

## Red Flags of Organic Recurrent Abdominal Pain in Children: Study on 100 Subjects

Farzaneh Motamed<sup>1,2</sup>, MD; Reihaneh Mohsenipour<sup>\*3</sup>, MD; Soroush Seifirad<sup>4</sup>, MD; Azizolah Yusefi<sup>3</sup>, MD; Fatemeh Farahmand<sup>1</sup>, MD; Ahmad Khodadad<sup>1,2</sup>, MD; Gholamhosein Falahi<sup>1</sup>, MD, and Mehri Najafi<sup>1,2</sup>, MD

1. Department of Pediatrics, Tehran University of Medical Sciences, Tehran, Iran
2. Growth and Development Research Center, Tehran University of Medical Sciences, Tehran, Iran
3. Children Medical Center, pediatric Center of Excellence, Tehran, Iran
4. Endocrinology and Metabolism Research Center, Tehran University of Medical Sciences, Tehran, Iran

Received: Feb 20, 2012; Final Revision: Mar 15, 2012; Accepted: Jun 06, 2012

### Abstract

**Objective:** A variety of sign, symptoms and laboratory findings are more common in children with organic abdominal pains. This study was performed to evaluate the prevalence of organic and functional abdominal pains and relation of red flags to organic pains in 100 children with recurrent abdominal pain (RAP).

**Methods:** One hundred consecutive patients with RAP were enrolled in the study. A complete interview and physical examination was made for each patient, accompanied by a series of laboratory, clinical and para-clinical examinations. The data were recorded and analyzed. Logistic regression analysis was used to model and formulize correlations between sign, symptoms, and laboratory findings with organic and functional abdominal pain.

**Findings:** Among 100 patients (52% male, 48% female, Age:  $9.29 \pm 3.17$ ) diagnostic works up revealed organic pain for 57 patients. The most common symptoms of the patients included constipation, diarrhea, chest pain, cough, headache, vomiting, hematuria, and dysuria. Fecal incontinence, delayed puberty, organomegaly, jaundice, and family history of inflammatory bowel disease were reported in none of the patients with RAP. Fever, pain not located in periumbilical area, nocturnal pain, elevated erythrocyte sedimentation rate, weight loss, growth disorder, and abdominal tenderness were among the red flags which revealed diagnosis of organic pain in this study.

**Conclusion:** A series of red flags could increase likelihood of finding organic pain in children with RAP.

*Iranian Journal of Pediatrics, Volume 22 (Number 4), December 2012, Pages: 457-462*

**Key Words:** Abdominal Pain; Children; Fever; Constipation; Red Flag

### Introduction

Recurrent abdominal pain (RAP) is defined as three or more episodes of abdominal pain which persists for more than 3 months, and is severe enough to interfere with normal activities. In

children this condition is ambiguous, because pain thresholds are diverse<sup>[1]</sup>. For most of the physicians, making decision on choosing diagnostic modalities in RAP is confusing<sup>[2]</sup>. Recurrent abdominal pain, is categorized into two groups of organic or nonorganic (functional)

**\* Corresponding Author;**

**Address:** Children Medical Center, No 62, Dr Gharib St, Tehran, Iran

**E-mail:** rmohsenipour@yahoo.com

© 2012 by Pediatrics Center of Excellence, Children's Medical Center, Tehran University of Medical Sciences, All rights reserved.

pains, if the diagnostic work up revealed a definite etiology for the pain or not<sup>[3]</sup>.

Infection, inflammation, obstruction (malrotation- concomitant intussusceptions), malabsorption syndromes (celiac), gynecologic disorders (dysmenorrhea, Pelvic inflammatory disease (PID)), neurologic disorders (abdominal epilepsy, migraine) and others (i. e. food allergies) are among common etiologies of organic recurrent abdominal pains<sup>[3-5]</sup>. Prevalence of organic abdominal pain is reported between 9 to 25% in different studies<sup>[1]</sup>.

It seems that a variety of sign, symptoms and laboratory findings are more common in children with organic abdominal pains<sup>[5,6]</sup>. This study was therefore undertaken to evaluate the prevalence of organic and functional abdominal pains and relation of red flags to organic pains in 100 children with recurrent abdominal pain.

## Subjects and Methods

One hundred consecutive patients aged between 4 to 18 years old, with chronic abdominal pain were enrolled in this cross sectional study. The patients were selected among the patients referred to gastroenterology clinic of Children Medical Center in 2009-2010. A complete interview and physical examination was done for each patient and was accompanied by a series of laboratory, clinical and para-clinical studies. Patients with acute and surgical abdominal pain were excluded from this study.

### History and Physical examination

The patients were asked and examined for pain (including type of pain, location, radiation, time of onset, duration of symptoms, associated symptoms, presence or absence of red flags including weight loss, nocturnal pain, increased erythrocyte sedimentation rate (ESR), anemia, pain not located in periumbilical area), anemia, jaundice, organomegaly, skin rash, abdominal tenderness, abnormal growth and puberty. Rectal exam was also performed for each patient.

Urine analysis and culture (U/A, U/C), ESR, complete blood count with differentiation (CBC diff), and stool exam (S/E) was ordered for of all patients. Additive studies including plain abdominal X-ray, abdominal ultrasound, upper gastrointestinal (GI) endoscopy, barium contrast, colonoscopy, examination of *Helicobacter pylori* antigen in stool, urea breath test (UBT) and celiac panel review were ordered for the patients if indicated. In the likelihood of GI etiology and also after excluding non-GI etiologies Upper GI endoscopy was performed for the patients; Samples were obtained from all of the patients for pathologic studies.

### Statistical Analysis

Statistical Package for the Social Sciences, Version 16.0 (SPSS Inc. Chicago, IL, USA) was used to appraise statistical analysis. Statistical significance was set at 0.05. Results are expressed as mean  $\pm$  SD. Kolmogorov-Smirnov test were applied to evaluate the normal distribution of the results (i.e distribution of age in two groups of organic and functional pains). Parametric and nonparametric studies were applied if the data had normal distribution or not. T- test was used for the data with normal distribution. Man Whitney test, and Fisher Exact test were used to compare the other results.

Finally, logistic regression analysis was done to model possible correlations between sign, symptoms, and laboratory findings with organic and functional abdominal pain. Using logistic regression analysis, we tried to provide a formula to predict likelihood of organic abdominal pain with respect to the red flags in history, physical examination and laboratory findings.

### Ethics

The study protocol was reviewed and approved by ethics committee of Tehran University of Medical Sciences. No additive evaluation was ordered for the patients enrolled in this study; hence, no informed consent was requested from the patients and their parents. However study aims was explained for the patients and/or their parents and they were informed that they were entered in our study.

## Findings

One hundred patients were entered to the study (52% male, 48% female, age:  $9.29 \pm 3.17$ , range 4-17 years). Among 100 patients diagnostic work up were revealed organic pain for 57 patients. The patients reported  $10.9 \pm 9.6$  (range 3-60) months of RAP.

The age distribution was normal in both groups and no difference in the term of age distribution was observed between organic and non organic diseases. Fifty percent of the girls and 64.4% of the boys had organic RAP.

The most common symptoms of the patient in this study were included constipation, diarrhea, chest pain, cough, headache, vomiting, hematuria, and dysuria.

## Pain

Persistent pain was reported in 13 patients while 84% of them were among patients with organic pain. On the other hand, 87 patients were reported colic cramps (46 organic, 41 functional). Colicky

character of the pain were increase likelihood of functional RAP ( $P=0.03$ , odds ratio=0.20). A positive relation between pre-umbilical pains and functional RAP was also observed in our study. It seems that location of abdominal pain could predict likelihood of RAP type ( $P=0.002$ , odds ratio=0.27). There was no correlation between localized or generalized abdominal pain and type of RAP (Table 1).

## Red Flags

Fecal incontinence, delayed puberty, organomegaly, jaundice, and family history of inflammatory bowel disease were reported in none of the patients with RAP. Table 2 shows final diagnosis of the patients with organic and functional RAP.

Fever, pain not located in periumbilical area, nocturnal pain, elevated ESR, weight loss, growth disorder, and abdominal tenderness were among the red flags for organic RAP. The most common causes for functional RAP in our study were as follows: constipation (32.6%), irritable bowel

**Table 1:** Correlations between sign and symptoms and organic recurrent abdominal pain

Red Flags	Recurrent Abdominal Pain				95% CI	
	Organic	Non-organic (functional)	P value	Odds ratio	Lower	Upper
Fever	7	0	0.02			
Pain not located in periumbilical area	39	15	0.001		1.7	9.3
Nocturnal pain	23	3	<0.001	9.2	2.4	32.6
Anemia	6	3	0.5	1.5	0.36	6.6
Elevated ESR	6	0	0.03			
Blood in stool examination	3	0	0.2			
Weight loss	18	1	<0.001	19.3	2.4	152.1
Fecal incontinence	0	0				
Positive familial history for Peptic ulcer	6	1	0.2	4.9	0.57	42.6
Growth disorder	12	2	0.02	5.4	1.1	25.9
Diarrhea and vomiting	17	10	0.5	1.4	0.56	3.4
Abdominal tenderness	25	7	0.003	4.01	1.5	10.5
Extra intestinal symptom	3	1	0.6	2.3	0.23	23.2
Perianal complications	2	4	0.4	0.35	0.06	2.03
Dysphagia	2	0	0.5			
Hematemesis	2	0	0.5			
Rash	1	0	1			
Hematochezia	2	0	0.5			
Hematuria	1	0	1			
Organomegaly	0	0				
Icterus	0	0				
Frequency and dysuria	5	0	0.06			
Positive familial history for IBD	0	0				
Delayed puberty	0	0				

ESR: Erythrocyte Sedimentation Rate; IBD: Inflammatory Bowel Disease

**Table 2:** Final diagnosis of patients with organic and functional recurrent abdominal pain

Etiology	Number of patients (%)	
<b>Organic</b>	<b>Gastritis (H.pylori +)</b>	12 (21.1)
	<b>Erosive gastritis</b>	2 (3.5)
	<b>Gastro-Esophageal Reflux Disease</b>	23 (40.4)
	<b>Vascular ring, GERD</b>	1 (1.8)
	<b>Urinary Tract Infection</b>	4 (7)
	<b>PUD, H.Pylori +</b>	1 (1.8)
	<b>PUD, H.Pylori -</b>	5 (8.8)
	<b>Malrotation, PUD</b>	1 (1.8)
	<b>Diabetic Ketoacidosis</b>	1 (1.8)
	<b>Familial Mediterranean Fever</b>	4 (7)
	<b>Eosinophilic colitis</b>	1 (1.8)
	<b>Lymphoma</b>	1 (1.8)
	<b>Renal Stone</b>	1 (1.8)
<b>Functional</b>	<b>Irritable Bowel Syndrome</b>	11 (25.6)
	<b>Abdominal migraine</b>	6 (14)
	<b>Constipation</b>	14 (32.6)
	<b>Functional Abdominal Pain</b>	9 (20.9)
	<b>Psychological Problem</b>	3 (7)

H. Pylori: Helicobacter Pylori, PUD: Peptic Ulcer Disease

syndrome (IBS) (25.6%), functional abdominal pain (20.9%), abdominal migraine (14%), and psychological causes (7%).

Table 1 shows correlations between sign and symptoms, red flags, and organic RAP. Using logistic regression analysis, we tried to formulize and predict likelihood of organic RAP with respect to the known red flags in this study.

## Discussion

Fifty two percent of the patients in our study were female which was fairly similar to the other published studies<sup>[7,8]</sup>. Average duration of recurrent abdominal pain in our patients was 10.9 months whereas a range of 7 to 28.3 months were reported in other published studies<sup>[5,6]</sup>.

In this study, 57% of the patients have organic RAP, while reported prevalence of organic disease varied between 23% and more than 80% in the other populations<sup>[3,7]</sup>.

It seems that external validities of different studies are influenced by their populations; while our study and most of the other studies are conducted in tertiary care centers, prevalence of organic and functional RAP is affected by selecting patients from a tertiary care center. Actually, most

of the patients in these centers are more complicated and sophisticated than the others in the society. For example, common infectious etiologies such as amebiasis and giardiasis were not observed in our patients, which is contradicts the results of other published studies<sup>[2,3,7]</sup>. It seems that stool examination (S/E) and stool culture (S/C) were requested for every patient before refer to a tertiary care center. Hence, patients with these common etiologies were excluded from our study population. Surprisingly Familial Mediterranean Fever (FMF), as a rare disease, was observed in 4% of our patients, which was higher than similar studies<sup>[8-10]</sup>. This also could be explained by weight of selecting patients from the largest pediatric tertiary care center in Iran. Nevertheless, diagnosis of FMF should be considered in patients with RAP, especially in patients from western southern areas of Iran<sup>[11]</sup>.

Additionally, observed differences in studies results are also influenced by differences in epidemiologic factors. For example, 22.9% of our patients were positive for *Helicobacter Pylori* (HP) which was similar to the results of a study in Finland, while 77% of the patients in another study in India were HP positive<sup>[12-14]</sup>. This observed difference could be explained with this fact that a higher prevalence of HP was reported in countries with lower economic status<sup>[15]</sup>. It was hypothesized that *Helicobacter pylori* could be

one of the recurrent RAP etiologies in children; However, according to the results of a later published study, no correlation was observed between RAP and HP infection in children in Iran<sup>[16]</sup>.

Gastro-esophageal reflux disease (GERD), was observed in 40.4% of our patients with organic disease, and was the most prevalent etiology in our study. Our results are not in accordance with the others results in this issue<sup>[1,5,7]</sup>. Upper GI endoscopy was performed for almost all of our patients with red flag which revealed a higher diagnosis of GERD. Additionally, esophagitis in the other studies was separately evaluated while in this study, esophagitis was interpreted as GERD.

Our results for common causes of functional RAP are in accordance with similar published studies<sup>[1,8,10]</sup>.

A wide range of prevalence for constipation (2.9%- 57.3%) is reported in different studies<sup>[1,9]</sup>. Different life style and diet in different populations and also loss of evaluation of occult constipation may explain this observed wide range of prevalence.

Abdominal pain was the most common complaint of patients with Crohn's disease in our country<sup>[17]</sup>. Nevertheless, it was not among the etiologies of RAP in our patients.

IBS was observed in 25.6% of the patients with functional RAP in our study. In a recent published study in Iran, approximately 51.1% of patients with functional RAP experienced at least one psychiatric disorder <sup>[18]</sup>. However, for 7% of our patients with functional RAP, a psychological problem was diagnosed to be responsible for their complaints.

Organic RAP was found in 57% of our patients while 30% of the patients with RAP in a similar published study had functional RAP <sup>[19]</sup>. Although there was no diagnosed case of celiac disease in this study, in a recently published study on 301 patients with functional abdominal pain we have shown that a higher prevalence of celiac disease (1.3%) is estimated in Iranian population compared to the normal population<sup>[20]</sup>.

A larger sample size could increase the power of this study. We have not evaluated if there is any relation between age and RAP etiologies in different age groups.

The following formula could predict likelihood of organic RAP with respect to the known red flags in this study:

$$Y = -96.939 + 20.958 (\text{fever}) + 1.555 (\text{pain not located in periumbilical area}) + 2.103 (\text{nocturnal pain}) + 19.971 (\text{elevated ESR}) + 2.750 (\text{weight loss}) + 1.389 (\text{growth disorder}) + 0.695 (\text{Abdominal tenderness}).$$

"Y" shows likelihood of finding organic RAP. Presence or absence of seven red flags gives scores of "0" or "1".

Conducting a multicenter large study could enhance power and external validity of this study; in that case we could develop statistical analysis to a scoring system. Furthermore, future studies could evaluate validity of our provided formula in predicting likelihood of organic RAP.

## Conclusion

In conclusion a series of red flags could increase likelihood of finding organic pain in children with RAP. Fever, pain not located in periumbilical area, nocturnal pain, elevated ESR, weight loss, growth disorder, and abdominal tenderness were among the red flags which revealed diagnosis of organic pain in this study.

## Acknowledgment

This study was financially supported by Tehran University of Medical Science.

**Conflict of Interest:** None

## References

1. El-Matary W, Spray C, Sandhu B. Irritable bowel syndrome: the commonest cause of recurrent abdominal pain in children. *Eur J Pediatr* 2004;163(10):584-8
2. Di Lorenzo C, Colletti RB, Lehmann HP, et al. Chronic Abdominal Pain In Children: a Technical

- Report of the American Academy of Pediatrics and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr* 2005;40(3):249-61
3. Buch NA, Ahmad SM, Ahmed SZ, et al. Recurrent abdominal pain in children. *Indian Pediatr* 2002;39(9):830-4.
  4. Thiessen PN. Recurrent abdominal pain. *Pediatr Rev* 2002;23(2):39-46.
  5. Stordal K, Nygaard EA, Bentsen B. Organic abnormalities in recurrent abdominal pain in children. *Acta Paediatr* 2001;90(6):638-42.
  6. Devanarayana NM, de Silva DG, de Silva HJ. Aetiology of recurrent abdominal pain in a cohort of Sri Lankan children. *J Paediatr Child Health* 2008;44(4):195-200.
  7. Devanarayana NM, Rajindrajith S, De Silva HJ. Recurrent abdominal pain in children. *Indian Pediatr* 2009;46(5):389-99.
  8. Stordal K, Nygaard EA, Bentsen BS. Recurrent abdominal pain: a five-year follow-up study. *Acta Paediatr* 2005;94(2):234-6.
  9. Eidlitz-Markus T, Mimouni M, Zeharia A, et al. Occult constipation: a common cause of recurrent abdominal pain in childhood. *Isr Med Assoc J* 2004;6(11):677-80.
  10. Devanarayana NM, de Silva DG, de Silva HJ. Recurrent abdominal pain syndrome in a cohort of Sri Lankan children and adolescents. *J Trop Pediatr* 2008;54(3):178-83.
  11. Salehzadeh F, Emami D, Zolfegari AA, et al. Familial Mediterranean fever in northwest of Iran (Ardabil): the first global report from Iran. *Turk J Pediatr* 2008;50(1):40-4
  12. Ashorn M, Maki M, Ruuska T, et al. Upper gastrointestinal endoscopy in recurrent abdominal pain of childhood. *J Pediatr Gastroenterol Nutr* 1993;16(3):273-7
  13. Das BK, Kakkar S, Dixit VK, et al. Helicobacter pylori infection and recurrent abdominal pain in children. *J Trop Pediatr* 2003;49(4):250-2.
  14. Macarthur C, Saunders N, Feldman W. Helicobacter pylori, gastroduodenal disease, and recurrent abdominal pain in children. *JAMA* 1995;273(9):729-34.
  15. McCallion WA, Bailie AG, Ardill JE, et al. Helicobacter pylori, hypergastrinaemia, and recurrent abdominal pain in children. *J Pediatr Surg* 1995;30(3):427-9.
  16. Masoodpoor N, Darakhshan, Sheikhvatan M. Helicobacter pylori infection in Iranian children with recurrent abdominal pain. *Trop Gastroenterol* 2008;29(4):221-3.
  17. Aghazadeh R, Zali MR, Bahari A, Amin K, Ghahghaie F, Firouzi F. Inflammatory bowel disease in Iran: a review of 457 cases. *J Gastroenterol Hepatol* 2005;20(11):1691-5.
  18. Ghanizadeh A, Moaiedy F, Imanieh MH, et al. Psychiatric disorders and family functioning in children and adolescents with functional abdominal pain syndrome. *J Gastroenterol Hepatol* 2008;23(7 pt 1):1132-6.
  19. Shahraki T, Farahmand F; Khatami GhR; et al. Recurrent Abdominal Pain: an Etiological Study among in a Referral Children's Medical Center in Iran. *Iran J Pediatr* 2007;17(3):235-40.
  20. Farahmand F, Modaresi V, Najafi M, Khodadad A, Moetamed F, Modarres Z. Prevalence of Celiac Disease in Iranian Children with Recurrent Abdominal Pain Referred to a Pediatric Referral Center. *Iran J Pediatr* 2011;21(1):33-8.