, and an infantile weak muscle tone are the major syndromic features of these patients (3). In the phenotype of the syndrome, intellectual disability, developmental delay, typical facial features such as brachycephaly and microcephaly, an unusual form of eyebrows, hypertelorism, thickened lower lip, short nose with anteverted nostrils, flat face, macroglossia, and childhood hypotonia are usually present in all the patients (4).

No specific evidence has been provided about the correlation of genotype and phenotype correlation throughout the clinical and molecular characteristics of both the 9q34.3 microdeletion patients and the ones with an intragenic EHMT1 mutation in Kleefstra syndrome (5). Therefore, genetic identification of patients with such clinical symptoms is beneficial. In this case report, we present a case with Kleefstra syndrome.

Case presentation

A 10-year-old mentally retarded male patient was referred to our pediatric neurology depart-

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ment with a generalized tonic-colonic seizure. He was under treatment by carbamazepine. In his medical history, he had a hospitalization in the neonatal intensive care unit (NICU) for five days due to tachypnea, low APGAR score, and meconium aspiration syndrome. There was however no hydrocephaly or other pathologic exams in his neonatal examination reports. He had had no problem until five months after birth, but he had recurrent upper respiratory infections during his infancy. At the age of 5.5 months, his parents noticed his neurodevelopmental delay. A sample patient with Kleefstra syndrome is presented in Figure 1.

Figure 1. A sample patient with Kleefstra syndrome

A brain magnetic resonance imaging (MRI) had been performed for him, and a genetic analysis had been done. His deep tendon reflexes had decreased during the examination. His brain MRI showed some degree of distension of the lateral cerebral ventricles with the basal cistern. The electromyography and the nerve conduction velocity were normal. His high-performance liquid chromatography of amino acids was normal as well. Mucopolysaccharidosis disorders and inborn errors of metabolism were ruled out for him. Cardiology consultation was normal too. He had caught seizures with a tonic-colonic presentation at three years of age. In the electroencephalogram, there were epileptic discharges. His walking and speech had delayed. There was no pathologic point in his cerebellar, and other exams were normal. His seizure was controlled for four years, but his walking was disturbed. He had hearing loss and was a candidate for a cochlear implant because of the disturbed auditory brainstem response (ABR) test, but his hearing gradually improved.

His seizure relapsed at the age of seven and nine years. Thereafter, his seizure had being managed with carbamazepine. His intelligence quotient (IQ) was calculated as 60-70, and he had mental retardation. His gait is now ataxic and spastic and has a wide-based pattern. A chromosomal array study showed chromosome 9 (9q34.3) deletion in EHMT1 gene syndrome indicating Kleefstra syndrome. He is now under treatment by piracetam and work-therapy. Figure 2 shows his karyotype indicating a normal male pattern.

Discussion

Here, we report a case of an Iranian 10-year-old male with Kleefstra syndrome. Our reported case had recurrent upper respiratory infections, neurodevelopmental delay, decreased deep tendon reflexes, brain ventriculomegaly, seizures, delay in walking and speech development, and mental retardation. By a chromosomal array study, we confirmed the syndrome.

Kleefstra syndrome has recently been found to be associated with intellectual disability, presented with childhood hypotonia and typical facial dysmorphism. In around 75% of the reported cases, a subtelomeric deletion at chromosome 9q34.3 has been reported, and the other cases were associated with a heterozygous pathogenic variant of the EHMT1 gene (6). For the two genotypes, similar phenotypic features such as cardiac defects, obesity, and seizures have been reported.

Different manifestations for this syndrome have been reported. Torga et al. presented an 11-year-old male with Kleefstra syndrome, who had an isolated micropenis, and was suffering from possible hypogonadotropic hypogonadism (7). Prenatal diagnosis of this syndrome is rarely reported. Only three prenatally diagnosed cases were featured 'pure' deletions, in which only the 9q34.3 region was involved (8-10). In the case reported by Guterman et al. (8), similar to our study, the karyotype was normal, and there were no chromosome rearrangements. However, in some other cases, the 9q34.3 deletion was accompanied by additional chromosomal anomalies, such as a ring chromosome 9 with deletion of the chromosome's short and long arms reported in two cases (11, 12), and an unbalanced chromosome translocation seen in one case (13). Kleefstra syndrome has been characterized well with details (14), and some reports presented the Kleefstra syndrome descriptions (15, 16). Maternal somatic mosaicism for interstitial 9q34.3

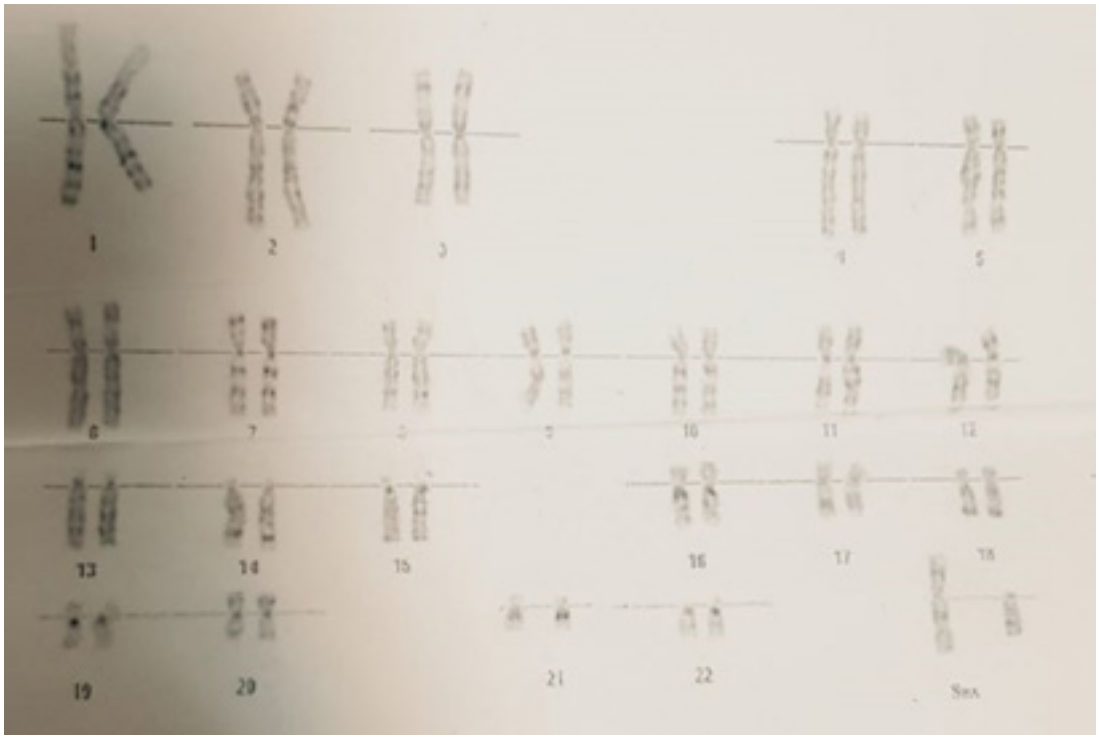

Figure 2. karyotype of normal male pattern

microdeletions is recorded in familial cases (17), while donor splice site mutation in EHMT1 (18) and ring chromosome 9 (19) are the other scenarios behind the Kleefstra syndrome. The reported etiology of this syndrome in most studies is linked to the malfunction of the EHMT1 gene (20). The encoded protein is a histone methyltransferase that methylates the histone H3 in Lys-9 and marks it for transcriptional repression and silencing of MYC-responsive and E2F-responsive genes. It could therefore be involved in the G0/G1 cell cycle transition (21).

Conclusion

We report a 10-year-old mentally retarded male patient diagnosed with Kleefstra syndrome. The presented case is the second report of Kleefstra syndrome in Iran. The 9q34 microdeletion has a critical role in Kleefstra syndrome by haploinsufficiency of the EHMT1 gene. This case report aimed to improve the diagnosis of such Kleefstra syndrome patients that suffer from developmental delay, epilepsy, and recurrent upper respiratory infections. This report could be beneficial to the diagnosis of such rare cases and the management of families with Kleefstra syndrome patients with no history in their family. According to the principles of follow-up in Kleefstra syndrome diagnosis, a cardiac consult is recommended to be performed.

Conflict of Interest: None

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