

Infantile hypertrophic pyloric stenosis in monozygotic twins: a case report and review of genetic and modifiable risk factors

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Infantile hypertrophic pyloric stenosis is the most common surgical pathology resulting in emesis presenting in infancy and is usually encountered between the second and eighth weeks of life. It is the most common indication for surgery in infants less than 1 month of age. Prior to the pyloromyotomy developed by Ramstedt in 1911, the mortality for the condition exceeded 50%. Current epidemiologic data indicate that the ailment affects between two and five infants per 1000 live births. Despite the incidence of the condition, the etiologic factors, genetic or environmental, have yet to be clearly elucidated. The incidence in twins has been previously described and noted to be nearly 200 times higher in monozygotic twins. The incidence in dizygotic twins is similar to that between siblings, but nearly 30 and 20 times higher than that of the general population, respectively. This observation continues to stress the importance of genetics in the development of

pyloric hypertrophy. Presented here are two cases of idiopathic infantile hypertrophic pyloric stenosis in monozygotic twins with a review of the literature of both genetic and environmental predisposing factors. *Ann Pediatr Surg* 14:182–186 © 2018 Annals of Pediatric Surgery.

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Introduction

Infantile hypertrophic pyloric stenosis occurs with an incidence in the Western world of two to five per 1000 live births. The onset of symptoms is usually abrupt and dramatic, presenting with nonbilious emesis resulting from hypertrophy and hyperplasia of the pylorus. This hypertrophy causes a functional gastric outlet obstruction, usually between the second and eighth week of life [1]. Prior to recognition of the disease as an entity by Hirschsprung in 1888 [2] followed by the first pyloromyotomy performed by Ramstedt in 1911 [3], mortality rates exceeded 50% [4]. Although our current understanding of the diagnosis and management of the ailment has resulted in excellent results with present day mortality rates being close to 0%, the exact etiology remains enigmatic. The skewed sex distribution, familial clustering, and high concordance in twins that have been demonstrated by multiple studies suggest a genetic cause, but without following any mode of Mendelian inheritance. Current models of inheritance that have been proposed include the multifactorial threshold model and the single major locus model, the latter of which proposed environmental modification of a single gene [5,6]. Presented here are cases of pyloric stenosis in monozygotic male twins and a review of the current understanding of the pathogenesis and genetic and environmental factors that have been implicated in the process. Prior reports of twins with pyloric stenosis in the literature have largely been limited to isolated case reports [7–19].

Case report

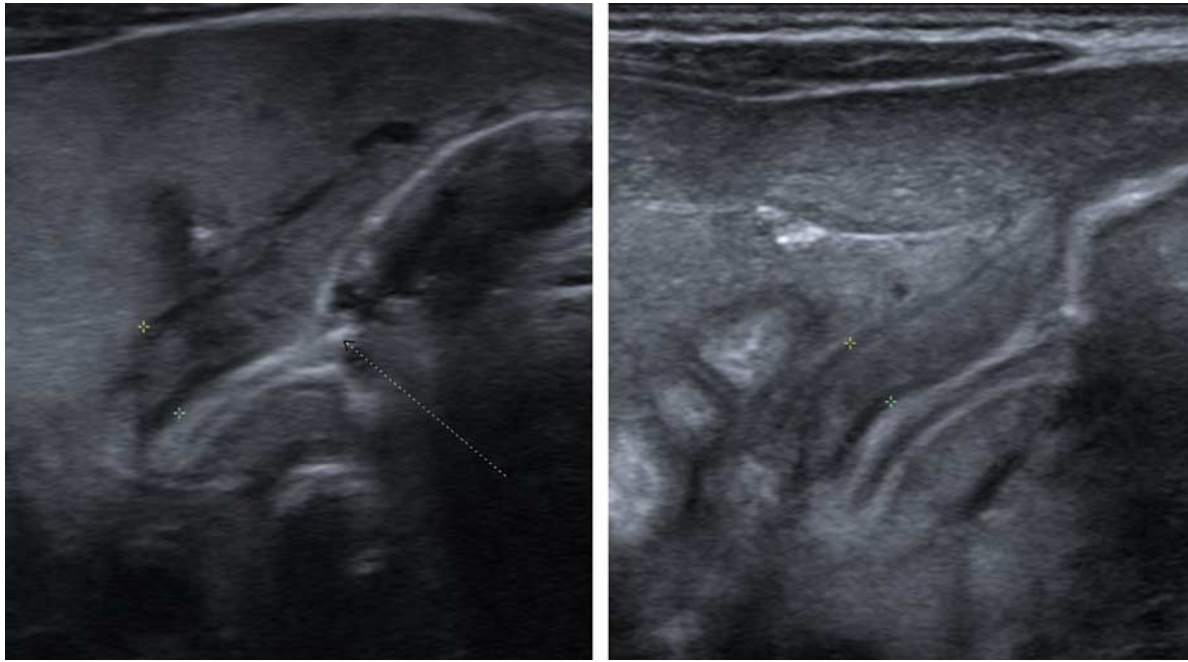
Both twins were born at 30 weeks and 2 days gestation to a 28-year-old G1P0 nonsmoking nonobese Caucasian mother via spontaneous vaginal delivery secondary to

preterm premature rupture of membranes. The twins were dichorionic, diamniotic, and both were males. Zygosity testing was completed postnatally, demonstrating the probability of monozygosity of 366 503 427 739 : 1.

The mother received steroids and magnesium in the late preterm period. The pregnancy was otherwise unremarkable. Twin A was born measuring 43 cm long and weighing 1.7 kg with APGAR scores of 8 and 9 at 1 and 5 min. Twin B was born 5 min after twin A, measured 42 cm and weighed 1.681 kg with APGAR scores of 7 and 8. Both twins spent a total of 4 weeks in the neonatal ICU for hyaline membrane disease, hyperbilirubinemia, and apnea of prematurity before being discharged home at 34 weeks and 1 day of gestation. Total parenteral nutrition was provided to both twins through 36 h of life, when nasogastric feeding tubes were placed. Nasogastric tubes were permanently removed at 24 days of life in twin A and 26 days of life in twin B. Of note, twin A had his nasogastric tube placed to a depth of 18 cm after 36 h of life, and underwent insertion of the nasogastric apparatus a total of five times before discharge from the neonatal ICU. Twin B had his nasogastric tube placed to a depth of 18 cm after 36 h of life, and underwent insertion of the nasogastric apparatus twice prior to discharge from the neonatal ICU. Both infants were fed exclusively breastmilk through the nasogastric tube, with breastfeeding and bottle-feeding occurring during daytime *ad lib* until nasogastric tubes were removed. After this period, both twins were exclusively fed breastmilk by bottle.

Both infants were placed in a supine position when sleeping. No prenatal exposure to thalidomide, hydantoins, or trimethadione, or postnatal exposure to erythromycin was present. Family history is significant for

Fig. 1



Abdominal ultrasound. Twin A at 33 days of life (left) measuring 6 mm in thickness and 2 cm in length with antral nipple sign (arrow) representing protruding pyloric mucosa. Twin B at 44 days of life (right) measuring 5 mm in thickness over 2 cm in length.

classic phenylketonuria (PKU) in the father. Both twins received negative newborn screening results for PKU. No known familial history of pyloric stenosis was noted in the immediate or extended family.

Twin A presented at 33 days of life with a short history of nonbilious projectile emesis and intolerance to feeds. Abdominal examination and electrolytes at presentation were unremarkable. An ultrasound was obtained (Fig. 1) which demonstrated a pyloric wall of 6 mm in thickness and measured at least 2 cm long with an antral nipple sign. An open Fredet-Ramstedt pyloromyotomy was performed on the day of presentation and was without complication. Postoperatively, the patient suffered a transient emesis and intolerance to feeds. This resolved after 12 h, at which time feeds were advanced. The remainder of the hospital course was unremarkable and discharge was achieved on postoperative day 2.

Twin B presented at 44 days of life with a history of nonbilious nonprojectile emesis for 4 days followed by 1 day of projectile emesis. Abdominal examination and electrolytes at presentation was unremarkable. Ultrasound imaging demonstrated a pyloric wall measuring 5 mm in thickness and was at least 2 cm in length (Fig. 1). An open Fredet-Ramstedt pyloromyotomy was performed and was complicated by a small mucosal perforation on the duodenal side of the myotomy. The perforation was repaired primarily with polydioxanone suture. The remainder of the procedure was unremarkable. Postoperatively, initiation of feeds was delayed by 12 h, given the mucosal repair. Feeds were started, advanced, and tolerated without issue, and the infant was discharged home on postoperative day 1.

At follow-up at 9 months of age, both twins continue to tolerate advancements in feeding and demonstrate satisfactory weight gain and achievement of developmental milestones.

Discussion

The etiology of pyloric stenosis remains enigmatic despite an excellent understanding of the diagnosis and management of infants with this pathology. An interaction between environmental factors and a genetic predisposition likely explains the complex inheritance. The general consensus is that no single gene model, regardless of penetrance, is responsible for the observed patterns of inheritance [5,20]. The first feature that suggested a genetic influence is the male predominance. Multiple epidemiological studies demonstrated a male: female ratio of 4–5 : 1 across multiple countries [1]. The incidence is highest in white non-Hispanic infants and lowest in Asians, the latter occurring at a quarter of the rate of non-Hispanic white infants [1,21]. In addition to male predominance, birth order was noted as early as 1927 to be associated with pyloric stenosis. Although multiple studies have looked at birth order, they have not demonstrated a first-born predominance, but rather a decreasing risk with increasing birth order with an odds ratio (OR) for first born of approximately two and decreasing to close to one by the fourth birth [1,22].

Additional evidence of a possible genetic influence comes from the association with multiple syndromes and malformations. Associated anomalies including diaphragmatic hernias, esophageal atresia, and urinary malformations have been reported in association with pyloric

Table 1 Candidate genetic factors in the pathophysiology of infantile hypertrophic pyloric stenosis

Gene/protein/cofactor	Normal function	Proposed mechanism of influencing pathogenesis
Neuronal nitric oxide synthase	Generates nitric oxide→activates guanylyl cyclase→smooth muscle relaxation	Reduced generation of inhibitory neurotransmitter increasing smooth muscle tone leading to hypertrophy
Transient receptor potential cation channels	Smooth muscle mechanoreceptors	Stimulation increases calcium inflow into smooth muscle increasing tone and leading to potential hypertrophy
Heme oxygenase-2	Produces carbon monoxide used in signal transduction	Dysfunctional communication between interstitial cells of Cajal and pyloric smooth muscle cells
Glucagon-like peptide-2	Trophic factor for intestinal epithelium, inhibitory of apoptosis, role in motility	Possible role in pyloric hypertrophy
Neuropeptide Y	Inhibitory enteric neurotransmitter	Involved in smooth muscle relaxation
Phenylalanine hydroxylase	Rate-limiting enzyme in the degradation of phenylalanine to tyrosine. Association in linkage analysis	Shares common cofactor, tetrahydrobiopterin, with nitric oxide synthase
Motilin	Role in initiating myoelectric motility complex. Association in linkage analysis	Erythromycin, a motilin agonist, associated with disease development

stenosis [23], as well as syndromes including trisomy 21, trisomy 18, Denys-Drash, Smith–Lemli–Opitz (defect in cholesterol metabolism), Cornelia de Lange (dysfunctional Notch signaling pathway), nephrotic syndrome type I, PKU, congenital lipodystrophy type IV, FG syndrome, familial visceral neuropathy, Costello (H-Ras mutation), Alpert, Opitz, Marden–Walker, X-linked ichthyosis, duplications 1q, 9q, deletion 11q, and fetal alcohol syndrome [21,24].

Genetic analyses have localized multiple candidate genes that may predispose to the development of pyloric stenosis (Table 1). The most thoroughly investigated of these has been the gene for neuronal nitric oxide synthetase (nNOS, *NOS1*, *IHPS1*, 12q24). Both gene expression at the mRNA level and protein expression are reduced or dysfunctional in some infants with pyloric stenosis [25,26]. It has been postulated that nitric oxide, an inhibitory neurotransmitter in the gastrointestinal tract that acts via guanylyl cyclase and generation of cGMP, is decreased. This results in pylorospasm, a prolonged inappropriate contraction that result in pyloric muscular hypertrophy, particularly of the circular layer [18,26,27]. Histologic analysis demonstrated distorted and enlarged enteric nerve fibers which also demonstrated reduced nNOS expression [26,28]. Genome-wide linkage analyses demonstrated multiple novel sites, as well as a linkage to locus 12q24, the site of the *NOS1* gene [29,30]. However, others demonstrated that while variants of the gene are present in some pyloric stenosis patients, they did not demonstrate an increased association with pyloric stenosis [31]. Although a promising candidate gene, immunohistologic analysis demonstrated reduced or absent expression of nitric oxide synthetase in only a minority of patients with pyloric stenosis [32]. Tetrahydrobiopterin, a cofactor for the phenylalanine hydroxylase enzyme, is also a cofactor for neuronal nitric oxide synthase [33,34]. Given the infants' paternal history of classic PKU and the autosomal recessive inheritance, the infants can be assumed to be heterozygous carriers of the phenylalanine hydroxylase enzyme deficiency.

Other candidate genes, some X-linked, include those coding for transient receptor potential cation channels that are expressed on smooth muscle cells. These membrane channels are thought to be mechanosensitive, possibly responding to luminal boluses in the region, eventually leading to smooth muscle hypertrophy [21,30,33]. Recent

molecular research has demonstrated a lack of c-Kit expression and cells of Cajal in the pylorus [34,35], suggesting a dysfunction of myenteric innervation of smooth muscle may be an important factor in the pathogenesis [36]. This is further supported by the decreased expression of heme oxygenase-2, which produces carbon monoxide that functions in signal transduction between cells of Cajal and pyloric smooth muscle cells [37]. Other candidate genes identified with linkage analysis but of uncertain significance include glucagon-like peptide-2, motilin, neuropeptide Y [29], and those related to cholesterol metabolism [38]. The infants in this case study presented 11 days apart with pyloric stenosis, with twin A having had triple the number of insertions of nasogastric feeding tubes compared with twin B prior to the diagnosis of this condition, bringing into question whether stimulation of the pylorus with either a foreign body or luminal bolus can result in transient receptor potential cation channel activation, possibly relating to pathophysiology of pyloric hypertrophy.

Familial aggregation studies have demonstrated a clear increased incidence of pyloric stenosis in Denmark, suggesting a strong genetic influence. Rate ratios were evaluated for monozygotic and dizygotic twins, siblings, half-siblings, cousins, and half cousins, which were 182, 29.4, 18.5, 5, 3, and 1.6, respectively, clearly demonstrating that the more genetic information shared, the greater the chance of concordance [11]. The relatively minor difference in the risk between siblings and dizygotic twins suggests that the influence of the in-utero environment is likely minor. The influence of parents with a history of pyloric stenosis on the offspring demonstrates an increased risk, but it was much more pronounced if the mother is affected, with increased risk ratio of 10 for an affected father, and 40 for an affected mother [39]. No direct family history of pyloric stenosis is described in this case.

Prenatal and postnatal exposure to a variety of drugs is associated with an increased incidence, the most notable being erythromycin. Concerns for a causal relationship between postnatal erythromycin exposure and the development of pyloric stenosis developed after two clusters of disease developed after postnatal exposure [40,41]. Motilin induces gastric contractions, is the target for erythromycin in the gastrointestinal tract, and has

been the center of investigation for a drug-induced etiology for pyloric stenosis. However, no association between the gene sequence variants of motilin and pyloric stenosis has been demonstrated [42]. Metanalysis involving nine studies, two of which were randomized control trials, demonstrated an OR with any erythromycin exposure of 2.45, but increased to 10.5–12.89 when looking at infants exposed in the first 14 days of life [43,44]. In addition, prenatal exposure to hydantoins, trimethadione, and thalidomide increased the incidence of pyloric stenosis [45]. Prostaglandin therapy for infants with a patent ductus arteriosus was suggested as a possible risk factor [46]. Maternal tobacco smoking has been explored and demonstrated an ORs of 1.82–2.1 in multiple epidemiologic analyses [47,48]. The twins presented here were unexposed to these substances prenatally and postnatally.

A number of environmental factors have been implicated as etiologic factors in the pathogenesis. A case-control study in Sweden examining the factors related to pregnancy and in-utero exposure determined that prematurity (OR: 2.54), cesarean delivery (OR: 1.67), and maternal age less than 20 years (OR: 1.42) are associated with an increased incidence of pyloric stenosis. In addition, birth order 2 or more (OR: 0.78) was associated with a decreased risk [47]. Maternal breastfeeding is protective [49,50]. The infants here were both premature, born vaginally at 30 weeks and 2 days gestation, and were exclusively fed breastmilk, yet presented 11 days apart.

Studies from Denmark and Sweden, where there has been the largest decline in the incidence of pyloric stenosis noted in the literature, have demonstrated a parallel decrease in the rate of sudden infant death syndrome (SIDS) after a countrywide recommendation that all infants be placed in a supine sleeping position to prevent SIDS [51–53]. Radiologic evidence demonstrated that feeds preferentially accumulate in the fundus and proximal stomach when the infant was supine, but in the antrum and pylorus when prone [52]. These findings have the potential to both offer a mechanical cause to explain the parallel decline in SIDS and pyloric stenosis, as well as provide a simple, highly effective means of disease prevention. The infants described here were bottle-fed in the right lateral decubitus position prior to their diagnosis.

Gastric hyperacidity has been implicated as another possible etiologic factor in the pathogenesis of pyloric stenosis. Infants display elevated gastrin levels through the fourth week of life which, coupled with immature epithelium, can lead to mucosal thickening. This latter finding is proposed as the primary alteration leading to pyloric stenosis secondary to chronic contractions in response to hyperacidity [54]. Others have suggested an inherited higher parietal cell mass as being a possible factor [55]. Studies evaluating *Helicobacter pylori* infection in infants as a factor failed to show any association [36,56,57].

Conclusion

Despite the excellent current knowledge of disease diagnosis and management, the etiological factors leading to the development of pyloric stenosis remain elusive. The

exact mechanism is likely polygenetic susceptibility that is influenced by postnatal environmental factors. Given the high concordance and familial aggregation, strong consideration should be given to ultrasound screening of infants that are siblings or twins of an infant diagnosed with pyloric stenosis.

Conflicts of interest

There are no conflicts of interest.

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