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RESEARCH ARTICLE

Hirschsprung's disease and Mowat-Wilson syndrome: should a pull-through be performed?

*Itzamara Martain-Pérez[1], Roberto Dávila-Pérez[1], Emilio Fernández-Portilla[1], Itzel Lizárraga-Rodríguez[1], Rodrigo Moreno-Salgado[2], Jaime Nieto-Zermeño[1], Adria Costa-Roig[1], and Alfredo Domínguez-Muñoz[1]**

[1]Colorectal Center, Department of Pediatric Surgery; [2]Department of Genetics. Hospital Infantil de México Federico Gómez, Mexico City, Mexico

Abstract

Background: *Hirschsprung's disease (HSCR) is characterized by the absence of ganglion cells. Five percent of cases are associated with syndromic conditions, one of which is Mowat-Wilson syndrome (MWS), with an incidence rate of 50%. HSCR may be the first feature of this syndrome to be diagnosed. MWS is an autosomal dominant genetic disorder caused by a variant in the ZEB2 gene (ZFHX1B). OMIM #235730. It involves severe clinical manifestations such as ocular hypertelorism, intellectual disability, congenital heart defects, epilepsy, and HSCR. The association between MWS and HSCR is regarded as a serious condition with unpredictable post-operative outcomes, and many reported complications related to motility disorders are noted.* **Methods:** *We conducted a retrospective study and reviewed the medical records of patients with MWS treated at our center. We examined the relationship among HSCR, clinical features, molecular characteristics, surgical complications, and pre-operative and post-operative enterocolitis events.* **Results:** *The study included four patients with MWS. Three (75%) were found to be associated with HSCR. Rectal biopsy confirmed HSCR in all patients. Two patients underwent a transanal pull-through Swenson procedure, and both experienced surgical complications. Both cases encountered multiple episodes of enterocolitis, and one of them required a permanent stoma. The third patient has not undergone surgical correction but has responded well to medical treatment (laxatives).* **Conclusions:** *The association between MWS and HSCR presents a severe condition with high morbidity. The outcome after the pull-through procedure is unpredictable. Further studies are necessary to gain a deeper understanding of this condition. We recommend evaluating these patients in a multidisciplinary consensus based on the existing literature and our findings. Those without recurrent enterocolitis or chronic motility disorders are suitable candidates for conservative management.*

Keywords: *Hirschsprung's disease. Mowat-Wilson syndrome. ZEB2.*

Enfermedad de Hirschsprung y síndrome de Mowat-Wilson: ¿debería realizarse un descenso transanal?

Resumen

Introducción: *La enfermedad de Hirschsprung es una entidad caracterizada por ausencia de células ganglionares; en el 5% de los casos llega a ser sindrómica. Uno de los síndromes más asociados (hasta 50%) es el síndrome de Mowat-Wilson, que es una enfermedad genética con variante en el gen ZEB2 (ZFHX1B), OMIM #235730. Localizada en el cromosoma*

***Correspondence:**
Alfredo Domínguez-Muñoz
E-mail: dominguezaalfredo@gmail.com

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2 (2:144,384,081), esta asociación sindrómica se considera una condición grave con resultados poco predecibles y complicaciones posquirúrgicas graves hasta en el 80% de los pacientes. **Métodos:** *Se llevó a cabo una revisión retrospectiva de registros hospitalarios de pacientes con diagnóstico molecular de Mowat-Wilson tratados en nuestra institución. Se analizaron los siguientes datos: asociación con enfermedad de Hirschsprung, características clínicas, estudio molecular, complicaciones quirúrgicas y eventos de enterocolitis preoperatorios y postoperatorios.* **Resultados:** *Se incluyeron cuatro pacientes con variantes patogénicas en ZEB2 con diagnóstico de Mowat-Wilson (tres de ellos [75%] asociados a enfermedad de Hirschsprung). Dos de los tres pacientes se detectaron en la etapa neonatal, cursando con eventos de enterocolitis; ambos se sometieron a descenso transanal tipo Swenson y ambos requirieron un redescenso transanal secundario a enterocolitis de repetición. El 100% cursó con complicaciones postoperatorias. La cuarta paciente ha cursado asintomática, sin tratamiento quirúrgico.* **Conclusiones:** *La asociación de enfermedad de Hirschsprung con Mowat-Wilson es una condición grave con alta morbilidad, con evolución posterior al descenso transanal poco predecible. A pesar de que se necesitan más estudios en el futuro recomendamos que el abordaje de los pacientes con esta asociación sea de manera multidisciplinaria y aquellos sin episodios frecuentes de enterocolitis son buenos candidatos para tratamiento conservador.*

Palabras clave: *Enfermedad de Hirschsprung. Síndrome de Mowat-Wilson. ZEB2.*

Introduction

Hirschsprung's disease (HSCR) is characterized by the congenital absence of enteric ganglion cells, at the Meissner's plexus (submucosa) and Auerbach's plexus (muscularis) of the terminal rectum that extends in a variable distance proximally[1-3], with the rectosigmoid segment being the most frequent. The estimated incidence rate is 1 in 4,417 live births, and approximately 5% of the cases show syndromic associations such as Mowat-Wilson syndrome (MWS)[3].

The MWS is an autosomal dominant genetic disease with an incidence of 1:50,000-1:70,000, resulting from a variant in the *ZEB2* gene (*ZFHX1B*), OMIM #235730, located on 2q22-q23 chromosome. *ZFHX1B* is a transcription factor with a critical role in the migration and maturation of the vagal crest cells during the embryonic period[4] and involves severe clinical manifestations such as ocular hypertelorism, intellectual disability, congenital heart defects, epilepsy, and HSCR. More than 300 individuals with MWS have been reported in the literature, with approximately 280 variants in the gene *ZEB2* (*ZFHX1B*), OMIM #235730[2,5].

One of the most classical components in the constellation of features found in children with MWS is the association with HSCR. This clinical association is present in 45-50% of patients[1,4,6,7] and is considered a severe condition. The phenotype also includes stereotypical movements and various congenital malformations, heart defects, corpus callosum agenesis, genitourinary system anomalies, and eye abnormalities[8]. The only genotype-phenotype correlation is based on differences in the clinical course of disease in patients with a point mutation in the *ZEB2*. Post-operative outcomes for patients with HSCR and MWS are unpredictable, and many issues regarding motility disorders have been reported. This study aims to analyze the management and outcome of patients with HSCR and MWS association.

Methods

We conducted a descriptive study of a series of cases. We included all patients with MWS who were treated at our institution between January 2011 and January 2024. We reviewed the patient's medical records to collect demographic, molecular, and clinical data.

We categorized the population into two groups: patients with MWS and HSCR and those without MWS and HSCR. Finally, we divided the patients into two subgroups: those who underwent surgical correction and those who received medical treatment. A detailed analysis was performed to determine postoperative complications (anastomosis leak or stenosis, small bowel obstruction, and the need for a reoperation) and long-term outcomes (recurrent enterocolitis, soiling, chronic motility disorder, and the need for a stoma diversion).

In our institution, the surgical technique used for HSCR is the transanal pull-through Swenson (TPTS) procedure. The protocol for recurrent enterocolitis after the pull-through procedure involves initiating rectal irrigations as the first step. In addition, a digital rectal exam is performed to exclude stenosis of the anastomosis, a contrast enema is performed to rule out twisting of the neorectum, and a histopathological review of the proximal margin of the resected colon is performed to exclude a histological

Table 1. Demographic data, molecular variant, and Mowat-Wilson syndrome characteristics

Patient	Gender	Age (years)	Gene mutation	Zygosity	OMIM	Variant in *ZEB2* gene	MWS characteristics	Rectal biopsy	HSCR type
1	Female	6	*ZEB2*	Heterozygous	16053902	*c.2761C>T* (P.Arg921)	Cardiac defect: ASD + PDA Brain defect: ID + DD + microcephaly Others: facial dysmorphic features, asplenia	Positive for HSCR	Rectosigmoid
2	Female	6	*ZEB2*	Heterozygous	16053902	c.2761C>T (P.Arg921)	Cardiac defect: PDA + ASD + PLVC. Brain defect: ID + DD + microcephaly Others: myopia, facial dysmorphic features.	Positive for HSCR	Short (according to contrast enema)
3	Male	12	*ZEB2*	Heterozygous	16053902	*c.425C>G* (p.Ser142)	Cardiac defect: Dextrocardia. Brain defect: ID + DD + ACC, Epilepsy Others: hypospadias, pyloric stenosis, facial dysmorphic features	Positive for HSCR	Rectosigmoid
4	Male	6	*ZEB2*	Heterozygous	235730	c.808-2A>G (p.?)	Cardiac defect: PDA + AS Brain defect: ID + DD + microcephaly, Epilepsy Genito-urinary: hypospadias, cryptorchidism Others: facial dysmorphic features, hypopigmentation of the skin, asplenia	No	No

ACC: agenesis of the corpus callosum; AS: aortic stenosis; ASD: atrial septal defect; DD: developmental delay; HSCR: Hirschsprung's disease; ID: intellectual disability; PDA: patent ductus arteriosus; PLVC: persistent left vena cava.

transition zone. In the scenario where all the mentioned studies are negative, we proceed to inject botulinum toxin into the anal sphincter, and we keep the patient on rectal irrigations and metronidazole for 3 months.

Results

Four patients diagnosed with MWS were included in the study. All had a pathogenic variant of the *ZEB2* gene (*ZFHX1B*), OMIM #235730. Three (75%) exhibited HSCR; two identical twins were among the four analyzed patients. The distribution included two males (50%) and two females (50%). Two males were full-term neonates, whereas the two females were premature. Furthermore, the two females were identical twins (Table 1).

MWS characteristics

All patients exhibited typical clinical manifestations, including facial dysmorphism (square-shaped face, large eyes), cardiac defects, moderate intellectual disability, and brain abnormalities. Further characteristics are detailed in table 1.

HSCR characteristics and surgical outcomes

Of the three patients with HSCR, two experienced the onset of symptoms during the neonatal period, marked by neonatal enterocolitis. The remaining patient exhibited constipation at the age of 5 years, and the diagnosis was suspected due to the presence of the association in his identical twin, along with the pathogenic variant of the *ZEB2* gene (*ZFHX1B*), OMIM #235730.

The rectal biopsy confirmed the diagnosis in all three patients. During the TPTS, the histopathological study identified a rectosigmoid variant in two cases (66%) that underwent surgical correction. The remaining patient has not had surgery, so the affected segment of the colon was estimated based on the contrast enema, which showed a short-segment variant.

Table 2. Hirschsprung's disease and surgical outcomes

Patient	Onset of symptoms	HSCR type	TPTS	Age at TPTS	Surgical complication	Number of enterocolitis events after TPTS	Second rectal biopsy	Redo TPTP	Surgical complication after redo TPTP	Others colorectal surgical procedures	Current managment
1	1 month (neonatal enterocolitis)	Rectosigmoid	Yes	2 months	No	13	Transition zone	2-year after TPTS	Anastomosis leak	4 botulism toxin application	Metronidazole + rectal irrigations
2	1 month (neonatal enterocolitis)	Short-segment	No	No	-	-	No	-	-	No	Senna (senosidos)
3	6 months (chronic constipation)	Rectosigmoid	Yes	2 months	Small bowel obstruction. Stoma creation	9	Transition zone	2-year after TPTS	No	Colostomy closure with anastomosis leak. Permanent stoma	Permanent colostomy

HSCR: Hirschsprung's disease; TPTS: transanal pull-through Swenson.

The clinical details for each patient are outlined table 2.

Patient one

At 2 weeks of age, an episode of neonatal enterocolitis was recorded. A rectal biopsy confirmed HSCR. A TPTS was performed at 2 months of age, and multiple episodes of enterocolitis and repeated hospitalizations were documented. Two years later, a second rectal biopsy showed a transition zone. The patient underwent a redo pull-through TPTS, complicated by an anastomosis leak that was treated with conservative management, but the episodes of enterocolitis persisted. She has received four injections of botulinum toxin and is undergoing rectal irrigations every 12 h, along with metronidazole.

Patient two

Started constipation at 6 months, and at 5 years of age, was seen for the 1st time in our institution due to fecal impaction. At the physical examination, the clinical findings of MWS were documented. This is due to family history (identical twin with the association), including the pathogenic *ZEB2* gene (*ZFHX1B*) variant, OMIM #235730. We decided to take a rectal biopsy to confirm an HSCR. A contrast enema was performed, which suggests a short-segment variant; however, the patient has never experienced an enterocolitis event and is doing well with the senna. The sister (patient one) had a poor outcome after the surgical correction, so we discussed the scenario with the family, and the decision for conservative management was made.

Patient three

At 1 week of age, the patient experienced a neonatal enterocolitis event, and a rectal biopsy was performed, confirming HSCR. At 2 months of age, the patient underwent a pull-through surgery (TPTS). Four days later, the first post-procedure enterocolitis event occurred, necessitating management in the neonatal intensive care unit and treatment with broad-spectrum antibiotics. Recurrent episodes of enterocolitis continued. Two months later, the patient developed a small bowel obstruction, leading to an exploratory laparotomy and colostomy creation. A second rectal biopsy was conducted, which indicated a transition zone pull-through. Two years later, a redo pull-through was performed. One year afterward, the patient was taken to the operating room for colostomy closure; however, 6 days later, an anastomosis leak was noted. After discussing the case with the family, they opted for a permanent colostomy. The patient is currently doing well.

Discussion

MWS is a rare genetic syndrome characterized by various symptoms, some of which are specific, including seizures and congenital heart defects[8]. We present a case series of patients with MWS and their association with HSCR. Our study included identical twins, both of whom had a heterozygous variant with the same genetic alteration, clinically manifesting across the broad spectrum of the disease. It is well known that the outcome of HSCR in patients with MWS is unpredictable, presenting numerous challenges[1,4,6,7]. Bonnard et al. reported on five patients with this association, and only one achieved a satisfactory outcome[7].

To the best of our knowledge, this is the first report from Mexico regarding patients with HSCR and MWS. In this study, 75% of patients with MWS presented with an associated HSCR, a higher rate than reported in the literature, which indicates a 45-50% association. Regarding the type of HSCR, 66% of our patients had a rectosigmoid variant, while 33% had a short-segment variant. This differs from Dagorno et al., who reported that 50% of their patients had the long variant, 30% had the total variant, and 20% had the rectosigmoid variant.

A retrospective study conducted by Dagorno et al.[4] found that over 15 years, 43% of patients had the association. HSCR was suspected in the neonatal period in 80% of cases, while it was identified later in life as chronic constipation in 20% of cases. All patients underwent surgical correction, and 80% required a second surgery due to complications (28% of patients underwent a redo pull-through). The complications included: 10% with abdominal wall necrotizing cellulitis, 10% with intestinal perforation, 10% with anal margin abscess, 10% with intra-abdominal abscess secondary to rectal stump leakage after the Duhamel procedure, 10% with anastomotic stenosis, 10% with intra-abdominal bleeding, 10% with septic shock and cardiac failure due to septic shock from enterocolitis, 10% with adhesive small bowel obstruction, 10% with sphincter hypertonia, and 10% with rectovaginal fistula. In addition, 50% of patients experienced symptoms of sub-occlusion, and one patient died from enterocolitis 1 month after the pull-through.

About 50% of the patients had a long variant, 30% patients had a total variant, and 20% had a

rectosigmoid variant of HSCR. In our study, all patients required a second surgery due to an anastomotic leak (colorectal anastomosis from TPTS and colo-colonic anastomosis from colostomy closure). It is essential to note that both patients in the present study were in the "Transitional zone," which could be a factor in the failure of the first procedure. However, Torre et al.[9] suggested that receiving a final report indicating a transitional zone creates a dilemma. In his retrospective study, he does not recommend performing a reoperation in the transitional zone; instead, he suggests a wait-and-see approach regarding the patient's progress before considering a new pull-through. A biopsy of the neorectum is applicable only to diagnose or confirm a ganglionic rectum.

The literature frequently reports this complication in patients with this association, leading us to speculate, as Dagorno[4] suggested, that the musculoskeletal anomalies associated with MWS may be connected to soft-tissue anomalies and impaired healing. However, further studies and molecular analyses are needed to support this conclusion.

Similarly, Coyle et al.[1] reported that 46% of patients with the association had a long-term colostomy or ileostomy. In this study, 33% of the cases required a permanent colostomy due to recurrent enterocolitis and surgical complications. In some cases, patients may also experience a severe chronic motility disorder, which could lead to the need for a stoma diversion[1,7,8].

Bonnard et al.[7] analyzed their retrospective study of five patients and concluded that this association (MWS and HSCR) is a serious condition leading to a poor quality of life, mainly due to prolonged parenteral nutrition and stoma diversion. Therefore, parents should be aware of this potential progression, and the surgical team should be fully involved in managing HSCR and related disorders, which require high levels of expertise in pathological examination and specific management.

Patients with MWS exhibit various clinical features with differing phenotypic penetrance[10]. As Birkhoff described, there is a haploinsufficiency in *ZEB2* that causes this new and rare, well-defined, monogenic syndrome[10]. In this study, we observed identical twins with the same heterozygous mutation and pathogenic variant in the *ZEB2* gene (*ZFHX1B*), OMIM #235730. However, they displayed different clinical manifestations of the disease. One of the twins (patient one) was diagnosed with HSCR in the neonatal period. In contrast, the other twin was diagnosed later due to a high suspicion index and current episodes of constipation (patient two). Further studies are necessary to understand the manifestations of the syndrome and the correlations between phenotype and genotype.

The *ZEB2* gene comprises ten exons of varying lengths and encodes six protein domains of different sizes and functions, as described by St Peter et al.[11]. They found that exon 8 encodes at least three of the six protein domains of the *ZEB2* gene and accounts for 66% (198/298) of the variants identified. One of the most common variants, *c.2083C>T*, OMIM #235730, in exon 8, contrary to two of our female patients, presents a *ZEB2* gene variant at exon 8, *c.2761C>T*, OMIM #16053902. In contrast to the two males identified in our study, patient three had a variant located in exon 5, which is not present in population databases. Finally, patient four had an unknown inheritance of a variant located in exon 7, *c.808-2A>G*, OMIM #235730. In this case, a segregation analysis was recommended.

The prevailing notion in clinical and surgical fields is that HSCR has a polygenic or multifactorial etiology. Consequently, genetic evaluation is not routinely pursued when a patient is diagnosed with this condition. However, this is not true for all patients, as various monogenic disorders, such as megacystis microcolon intestinal hypoperistalsis syndrome, can present a ganglionic colon as one of their features[8]. This requires physicians caring for patients with chronic constipation to consider rare diseases whenever they encounter one of these children, as specific treatments or protocols may need to be implemented.

As massive parallel sequencing technologies become more available, even in low- and middle-income countries, the only genotype-phenotype correlation is based on differences in clinical courses of disease in patients with point mutations in the *ZEB2* gene and patients with *ZFHX1B* deletions, OMIM #235730. However, still, not all mutations tend to develop aganglionosis affecting longer segments[12], which is expressed in most human tissues and is essential for the development and migration of neural crest cells[5].

The active pursuit of genetic diagnosis in every patient with HSCR should be considered, as improved care could be achieved with knowledge of the genetic etiology. MWS is a rare genetic syndrome characterized by various symptoms, and a distinctive facial appearance in patients with developmental delays or intellectual disabilities should prompt consideration of this syndrome[5,8,13].

The association between HSCR and MWS is a severe condition with unpredictable outcomes after surgery. Numerous studies, including this one, report a high rate of surgical complications and poor long-term outcomes following the pull-through procedure[1,7,8]. Currently, there are no established guidelines for performing rectal biopsies on these patients. However, considering the literature

and the results presented in this study regarding long-term outcomes and surgical complications experienced by these patients, we recommend conducting a rectal biopsy for every patient with MWS. Patients without clinical complications, such as severe episodes of abdominal distention, recurrent enterocolitis, or failure to thrive, must be assessed to determine if they are suitable candidates for conservative management. Conversely, consulting with an interdisciplinary and specialized colorectal team is crucial for patients who require surgery. Effectively communicating potential outcomes to the family is vital.

Conclusions

The association between MWS and HSCR is a serious condition with high morbidity. The outcome following the pull-through procedure is unpredictable. Based on the existing literature and our findings, we recommend that these patients be assessed through a multidisciplinary consensus. Those without recurrent enterocolitis or chronic motility disorders are suitable candidates for conservative management. Further studies are needed to determine surgical and long-term outcomes and to identify the most effective approach to treating and managing these patients.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical considerations

Protection of human subjects and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. This study does not involve personal patient data, medical records, or biological samples, and does not require ethical approval. SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

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