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Early-Life Factors Associated with Pediatric Functional Constipation: an Italian Multicenter Prospective Study

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Short Title: Early-Life Risk Factors for Pediatric Functional Constipation

Abbreviations: FC, Functional Constipation; FGIDs, Functional Gastrointestinal Disorders; ID, Infant Dyschezia; IBS, Irritable Bowel Syndrome; CMA, cow's milk allergy.

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Abstract

Objective: This multicenter prospective study sought to establish possible risk factors for Functional Constipation (FC) in the first year of life. **Study design**: At the infant's age of 3, 6 and 12 months, parents of all included infants complete two questionnaires: one about the presence of FC and the second screened the possible risk factors for FC. Parents of 465 infants completed the questionnaires at 3 and 6 months and of 402 infants at 12 months of life. **Results**: According to the Rome III Criteria, at 3 months FC was found in 11.6% of the infants, in 13.7% at 6 months and in 10.7% at 12 months after birth. Family history of atopy was present in 38.8% and in 45.3% of constipated infants at 3 and 6 months (p=0.04 and p=0.02; respectively), but no significant association was found at 12 months (p=0.80). Breastfeeding was significantly related to a normal evacuation pattern at 3 months (p=0.05), but not at 6 and 12 months (p=0.12 and p=0.9 respectively). Acetaminophen and female gender resulted to be a risk factor for FC at 12 months. After adjustment for all analyzed variables, FC in infants was significantly associated with the use of acetaminophen (OR: 6.98; 95% confidence interval: 0.0082-0.1350). **Conclusions**: Our results confirm that breast-feeding is a protective factor for FC in the first 3 months of life and that female gender is at risk to have FC. We found that the use of acetaminophen was associated with a higher incidence of FC in the first year of life.

Key words: Functional Constipation, Infants

Introduction

Functional Constipation (FC) is a widespread symptom in infants accounting for approximately 3% of consultations in an average pediatric practice and up to 25% of referrals to pediatric gastroenterologists (1, 2).

Stool frequency depends on age of infants. A number of studies revealed a decline in stool frequency from > 4 stools per day during the first week of life to 1.7 per day at 2 years of age and to 1.2 per day at 4 years of age (3, 4). Fontana *et al.* showed that in the first 3 years of life, 97% of healthy infants had at least 1 bowel movement every other day (5).

It's known that approximately 16-40% of infants with FC develops symptoms during the first 6 months of life (6, 7) and that the prevalence of FC in infants in the first year of life is estimated to be 2.9% with a ratio males/females: 1.1/1 (8).

Even if the pathogenesis of FC remains incompletely understood, the most common FC cause appears to be an acquired behavior of withholding of stools after the experience of painful defecation. Because of the withholding, the rectal mucosa absorbs water from fecal mass that becomes hard and difficult to be eliminated. This process leads to a vicious circle of stool retention, which is the basis of the persistence of FC in infants (9).

Factors that lead to painful defecation during the first months of life are not completely known. It has been reported that FC is less common in breast-fed infants than formula-fed infants, both in term and in preterm infants (10, 11). In a study conducted in children aged > 2 years, FC was significantly associated with the female gender, with a low level of maternal education, with the residence in a community with more than 3000 inhabitants and with the absence of older brothers (12). Nevertheless, the timing, style or techniques used for toilet training were not significantly associated to the development of FC in infants (13).

On the other hand, in adults the use of certain medications such as antacids, diuretics, antidepressants, anti-epileptics, antihistamines, has been associated with an increased risk of

chronic constipation (14, 15). Moreover, a significant association between acetaminophen, aspirin, NSAIDs and chronic constipation has been observed in adult population (16, 17, 18).

Despite the development of painful defecation during the first year of life is universally recognized as an important trigger for the pathogenesis of FC in the successive years of life, no studies have been conducted in this specific age. This multicenter prospective study sought to assess: 1) possible risk factors for an alteration of stool habit in infants and 2) the incidence of FC in the first year of life.

Subjects and Methods

This study was based on a birth cohort of 465 consecutive healthy term newborns, with a weight appropriated to gestational age, enrolled from the 1st June to the 30 September 2009 from the following Departments of Pediatrics: University of Naples "Federico II", University of Catanzaro "Magna Graecia", "University of Foggia", University "La Sapienza" Rome, University of Messina and University of Padua. The mothers of all infants were informed of the study during their hospitalization for childbirth.

Then, we prospectively followed up the infants up to the first year of life, to evaluate possible risk factors for development of FC. Four-hundred-two infants (86.4%) completed the study while the remaining infants (13.6%) were lost during the follow up.

At the child's age of 3, 6 and 12 months, parents who expressed interest in the study, were contacted by telephone by specifically trained physicians to complete two questionnaires: one evaluated the presence of FC according to the Rome III Criteria (Table 1) and the second screened the possible risk factors for FC.

The bowel habit of infants were assessed by a questionnaire made on the following variables, related to the month preceding each interview: stool consistency (hard, soft or firm), stool frequency per week, pain or difficulty in evacuating, mucus in stools, presence of a large fecal mass in the rectum observed with a previous rectal examination, retentive posturing during defecation. Infants

younger than 6 months of life, who presented with straining and crying before successful passage of soft stools and who did not fulfilled the Rome III criteria for FC, were considered to be affected by Infant Dyschezia according to Rome III Criteria.

The second questionnaire, as reported in the Appendix (*http://links.lww.com/MPG/A273*), included the evaluation of the following possible risk factors for FC: breast-feeding duration, intake of vitamins and food supplements, family history of Functional Gastrointestinal Disorders (FGIDs), family history of atopy, weaning and nursery-school age, episodes of fever within 2 weeks before the onset of FC and use of drugs (acetaminophen, anti-inflammatory drugs, corticosteroids and antibiotics).

Parents were asked about the modality of feeding of their infants at each interview with the responses (1) ever breast-feeding; (2) receiving breast-feeding; and (3) receiving mixed breast-feeding and formula-feeding.

If the infant's parents and siblings have had any medical treatment for FGIDs and /or asthma, allergic rhinitis, food allergy, allergic dermatitis, anaphylactic shock they were considered to have "family history of FGIDs" and /or "family and/or personal history of atopy", respectively. Regarding the drug's use, information on duration of treatment and the symptoms for which infants took these medications were annotated.

Moreover, socio-demographic factors were screened and included the following: education and profession level of the parents, number of siblings and residence in a community with more or less than 3000 citizens.

The infants were excluded if they had symptoms or findings suggestive of illnesses that could cause gastro-intestinal symptoms, a history of major abdominal surgery, acute or chronic physical disease, a development disability or diagnosis of organic causes of FC such as: ano-rectal malformations, changes in the intestinal nerve and muscle structures (Hirschsprung), endocrine and metabolic disorders (hypothyroidism, hypercalcemia), neurological and neuromuscular diseases (central nervous system disorders, spinal cord injuries, muscular dystrophy), side effects of drugs. At each

interview, parents had to answer about the presence or the absence of the mentioned conditions and the eligibility for the study was from time to time decided.

Written, informed consent for participation in this study was obtained from all infants' s parents and the experimental design was approved by the Institutional Review Board of all participating centers.

Statistical analysis

The statistical analysis of the questionnaires was based on the answered questions. All data were stored in a common database and statistically analyzed using the SPSS version 8.0 program (SPSS Inc., Chicago, IL, USA). Variables were screened for their distribution and appropriate parametric or nonparametric tests were adopted as required. Cross-tabulations were evaluated by using the Fisher test and χ^2 test. Statistical significance was predetermined as $p < 0.05$. Multivariate conditional logistic regression analysis was used to explore odds associated with onset of FC. The dependent variable was FC, while the effect of all the above-mentioned variables were analyzed by a stepwise procedure.

Results

Four-hundred-sixty-five parents of infants (M/F, 213/252) enrolled at birth, completed the questionnaires at 3 and 6 months whereas 402 infants (M/F, 184/218) were evaluated at 12 months follow up (86.4%). The remaining were lost at the follow-up since their parents refused to complete the questionnaires.

In our study population 11.6% of the infants fulfilled the Rome III Criteria for FC at 3 months, 13.7% at 6 months and 10.7% at 12 months after birth.

We showed that 23.3% of constipated infants at 3 months was still constipated at 12 months, while 8% of non-constipated infants become constipated at 12 months (p=0.2).

Comparing the presence of FC and gender, we observed that at 3 and at 6 months no statistically differences existed between constipated and non-constipated infants, while at 12 months 29 (67.5%) out of 43 constipated infants were female compared with 189 (52.7%) out of 350 non-constipated infants (p=0.04). In addiction, at 12 month follow-up no significant difference was found for the following variables: standard of living, number of children for each family, mother's education and occupation level and father's education and occupation level.

Tables 2, 3 and 4 report the proportion of infants with FC according to categories of each potential risk factor at 3, 6 and 12 months, respectively.

When compared with non-constipated infants, the presence of familiarity for FGIDs didn't result to be a significant risk for the development of FC at any follow-up age (p=0.8, p=0.6 and p=0.6 of the three follow-up respectively).

Exclusively breast-feeding was significantly related to a normal evacuation pattern at 3 months (p=0.05), while it resulted to have no influence at 6 and 12 months of age (p=0.12 and p=0.9 respectively). Results regarding the family history of atopy were reported in Figure 1. We observed a significant association between family history of atopy and FC at 3 and 6 months (p=0.04 and p=0.02; respectively) but no association at 12 months (p=0.8).

Acetaminophen didn't result to be a risk factor for the onset of FC at 3 months (p=0.13), but at 6 months we found a trend toward the significance for the use of this drug in constipated infants compared with non-constipated infants (p=0.06). At 12 months of life we observed that 79.1% constipated infants had done use of acetaminophen respect to 58.2% non-constipated infants (p=0.005). Moreover, any significant association was evaluated by the use of different formulations (syrup, drops, suppositories) of acetaminophen (p=0.09). We observed that the main indications for intake of acetaminophen were: fever (75%), cold (30%), and dental eruption (15%), other symptoms (crying, infant colics, vaccination; 5%). Overall, no statistically significant association was detected for the use of antibiotics, anti-inflammatory drugs and corticosteroids.

No statistically significant association with FC in infants was observed for intake of vitamins and food supplements, weaning and nursery-school age, episodes of fever within 2 weeks before the onset of FC, education and profession level of the parents, number of siblings, residence in a country with more or less than 3000 citizens, at any studied age.

Twenty-nine infants younger than 6 months (6%) had Infant Dyschezia (ID) according to Rome III criteria. The data for these infants were not included in the data on symptoms of FC. Nevertheless we evaluated if an association between ID and the onset of FC could exist and we observed that only 3 (6.9%) infants with FC at 12 months have had a diagnosis of ID in the first months of life (p=0.07).

Overall, after adjustment for all analyzed variables, FC in infants was significantly associated with the use of acetaminophen (OR: 6.98; 95% confidence interval: 0.0082-0.1350). In the first year of life, none of the other analyzed variables resulted to be associated with the onset of FC at 12 months of life.

Discussion

In this multicenter study we found that breast-feeding is a protective factor for FC in the first 3 months of life and that female gender and the use of acetaminophen are associated with development constipation in the first year of life.

We observed that breast-feeding has a protective role in the first months of life for the development of FC. Exclusively breast-feeding resulted to be related with a normal defecation pattern until 3 months of age, while it didn't affect the bowel habit at 6 and 12 months of age, respectively. It is known that breast-fed infants have a number of stool per day significantly higher respect to formula-fed infants (5, 19). In addition, it has been reported that the influence of breast-feeding on the bowel habit disappears after the 16th week of life (10). Tunc et al. (20) observed a significantly

difference between breast-fed and formula-fed infants in term of stool consistency and stool frequency in the first 4 months and 6 months of age, respectively. A possible explanation may be researched in the different composition of breast and formula milks. As a matter of fact, Quinlan et al. demonstrated that formula milk contains higher levels of lipids and minerals, concluding that calcium fatty acid soaps are positively related to stool hardness (21).

In the present study we report that the use of acetaminophen is a potential risk factor for FC in infants at 12 months of life with a significant trend at 6 months of life. To our knowledge, this is the first multicenter study investigating the relationship of FC with drugs commonly used in infants. In 2007 Chang et al. (16) reported a significantly association between chronic constipation and use of acetaminophen in adult patients. The exact role of acetaminophen in inducing chronic constipation is not well known. The authors postulated three possible mechanisms: 1) an increased intake due to the higher frequency of abdominal pain and/or somatic complaints; 2) the use of a formulation with the addition of an opiate; 3) the possible anti-serotoninergic effects of acetaminophen. Serotonin is involved in GI motility, secretion and sensation. Considering the role of serotonin signaling in gastrointestinal tract and the use of serotonin agonists as anti-constipation drugs, is plausible that an anti-serotonergic pathway may be responsible of the association between acetaminophen and constipation. As reported in the study of Chang, we excluded the first two hypotheses. The main indications for acetaminophen in our infants were fever, cold, and dental eruption and no formulation with the opiate addition has been used. Moreover, considering the large use of suppositories in pediatric age we thought to a possible correlation whit this kind of formulation. However, we didn't find any significant association between different formulations of acetaminophen and FC. So, we speculate that the anti-serotoninergic action of acetaminophen may be a possible explanation for this association, even if, this mechanism remains controversial (22). No significant association between FC and the other analyzed drugs such as anti-inflammatory drugs, corticosteroids and antibiotics was found in our study.

We observed a higher prevalence of FC in females compared to males, with a ratio females/males of 2 at 12 months of age. In literature a variance of gender prevalence of constipation is reported. In particular some studies found a slight higher prevalence of constipation in females compared to males (23, 24) and other reported a similar prevalence rates between male and female (8). The reasons for a female predominance can not be explained in our population on the basis of data collected.

Chang et al. (25, 26) reported that adults with FC showing a familial aggregation had more severe or refractory symptoms. In a previous study we found that 41% of children with FC had mothers with FC (27). FC, as the other Functional Gastrointestinal Disorders (FGIDs), seems to have a multifactorial etiology. Levy et al. (28) found evidence for both a genetic and a social learning contribution to the intergenerational transmission of Irritable Bowel Syndrome (IBS) symptoms. Although heredity may contribute to the tendency of IBS to familial aggregation, concordance rates between parents and children compared with those between identical twins, indicate that the environmental factors, such as learning, are likely to have an equal or greater influence on the development of IBS (29). In the present study we didn't find any association between FC and familiarity for FGIDs. This finding may be explained by the early age of the studied population. As a matter of fact, in the first year of life, it's plausible that the environmental components don't have yet such an important role in determining the onset of FC.

The family history of atopy didn't result an independent risk factor for FC, by the multivariate conditional logistic regression analysis, at any studied age. However, we observed a higher prevalence of family history of atopy in constipated children compared with non- constipated children at 3 and 6 months of life. Regarding the relationship between cow's milk allergy (CMA) and FC, conflicting data have been reported. Iacono et al. (30) and Daher et al. (31) reported that in young children, FC can be a manifestation of CMA. Conversely, Loening-Baucke found a very low prevalence (2%) of food allergy in children less than 2 years of age with FC (8) and a lack of improvement of the FC after 2-week elimination diet (32). In an Italian population study, it has

been reported that the prevalence of atopy among children with FC (27.3%) is similar to that of the general population (20%) (33). Moreover, Irastorza et al. observed that no significant statistical difference was found in terms of atopy or allergic history between constipated children who responded to CM-free diet and constipated children who did not respond (34). Recently, Saps et al. (35) showed that even if 44.2 % of children with a history of CMA reported GI symptoms including constipation, the association between constipation and CMA was not significant.

Socioeconomic status and education level seem to be related to the development of FC in both adults and children (12). However, we didn't find any correlation between FC and intake of vitamins and food supplements, weaning and nursery-school age, episodes of fever within 2 weeks before the onset of FC and socio-demographic factors such as the education level of parents, the income level of the family, parents' occupation and living in a highly densely populated community. This is probably due to the early age of our study population.

One point of strength of our study is certainly the relevance of the problem. The majority of patients develop constipation during the first year of life and 1/3 of them is still constipated after puberty, with an enormous cost for national health systems. Therefore, it is extremely important to recognize the early risk factors, especially in female gender, in order to build a prevention strategy to minimize the becoming of FC.

This multicenter study examined several potential risk factors for FC and identified an association with use of acetaminophen and the female gender, while confirming the protective role of breast-feeding. The association with acetaminophen has not been previously reported in pediatric population but this warrants further investigation.

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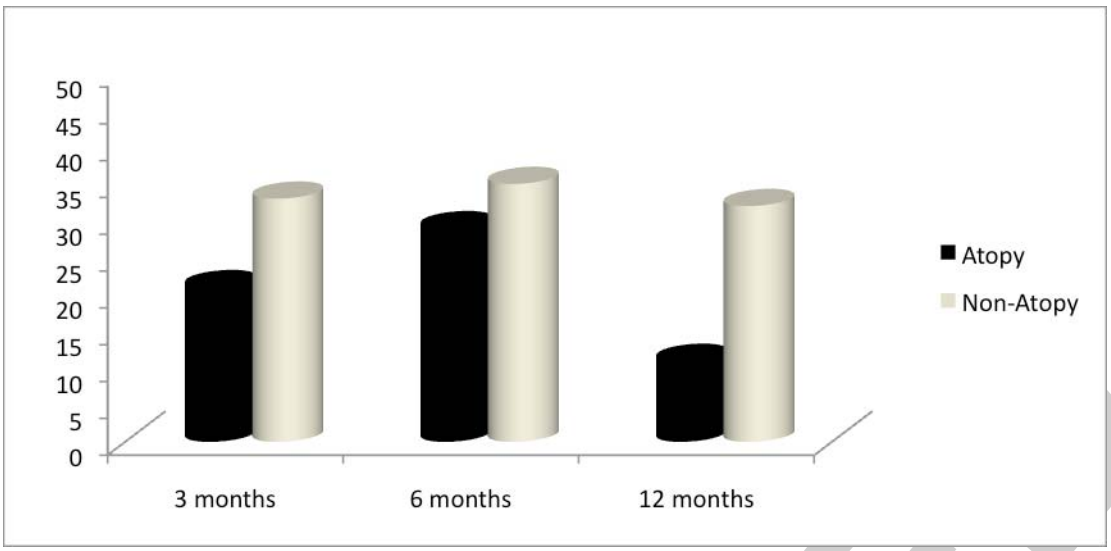
Figure Legend

Figure 1. Family history of atopy in constipated

(1A) and in non-constipated

(1B) children at the age of 3, 6 and 12 months.



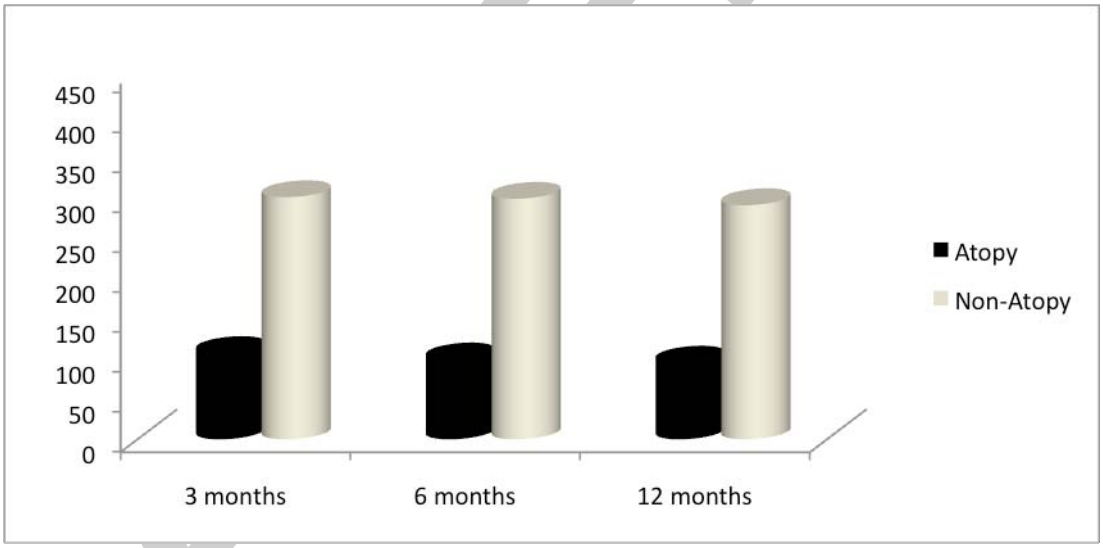


Table 1. Functional Constipation according to Rome III criteria (*)

FC was defined on the presence of 2 or more of the following conditions:

1) two or fewer defecations per week;

2) at least 1 episode per week of incontinence after the acquisition of toileting skills;

3) history of excessive stool retention;

4) history of painful or hard bowel movements;

5) presence of a large fecal mass in the rectum;

6) history of large-diameter stools that may obstruct the toilet.

- Symptoms must continue for at least 1 month.
- No information regards to the second point was collected taking in account the young age of our study population.

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Table 2. Risk factors for Functional Constipation at 3 month of follow up

Infants	**Constipated infants**	**Non-constipated infants**	**p***
Family History and/or personal history of Atopy(%)	21/54 (*38.8*)	108/411 (*26.2*)	*.04*
Family History of FGDIs (%)	17/54 (*31.4*)	150/411 (*36.4*)	NS
Breastfeeding (%)	33/54 (*61.1*)	323/411 (*78.6*)	*.05*
Acetaminophen (%)	13/54 (*24*)	115/411 (*27*)	NS
Anti-inflammatory drugs or corticosteroids (%)	8/54 (*18.5*)	64/411 (*15.5)*	NS
Antibiotics (%)	10/54 (*18.5*)	94/411 (*22.8*)	NS
Gender (%)			NS
Male	28/54 (*52*)	185/411(*45*)	
Female	*26*/54 (48)	226/411(*54*)	

*Chi Square test
NS= not significant

Table 3. Risk factors for Functional Constipation at 6 months of follow up

Infants	**Constipated infants**	**Non-constipated infants**	**p***
Family History and/or personal history of Atopy(%)	29/64 (*45.3*)	100/401 (*24.9*)	*.02*
Family History of FGDIs (%)	20/64 (*31.3*)	147/401 (*36.6*)	NS
Breastfeeding (%)	45/64 (*70.3*)	303/401 (*75.5*)	NS
Acetaminophen (%)	24/64 (*40*)	44/401 (*10.9*)	.06
Anti-inflammatory drugs or corticosteroids (%)	11/64 (*17*)	68/401 (*16.9)*	NS
Antibiotics (%)	17/64 (*26*)	77/401 (*19*)	NS
Gender (%)			NS
Male	30/64 (47)	183/401(*45.6*)	
Female	34/64 (*53*)	218/401(*54.4*)	

*Chi Square test
NS= not significant

Table 4. Risk factors for Functional Costipation at 12 months of follow up

Infants	**Constipated infants**	**Non-constipated infants**	**p***
Family History and/or personal history of Atopy(%)	11/43 (25.6)	96/359 (*26.7*)	NS
Family History of FGDIs (%)	16/43 (*37.2*)	135/359 (*37.6*)	NS
Breastfeeding (%)	34/43 (*79.0*)	303/359 (*75.7*)	NS
Acetaminophen (%)	34/43 (79.1)	209/359 (58.2	.005
Anti-inflammatory drugs or corticosteroids (%)	2/43 (4.6)	23/359 (*6.4)*	NS
Antibiotics (%)	15/43 (34.8)	98/359 (27.2)	NS
Gender (%)			.04
Male	14/43 (32.5)	170/359(*47.3*)	
Female	29/43 (67.4)	189/359(52.6)	

*Chi Square test
NS= not significant