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Functional Abdominal Pain in Children

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Functional abdominal pain (FAP) is one of the most common pain syndromes in childhood and is a functional gastrointestinal disorder (FGID). Recurrent abdominal pain (RAP) is characterized by three or more episodes of abdominal pain that occurover at least 3 months and are severe enough to interfere with activities. It may be caused by many conditions, including inflammatory bowel disease, peptic ulcer, pancreatitis or, functional abdominal pain. The most common clinical manifestation is periumbilical pain related to autonomic and functional symptoms like nausea, vomiting, pallor and other painful conditions like headache and limb pains. RAP requires accurate diagnostic tests to rule out organic causes of pain based on 'red flag' sign. Furthermore, to diagnose and classify functional abdominal pain, Rome III criteria were published and updated with multiple discussions of FGIDs. Conventional interventions for RAP include reassurance and general advice, symptom-based pharmacological therapies, and psychological and behavioral treatments. But further research should be conducted to advance our understanding of the multiple factors involved in the pathogenesis of this group of conditions and to provide evidence for its therapeutic benefit. **(Korean J Pediatr Gastroenterol Nutr 2011; 14: 222～231)**

Key Words: Functional abdominal pain, Functional gastrointestinal disorder, Recurrent abdominal pain, Rome III criteria, Children

INTRODUCTION

Functional abdominal pain (FAP) is the one of the most common pain syndrome in children and can be categorized as a functional gastrointestinal disorder (FGID). For the past few years, "recurrent abdominal pain (RAP)" was accepted in describing children with functional abdominal pain[1]. In Apley's report, RAP is defined by more than

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three times of pain within 3 months and interference with normal functions such as school activities, social activities, and sports performances[2]. These events characterized as cramps, blunt or dull pain, usually localized around periumbilical area, and persists below 1 hour[2,3]. RAP may have several causes such as inflammatory bowel disease, peptic ulcer, pancreatitis or functional causes. Functional gastrointestinal disorders are conditions that report clusters of symptoms related to disordered function in the gastrointestinal tract (GI) or in the central processing of information originating from the GI tract[4]. The understanding of FGIDs has altered our concept of illness and diseases shifted away from the simplistic model of disease[5]. A more comprehensive, biopsychosocial concept of illness has replaced the approach in which the pediatrician's efforts were always directed to identify underlying etiology to symptoms[6,7]. This concept of illness takes into account not only the detection of a biological abnormality, but also the patient's perception of their own wellbeing.

EPIDEMIOLOGY

RAP is accepted as a functional disorder that accounts for 25% of referrals to tertiary gastroenterological clinics and often gives a negative effect on children[8,9]. According to the reports of the incidence of RAP, disparate results have been reported with prevalence ranged from 10 to 25%[10~12]. The suggestion of population-based reports showed 10～20% of school- aged and especially about 15% of middle- and high school-aged adolescents experienced RAP[13,14]. Furthermore, almost 10～18% of school-aged children in developed countries experienced RAP[15]. The prevalence of RAP tends to decline in boys, not in girls as they grow older[16].

The similar prevalence was reported in Asian epidemiological studies. In Sri Lanka, prevalence of RAP is almost 11%[17]. It has been shown by Boey et al.[18,19] that RAP among school-age children had a prevalence of almost 10%. Similarly, it has been reported by Rasul and Khan that the prevalence of RAP is approximately 11.5% of Bangladesh school-age children[20]. Most of the studies documented that girls are more affected than boys[2,17~19,21].

ETIOLOGY

The etiology of RAP has become increasingly complex after Apley's report. Current concepts are diverse and recognize the factors of biological-psychosocial factors[22,23]. In a child with recurrent abdominal pain who has no psychological and social factors, furthermore, well-being is predicted to show a better result than the child with pain and any other problems. Also, the severity of the disorder can be affected to the child's clinical outcome[24]. The causes of RAP are complex and do not provide a single concept of causations. In the Apley and Naish study[2], they supposed that organic cause cannot be qualified in approximately 90% of children with RAP. It has been documented that the portion of children with organic cause of RAP was identified to be increased more than previous reports[25~28]. During the past, new diagnostic tools have been used for the evaluation of children with RAP, and have a contribution to improved evidences of the pathophysiology of pain[22]. So, the portion of organic RAP was found to be higher than 80% in some of these reports[28]. The large majority of reports were performed in secondary or tertiary hospitals where children were selected highly and it was more likely that an organic cause was existed[25~28]. Most of the organic disorders lead to abdominal pain and the pathophysiology is related to infection, inflammation, distension or obstruction. Table 1 demonstrates common causes for RAP among children[29,30].

1. Alteration of gastrointestinal motility

The studies of motility alterations were noted in adults with FGIDs and their symptoms could be explained by this alteration[31]. The small and large bowel with dysmotility and variations in transit time were also documented in several stuidies[32]. Especially in irritable bowel syndrome (IBS) patients, it seems to be higher in

Table 1. Common Causes of Recurrent Abdominal Pain

Chronic constipation	Functional dyspepsia
Inflammatory bowel disease	Irritable bowel syndrome
Parasite infection	Functional abdominal pain/syndrome
Dietary intolerance	Abdominal migraine
Gastroesophageal reflux disease	Aerophagia
Helicobacter pylori infection	Urinary tract infection
Peptic ulcer	Urinary calculi
Gastritis	Pelvouretic junction obstruction
Celiac disease	Ovarian cyst
Hepatitis	Endometriosis
Gallbladder calculi	Pelvic inflammatory disease
Chronic appendicitis	Abdominal epilepsy
Chronic pancreatitis	Physical, emotional, sexual abuse

the amplitude and number of colonic contractions rather than control. Also there is an association between rectal balloon distention and abnormal motor responses[33,34]. Episodes of abdominal pain frequently coincided with abnormal contractions[35]. Impaired clearance and propulsion of intestinal gas are present in patients with inflammatory bowel disease (IBD)[36]. However, it remained unclear that motility alteration in patient could be the cause in patient with IBS in the field of the physiologic and clinical significance. It has been shown that the small and large bowel motility patterns are alike with the contractions noted in control grouop[37].

2. Visceral hypersensitivity

The well-known hypothesis which can explain the clinical features in patient with IBS is visceral hypersensitivity[31]. It has been documented that the patients with IBS seem to have more sensitivity than control group at the time of balloon distention in colon[38~40]. The volumes of retained gas in IBS patients who developed pain were retained and well tolerated by healthy individuals[41]. In functional dyspepsia (FD), it is shown that intolerance to gastric distention exited[42,43]. Furthermore, high school-aged children with FD showed slower gastric emptying time and feeling of nausea after meal time[44].

3. Genetic effects

It is well known that some investigations have proven a familial history of FGIDs[45~47]. Children with RAP seem to have parents who have the similar symptoms[45]. It has been documented that the evidences of genetic effects were found in the monozygotic twins as two times as developing IBS in dizygotic twins[48]. It has also been reported that an independent and stronger predictor is a parent with IBS[48]. In spite of several investigations of multiple gene studies, the results are still inconclusive. There were researches which have focused on essential element (proteins) which has an effect on the serotonin function and serotonin transporter protein. Link between these proteins showed co-morbid stressful conditions that frequently showed in patient with IBS[49~52]. Serotonin transporter protein has a function to inactivate serotonin, which act in pain control and connection between the visceral and the central nervous system. The similarity which a different feature of diarrhea and constipation can be existed in patients with IBS was documented[53]. It is reported that in patients with IBS, the level of serotonin transporter protein mRNA and serotonin transporter protein decreased significantly in the intestinal epithelial cell[54]. Interestingly, these findings have not been proved in a current study[55]. But, some studies showed the description of a link between a protein critical to serotonin

receptor functions and IBS[55]. IBD patients showed high level of p11. Recognition of gastric distention of hypersensitive patients with FD can be reduced by 5-HT 1B receptor enhancers[56]. The modulation of p11 could be responsible for acceleration of serotonergic receptors, including serotonin receptors[55], and p11 could be decreased due to involvement of slow colonic transit time from stimulation of serotonergic receptor.

4. Psychological factor and stress

Psychological factors and stress can have effect on the characteristics of symptoms and clinical manifestation, moreover outcome in child with FGIDs[31]. Familial responses affect the experience of illness, school activities, and hospital visit[57]. Children whose parents with IBS tend to visit the hospital more than healthy control[58]. It has been demonstrated that the severity of pain and the level of parental distress were independent factors predicting behavior in children with RAP[59]. Two samples of social learning were documented as a positive reinforcement and modeling in children with IBS[60,61]. Furthermore, it has been suggested that parents who give special advantages to children with GI symptoms tend to enhance their complaints[62]. A model of illness behavior with GI symptoms can be provided by parents evading unpleasant works or looking forward to special consideration when they are sick[60,62]. It has been reported in retrospective and prospective studies that parents who tend to reinforce their symptoms could make their children's behaviors more severe than healthy control[59,61]. The higher levels of depression and anxious feeling can be detected in children with RAP rather than healthy control. Also the severity of anxiety and depression was documented in children with long term of GI symptom and signs[63]. Besides, it is demonstrated that a poor ability to deal with stressful conditions was noted in children with FAP rather than healthy controls[64]. A recent prospective investigation has been proven that the psychosocial indicators and development of IBS have an association in patient with IBS[31]. Another research reported that behavior of ill patients, symptoms, sleep discomforts, depression, anxious feeling, psychosocial stress had significant correlation with the onset of IBS[65]. Although the psychosocial factors have a possibility to predict the onset of IBS, it is impossible to explain the correlation between the development of FGIDs and psychological conditions completely[31]. Most of the psychological situation can be produced after the development of GI symptoms and it is considered to be the part of the effects of FGIDs[31]. It is supposed that systemic homeostasis against physical, immune, and psychological stress can be defined paradoxically as a stress. Stress can augment the gut sensitivity and relaxation can reduce its sensitivity. Slow gastric emptying can be leaded by anger, anxiety, and pain[66,67] and colonic motional activity can enhance[66]. The greater physiologic response in FGIDs patients seems to make psychosocial stress[66]. It have been proven that in the field of pathophysiology, stress plays an important role[67] on clinical presentation of IBS[68].

CLINICAL MANIFESTATION

In generally, the complaint of pain in RAP children is somewhat genuine, and cannot be defined as a social modeling, a copy of care-givers' pain, or tools to avoid an unpleasant experience[21]. The most common clinical symptoms are periumbilical pain, related to functional and autonomic manifestations like vomiting, nausea, paleness and other conditions such as headache[2,17,20,21]. In this way, on initial clinical manifestation, RAP may copy any kind of sudden onset abdominal disorders, and may stimulate unnecessary and extensive investigations. It has been found that there were severe family history of FGID[2,15,17,19,20]. Furthermore, there were some reports that bowel disorder causing abdominal pain is associated with IBS[69]. Genetic or environment vulnerability might be a cause of this phenomenon and further researches should be needed to solve a definite genetic predisposition[21].

DIAGNOSIS

Clinician should not perform many investigations to rule out organic etiology of pain in children with RAP. Too much evaluation may increase parental concern and make the child unnecessarily stressfull[21]. On the other hand, indefiniteness of the diagnosis and basis of the symptoms have a tendency to damage the trust between pediatrician and parent. Hence, it is important from parent-child's purpose and the pediatrician's purpose to approach an equitable diagnosis at initial visit[21]. There were no reports that showed the basis, severity, duration or focus of the abdominal pain to rule out organic causes. In spite of insufficient studies to document differentiations between functional and organic disorders, it had been demonstrated that children with RAP tend to have headache, nausea, vomiting, anorexia, altered bowel movement than children without RAP[70]. Besides, there were no reports that have validated the physical signs and symptoms to identify organic causes in RAP patients. 'Red flag signs' in Table 2 have been applied by many pediatricians to confirm organic causes in children[29,30].

1. Pediatric Rome III criteria

In 1984, the XII International Congress of Gastroenterology was held in Lisbon, and adults investigators who had an interest in FGID were requested to develop diagnostic criteria of IBS[71,72]. Four years after the initial committee[73], the recommendations of International Congress of Gastroenterology was presented and named 'Rome criteria'. There were a few published reports to reference to validate the recommendations of criteria. Finally they reviewed several researches and discussed to reach a consensus[73]. From this effort, production of complete classification system could be formed with criteria for 24 FGIDs as Rome I criteria[72]. The Rome I criteria was revised with addition of more information about clinical, pathophysiological, diagnostic features and management methods for each FGIDs[74]. Psychological and social aspects of FGIDs and guideline for managements was also provided by this committees[74]. From this publication and application of the Rome criteria, a better understanding of childhood FGIDs could be obtained and patient care improved associated with this development[4]. This recent effort induces the development of the Rome III criteria in April 2006[75,76]. From the introduction of Rome II criteria in 1999[77], over 200 Medline quotations were developed, but from the introduction of Rome III criteria, over 600 quotations were developed. The neonate/toddler and the child/adolescent committees published the Rome III criteria, separately. In Table 3, pediatric FGIDs were presented from the Rome III criteria[75,76,78]. Most important changes of the

Table 2. Red Flag Sings in History and Physical Examination

History	Physical examination
Patient age < 5 years	Growth deceleration, delayed puberty
Constitutional symptom: fever, weight loss, joint symptom, recurrent oral ulcer	Scleral icterus/jaundice, pale conjunctiva/pallor
Dysphagia	Rebound, guarding, organomegaly
Emesis, particularly if bile or blood stained	Perianal disease (tags, fissures, fistulas)
Nocturnal symptoms awaken child from sleep	Occult or gross blood on stool
Persistent right upper or right abdominal pain	
Referred pain to the back, shoulders, or extremities	
Dysuria, hematuria, or flank pain	
Chronic dedication use: NSAIDs, herbals	
Family medical history of IBD, peptic ulcer disease, celiac disease, atopy	

Table 3. Rome III Diagnostic Criteria for Pediatric Functional Gastrointestinal Disorders

H1. Vomiting and aerophagia
H1a. Adolescent rumination syndrome
H1b. Cyclic vomiting syndrome
H1c. Aerophagia
H2. Abdominal pain – related functional gastrointestinal disorders (FGIDs)
H2a. Functional dyspepsia
H2b. Irritable bowel syndrome
H2c. Abdominal migraine
H2d. Childhood functional abdominal pain
H2d1. Childhood functional abdominal pain syndrome
H3. Constipation and incontinence
H3a. Functional constipation
H3b. Nonretentive fecal incontinence

Rome III pediatric criteria were the decline in the duration of symptoms from 3 to 2 months except for cyclic vomiting syndrome and abdominal migrain[4].

MANAGEMENT

Reassurance, careful advices, pharmacological therapies, behavioral and psychosocial modulations should be included in conventional management for RAP[79]. Especially, reassurance including information of no serious organic causes and general advices should be consisted in the care of child with RAP because it is helpful to control or overcome painful conditions. The pediatrician should recognize that the pain is real and not harmful[80]. Based on the necessity of medication and psychological intervention, the association between the level of management and improvement is so much important in RAP children's function[81]. It is helpful to give symptom-associated pharmacologic treatment in typical cases. For example, desipramine hydrochloride and amitriptyline (tricyclic antidepressants) could be used to manage the pain of visceral origin. Dicyclomine and hyoscyamine (anticholinergics) could be also applied to control antispasmodic properties. Laxatives and stool softeners in childhood constipation might be helpful to decrease symptoms and signs. It is recommended that pediatricians should have an effort to decrease prescription of medicines to children who have the higher level of symptoms not responding to initial therapy[82]. They also demonstrated that when applying therapeutic use of drugs, clinicians should notice that RAP is a fluctuating situation. Multiple recent literatures on behavioral and psychological treatments of children with RAP have been resumed[83~85]. Recent study showed three different therapeutic approaches such as voluntary procedures[86,87], dietary fiber[88~90], and behavioral-cognitive managements[82,91~94]. According the guidelines of recent research[24], cognitive and behavioral therapies arise as a promising and efficacious management for RAP. Dietary fiber therapy for children with constipation comes out as a probable management. Voluntary procedures do not satisfy the most alleviated concept of empirical or supportive therapies one and only, and there were no therapeutic approach to meet the criteria for a well-known management[24].

CONCLUSION

Importantly, we approach so much closely in the understanding of childhood FGIDs because of the developing study into this area expedited by publications with the Rome criteria. Childhood FGIDs could be caused by the complex interaction among gut sensitivity, motility, environmental factors, early life events, and psychosocial factors. The comprehensive investigation, consideration of various treatment options is important for children with RAP, along) with consideration of the efficacy and safety of other management tools. It is necessary to perform further research to improve in knowledge of the factors concerned with the pathogenesis and to provide evidence for helpful therapies.

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