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ORIGINAL ARTICLE

Consanguinity and its relevance for the incidence of megacystis microcolon intestinal hypoperistalsis syndrome (MMIHS): systematic review

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Abstract

Background/purpose Megacystis microcolon intestinal hypoperistalsis syndrome (MMIHS) is a rare congenital and generally fatal cause of functional intestinal obstruction in the newborn. The cause of this syndrome is unknown. Familial occurrence and reports of consanguinity in MMIHS implies that genetic factors may have an important role in the pathogenesis of this syndrome. The aim of the study was to determine the consequence of consanguinity for the incidence of MMIHS.

Methods A literature search was performed using the keywords "megacystis microcolon intestinal hypoperistalsis" for studies published between 1976 and 2018. Retrieved articles, including additional studies from reference lists, were reviewed for consanguinity between parents and recurrence of MMIHS between siblings. Data were extracted for cases where familial MMIHS was present.

Results A total of 450 patients with the diagnosis of MMIHS have been reported in the literature. There were 56 (12%) cases in which familial MMIHS was confirmed, 25 families with multiple siblings and 3 families with single affected infant. Of the 25 families with multiple siblings, 22 families had 2 siblings with confirmed MMIHS and 3 families had 3 children each with MMIHS. Consanguinity between parents was confirmed in 30 cases (18 siblings and 12 individual cases). Female-to-male ratio in the 30 patients was 4.4:1.

Conclusion The occurrence of MMIHS in the offspring of consanguineous parents and recurrence in siblings of healthy parents suggest that MMIHS is an autosomal recessive disorder. Pre-marital and pre-conception counselling of consanguineous populations is recommended to prevent harmful consequences.

Keywords Megacystis microcolon intestinal hypoperistalsis syndrome · Berdon syndrome

Introduction

Megacystis microcolon intestinal hypoperistalsis syndrome (MMIHS) is a rare congenital and generally fatal cause of functional intestinal obstruction in the newborn [1]. MMIHS was first reported by Berdon et al. [2] in 1976, as the combination of a giant bladder and aperistaltic intestine in the newborn. This syndrome is characterized by distended abdomen caused by a non-obstructed dilated bladder, microcolon with malrotation, and a decrease and/or absence of intestinal peristalsis [2]. MMIHS is usually diagnosed in the prenatal or the immediate neonatal period. Since MMIHS is a severe condition, the patients would have supportive medical or surgical treatment [3]. Due to the gastrointestinal dysmotility, enteral nutrition is not tolerated and patients require parenteral nutrition. The majority of MMIHS patients have been reported to die due to complications of the parenteral nutrition and/or renal insufficiency [4].

Several hypotheses have been proposed to explain the pathogenesis of MMIHS [1]: genetic [5–8], neurogenic [9–11], myogenic [12–15] and hormonal factors [16]. However, the cause of this syndrome is still unclear. Familial occurrence and reports of consanguinity in MMIHS implies that genetic factors may have an important role in the pathogenesis of this syndrome [17]. The aim of this study was to

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determine the consequence of consanguinity for the incidence of MMIHS.

Materials and methods

A systematic review was conducted based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A systematic search of the literature was performed in the Pubmed, Embase, Medline and Cochrane Library electronic database for the keywords "megacystis microcolon intestinal hypoperistalsis" for studies published between 1976 and 2018. Reference lists of relevant articles were manually searched for further cohorts. Duplicates were deleted. The relevant articles were reviewed by title, keywords and abstract by the authors (H.N. and P.P.) and a full-text assessment of selected articles was performed. Resulting publications were reviewed in detail for recurrence of MMIHS between siblings and consanguinity between parents of affected cases. Data for key epidemiological parameters, presenting features and outcome were extracted and analysed.

Results

A total of 450 patients with the diagnosis of MMIHS have been reported in the literature [1, 4, 5, 7, 8, 17–94]. There were 56 (12.4%) cases in which familial MMIHS was confirmed, 25 families with multiple siblings and 3 families with a single affected infant. Seven further confirmed index cases of MMIHS had a probable afflicted sibling and one of the sibling pairs had a probable third affected sibling. The probable cases suffered intrauterine death or passed away in the early neonatal period with evidence of bladder and bowel pathology consistent with MMIHS, but without a confirmed diagnosis. Of the 25 families with multiple siblings, 22 families had 2 siblings with confirmed MMIHS and 3 families had 3 children each with MMIHS. Consanguinity between parents was confirmed in 30 (6.7%) cases (18 siblings and 12 individual case) (Tables 1, 2). One of these individual cases was a double first cousin to one of the sibling pairs, sharing both maternal and paternal grandparents and, therefore, a common genetic pool. Prenatal ultrasonography detected a megabladder in 15 (50%) cases and a dilated stomach in 2 (6.7%) cases with MMIHS in consanguinity. The overall female-to-male ratio of MMIHS cases was 2.3:1, while female-to-male ratio in the 30 patients from consanguineous parents was 4.4:1. Four (13%) survivors with MMIHS in consanguinity were reported at the time of publication. The eldest surviving patient with consanguinity parent was a 3-year-old female.

Table 1 Cases in siblings with MMIHS and consanguinity

Author	Year	Number of siblings		Consanguinity
Winter	1986		2	+
Penman	1989		2	+
Gakmak	1989		3	+
Anneren	1991		2	+
Moreno	2016		2	+
Halim	2016		2	+
Halim	2017	Family 1	3	+
		Family 2	2	+

Table 2 Individual Cases with MMIHS and consanguinity

Author	Year	Number of individual case	Consanguinity
Kirtane	1984	1	+
Mc Namara	1994	1	+
Junior	1996	1	+
Al Harbi	1999	1	+
White	2000	1	+
Narayanan	2007	1	+
Melek	2009	1	+
Hiradfar	2013	1	+
Gauthier	2015	1	+
Garcia	2015	1	+
Halim	2016	1	+
Halim	2017	1	+

Discussion

Several studies have investigated the cause of this condition. It has been suggested that MMIHS is inherited in an autosomal recessive manner as consanguinity between parents and recurrence in siblings is frequently seen [17]. However, since the majority of cases of MMIHS occur sporadically, it has been hypothesized that locus heterogeneity exists, and the genetic etiology of sporadic and familial MMIHS cases may differ. To date, four genes are known to be involved in the pathogenesis of MMIHS: *ACTG2, MYH11, MYLK* and *LMOD1*. Heterozygous missense variants in *ACTG2* gene have been reported as a cause of sporadic MMIHS cases in several independent studies [58, 61, 62], while homozygous missense variant in *MYH11* was identified in a newborn patient with consanguineous parents [60] and homozygous variants in *MYLK* were found in three MMIHS patients from two

consanguineous families [7]. *ACTG2* is the main actin isoform expressed in smooth muscle cells, and changes affecting its structure lead to severe disruption of smooth cell development and function. The *MYH11* gene is highly specific contractile gene for smooth muscle linages. Mice with homozygous deletion of *MYH11* show several smooth muscle cell abnormalities including a large and thin walled bladder and abnormal intestinal movement, the typical features of MMIHS. *MYLK* gene is an important kinase required for myosin activation and subsequent interaction with actin filaments and its absence leads to impairment of smooth muscle cell contraction. *LMOD1* gene is involved in the smooth muscle cytoskeletal-contractile coupling and loss of *LMOD1* results in a reduction of filamentous actin, elongated cytoskeletal dense bodies, and impaired intestinal smooth muscle cell contractility.

The present study showed highly significant sex related differences in MMIHS cases from consanguineous parents. The overall female-to-male ratio of MMIHS cases is 2.3:1 whereas female-to-male ratio in 30 MMIHS patients from consanguineous parents was 4.4:1, thus showing a female predisposition to MMIHS in consanguineous parents. This has implications for genetic counselling and modelling inheritance in MMIHS.

The management of patients with MMIHS is frustrating. A number of prokinetic drugs and gastrointestinal hormones have been tried without success [17, 40]. The outcome of this condition is generally fatal: in the present study only 4 of the 30 reported patients with MMHIS form consanguineous parents were alive, the oldest being 3 years old. The need for surgical intervention should be carefully evaluated, and the intervention individualized, since most explorations have not been helpful and probably were not necessary.

In conclusion, the occurrence of MMIHS in the offspring of consanguineous parents and recurrence in siblings of healthy parents suggests that MMIHS is an autosomal recessive disorder. Pre-marital and pre-conception counselling of consanguineous populations is recommended to prevent harmful consequences. The advancing technology of whole exome sequencing may allow better insights into the genetic basis of MMIHS.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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