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Case Reports

Kleefstra Syndrome: One Diagnosis to Remember

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Abstract

Introduction: Kleefstra Syndrome is a rare genetic neurodevelopmental syndrome characterized by the presence of multiple congenital defects. Patients present a large variety of clinical symptoms: psychomotor delay and speech development, intellectual disability, muscular hypotonia and characteristic facial dysmorphic features. The cause of the syndrome is submicroscopic deletion in the chromosomal region 9q34.3 or an intragenic mutation of the Euchromatin Histone Methyltransferase 1 (EHMT1) gene.

Case Report: We present the case of a 3-year-old girl with psychomotor developmental delay and distinctive facial features in whom the diagnosis of the genetic syndrome was established at the age of 2 years by chromosome analysis using array-base comparative genomic hybridization (aCGH), which showed a pathogenic variant involving EHMT1. On physical examination, she had peculiar facies, with mild and nonspecific dysmorphia, and important hypotonia. She is currently doing progresses, supported by rehabilitation and with a multidisciplinary medical approach.

Discussion: Early diagnosis is extremely important for children and their families as it allows quick establishment of an adequate surveillance program, which has a great impact on improving the quality of life and prognosis for this children. This case presentation aims to alert for the diagnose of Kleefstra syndrome, as a rare syndrome with non-characteristic manifestations.

Keywords: Kleefstra syndrome; 9q34; Global Developmental Delay; Autism Spectrum Disorder; Childhood Hypotonia.

Abbreviations

KS: Kleefstra Syndrome; EHMT1: Euchromatin Histone Methyl Transferase 1; aCGH: Array-Base Comparative

Genomic Hybridization; ASD: Autism Spectrum Disorder; WES: Whole-Exome Sequencing

Introduction

Kleefstra syndrome (KS) is a rare autosomal dominant disorder caused by either a deletion of the subtelomeric region of the chromosome 9q or by a loss of function mutation in the EHMT1 gene. EHMT1 encodes a histone H3 Lys 9 methyltransferase and is thereby involved in chromatin remodeling [1-3].

Males and females are affected equally and almost all cases reported to date are sporadic [1,3].

KS is estimated to affect 1:25,000 to 1:35,000 individuals but the real prevalence may be higher as many individuals are not diagnosed properly [1].

Common features associated with KS are developmental delay, intellectual disability (usually moderate to severe and associated with severe speech delay), autism spectrum disorder, childhood hypotonia, hearing and visual impairment and distinct facial features (hypertelorim, synophrys, midface hypoplasia, microcephaly, full everted lower lip, cupid bowed upper lip, protruding tongue and prognathism) [2-4].

Additional clinical features include congenital heart and urogenital defects, severe respiratory infections, epilepsy / febrile seizures, nonspecific brain abnormalities (structural defects, cortical hypoplasia or white matter defects) and overweight. In adolescence and adulthood patients may also experience developmental regression and psychiatric disorders [1-3].

There are some disorders to consider in the differential diagnosis of KS: Down syndrome, Smith-Magenis syndrome, Pitt-Hopkins syndrome, Angelman Syndrome, autism spectrum disorder (ASD), attention deficit and hyperactivity disorder, KMT2C-associated syndrome and MBD5 haploinsufficiency [1].

Treatment is primarily supportive. Ongoing routine pediatric care by a pediatrician or neurologist and psychiatrist is recommended [1].

Case Presentation

We report the case of a caucasian girl, with no familiar background of interest. She was born at 40 weeks after a normal vaginal delivery, with the appropriate weight for gestational age, Apgar score 9/10 and no reported complications.

In the first days of life it was detected a heart murmur along the left edge of the sternum requiring consultation. The echocardiogram examination revealed a large patent ductus arteriosus, without hemodynamic consequences.

Within the first five months of life, she evolved to psychomotor developmental delay and notable findings on examination that includes hypotonia, hypertelorism, epicanthus, slight midfacial hypoplasia, short nose, depressed nasal bridge and protruding tongue.

Inability to follow objects properly led to ophthalmologic observation, leading to the diagnosis of hyperopia and congenital strabismus.

At this time an audiometry test was also conducted but it did not reveal any signs of hearing loss.

Cerebral ultrasound was performed at 3 months old and was normal. Considering all of these findings, she made and MRI that revealed mild ponto-mesencephalic hypoplasia and right frontal subcortical white matter hypomyelination, with uncertain pathological significance.

The girl was evaluated in neuropediatric and neurodevelopment pediatrics consultation every 3-6 months, maintaining severe psychomotor delay, supported by multi-profile rehabilitation.

Array-base comparative genomic hybridization (aCGH) has been requested but only detected a variant of unknown significance.

Therefore genetic study progressed to clinical whole-exome sequencing (WES) which detected a nonsense variant c.3178C>T (p.GIn1060Ter) in EHMT1 gene on heterozygosity.

She is currently 3 years old and shows a better eye contact, doesn't have functional language and presents wide base gear. Maintains a multidisciplinary approach in neurodevelopment, neurology, cardiology and ophthalmology consultation.

Neurodevelopmental assessment performed with the Griffiths Mental Developmental III Scale at 34 months indicates a global developmental delay (developmental quotient (DQ)< 50, P<1), with language, communication and social function as the worst areas (DQ<1, P<1).

Most recent echocardiogram showed mild pulmonary valve stenosis and small interauricular communication.

Till date she never had other problems related to his disease. She maintains speech therapy, occupational therapy and physiotherapy and is also accompanied in school by a local intervention team.

Discussion

KS can be a diagnostic challenge due to its rarity and very limited reports of this syndrome in the literature, therefor our case

report pretends to add further knowledge and emphasize the importance of a multidisciplinary approach in this condition.

This case had several clinical manifestations commonly observed in KS, including intellectual disability, delayed psychomotor development, autistic-like features, childhood hypotonia, child's characteristic facial morphology and congenital heart defects.

Diagnosis was established by genetic testing but it is important to reinforce that one of the most used methods (chromosomal microarray analysis) can sometimes be insufficient. WES generally enables a more precise delineation of the breakpoints, though many array platforms have poor coverage of the 9q subtelomeric region. We believe that identification of increasing numbers of patients with (smaller) deletions and EHMT1 mutations will probably further increase our knowledge of the phenotypic and genotypic spectrum of KS and will contribute to early diagnosis in other children. And so we will be able to implement appropriate therapeutic management and comprehensive care, which has a great impact on improving the quality of life and prognosis of this patients.

Conflict of Interest

The authors have no conflicts of interest to declare.

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