

Functional Gastrointestinal Disorders Induced by Esophageal Atresia Surgery: Is It Valid in Humans?

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Background/Aims

Functional gastrointestinal disorders (FGID) affect 15%-20% of the general pediatric and adult population. Animal models suggest that a neonatal stress such as invasive procedures and maternal separation could be responsible for visceral hypersensitivity and FGID. We tested the hypothesis that congenital esophageal atresia (EA), a condition corrected during the neonatal period and associated with multiple stresses, is a clinically significant risk factor for the development of FGID later in life. We postulated that, to be clinically significant, the effect of neonatal stress on the incidence of FGID should be as strong as that of enteric infections in the development of irritable bowel syndrome in children.

Methods

Subjects with EA and healthy controls were enrolled in this multicenter cohort study. Gastrointestinal symptoms were assessed by a questionnaire and FGID was diagnosed using the Rome III criteria.

Results

Fifty-three children (25 girls; median age, 12 years) with EA were compared to 72 age- and sex-matched controls. Although 11 children with EA (21%) had a FGID diagnosis versus 8 controls (11%), this difference was not significant ($\chi^2 = 2.20$, $P > 0.05$). In subjects with EA, the presence of associated malformations, the occurrence of complications during the first month, and the length of hospital stay > 30 days did not influence the incidence of FGID. Chronic abdominal pain was present in 38% of subjects with EA versus 25% of controls ($P > 0.05$).

Conclusions

Neonatal stress secondary to surgical correction of EA is not a clinically significant risk factor for the development of FGID in childhood.

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Key Words

Esophageal atresia; Irritable bowel syndrome; Life change events

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Introduction

Functional gastrointestinal disorders (FGID) are defined as recurrent symptoms that are not yet explainable by structural or biochemical anomalies. In children, the most frequent FGIDs include irritable bowel syndrome (IBS), functional abdominal pain (FAP) and functional dyspepsia (FD), which are defined by the symptom-based Rome criteria.¹

The mechanisms underlying the pathophysiology of FGID are not unique and rather the result of various mechanisms. FGID may result from the interaction of multiple genetic, biologic, psychological and social factors. Among them, early-life adverse events in the neonatal period either somatic or psychological have been implicated as possible contributing factors. Animal studies have shown that the neonatal period is characterized by a very high susceptibility to stress including colonic irritation² and maternal deprivation³ which lead to visceral hypersensitivity in adulthood.^{2,3} The latter has been closely related not only to central² but also to peripheral sensitization.^{3,4} In humans, studies have attempted to confirm these findings, suggesting the putative key role of birth weight < 1.5 kg, repetitive gastric suction in neonates, and surgical correction of pyloric stenosis.⁵⁻⁷

Esophageal atresia (EA) occurs in about 1 out of 3,000 live births.⁸ Surgical repair is obligatory and performed in the first day of life followed by a stay in the neonatal intensive care unit (NICU). Therefore, patients operated at birth for EA experience highly stressful neonatal events including surgery, painful procedures, gastric tube placement and NICU stays with prolonged maternal separation.

We hypothesized that subjects operated for EA (exposed group) were more prone to develop FGID and abdominal pain compared to control subjects without a complex neonatal history. In this multicenter cohort study, we sought to measure the incidence of abdominal pain and abdominal pain-related FGID (IBS, FD and FAP), using the Rome III criteria, in patients with congenital EA corrected during the neonatal period, and compared it to subjects without a complex neonatal history. We also aimed to determine if complications and events following surgery in the first month of life influence long-term development of abdominal pain-related FGID in childhood.

Materials and Methods

Subjects

All subjects with EA, aged 8 to 18 years, followed at the EA Clinics at Hôpital Sainte-Justine (Université de Montréal, Québec, Canada) and at Hôpital Jeanne de Flandre (University of Lille, Lille, France) were approached for inclusion. Exclusion criteria included a history of inflammatory bowel disease, an acute enteric infection (gastroenteritis) or an abdominal surgery in the previous 4 weeks, and an intellectual disability. Data was gathered from patients' charts using standardized data collection forms. We included patient demographics (sex, gestational age, birth weight, type of atresia and associated malformations), occurrence of post-operative complications in the first month of life (pneumothorax, chylothorax, anastomotic leak and early recurrent fistula), duration of intubation, age of oral feeding, duration of NICU stay and duration of hospital stay.

Controls \geq 8 years of age were enrolled using the same exclusion criteria from orthopedic clinics in each hospital. Control subjects had a benign neonatal course (absence of neonatal surgery and neonatal maternal separation) and no history of surgery for scoliosis.

Methods

All participants had to complete the Questionnaire of Pediatric Gastrointestinal Symptoms (QPGS). The QPGS is a questionnaire, validated in English and French, that assesses symptoms associated with FGID in children, and has been adapted to the pediatric Rome III criteria.^{1,9} This structured questionnaire includes sections assessing bowel habits, abdominal pain (pain duration and frequency), dysphagia, heartburn, regurgitations and data on limitations of activities (missed days of school and missed activities with friends due to pain). The questionnaire was completed by each child or with the help of a parent for children less than 10 years old. The primary outcome was the prevalence of abdominal pain-associated FGID (IBS, FD and FAP) according to Rome III criteria. The secondary outcome was the prevalence of chronic abdominal pain defined as abdominal pain reported either continuously or intermittently at least once a week for more than 8 weeks of duration.

The protocol was approved by the institutional ethics committees of the 2 hospitals, and appropriate consent was obtained from all participants. Consent was signed by the parents or legal

guardian and by the child himself if older than 14 years of age.

Sample Size Calculation and Statistical Analysis

We postulated that, to be clinically significant, the effect of neonatal stress on the incidence of abdominal pain-related FGID in the exposed subjects should be as strong as the effect of enteric infections in the development of IBS in childhood.¹⁰ Studies have shown that the prevalence of abdominal pain-related FGID in the general pediatric population is 10%-12%¹¹ and increases to 30%-32% in those that have had a recent enteric infection (relative risk ~ 3.2).¹⁰ We therefore hypothesized that 30%-32% of exposed subjects (with EA) should be affected by FGID and calculated that 52 patients and 52 controls were necessary in each cohort to achieve a uni-directional alpha of 0.05 with power of 80%. The percentage of children who reported abdominal pain-related FGID in each group was compared and odds ratio was obtained. In the group of patients operated for EA (exposed group), further analysis was conducted between subjects with and without FGID: continuous variables (gestational age, birth weight, age at extubation, age at oral feeding, length of NICU stay and length of hospital stay) and dichotomous variables (presence of associated malformations, post-operative complications during the first month, and hospital stay duration > 30 days) were compared.

Appropriate descriptive statistics were used to summarize the general features of the population and questionnaire findings. We performed comparisons between the groups using the Student's *t* test and Wilcoxon test to compare means and medians for the continuous variables, and the χ^2 test or Fisher exact test for discrete variables. Statistical significance was expressed as $P < 0.05$ and SPSS software (version 18.0; SPSS Inc., Chicago, IL, USA) was used for all analyses.

Results

Fifty-five subjects with EA fulfilled the inclusion criteria. Fifty-three of them, 23 from Hôpital Ste-Justine and 30 from Jeanne de Flandres Hospital, (25 girls; median age, 12.3 years; range, 7.8-18.0) accepted to participate to the study. Seventy-two controls (34 girls; median age, 13.4 years; range, 7.8-18.5) were also included ($P > 0.05$ for age and sex ratio of patients vs controls).

Based on the answers from the QPGS, 11 out of 53 children (21%) with EA complained of FGID (IBS, $n = 5$; FAP, $n = 5$;

FD, $n = 1$) according to pediatric Rome III criteria compared to 8 out of 72 controls (11%) (IBS, $n = 3$; FAP, $n = 3$; FD, $n = 2$) ($\chi^2 = 2.20$, $P > 0.05$). Odds Ratio of developing a FGID following EA repair was 2.09 (95% CI, 0.77-5.64; $P > 0.05$). There were no significant differences in symptom duration, intensity or limitation of activities, between exposed subjects and controls with FGID (Table 1).

In addition, we sought to determine if patient variables such as associated malformations, occurrence of post-operative complications, duration of intubation, age at oral feeding, duration of NICU stay or duration of hospital stay, which could all be con-

Table 1. Gastrointestinal Symptoms Severity Variables in Pediatric Subjects and Controls With Functional Gastrointestinal Disorders

	Subjects with FGID (n = 11)	Controls with FGID (n = 8)
FGID type (n [%])		
IBS	5 (45.0)	3 (37.5)
FAP	5 (45.0)	2 (25.0)
FD	1 (10.0)	3 (37.5)
Pain frequency (n [%])		
< Once/wk	0 (0.0)	0 (0.0)
Once/wk	6 (54.0)	4 (50.0)
Many times/wk	4 (36.0)	3 (37.5)
Everyday	1 (10.0)	1 (12.5)
Duration of pain (n [%])		
2-3 mo	2 (18.0)	2 (25.0)
4-11 mo	0 (0.0)	0 (0.0)
≥ 1 yr	9 (82.0)	6 (75.0)
Duration of pain (n [%])		
< 1 hr	8 (72.0)	6 (75.0)
1-2 hr	2 (18.0)	1 (12.5)
3-4 hr	0 (0.0)	0 (0.0)
Majority of the day	0 (0.0)	1 (12.5)
≥ 1 day	1 (10.0)	0 (0.0)
Quantification of pain (n [%])		
A little	4 (36.0)	5 (62.5)
From a little to a lot	4 (36.0)	3 (37.5)
A lot	3 (28.0)	0 (0.0)
Hugely	0 (0.0)	0 (0.0)
Missed days of school (n [%])		
Never or < once/mo	9 (82.0)	8 (100.0)
1-4 times/mo	2 (18.0)	0 (0.0)
Everyday	0 (0.0)	0 (0.0)
Missed social activities (n [%])		
Never or < once/mo	9 (82.0)	7 (87.5)
1-4 times/mo	2 (18.0)	1 (12.5)
Everyday	0 (0.0)	0 (0.0)

FGID, functional gastrointestinal disorders; IBS, irritable bowel syndrome; FAP, functional abdominal pain; FD, functional dyspepsia.

Table 2. Distribution of Stress-related Factors in Pediatric Subjects Operated for Esophageal Atresia With or Without Functional Gastrointestinal Disorders

	EA with FGID (n = 11)	EA without FGID (n = 42)	OR and <i>P</i> -value
Gestational age (median [range], wk)	38 (33-42)	38 (29-40)	<i>P</i> = 0.912
Birth weight (median [range], g)	2,400 (1,465-3,270)	2,835 (1,050-3,750)	<i>P</i> = 0.123
Birth weight < 2,500 g (n [%])	6 (55)	12 (29)	OR = 0.36 (0.77-11.72) <i>P</i> = 0.135
Age at extubation (median [range], days)	3 (1-18)	2 (0-60)	<i>P</i> = 0.971
Age at oral feeding (median [range], days)	6.5 (0-19)	7 (2-26)	<i>P</i> = 0.872
NICU stay duration (median [range], days)	7 (1-73)	8 (1-145)	<i>P</i> = 0.828
Hospital stay duration (median [range], days)	14.5 (4-140)	15.5 (7-154)	<i>P</i> = 0.494
Presence of associated malformations (n [%])	8 (72)	21 (50)	OR = 2.67 (0.62-11.48) <i>P</i> = 0.177
Post-operative complications during first month (n [%])	4 (36)	22 (52)	OR = 0.52 (0.12-1.73) <i>P</i> = 0.344

EA, esophageal atresia; FGID, functional gastrointestinal disorders; NICU, neonatal intensive care unit.

sidered as a proxy for assessing the intensity of neonatal stress, influencing the development of FGID. None of these parameters was a significant risk factor for the development of FGID in childhood and adolescence (Table 2).

Chronic abdominal pain as previously defined was present in 20/53 patients (38 %) and 18/72 controls (25%) ($P > 0.05$).

Compared to controls, the children with EA reported more frequent dysphagia (49% vs 11%, $P < 0.001$), heartburn (25% vs 10%, $P < 0.05$), regurgitations (23% vs 8%, $P < 0.05$), symptoms related to esophageal dysmotility and gastroesophageal reflux which were both associated to EA in the literature.¹²

Discussion

We showed that the neonatal stress induced by EA repair which involved many stressful events (repeated invasive procedures, maternal separation), was not a clinically significant risk factor for subsequent development of pain-associated FGID in later childhood. We have reported similar results even when less rigorous criteria of "chronic abdominal pain" were used. Furthermore, we showed that subjects suffering from FGID had not been exposed to more severe neonatal stressful conditions.

These results contrast with those of previously published human studies on consequences of neonatal stress on the occurrence of FGID. Indeed, a case-control retrospective study found that 22.4% of 108 patients hospitalized with FGID at a median age of 14 (range, 2-31) had experienced gastric suction at birth versus 11.2% in a control group. However, this retrospective study was

prone to recall bias and gastric suction might thus be a confounding factor.⁵ A recent work by Saps & Bonilla reported that infants operated for pyloric stenosis at a mean age of 39 days, developed at the age of 7.5 days, showed a significantly higher incidence of chronic abdominal pain (but not of FGID) compared to controls (OR, 4.27; 95% CI, 1.43-12.70).⁷ Although the incidence of chronic abdominal pain was comparable to our present data (25% in Saps & Bonilla's study vs 38% in the present study), the incidence of abdominal pain was surprisingly very low (5%) in the control group compared to the previously published data in children^{11,13}; including those from this group.¹⁰

The strengths of the present work are that: (1) this is a prospectively designed multicenter study. We included a homogeneous cohort of subjects with a history of severe neonatal stress who therefore represent an appropriate population to test the hypothesis of the role of early-life stress in the development of FGID; (2) the incidence of pain-related abdominal symptoms in control subjects is in agreement with previously published pediatric data suggesting that the control group was adequately selected^{10,11,13}; and (3) the expected high incidence of dysphagia and gastroesophageal reflux symptoms in patients with operated EA as compared to controls shows, as an internal control, that the subjects correctly answered the questionnaires.

This study was conducted exclusively in patients with EA. One can argue that surgical damages, mainly towards vagal afferents, during EA repair may have influenced visceral pain processing. However, vagal afferents are believed to mediate physiological rather than harmful sensations transmitting information

on nature and composition of the intestinal content and motility and contractile tension of the smooth muscle.¹⁴ It can also be argued that since children with EA may have “upper” gastrointestinal discomfort such as gastroesophageal reflux disease and dyspepsia, a risk of confusion between symptoms accompanying EA and those secondary to the neonatal stress induced by the EA surgery is possible. However, in this study, a majority of patients with EA presenting with a FGID diagnosis had mainly IBS or FAP (based on “lower digestive tract” complaints) enhancing the reliability of the results. Another pitfall is related to the number of subjects included, which may preclude the demonstration of differences between 2 groups of subjects by a possible type II error. We postulated that, to be clinically significant, the effect of neonatal stress on the incidence of FGID should be as strong as that of enteric infections in the development of IBS symptoms.¹⁰ Although this study was based on this hypothesis, we cannot rule out that a less profound effect of neonatal stress is present.

The putative role of early life events in the development of FGID comes from studies conducted in rodents indicating that the neonatal period is characterized by a very high susceptibility to stress leading to visceral hypersensitivity in adulthood. Neonatal colonic² or gastric¹⁵ irritation, maternal deprivation³ and gastric suctioning¹⁶ have been shown to induce visceral (colonic^{2,3,16} or gastric¹⁵) hypersensitivity in animal models. The mechanisms include peripheral^{3,4} and central sensitization² and involve corticotrophin releasing factor,¹⁶ nerve growth factor¹⁷ and transient receptor potential vanilloid 1.¹⁸ Indeed, this period is a particularly sensitive window for experience-induced neuronal plasticity due to the ongoing maturation of sensory¹⁹ and pain processing.²⁰

How do we explain the discrepancies between animal studies and the results of the present study? It is well known that early traumatic and painful experiences such as burns can induce long-term alterations in sensory and pain processing in children.²¹ Similarly, though different from neonatal stress, childhood trauma and abuse that are strongly associated to IBS in adults result in modifications in the hypothalamic-pituitary-adrenal axis.²² However, somatic pain researchers have also shown that long-term consequences of NICU admission are not only characterized by enhanced perceptual sensitization to prolonged painful stimulation but also by hypoalgesia to brief heat pain stimuli²³ suggesting that modifications of pain processing may occur in various directions. Ren et al²⁴ corroborated this idea by showing in a rat model of neonatal local inflammation that global elevation of pain thresholds (ie, hypoalgesia) and excessive hyper-

algesia upon re-inflammation in response to thermal and mechanical stimuli could occur both in the same animal.²⁴ Furthermore, translational studies in FGID have shown that results obtained in animal models are only partially correlated to human symptoms.²⁵ This is also illustrated in a study of somatic pain sensitivity to mechanical stimulation in children that was not significantly altered by painful neonatal experiences²³ contrasting with results found in animals.²⁴ All of these elements must be carefully taken into account when the replication of animal studies in the field of pain and visceral sensitivity is attempted on humans. Since visceral sensitivity processing is highly complex with involvement of peripheral and central nervous systems influenced by cognitive and psychological processes, it is easy to imagine that animal models only partially reflect human pathophysiology. In keeping with this idea, it has been shown that response to pain in school-aged children with previous experience in NICU was highly influenced by the mother’s behavior.^{26,27}

We conclude that severe neonatal stress (surgery, repeated physical aggressions and maternal separation) secondary to EA repair is not a clinically significant risk factor for pain-associated FGID later in life either in childhood or in adulthood. Invaluable pathophysiological knowledge gathered by animal models must be carefully interpreted in that context. To further understand the results of this study and the consequences of neonatal stress on visceral sensitivity, objective measurements of somatic pain, visceral sensitivity and psychological and cognitive assessment of the patients (and their parents) should be conducted. Measure of the response to stress is also warranted as suggested by recent work on epigenetic consequences of early life adverse events.²⁸

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pediatric patients in the French team, and critically revised the manuscript. Christophe Faure designed the study. He recruited pediatric patients in the Canadian team, participated in the statistical analysis and wrote the manuscript.

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