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Formula-feeding and hypertrophic pyloric stenosis: is there an association? A case–control study

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ABSTRACT

Background: The etiology of infantile hypertrophic pyloric stenosis (HPS) is not fully understood. The objective of this study was to determine whether formula-feeding is associated with increased incidence.
Methods: This case–control study included HPS cases and controls admitted between 1992 and 2012. Demographic data including feeding method were collected from patient charts and analyzed.
Results: We identified 882 HPS cases and 955 controls. The highest incidence of HPS presentation was in summer ($P = 0.0028$). Infants with HPS were more likely to have been exclusively formula-fed, have a family history of HPS, and be male compared to infants in the control group ($P < 0.001$); they were also more likely to live in rural areas, although not significantly so. After adjusting for family history, sex, place of residence, and season of presentation, exclusively formula-fed infants were 1.36 times more likely to develop HPS compared with exclusively breastfed infants (RR 1.36, 95% CI 1.18–1.57, $P < 0.005$).
Conclusions: Formula-feeding is associated with significantly increased risk of HPS. Further investigation may help to determine the components of formula that simulate hypertrophy of the pylorus muscle, or the components of breast milk that are protective, as well as other influencing factors.
Level of evidence: 3b.

Infantile hypertrophic pyloric stenosis (HPS) is the most common condition requiring surgery in the first months after birth [1,2]. Although the presentation is well-known, and diagnostic methods and treatment for HPS are fairly standard, its cause remains unclear.

Male gender and a family history of HPS are consistently reported as risk factors, suggesting a genetic component to the etiology of HPS [1,3–5]. However, the recent increase in HPS incidence reported in several countries indicates that environmental factors likely play a role [3]. Symptoms usually do not arise until the second or third week of life, which may point to early exposures. The most commonly suggested exposure – likely because this condition affects the digestive system – is choice of breast- or formula-feeding [6–9], although this association has not been conclusively proven. In addition, other factors such as seasonal variations in environment [10,11], and location of dwelling [12,13] may contribute.

The objective of this study was to determine whether feeding practice is associated with rates of HPS, after controlling for other possible influences.

1. Methods

1.1. Study design

After obtaining institutional research ethics board approval (13/78X), we performed a case–control retrospective chart review including patients admitted to the Children's Hospital of Eastern Ontario (CHEO) between January 1992 and December 2012. We identified all patients who had undergone pyloromyotomy during this period, and randomly selected controls admitted during the same period for a reason other than HPS. We collected data on patient sex, gestational age at birth, whether there was a family history of HPS, parental postal code (used to determine whether the family lived in a rural or urban area according to data provided by Statistics Canada [14]), and feeding practices since birth (exclusively breastfed, exclusively formula-fed, or a combination).

1.2. Covariates of interest

1.2.1. Feeding method

Our primary variable of interest was feeding method. Patients were categorized into three groups based on the feeding practice reported in their medical charts: exclusively breastfed, exclusively formula-fed, or a combination. Patients who were fed a combination of breast milk and

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formula since birth were excluded from the analyses on feeding, as were patients for whom feeding practice since birth could not be determined from the patient's chart.

1.2.2. Seasonal variation

As season of presentation has been reported to be a risk factor for HPS, we included it as a covariate. Seasons were defined as follows: winter (December, January, and February), spring (March, April, and May), summer (June, July, and August), and autumn (September, October, and November) [11].

1.2.3. Geographic variation

Patients were categorized into two groups according to place of residence, determined by parental postal code in combination with data provided by Statistics Canada: urban area (centres with population of 10,000 or more) and rural area (towns and municipalities outside the commuting zone of larger urban centers) [14]. This variable was used in a multivariate analysis as a surrogate for possible environmental etiological factors.

1.2.4. Statistical analysis

Data were analyzed using Student's t-tests for continuous variables and chi^2 tests for categorical ones. The HPS cases and the control cases were compared in a univariate analysis. This was then followed by a multivariate analysis. Independent factors considered in the regression model included gender, feeding (breastfed vs formula-fed), geographic location of dwelling, and season of presentation. Statistical significance was based on a two-tailed P-value of 0.05.

2. Results

We identified 882 infants with HPS and 955 controls admitted during the study period (January 1992 to December 2012). Approximately 40% of control group patients were admitted for respiratory symptoms; 5% were admitted for each of orthopedic problems, urinary tract infection, and inguinal hernia; and the rest were admitted for a wide variety of other conditions. The demographic characteristics of study subjects are presented in Table 1. Gestational age at birth was similar in HPS cases and controls. In comparison to controls, HPS cases were more likely to be male and to have a positive family history of HPS ($P < 0.001$). The difference in the proportion of infants living in rural areas between the HPS and control group approached significance, with HPS patients being more likely to live in a rural environment ($P = 0.0681$). After excluding patients whose feeding history was unknown or who were fed a combination of breast milk and infant formula since birth, HPS cases were more likely to have been exclusively formula-fed compared to controls ($P < 0.001$; Table 2).

Table 1
Patient characteristics.

	HPS cases (%)	Control cases (%)	P value
Sex			
Male	755 (86)	599 (62)	<0.001
Female	127 (14)	356 (38)	
Gestational age at birth			
<37 weeks	91 (10)	260 (27)	NS
37–40 weeks	671 (76)	591 (62)	
>40 weeks	102 (12)	73 (8)	
Unknown	18 (2)	31 (3)	
Positive family history	83 (9)	3 (<1)	<0.001
Dwelling			
Rural area	222 (25.2)	206 (20.9)	0.0681
Urban area	660 (74.8)	749 (79.1)	
Total	882	955	

HPS: hypertrophic pyloric stenosis; NS: not significant.

Table 2
Feeding method.

	HPS cases (%)	Control cases (%)	P value
Exclusively breastfed	132 (15)	214 (22)	<0.001
Exclusive formula-fed	563 (64)	496 (52)	<0.001
Combined	169 (19)	183 (19)	
Unknown	18 (2)	62 (6)	
Total	882	955	

HPS: hypertrophic pyloric stenosis.

We compared numbers of HPS patients by the month of presentation. July had the most HPS cases, while February had the fewest. The difference in case numbers between months of presentation was statistically significant ($P = 0.0031$; Fig. 1). Correspondingly, when we compared number of cases by the season of presentation, the highest number was recorded during the summer, followed by autumn; winter had the lowest number of cases. The difference in case numbers between seasons was statistically significant ($P = 0.0028$; Fig. 2).

The association between HPS, feeding method, sex, family history, area of residence (urban vs. rural), and season of presentation was modeled by logistic regression (Table 3). After adjusting for these other variables, exclusive formula-feeding remained significantly associated with the development of HPS. The risk of HPS for an infant who was exclusively breastfed since birth was 0.57 (95% confidence interval (CI) 0.42–0.78, $P < 0.005$). Exclusively formula-fed infants experienced a risk of developing HPS that was 1.36 times higher compared with exclusively breastfed infants (relative risk 1.36, 95% CI 1.18–1.57, $P < 0.005$). In this analysis, family history of HPS and male sex remained positively associated with risk of HPS ($P < 0.005$), however differences based on location of residence and season of admission were not significant.

3. Discussion

Although a number of etiological theories exist, the cause of HPS has not been fully explained. Several recent publications have indicated that the etiology of HPS is multifactorial [15–18], however there is a paucity of large-scale studies investigating the relative contributions of genetic and environmental factors, and their interactions, to the development of pyloric muscle hypertrophy in infants.

In this large case–control study we demonstrate that after controlling for genetic factors (sex, family history) and environmental factors (season, location of residence), exclusive formula-feeding remains positively associated with the development of HPS. In our study, formula-fed infants experienced a 1.36-fold higher risk of HPS compared with exclusively breastfed infants. To our knowledge, no previous studies have evaluated the interaction between feeding method, genetics, and environmental factors, and their contribution to the risk of developing HPS.

3.1. Feeding method

Feeding method during early infancy has long been believed to contribute to the etiology of HPS, given its clinical presentation and pathophysiology. Early epidemiological studies reported increased rates of HPS during a time when breastfeeding also increased in popularity [6,7,19,20]. However, in more recent population-based case–control and cohort studies, exclusive breastfeeding has been associated with a lower risk of HPS compared to formula-feeding [15,21–23]. The results from our study support the association between formula-feeding and an increased risk for HPS. The question remains, however, whether breastfeeding confers protection against HPS, or formula-feeding contributes to its development. The presence of high levels of hormones such as vasoactive intestinal peptide in human milk [24,25] and breast milk's lower osmolarity compared to infant formula [26], as well as the probiotics introduced through breastfeeding [27,28] have all been suggested as protective factors against HPS. Authors of a recent