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Ohdo-Madokoro-Sonoda Syndrome with a De Novo MED12 Mutation

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Case Report

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ABSTRACT

Ohdo syndrome is extremely rare and comprises a heterogeneous group of disorders characterized by intellectual disability (ID) and typical facial features, including blepharophimosis, ptosis, dental hypoplasia, hearing impairment and intellectual disability. So far, fewer than 30 patients have been reported with Ohdo syndrome, with a prevalence of 1/1 000 000. Most reported cases are sporadic, except the original cases of ohdo who described two affected sisters and a first cousin, suggesting autosomal recessive inheritance. Autosomal dominant, X-linked- and mithochondrial inheritance have also been suggested.

We report the case of a 5-year-old girl, born to healthy, non-consanguineous parents, with no other family members known to be affected by a similar disorder. She exhibited significant dysmorphic facial features, including blepharophimosis, dental hypoplasia, hypertélorism, rétrognatism, microcephaly, trigonocéphaly, microphthalmia, nasolabial furrow, badly hemmed ear, and a pointed palate. These features were associated with psychomotor and growth retardation of less than 2 Standard deviations. Using whole exome sequencing (WES), we discovered the variant

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NM_005120.3 (MED12):c.6352C>T(p.Gin2118Ter) in the heterozygous state and its absence in the parents, confirming the de novo nature of this variant, which is compatible with the diagnosis of ohdo syndrome due to a heterozygous mutation of the MED 12.

Keywords: Ohdo-Madokoro-Sonoda syndrome; dysmorphic facial features; intellectual disability; heterozygous mutation of MED 12.

1. INTRODUCTION

Ohdo et al. [1] delineated "a syndrome characterized by blepharophimosis, ptosis, dental hypoplasia, heart defect, and mental handicap, to which his name is currently attached. In the following years, other cases of ''Ohdo syndrome'' were reported, with large clinical variability beyond the presence of the palpebral anomaly. Most cases were sporadic".

2. CASE PRESENTATION

A 5 year-old girl was born on January 4, 2018, to healthy and non-consanguineous parents following a monitored pregnancy. The delivery was vaginally, the second for a gravida 3 Para 3 mother. Her Birth weight was 3300 g. Her medical history is notable for a hospitalization on the 7th day of life for 13 days due to neonatal respiratory distress. Although her two sisters are healthy, no other family members are known to be affected with a similar disorder. Developmental delays were noted: she began to sit at 24 months, walk at 03 years, and by the age of 4, she was able to speak a few words.

On physical examination, her height was 96, 5 cm (-2 SD), weight 15 kg (Median), and head circumference 46 cm (-2 SD). She had marked dysmorphic facial features, including blepharophimosis, dental hypoplasia, hypertélorism, rétrognatism, microcephaly, trigonocéphaly, microphthalmia, a nasolabial furrow, badly hemmed ears, and a pointed palate, all associated with psychomotor retardation and growth retardation below -2 SD, No heart murmur was noted.

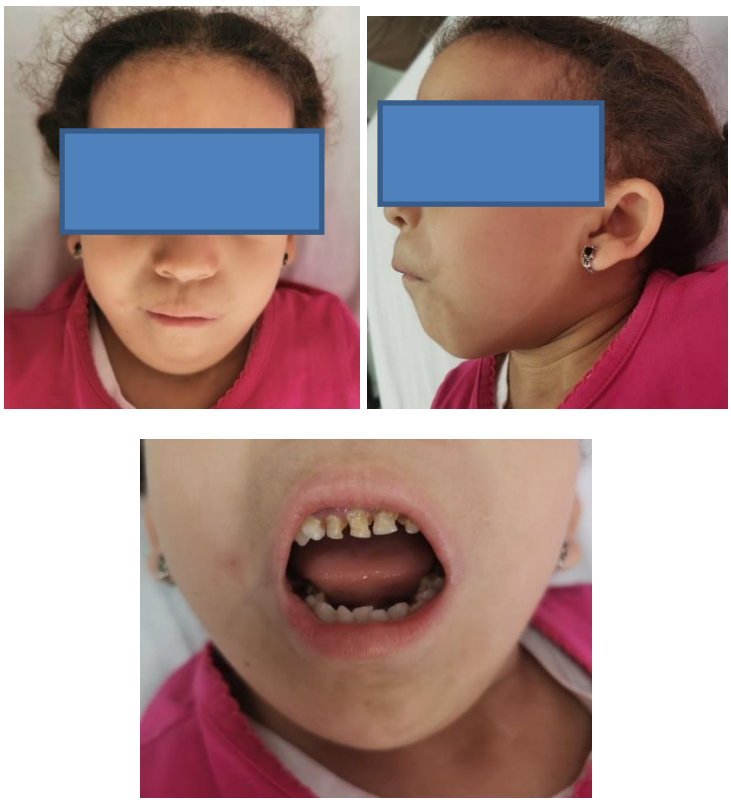

Fig. 1. Facial features of our patient include blepharophimosis, a wide and flat nasal bridge, small and simple ears, and small teeth

Ophtalmological examination: squamous blepharitis, severe hypertelorism and epicanthus, a limbic dermolipoma in the left eye, and hypoplastic papillae with tortous macula vessels having an appearance reminiscent of cherry-red spot, chorioretinal atrophy.

Heart and abdominal ultrasonography and a cranial CT scan were normal.

Karyotype and array-CGH did not show any pathogenic chromosomal imbalance.

Exome sequencing showed the presence of the variant NM_005120.3 (MED12):c.6352C>T(p.Gin2118Ter) in the heterozygous state and its absence in the parents, which confirms the de novo character of this variant , which is compatible with the diagnosis of ohdo syndrome by heterozygous mutation of MED 12.

3. DISCUSSION

Previous reports by Ohdo et al, Say and Barber have documented “the existence of a syndrome which includes dysmorphic facial features (most prominently blepharophimosis), intellectual disability, and limb anomalies” [2].

Ohdo syndrome is extremely rare, characterized by intellectual disability (ID) and typical facial features, including blepharophimosis, ptosis, dental hypoplasia, hearing impairment and intellectual disability, male patients may show cryptorchidism and scrotal hypoplasia, to which the syndrome’s name is currently attached.

So far, fewer than 30 patients have been reported with Ohdo syndrome, including both familial and sporadic cases, with a prevalence of 1/1 000 000.

“The blepharophimosis-ID syndromes have been classified into five distinct subgroups. The first group can be distinguished from the others as it is caused by deletions of the short arm of chromosome 3. The second group is designated as the Ohdo type”, based on the original report by Ohdo et al. [3,1] “These individual present with typical features of prognathism, a short philtrum, and proteinuria, while hypotonia, abnormal growth, and limb defects are absent. The Verloes type is a more severe condition with severe microcephaly, epilepsy, brain malformations, adducted thumbs, and abnormal genitals” [3]. “The most clinically distinctive phenotype is the Say/Barber/ Biesecker/Young/Simpson (SBBYS) type (MIM 603736), characterized by striking facial dysmorphisms, including a large to bulbous nasal tip; small and/or dysplastic, thick, simple, or overfolded pinnae; thick swollen cheeks; and retrognathia. Additionally, hypotonia, hyperextensible joints, cryptorchidism, and a wide range of congenital anomalies are present”. [3,4] “This type was recently shown to be caused by mutations in lysine acetyltransferase 6B (KAT6B [MIM 605880])” [5].

Beseecher’s case and that described by Say and Barber [4] offer little insight into the inheritance pattern of this disorder; the report of Ohdo et al [1] is puzzling in this respect. They propose that the pedigree is compatible with multifactorial, autosomal recessive, and autosomal dominant modes of inheritance. It is reasonable to propose multifactorial or autosomal dominant inheritance (with variable penetrance), but it is unlikely that a rare autosomal recessive disorder would affect cousins in the absence of consanguinity or non-paternity. Mitochondrial or X linked inheritance is unlikely with transmission through the father in the report of Ohdo et al. [1] Although it is possible that a submicroscopic chromosomal abnormality could be present in the case of Say and Barber [6] the cases of Ohdo et al. [1] would be incompatible with this etiology [2].

“The family reported by Ohdo had an inheritance pattern that was suggestive of a cryptic rearrangement” [3].

“The majority of reported cases are sporadic, with the exception of the initial cases of ohdo which involved two affected sisters and a first cousin, indicating autosomal recessive inheritance. Autosomal dominant, X-linked, and mithochondrial inheritance have also been proposed” [7].

Mhanni et al (1998) reported “vertical transmission of ohdo syndrome from mother to son, suggesting autosomal dominant inheritance. The possibility of X–linked or mitochondrial inheritance cannot be ruled out based on this case. Considering previously reported cases, the authors suggested that autosomal dominant inheritance with incomplete penetrance is most likely. Genetic heterogeneity is also possible”.

Moncla et al. [1995] first noted to “the overlap between Young–Simpson syndrome, Ohdo syndrome, and del (3) (pter) syndrome”. Clayton-

Smith et al. [5] proposed “distinguishing Ohdo syndrome (for the original family) from Ohdo-like syndrome, an entity that encompasses most of the patients described as Ohdo syndrome”. Finally, Marques-de-faria et al. [2000] hypothesized that “Ohdo syndrome and Young–Simpson syndrome may belong to the same clinical spectrum” [2].

White et al (2003) reported “2 cases of ohdo syndrome, one with mild and the other with severe features, illustrating the phenotypic variability of the condition. The authors noted that all cases with the severe phenotype were sporadic. Subtelomeric FISH studies of both 2 cases showed no abnormality”.

Using whole exome sequencing (WES), we identified the variant NM_005120.3 (MED12):c.6352C>T(p.Gin2118Ter) in the heterozygous state and its absence in the parents confirms the de novo nature of this variant , which is compatible with the diagnosis of ohdo syndrome caused by heterozygous mutation of the MED 12.

“MED12 is a part of a protein complex involved in the regulation of the majority of RNA polymerase II-dependent genes. It encodes the mediator of RNA polymerase II transcription subunit 12” [8]. “Mutations in the MED12 gene are known to alter cell-fate decisions and lead to a variety of pathologic conditions including developmental defects, cancers and heart development” [9,10].

“Mutations in MED12 have been linked to several forms of XLID, including Opitz-Kaveggia syndrome also known as FG syndrome (MIM #305450), Lujan-Fryns syndrome (MIM #309520) and the X-linked Ohdo syndrome (OSMKB subtype) (MIM #300895)” [11-13,7].

“Typically associated with X-linked disorders, most patients with MED12 mutations are males inheriting the missense variant from carrier mother unaffected by the condition” [14]. “Recently, however, females with MED12 variants have also been identified” [15,11,16]. Various types of variants including missense, nonsense and frame shift mutations have been observed.

4. CONCLUSION

Ohdo syndrome is a syndrome of multiple congenital malformations, very rare. Its managements require multidisciplinary collaboration and varies according to the deficiency, the child’s age, and the difficulties they face.

In this paper, we have substantiated the role of the MED12 gene in Intellectual Disability (ID). Despite the limited number reported of MED12 mutations, defining genotype–phenotype correlations remains challenging. Mutations across various protein regions may lead to variable clinical outcomes, potentially resulting in either more severe cognitive impairments or more prominent dysmorphic features.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

CONSENT

As per international standards, parental written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standards or university standards written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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