Case Report
Volume 17:06, 2023

Journal of Molecular and Genetic Medicine

ISSN: 1747-0862 Open Access

Mowat Wilson Syndrome – Expanding the Phenotype by Mutation ZEB2: A Case Report of a Rare Entity and Literature Review

Danielly Viana Monteiro Santos*[1], Danilo Tokechi Amaral[1], Nathalia Teixeira Hatano[2], Leonardo Furtado Freitas[3], Catherine Marx[4] and Lazaro Luis Faria do Amaral[1]

[1]*Department of Radiology, Hospital Beneficência Portuguesa of São Paulo University, São Paulo, Brazil*
[2]*Department of Radiology, Hospital DF Star, Federall District, Brazil*
[3]*Department of Radiology, University of Iowa Health Care, Iowa, United States*
[4]*Department of Neurology and Neurosurgery, Federal University of Sao Paulo, São Paulo, Brazil*

Abstract

Mowat-Wilson Syndrome (MWS) is a syndrome with multiple congenital abnormalities first clinically delineated by Mowat DR, et al. in 1998. All affected patients exhibit typical dysmorphic features in association with severe intellectual disability and most have microcephaly and seizures. Congenital anomalies such as Hirschsprung disease, congenital heart disease, hypospadias, genitourinary malformations, corpus callosum agenesis and short stature are also common. There is no consensus on clinical diagnostic criteria, but MWS should be suspected in individuals with the aforementioned clinical features and head imaging findings. We report a full-term male newborn with microcephaly, congenital megacolon, hypospadias, facial dysmorphism and heart defect. Thus, MWS was suspected and later confirmed by a mutation analysis of the ZEB2 gene.

Keywords: Review Mowat-Wilson syndrome • Identify the clinical features of this syndrome • List the main findings image • Know your main differential diagnoses

Introduction

Mowat–Wilson Syndrome (MWS) is a multiple congenital anomaly syndrome, first clinically delineated by Mowat DR, et al. in 1998. All afflicted patients exhibit typical dysmorphic features in association with severe intellectual disability and most have microcephaly and seizures. Congenital anomalies such as Hirschsprung disease, congenital heart disease, hypospadias, genitourinary anomalies, agenesis of the corpus callosum and short stature are also common. The syndrome is the result of heterozygous deletions or point mutations in the Zinc finger E-box-binding homeobox 2 gene (ZEB2), at locus 2q22-23. The exact incidence rate is currently unknown because MWS is still an underdiagnosed condition, but it is believed to be at least 1 in 70,000 live births. There is no consensus on clinical diagnostic criteria, but MWS should be suspected in individuals with the typical clinical features and head imaging findings.

Methods

Medical records including the diagnostic evaluations were reviewed. DNA was extracted from peripheral blood for molecular analysis by exome sequencing. A search of the relevant literature was conducted in the PubMed, EMBASE, Cochrane Library, CINAHL and LILACS online databases with the following keywords: “Mowat-Wilson Syndrome,” “mutation ZEB2” and “Magnetic Resonance Imaging".

Case Presentation

A male full-term newborn was admitted at the NICU due to failure to pass meconium for the first 72 hours following delivery, who received the diagnosis of congenital megacolon after complimentary diagnosis workup (abdominal radiographs showed multiple dilated loops of bowel with absence of distal air, consistent with a distal bowel obstruction). He was the third child of non-related parents, delivered by C-section after an uneventful gestation with Apgar scores of 9 and 10 at the 1st and 5th minutes, respectively. Birthweight was 3,340 g (appropriate for gestational age); length, 52 cm; head circumference, 33.5 cm. Other congenital abnormalities were described such as hypospadias and cardiac defect. Karyotype was normal (46, XY).

On his seventh month of life, he was referred to a child neurologist after failure to thrive. He was able to control head movements at the age of five months, hold objects and get them to the midline position, turn side to side, but was incapable of sitting or rolling. Upon neurological examination he presented head circumference of 39.5 cm (microcephaly), weighted 7,490 g, was alert, could follow the examiner´s face, established good eye contact and smiled. Parents referred he babbled to himself; however, this was not noted. He presented trunk hypotonia with normal deep tendon reflexes. Besides hypospadias, some other features were highlighted: such widely spaced eyes, broad eyebrows with medial flare, broad nasal bridge, prominent columella, low set ears, uplifted ear lobes and open mouth with M-shaped upper lip.

The Magnetic Resonance Imaging (MRI) of the brain revealed craniofacial disproportion with facial predominance (microcephaly), macrocerebellum, hypertelorism and dysplasia of the corpus callosum (thin, shortened and with the splenium turned posteroinferiorly).

Whole-Exome Sequencing (WES) displayed the c.2168del variant, identified in the ZEB2 gene, characterized by the deletion of a nucleotide at

***Address for Correspondence:** Danielly Viana Monteiro Santos, Department of Radiology, Hospital Beneficência Portuguesa of São Paulo University, São Paulo, Brazil; Tel: +55 79996282619, E-mail: danivms.dm@gmail.com, dvmsantos@outlook.com*

Received: 06 October, 2023, Manuscript No. jmgm-23-116021; **Editor assigned:** 09 October, 2023, PreQC No. P-116021; **Reviewed:** 20 October, 2023, QC No. Q-116021; **Revised:** 25 October, 2023, Manuscript No. R-116021; **Published:** 01 November, 2023, DOI: 10.37421/1747-0862.2023.17.633

the 2168 position of exon 8, which leads to a change in the reading frame (frameshift) by promoting the replacement of the amino acid threonine in codon 723 by a lysine, with consequent arrest protein translation 11 positions ahead (p.(Thr723Lysfs*11)), resulting in a truncated protein. According to the American College of Medical Genetics and Genomics (ACMG) guidelines for variant classification, this variant was considered "likely pathogenic".

Results and Discussion

MWS is an autosomal dominant disorder caused by a pathogenic variant in ZEB2, a heterozygous deletion of 2q22.3 involving ZEB2, or (rarely) a chromosome rearrangement that disrupts ZEB2. Almost all individuals reported to date have been simplex cases (i.e., a single occurrence in a family) resulting from a *de novo* genetic alteration; rarely, recurrence in a family has been reported when a parent has a low level of somatic or presumed germline mosaicism for a MWS-causing pathogenic variant. Individuals with MWS are not known to reproduce. Once the causative genetic alteration has been identified in the proband, prenatal testing may be offered to parents of a child with MWS because of the recurrence risk associated with the possibility of parental mosaicism or a balanced chromosome rearrangement.

The prevalence of MWS is estimated to be between 1:50,000 and 1:70,000 live births.

Formal clinical diagnostic criteria for MWS have not yet been published. However, the facial features are recognizable and, when accompanied by head imaging findings and other features of the condition, can establish the clinical diagnosis.

Distinctive craniofacial features are one of the most specific findings, present in more than 90% of affected individuals, include: large, deep-set eyes; hypertelorism; large medially flaring and sparse eyebrows; rounded nasal tip; prominent columella; M-shaped upper lip; pointed triangular chin; uplifted, fleshy ear lobes with a central depression; microcephaly.

Additional features are congenital heart defects with predilection for abnormalities of the pulmonary arteries and/or valves, Hirschsprung disease or chronic constipation, genitourinary anomalies (particularly hypospadias in males) and hypoplasia or agenesis of the corpus callosum. The majority of affected individuals have moderate-to-severe intellectual disability. Speech is typically limited to a few words or is absent, with relative preservation of receptive language skills. Growth restriction with microcephaly and seizure disorder are also common. Most have a happy demeanor and a wide-based gait that can sometimes be confused with Angelman syndrome.

Other syndromic forms of HSCR can be considered as a differential diagnosis of MWS, such as X-linked hydrocephalus and Coffin-Siris syndrome.

The spectrum of brain structural abnormalities in a neuroimaging study of MWS include anomalies of the complete or partial ACC, hypoplasia of corpus callosum (thin corpus callosum), hippocampal abnormalities (particularly malrotation), reduction of white matter thickness and anomalies in the cerebral ventricles such as dilatation and temporal horn enlargement. Less common but relevant findings are large basal ganglia, polymicrogyria, nodular periventricular heterotopia, cortical dysplasia, cerebellar hypoplasia, Chiari type 1 malformation and localized signal alteration of white matter [1-6] (Figures 1 and 2).

Figure 1. Physical examination of the patient shows facial dysmorphisms with such widely spaced eyes, broad eyebrows with medial flare, broad nasal bridge, prominent columella, low set ears, uplifted ear lobes (arrowhead) and open mouth with M-shaped upper lip (arrow).

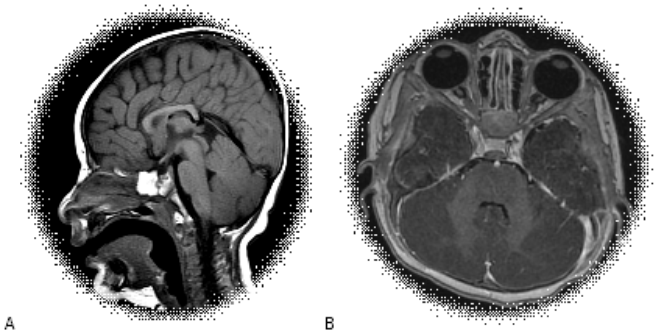

Figure 2. A) Sigittal T1WI and **B)** Axial T1WI Gd reveal craniofacial disproportion with facial predominance (microcephaly), macrocerebellum, hypertelorism and hypoplasia of the corpus callosum (thin, shortened and with the splenium turned posteroinferiorly).

Conclusion

MWS is still an underdiagnosed condition, but with careful and detailed observations of the neurological clinic with a detailed physical examination, previous history of Hirschsprung's disease and neuroimaging features, it seems likely that more patients will be described. With this case report, we wish to contribute to a further delineation of this quirky entity.

Informed Consent Statement

Written informed consent was obtained from the patient's guardian for the publication of this case report (including images, case history and clinical data).

Acknowledgement

None.

Conflict of Interest

None.

References

1. Garavelli, Livia, Ivan Ivanovski, Stefano Giuseppe Caraffi and Daniela Santodirocco, et al. "Neuroimaging findings in Mowat–Wilson syndrome: A study of 54 patients." *Genet Med* 19 (2017): 691-700.
2. Garavelli, Livia and Paola Cerruti Mainardi. "Mowat-Wilson syndrome." *Orphanet J Rare Dis* 2 (2007): 1-12.
3. Moore, S. W. "Hirschsprung's disease and the brain." *Pediatr Surg Int* 27 (2011): 347-352.
4. Mowat, D. R., G. D. Croaker, D. T. Cass and B. A. Kerr, et al. "Hirschsprung disease, microcephaly, mental retardation, and characteristic facial features: Delineation of a new syndrome and identification of a locus at chromosome 2q22-q23." *J Med Genet* 35 (1998): 617-623.
5. Paz, José Albino da, Chong Kim, Michael Goossens and Irina Giurgea, et al. "Mowat-Wilson syndrome: Neurological and molecular study in seven patients." *Arq Neuro-Psiquiatr* 73 (2015): 12-17.

6. Adam, Margaret P., Jessie Conta and Lora JH Bean. "Mowat-Wilson syndrome." (2019).

How to cite this article: Santos, Danielly Viana Monteiro, Danilo Tokechi Amaral, Nathalia Teixeira Hatano and Leonardo Furtado Freitas, et al. "Mowat Wilson Syndrome – Expanding the Phenotype by Mutation ZEB2: A Case Report of a Rare Entity and Literature Review." *J Mol Genet Med* 17 (2023): 633.