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ORIGINAL ARTICLE

Familial megacystis microcolon intestinal hypoperistalsis syndrome: a systematic review

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Abstract
Background Megacystis microcolon intestinal hypoperistalsis syndrome (MMIHS) is a rare and severe disorder of functional obstruction affecting bladder and bowel, usually diagnosed in the neonatal period. Over 230 cases have been reported since Berdon and colleagues first described this clinical entity in 1976. The exact pathogenesis of MMIHS is unknown. Familial occurrence of MMIHS has been reported and could offer insight into the aetiology of this disease. The purpose of this study was to systematically review the published literature for the evidence of familial MMIHS and to characterise these presentations.
Methods A literature search was performed using the keywords "megacystis microcolon intestinal hypoperistalsis" (1976–2013). 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 47 patients were reported in which familial MMIHS was likely or confirmed. 15 sibling sets were definitively diagnosed with MMIHS (14 pairs and one set of three siblings). Four further index patients with a confirmed diagnosis and also one of the sibling pairs were reported to have a sibling in which MMIHS was probable. Consanguinity between parents was present in four of the confirmed sibling sets and in an additional seven individual cases. The outcome for familial MMIHS is generally poor. Multiple sibling fatalities were frequent and in only one family were both siblings' survivors at the time of reporting.
Conclusion Consanguinity between parents and recurrence in siblings indicate that MMIHS is inherited in an autosomal recessive manner. With the advent of next generation sequencing, these familial clusters may be key to determining the genetic basis for MMIHS.

Keywords Megacystis microcolon intestinal · Hypoperistalsis autosomal · Recessive familial

Introduction

Megacystis microcolon intestinal hypoperistalsis syndrome (MMIHS) is a rare congenital disorder of functional bowel obstruction and failure to void urine spontaneously. It is typically diagnosed prenatally or in the immediate neonatal period. It is characterised by massive abdominal distension due to a dilated non-obstructed bladder, microcolon with malrotation, and decreased or absent intestinal peristalsis [1] (Fig. 1). MMIHS is a severe condition for which only supportive medical or surgical treatments have been available [2]. The majority of afflicted cases succumb to a fatal outcome within a short period of time, most often due to complications of parenteral feeding or renal insufficiency [3]. The advent of multi-visceral organ transplantation has given some prospect of survival in selected cases [4]. The aetiology of MMIHS is unknown. However, occurrence of MMIHS in the offspring of consanguineous parents and recurrence in siblings with healthy parents, suggests autosomal recessive inheritance. Indeed, the very first report on this condition by Berdon et al. [5] included a

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pair of affected sisters. It has been proposed that these familial patterns are evidence for the genetic basis of the disease [6], although it has not previously been investigated whether familial and sporadic MMIHS encompass the same clinical condition. The purpose of this systematic review was to characterise these familial presentations.

Methods

A literature search was performed for the keywords "megacystis microcolon intestinal hypoperistalsis" on the Pubmed® and Embase® electronic databases (1976–2013) with no language restrictions. Retrieved articles were examined for recurrence of MMIHS between siblings and consanguinity between parents of affected cases. Reference lists of retrieved articles were screened for additional cases. Data for key epidemiological parameters, presenting features and outcome were extracted and analysed. The diagnostic criteria for MMIHS were megacystis and microcolon with symptoms of hypoperistalsis, confirmed radiologically, at autopsy or at laparotomy.

Results

A total of 47 cases in which familial MMIHS was confirmed or likely were identified. 19 families had multiple affected siblings (Table 1). There were 14 pairs of siblings with confirmed MMIHS [3, 5, 7–17]. One family had three children with MMIHS [18]. Four further confirmed index cases of MMIHS had a probable afflicted sibling [19–22] and one of the sibling pairs had a probable third affected sibling [17]. 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. Consanguinity between parents was reported in four of the confirmed sibling sets [6, 10, 13, 18] and in a further seven individual cases [23–29] (Table 2). In addition, 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 [10, 24]. The ethnic background was heterogeneous overall. All of the individual cases with consanguineous parents were female. Within affected siblings, the gender was all female in seven sets, both male in two sets, mixed female and male in six, and unknown in the remainder. The overall female:male gender distribution in familial MMIHS approximated 2.5:1. Prenatal sonographic diagnosis of fetal megacystis or intra-abdominal mass was reported in 21 cases. Of 37 live–born infants, 22 (61 %) were born at term gestation (≥36 weeks). Abdominal distension at birth was the commonest presenting feature. 21 cases underwent laparotomy for intestinal obstruction. Outcome was described in 44 cases. There were seven survivors at the time of publication for all studies, five females and two males. The eldest surviving patient was a

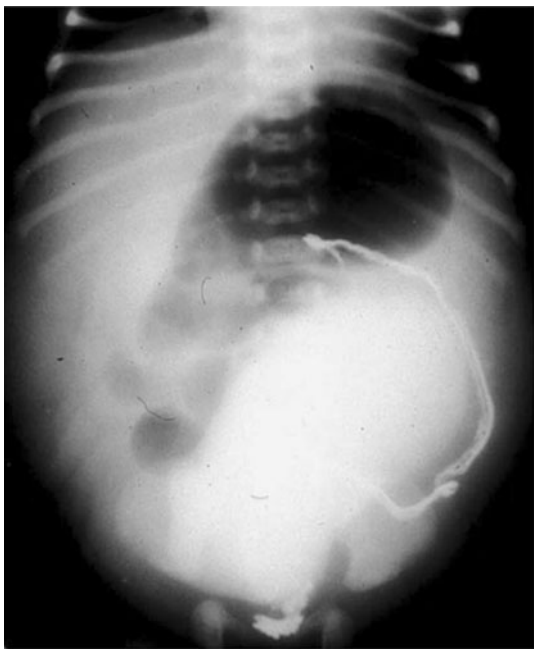

Fig. 1 Contrast enema showing microcolon. Note residual contrast in distended bladder from prior cystogram

Table 1 Families with multiple sibling MMHIS cases

References	Centre	Gender
Berdon et al. [5]	New York	F/F
Patel and Carty [7]	Liverpool, UK	F/F
Oliviera et al. [8]	Vitoria, Brazil	F/M
Winter and Knowles [6]	Herts/Harrow/Oxford, UK	F/F
Farrell [9]	Ontario, Canada	F/F
Penman and Lilford [10]	Leeds, UK	F/F
Young et al. [11]	Leicester, UK	M/M
Gakmak et al. [18]	Turkey	–/–/–
Garber et al. [12]	Los Angeles, California	M/M
Annerén et al. [13]	Uppsala, Sweden	M/F
Stamm et al. [14]	Denver, Colorado	F/F
Goldberg et al. [20][a]	Johannesburg, South Africa	F/–
Guzé et al. [21][a]	Carson/Orange, California	F/M
Bloom and Kolon [19][a]	San Diego, California	F/–
Hsu et al. [15]	Omaha, Nebraska	F/M
Köhler et al. [3]	Auckland, New Zealand	F/M
Boissier et al. [22][a]	Saint-Étienne, France	F/–
Lopez-Munoz et al. [16]	Mexico, Mexico	F/M
Lozoya-Araque et al. [17][a]	Valencia,Spain	F/–/F

[a] Includes probable case, dash denotes unknown gender

Table 2 MMHIS cases with consanguineous parents

References	Centre
Siblings	
Winter and Knowles [6]	Herts/Harrow/Oxford, UK
Penman and Lilford [10][a]	Leeds, UK
Gakmak et al. [18]	Turkey
Annerén et al. [13]	Uppsala, Sweden
Individual cases	
Kirtane et al. [23]	Bombay, India
Mc Namara et al. [24][a]	Leeds, UK
Junior et al. [25]	Brasilia, Brazil
Al Harbi et al. [26]	Riyadh, Saudi Arabia
White et al. [27]	Oxford, UK
Narayanan et al. [28]	Birmingham, UK
Melek et al. [29]	Van, Turkey

[a] Related families

10-year-old female at 2 years post bowel transplant. Frequently multiple sibling fatalities were reported (66 % of families) and in only one family were all affected children survivors [15]. Of the fatalities, four pregnancies were terminated following detection of fetal abnormality on prenatal sonography, three intrauterine deaths occurred and 23 died before 2 months of age. Seven children survived beyond this period but not longer than 20 months of age. Sepsis was the most commonly cited cause of death.

Discussion

In a recent systematic review, the overall gender distribution for all MMIHS cases was 2.4:1 female to male [30]. This female preponderance is maintained in the familial group. It has been suggested by some authors that the female predominance in MMIHS may be due to a more severe form of the condition in males resulting in intrauterine death [11]. In the familial cases, there were no reported male intrauterine deaths and genders were represented across neonatal deaths, later deaths and survivors in proportion to the reported gender distribution. However, this data may not capture early intrauterine deaths of severely afflicted males. The common presenting features did not differ from those described in the literature for sporadic MMIHS and in particular marked abdominal distension at birth appears to distinguish these cases [31]. Definitive diagnosis was made by ultrasonography and contrast imaging [32] or at autopsy in some cases but was most often confirmed at laparotomy for intestinal obstruction (performed in 57 %). Therapeutic surgical interventions such as stoma formation were commonly performed without gaining clinical benefit, a similarly frequent occurrence in the sporadic cohort [30]. Overall outcomes were poor (16.5 % survival rate) but reflect the overall outcomes for all MMIHS in the recent literature (12–20 % survival rate) [30, 33]. Parental consanguinity increases the risk of birth defects in offspring when compared to overall population risk [34, 35] and increases the rate of neonatal mortality by the expression of recessive genes [36]. The pattern of familial presentation described in this review conforms to the expectation of autosomal recessive inheritance, in the recurrence of MMIHS between progeny of healthy parents together with the frequency of consanguinity between parents of affected children [37, 38]. Parental history of functional bowel and bladder dysfunction was not reported for any cases with one exception [21]. MMIHS is referred to by some authors within a spectrum of functional bowel disorders collectively termed visceral myopathies or chronic intestinal pseudo-obstruction. Classified within these umbrella terms, there have been reports of familial severe neonatal functional bladder and bowel disorders following an autosomal recessive inheritance pattern [39–42]. Inadequate diagnostic detail prevented the inclusion of data for these ten families in the confirmed MMIHS familial group. A total of 227 cases of MMIHS have been reported in the literature according to a 2011 review (1976–2011) [30]. We have classified 47 cases reported between 1976 and 2013 as demonstrating autosomal recessive inheritance patterns while not differing from the phenotype described in sporadic MMIHS. Clearly a substantial proportion of all MMIHS cases may be familial in nature. Given the abysmal mortality rate and heavy morbidity burden associated with MMIHS, with children likely to require multi-visceral transplantation for long-term survival [43], the importance of recognising the potential familial nature of this disorder is highlighted. Genetic counselling for the family of an affected child is to be prioritised [44]. Candidate MMIHS genes have been identified both in the clinical setting and in experimental models. Nicotinic mechanisms are key in the autonomic control of organ function [45]. Nicotinic acetylcholine receptor (nAChR) subunit gene knockout in the mouse results in a phenotype resembling MMIHS for both α3 and β2/β4 subunits [46]. Richardson et al. [47] showed reduced α3 nAChR subunit expression in resected human MMIHS small bowel specimens versus controls. High frequency polymorphisms in CHRNA3 and CHRNB4 genes on the long arm of chromosome 15, coding for α3 and β4 nAChR subunits, respectively, were found in individuals and families of individuals affected by MMIHS [48]. In addition, Szigeti et al. [49] have reported a case of MMIHS with a de-novo deletion on the proximal long arm of chromosome 15. While familial patterns may not definitively prove that MMIHS can be inherited in an autosomal recessive fashion, they provide a strong indication for this. By utilising next generation sequencing techniques to

screen for candidate gene mutations such as nAChR gene deletions, these families may play a key role to reveal the genotype of MMIHS. Recruitment of such families for genetic testing could be highly beneficial in elucidating the aetiology of this distressing condition and could potentiate prenatal screening and gene therapy for affected families in the future.

Conclusion

Consanguinity between parents and recurrence between siblings strongly indicate that MMIHS can be inherited in an autosomal recessive manner. These familial presentations do not differ from sporadic MMIHS and may encompass a substantial proportion of all presentations of MMIHS. With the advent of next generation sequencing, investigating these familial clusters may be instrumental in establishing the genetic basis for MMIHS.

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