Early Life Events: Infants with Pyloric Stenosis Have a Higher Risk of Developing Chronic Abdominal Pain in Childhood

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Objective We hypothesize that children who had pyloric stenosis are at greater risk for developing chronic abdominal pain because this cohort combines various risk factors: an early stressful event, gastric surgery, and perioperative nasogastric tube placement in most cases.

Study design This was a case control study of all children diagnosed with pyloric stenosis during infancy (cases) between January 1, 2000, and June 31, 2005, at Children's Memorial Hospital, Chicago. Because of their similar genetic and socioeconomic backgrounds, siblings aged 4 to 20 years without a history of pyloric stenosis were selected as controls. Parents of children with symptoms completed the parental form of the Pediatric GI Symptoms Rome III version questionnaire for both cases and controls. The primary outcome was the prevalence of chronic abdominal pain, and the secondary outcome was the presence of pain-associated functional gastrointestinal disorder (FGID), in accordance with Rome III criteria.

Results Cases (n = 100; mean age, 7.49 ± 1.43 years; 29 girls) and controls (n = 91; mean age, 9.20 ± 4.19 years; 29 girls) participated in the study. Mean time to follow-up was 7.2 ± 1.6 years. Chronic abdominal pain was significantly more common in cases than in controls (20/80 [25%] vs 5/91 [5.8%]; OR, 4.3; 95% CI, 1.5-12; $P = .0045$). Seven out of 20 subjects (35%) met the Rome III criteria for diagnosis of a pain-associated FGID (3 with irritable bowel syndrome, 2 with functional dyspepsia, and 2 with functional abdominal pain), and 1 patient in the control group (with irritable bowel syndrome) met these criteria (OR, 6.8; 95% CI, 0.82-56; $P = .043$).

Conclusion We have described a new model to study early life events in infants. Our findings suggest that the presence of pyloric stenosis in infancy and factors involved in its perioperative care represent risk factors in the development of chronic abdominal pain in children at long-term follow-up. This study provides important data to sustain the multifactorial theoretical construct of pain-associated FGID and underscores the importance of early life events in the development of chronic abdominal pain in children. *(J Pediatr 2011;159:551-4)*.

Abdominal pain is among the most common complaints in childhood; 38% of school children report abdominal pain weekly, and 24% of school children report abdominal pain persisting for more than 8 weeks, meeting the Rome III temporal criteria for pain-associated functional gastrointestinal disorders (FGID).[1] Children with chronic abdominal pain have higher depression scores and greater school absenteeism.[1] Long-term follow-up studies have shown a higher prevalence of psychological ailments and use of psychotropic medications in adults who had a history of chronic abdominal pain during childhood.[2] The high prevalence and serious impact of chronic abdominal pain and the significant health care costs involved in the treatment of children and adults with pain-associated FGID call for an increased understanding of the disorder's pathogenesis.

The biopsychosocial model is the most accepted construct for explaining pain-associated FGID.[3] It proposes that FGID results from the interplay of multiple psychological, social, and biological factors throughout the individual's life. The effects of some of the factors that predispose children to develop FGID can be traced to the first hours or days of life. A controversial study suggested that the noxious stimulation caused by the simple maneuver of gastric suction at birth increases the risk of developing pain-associated FGID later in life.[4] Another study found that neonatal rats subjected to daily orogastric suctioning for 10 days developed global chronic somatic and visceral hyperalgesia as adults.[5] The increased serum levels of corticotropin-releasing factor-1 found in these animals suggested the involvement of stress mechanisms.[5] These previous studies suggest the existence of a period of early susceptibility and neural plasticity in which apparently minor noxious factors may lead to enduring alterations in pain perception.[6]

Gastric surgery may be one of several noxious factors leading to visceral hyperalgesia and pain-associated FGID later in life. Animal studies have shown the development of nerve remodeling and visceral hyperalgesia after gastric surgery.[7] Whether noxious agents affecting human neonates predispose to pain-associated FGID remains an interesting question. The

FGID	Functional gastrointestinal disorders
GI	Gastrointestinal
QPGS-RIII	Pediatric GI Symptoms Rome III questionnaire

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human study on orogastric suction has not been replicated, and the findings of experimental animal studies are not always translatable to humans. Advances in the understanding of the link between early life events and FGID have been hampered by a lack of human models.

Infantile hypertrophic pyloric stenosis is a condition of early infancy in which hypertrophy of the pylorus leads to gastric outlet obstruction. We hypothesized that children who had pyloric stenosis during infancy are at greater risk of developing chronic abdominal pain later in life. A cohort of infants affected by pyloric stenosis combines various risk factors thought to lead to visceral hyperalgesia and pain-associated FGID: an early stressful event, gastric surgery, and perioperatory nasogastric tube placement in most or all cases.

Methods

This was a cohort study aimed at assessing the long-term gastrointestinal (GI) outcome of infants diagnosed with pyloric stenosis. Data from all children who were diagnosed with pyloric stenosis during infancy (International Classification of Diseases, Ninth Revision codes 537.0 and 750.5) between January 1, 2000, and June 31, 2005, at Children's Memorial Hospital, Chicago were obtained from the hospital's Health Information Management Department. A single physician reviewed all charts and operative reports for the children diagnosed with pyloric stenosis during infancy (cases) to confirm the diagnosis. Parents of all cases were contacted by phone by a bilingual (English and Spanish) physician and were invited to participate in a study assessing the presence of GI symptoms. Because of their similar genetic and socioeconomic backgrounds, siblings aged 4 to 20 years with no history of pyloric stenosis were selected as controls. In cases of multiple siblings, the sibling of the same sex who was closest in age was selected as the control. Consenting parents of both cases and controls were requested to complete the parental form of the Questionnaire on Pediatric GI Symptoms based on Rome III criteria (QPGS-RIII). The QPGS-RIII is a validated questionnaire for diagnosing FGID according to the Rome III criteria and assessing its severity and related disabilities. Rome III criteria define minimum requisites for a disorder to be defined as a pain-associated FGID, including duration of pain at least 8 weeks and at least 1 pain episode per week.[8] Thus, based on the Rome III criteria, children with a history of abdominal pain of more than 8 weeks duration who did not have at least 1 episode of pain per week do not have an FGID despite the presence of chronic abdominal pain. The primary outcome was the prevalence of chronic abdominal pain, defined as continuous or intermittent abdominal pain of more than 8 weeks duration. The secondary outcome was the presence of pain-associated FGID according to the Rome III criteria (ie, abdominal pain of more than 8 weeks duration occurring at least once a week). The study was approved by the Children's Memorial Hospital Institutional Review Board.

Sample size calculation was conducted based on the assumption that 30% of the subjects with pyloric stenosis would develop chronic abdominal pain, compared with 5% of controls. Based on these estimates, with a nondirectional α value of 0.05 and a power of 0.90, 49 patients per group were required to detect this level of difference. Significance between groups was evaluated using OR and 2-tailed Fisher exact tests. Statistical significance was set at $P \leq .05$. Estimates for sample size calculation were based on data from previous studies by our group with a similar study design.[9,10] Data for the estimation of cases (30%) were based on a study designed to assess cow's milk allergy (another noxious early life event occurring in the first months of life) as a possible risk factor for FGID and chronic abdominal pain, which showed a 31% prevalence of chronic abdominal pain in long-term follow-up. Data for the estimation of controls was calculated by averaging the prevalence of chronic abdominal pain in controls in 2 previous studies by our group (2.6% and 9.4%).[9,10]

Results

A total of 100 cases (mean age, 7.49 ± 1.43 years; 29 girls) and 91 controls (mean age, 9.20 ± 4.19 years; 29 girls) participated in the study. Four patients were excluded after a review of charts and phone interview revealed wrongful entry to the database; data for these 4 cases are not included (**Figure**; available at www.jpeds.com). Nineteen patients (19%) were diagnosed with congenital pyloric stenosis, and 81 patients (81%) were diagnosed with acquired pyloric stenosis. None of the patients included in this study had any other GI abnormality. The study cohort was 56% Hispanic, 39% Caucasian, 4% Asian, and 1% African American; 91% of the children diagnosed with pyloric stenosis were born full term (73% by vaginal delivery and 27% by cesarean delivery). None of the cases had received erythromycin, a drug that has been associated with the development of pyloric stenosis.[11] Average age at diagnosis of pyloric stenosis was 39 days (range, 6 to 154 days; median, 33.5 ± 23.62 days; 95% CI, 33.3- 43.8 days). The mean interval from the time of diagnosis to follow-up was 7.22 ± 1.64 years.

Presence of abdominal pain in the previous 2 months was significantly more common in cases than controls (20/100 [20%] vs 5/91 [5.8%]; OR, 4.3; 95% CI, 1.541 to 11.99; 2-tailed $P = .0045$). There was no significant difference in age at the time of diagnosis of pyloric stenosis, type of delivery, and race or ethnicity between the patients with pyloric stenosis who developed chronic abdominal pain and those who did not (**Table**). Intensity of abdominal pain was rated on a 4-point scale. Pain was rated as "a little" in 2 cases, "some" in 8 cases, "a lot" in 8 cases, and "a very lot" in 2 cases. Some form of disability was present in 12/20 cases (60%; "most of the time," 5; "sometimes," 2; "once in a while," 5). Patients with congenital pyloric stenosis were as likely to develop chronic abdominal pain as those diagnosed with acquired pyloric stenosis