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ORIGINAL ARTICLE

Prevalence of Hirschsprung's disease in premature infants: a systematic review

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Abstract
Purpose Intestinal dysmotility in preterm infants has often been attributed to immature enteric nervous system. It is frequently reported that Hirschsprung's disease (HD) is rare in premature infants. The exact prevalence of HD in premature infants is not well documented. The classical signs of HD may often not be identified due to the complexity of symptoms of prematurity itself. This systematic review was designed to determine the prevalence and presentation of HD in premature infants.
Methods A systematic review of the literature using the keywords "Hirschsprung's disease", "aganglionosis", "congenital megacolon", "premature" and "preterm" was performed. Resulting publications were reviewed for epidemiology and morbidity. Only infants born <37 weeks of gestation or described as preterm birth by the authors were included. Reference lists were screened for additional relevant studies.
Results Twenty-six publications from 1964 to 2013 reported data on premature infants with HD. Out of a total number of 4,147 infants, prematurity was recorded in 257 cases, giving a prevalence rate of 6 % of preterm infants diagnosed with HD. During 1964–1999, reported prevalence of HD in premature infants ranged from 1.7 to 9.2 % (overall prevalence 5 %) and during 2000–2013 prevalence ranged from 4 to 19.4 % (overall prevalence 14 %). The prevalence of total colonic aganglionosis in premature infants was 13 % (15 out of 118 infants). Mean gestational age of preterm infants was 34.5 (±0.7) weeks and mean age at diagnosis ranged from 18.3 days to 3.9 months. Abdominal distension was observed in 80 % of preterm infants, delayed passage of meconium in 57 and 37 % of premature infants presented with bile-stained vomiting.
Conclusion In recent years, higher prevalence of HD has been reported in premature infants compared to previous years. Hirschsprung's disease should be considered in preterm infants presenting with features of intestinal obstruction.

Keywords Hirschsprung's disease · Congenital megacolon · Premature · Preterm · Prevalence

Introduction

Hirschsprung's disease (HD) is one of the more common causes of intestinal obstruction in the newborn, occurring in approximately 1 in 5,000 live births. It is characterized by a congenital absence of ganglion cells (aganglionosis) in the distal bowel, which extends for varying distances into the more proximal large bowel and rarely into the small intestine [1–3].

The aganglionosis is primarily reported to be attributed to cellular and molecular abnormalities during the development of the enteric nervous system (ENS), which plays a major role in the coordination of normal gut motility. In the human fetus, neural crest-derived neuroblasts migrate in a cranio-caudal direction from the developing esophagus to the anal canal during the 5th–12th week of gestation. Thus, an early arrest of migration in the developing fetus results in long-segment aganglionosis [4, 5]. In addition, intestinal

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dysmotility in preterm infants has also been described to be due to intrinsic immaturity of the ENS [6].

HD is frequently considered to be uncommon and rare in premature infants and, therefore, the exact prevalence of HD among this cohort is not well documented. In general, most neonates with HD present with bowel obstruction, delayed passage of meconium after 48 h of birth, abdominal distension, bilious emesis, and feeding intolerance [4, 7, 8]. However, these "classical" signs of HD may often not be identified in preterm infants due to the complexity of symptoms of prematurity itself, including associated congenital abnormalities, respiratory failure, heart rate abnormalities, and feeding intolerance requiring parenteral nutrition [1, 9, 10].

The aim of this systematic review was to determine the prevalence and clinical presentation of HD in premature infants.

Methods

A PubMed® search of the literature using the keywords "Hirschsprung's disease", "aganglionosis", "congenital megacolon", "premature" and "preterm" was performed. Detailed information on epidemiology and morbidity was recorded from resulting publications. Only infants born alive below 37 weeks of gestation or described as preterm birth by the authors were included. The reference lists of retrieved articles were screened for additional relevant studies. Case reports and articles reporting on infants born below 37 weeks of gestation without giving exact numbers or percentage were excluded.

Table 1 Prevalence of HD in premature infants from 1964 to 2013

Year	Reference	Infants with HD	Preterm infants with HD	Prevalence of preterm infants with HD (%)
2013	[12]	85	6	7.1
2013	[1]	129	24	18.6
2013	[13]	55	9	16.4
2010	[14]	45	7	15.6
2007	[15]	25	1	4
2005	[2]	36	7	19.4
2000	[16]	78	9	11.5
1997	[17]	180	3	1.7
1995	[18]	131	9	6.9
1994	[19]	65	3	4.6
1993	[20]	213	17	8
1992	[21]	127	9	7.1
1992	[11]	260	10	3.8
1987	[25]	32	1	3.1
1986	[22]	35	1	2.9
1984	[23]	26	1	3.8
1984	[24]	1,577	87	5.5
1979	[26]	28	2	7.1
1978	[27]	89	4	4.5
1977	[28]	120	11	9.2
1973	[29]	501	25	5
1973	[30]	13	1	7.7
1972	[31]	34	1	2.9
1967	[32]	53	3	5.7
1966	[33]	53	1	1.9
1964	[34]	157	5	3.2
		4,147	257	6.2

Results

During the time period from 1964 to 2013, 26 publications reported data on premature infants with HD (Table 1) [1, 2, 11–34]. Out of a total number of 4,147 infants in the included literature, prematurity was recorded in 257 cases, giving a prevalence rate of 6 % of preterm infants diagnosed with aganglionosis.

A total of 19 articles [11, 17–34] reporting premature infants with HD were published before the year 2000, whereas seven articles were found in or after 2000 [1, 2, 12–16]. During 1964–1999, a total number of 194 preterm infants out of 3,694 neonates with HD were recorded with an overall prevalence rate of 5 % (range 1.7–9.2 %). During 2000–2013, a total of 63 premature infants out of 453 neonates with HD were reported, giving an overall prevalence rate of 14 % (range 4–19.4 %).

Six articles reported 118 neonates diagnosed with total colonic aganglionosis (TCA). A total of 15 preterm infants were presented in this cohort, giving a prevalence rate of prematurity and TCA of 13 % in this subgroup.

Data on gestational age at birth was reported in seven articles. Mean gestational age was 34.5 (±0.7) weeks in preterm infants with HD. Mean age at diagnosis was mentioned in 427 cases with HD and ranged from 18.3 days to 3.9 months in preterm infants compared to 5.2 days–10 months in full-term neonates. Associated major congenital anomalies were stated in a cohort of 342 neonates with HD and occurred in 46 % of premature infants compared to 18 % of full-term infants.

In a cohort of 214 patients with HD, data on symptoms at presentation were reported in preterm infants and compared to full-term babies. Abdominal distension was observed in 80 % of preterm infants vs. 82 % of full-term neonates, delayed passage of meconium in 57 % of preterm vs. 50 % of full-term neonates and 37 % of premature infants presented with bile-stained vomiting in comparison

to 53 % of full-term infants. The location of aganglionosis was rectosigmoid in 70 % of preterm and 54 % of full-term neonates.

Discussion

HD is a frequent cause of intestinal obstruction in the newborn with an estimated incidence of 1 in 5,000 live births and a male-to-female ratio of 4:1. It is characterized by a congenital absence of enteric (intrinsic) neurons in the distal bowel (aganglionosis), which extends for varying lengths from the most distal large intestine into the more proximal bowel and less commonly into the small bowel. The extent of aganglionosis is generally classified as rectosigmoid, long-segment and TCA [1, 3, 35].

Preterm infants are often described to have feeding difficulties due to a functional disorder of the gastrointestinal tract, which is mainly attributed to immaturity of the ENS, represented as decreased organized intestinal motility [6, 36]. However, HD in preterm infants has generally been considered uncommon and, thus, the exact prevalence of intestinal aganglionosis among this subgroup is only sparsely documented. We designed this systematic review to determine the prevalence and presentation of HD in premature infants.

The "classical" signs of HD, including bowel obstruction, delayed passage of meconium, abdominal distension, and bilious emesis are often not recognized in preterm neonates due to their complex condition of prematurity itself. Associated congenital anomalies, requirement for parenteral nutrition, respiratory failure and bradycardia, might obscure the typical symptoms and lead to a delay or misdiagnosis of HD in this cohort [1].

A total number of 26 publications from 1964 to 2013 [1, 2, 11–34] presenting data on premature neonates with HD could be identified. Out of a total number of 4,147 infants, prematurity was recorded in 257 cases, giving an overall prevalence rate of 6 % of preterm infants diagnosed with HD. The first paper in our review published in 1964 reported a prevalence rate of 3.2 % out of 157 infants [34]. The lowest prevalence rate was recorded in a series of 302 patients with HD [17]. Out of the total number of these infants data on gestational age was available in 180 infants, giving a prevalence rate of 1.7 % of preterm infants with HD. The highest prevalence rate of 19.4 % was reported by Escobar et al. in 2005 focusing on patients with TCA [2]. In one of the latest publications in our systematic review, Baxter et al. analyzed all classifications of HD, determining an exact prevalence rate of 18.6 % of premature neonates with HD [1]. We then compared case series published before 2000 with more recent studies. During 1964–1999, the overall reported prevalence of HD in premature infants was 5 % and during 2000–2013 an overall prevalence of 14 % could be identified. Baxter et al. stated when comparing their high prevalence with lower rates in previous reports that possible contributing factors to the higher preterm prevalence might be the increased incidence of prematurity over time with recent advances in the care of preterm infants and improved diagnostic testing for HD, respectively [1].

TCA with varying lengths of small bowel involvement is a severe and rare form of HD occurring in about 2–14 % of infants with HD and is usually associated with higher morbidity and mortality. Nonetheless, the advent of current operative techniques, total parenteral nutrition and improvements in supportive care and diagnostic histochemical techniques have led to an increased survival rate in recent years [2, 15, 37]. In relation to our systematic review, we could identify 15 preterm infants out of 118 neonates with TCA, giving a prevalence rate of 13 %.

Lee et al. have shown that delayed diagnosis of HD in newborn infants beyond 1 week after birth significantly increases serious morbidities in the neonatal period and also affects the long-term outcome. Patients are reported to be at higher risk of HD-associated enterocolitis, which can progress to life-threatening conditions such as severe dehydration, shock and sepsis [38]. As the diagnosis of HD can often be delayed or missed in preterm infants, these neonates might have an increased risk of serious complications. Regarding the mean age at diagnosis in preterm infants, there was a huge range from 18.3 days to 3.9 months in our systematic review. Baxter et al. and Sharp et al. recorded a significantly higher mean age at diagnosis in their preterm neonates, whereas Klein et al. reported that the mean age at diagnosis was much less in this cohort [1, 12, 20].

HD occurs as an isolated defect in 70 % of infants. In contrast, associated congenital anomalies have been shown to be present in 21 % of all infants with HD. In particular, the association with chromosomal abnormalities is well described, with trisomy 21 being the most frequent, and has been stated to exist in 12 % of neonates. It addition, it can be related to other neurocristopathies as well, such as Haddad, Waardenburg or Goldberg-Shprintzen syndromes [8, 39, 40]. Furthermore, Honein et al. [10] have recently evaluated the association between preterm births and major birth defects and found a strong relation between these conditions. In our review, associated major congenital anomalies were also more frequently reported in premature infants compared to full-term neonates, ranging from 46 to 18 % in the included articles, which also emphasizes the potential complexity of a preterm infant's condition and aspects to be considered in the pre- and postnatal care.

In terms of clinical signs of HD, obstructive bowel symptoms in preterm infants can suggest several different intestinal morbidities with necrotizing enterocolitis (NEC) being the most important one [1, 6]. Therefore, HD might be far less considered in the differential diagnosis of intestinal obstruction in preterm compared to full-term neonates. Out of the 26 publications presenting data on prematurity and HD in this systematic review, only two studies [1, 12] specifically analyzed the characteristics of HD between premature and full-term infants. Abdominal distension was recorded in 80 % of preterm vs. 82 % of full-term infants, delayed passage of meconium in 57 vs. 50 % and bile-stained vomiting was observed in 37 % of premature infants compared to 53 % of full-term neonates. Overall, there does not seem to be a substantial difference between preterm and full-term infants with HD as regards the presence of obstructive signs and symptoms only. However, the majority of articles did not compare the clinical data of preterm neonates with full-term infants, which is a limiting factor for interpretation of these results.

In conclusion, this review shows that in recent years a higher prevalence rate of HD has been reported in premature infants compared to previous years. HD should be considered in preterm infants presenting with features of intestinal obstruction. More studies specifically analyzing the epidemiology of intestinal aganglionosis in premature neonates in comparison to full-term infants should provide essential data on the exact prevalence rate and the management of HD in premature infants.

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