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Colonic Transit Patterns and Plasma Cholecystokinin Levels in Children with Recurrent Abdominal Pain

Ki Sup Chung[1], Je Woo Kim[2], and Chang Han Lee[1]

Abstract

Plasma cholecystokinin levels were measured in children with recurrent abdominal pain to investigate the relationship of plasma cholecystokinin levels with colonic transit patterns and clinical symptoms. Subjects consisted of 120 children (mean age 9.6±2.6 years) for whom colonic transit study had also been done. Plasma cholecystokinin levels were 79.2±58.7 pg/mL in children with colonic inertia, 70.7±47.0 pg/mL in hindgut dysfunction, 57.4±53.1 pg/mL in pelvic outlet obstruction, and 67.6±47.9 pg/mL in normal colonic transit. These data showed that there was a tendency of increasing plasma cholecystokinin levels in children with proximal colon transit delay, although there was no significant difference among four groups. Plasma cholecystokinin levels in children of 10 years of age and under (54.5±40.4 pg/mL) were significantly lower ($p=0.01$) than in children over 10 years (79.1±59.8 pg/mL). Plasma cholecystokinin levels based on colonic transit patterns, however, were not significantly different between the two age groups. There was no significant difference in plasma cholecystokinin levels between groups based on defecation frequency per week, presence of defecation pain, symptoms of milk intolerance, or the presence of emotional stress. These results suggested that there was a tendency of increasing plasma cholecystokinin levels in the younger age group and in children with delay in proximal colonic transit, but further study is required in relation to plasma cholecystokinin levels based on colonic transit patterns in a large number of patients.

Key Words: Colonic transit patterns, cholecystokinin, children, recurrent abdominal pain

INTRODUCTION

It is well known that about 10 to 15% of school-age children have some disturbances in normal daily activity or performance due to recurrent abdominal pain and it has been called 'recurrent abdominal pain'.[1] Already in the past, recurrent abdominal pain (RAP) was defined by Apley[2] of "three or more episodes of abdominal pain occurring over a period of at least three months and affecting normal activities in children between the age of 4 and 16 years, but without signs of organic disease".

In about 70 to 75% of these children, recurrent abdominal pain results from functional causes in which the pathogenesis of pain involves disordered gastrointestinal motility and visceral hypersensitivity on the prevailing viewpoint.[3-5]

Pineiro-Carrero et al. described that the specific motility patterns associated with pain included high amplitude duodenal contractions and activity of the migrating motor complex (MMC).[6] And children with recurrent abdominal pain had more frequent migrating motor complexes, but these were shorter in duration and moved more slowly down the intestine (slower propagation velocities) than in normal controls.

It is well established that the gut hormones are one of the important factors of regulating gastrointestinal motility. Especially, cholecystokinin (CCK) has been known to inhibit gastric emptying by closing the pyloric sphincter and in stimulating intestinal motility. And it is also known that the gastro-colic reflex is caused by postprandial cholecystokinin release.[3-5] Alfven and Moberg reported that children with recurrent abdominal pain had high plasma cholecystokinin levels, but they described that whether or not this elevated cholecystokinin level is related to the clinical symptoms including abdominal pain remains to be

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[1]Department of Pediatrics, Yonsei University College of Medicine, [2]Department of Pediatrics, Hallym University College of Medicine, Seoul, Korea.
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Address reprint request to Dr. K. S. Chung, Department of Pediatrics, Yonsei University College of Medicine, C.P.O. Box 8044, Seoul 120-752, Korea. Tel: 82-2-361-5510, 5519, Fax: 82-2-393-9118, E-mail: kschung58@yumc.yonsei.ac.kr

established.[7] It thus appears necessary to investigate the role of plasma cholecystokinin levels in relation to recurrent abdominal pain.

The purpose of this study was to explore the relationships of plasma cholecystokinin levels to colonic transit patterns and to clinical symptoms in children with recurrent abdominal pain.

MATERIALS AND METHODS

Subjects

One hundred and twenty children who had recurrent abdominal pain and who also had colonic transit study at the Department of Pediatrics, Yonsei University College of Medicine from June 1997 to June 1998, were enrolled in this study.

Measurement of colonic transit time

Colonic transit times were measured by the method of Metcalf[8] with Sitzmarks® (Konsyl Pharmaceuticals, Inc, Fort Worth, Texas, USA). Each patient ingesed one Sitzmarks capsule containing 24 markers on three successive days at 8 : 30 a.m. and a plain abdominal radiograph was taken at the same hour on the fourth day. The location of markers in the right colon, left colon or rectosigmoid was determined on the basis of their position with respect to lines drawn from the midline to the fifth lumbar vertebra and from the latter to the right pelvic brim and to the left anterior superior iliac crest. The colonic transit patterns were determined by applying the normal segmental transit time of healthy Korean children that the authors had previously reported.[9] Delayed transit in the right colon refered to colonic inertia, that in the left colon to hindgut dysfunction, and that in the rectosigmoid colon to pelvic outlet obstruction.

Collection of blood samples and measurement of plasma cholecystokinin levels

Blood samples were withdrawn from children between 09 : 00 and 10 : 00 a.m. after overnight fasting. Collected blood samples were transferred into a polypropylene tube containing EDTA (1 mg/mL of blood) and Aprotinin (500 KIU/mL of blood) at 0°C using a chilled syringe. Plasmas obtained from centrifuging the samples at 1,600×g for 15 minutes at 0°C were transferred to a fresh polypropylene tube and stored at −70°C.

Plasma cholecystokinin levels were measured by radioimmunoassay (RIA) with the commercial kit; RIK 7181 CCK Octapeptide 26−33, non-sulfated kit (Peninsula Laboratories, Inc, Belmont, CA, USA). Before the assay, the plasma cholecystokinin was extracted under the general protocol (range; 1−128 pg/tube) for peptide radioimmunoassay supplied by Peninsula Laboratories, Inc.

Statistical analysis

Plasma cholecystokinin levels were analysed among groups based on age, sex, colonic transit patterns, defecation frequency per week, the presence of defecation pain, the presence of milk intolerance, or the presence of emotional stress.

The statistical analysis was made by the student t-test and ANOVA test using SPSS 7.0 for Windows. A p-value less than 0.05 was considered statistically significant.

RESULTS

Colonic transit patterns of patients

The subjects consisted of 120 children with a mean age of 9.6±2.6 years (range 4.8−14.5 years). There were 68 males and 52 females. Colonic transit patterns included 11 cases in colonic inertia, 18 in hindgut dysfunction, 49 in pelvic outlet obstruction, and 42 in normal transit (Table 1).

Table 1. Age and Sex Distribution of Patients and Colonic Transit Pattern

	No. of patients	Age (yrs)	Male : Female
Colonic inertia	11	9.5±2.6	5 : 6
Hindgut dysfunction	18	9.1±2.7	12 : 6
Pelvic outlet obstruction	49	9.6±2.6	26 : 23
Normal	42	9.8±2.6	24 : 18
Total	120	9.6±2.6	67 : 53

Plasma cholecystokinin levels and colonic transit patterns

The plasma cholecystokinin level was 79.2±58.7 pg/mL in colonic inertia, 70.7±47.1 pg/mL in hindgut dysfunction, 57.4±53.1 pg/mL in pelvic outlet obstruction, and 67.7±47.9 pg/mL in normal transit. And the mean plasma cholecystokinin level of all 120 children was 65.0±50.8 pg/mL. There was no significant difference among four groups based on colonic transit patterns ($p>0.05$) (Table 2).

Plasma cholecystokinin levels and age distribution

The plasma cholecystokinin levels were lower in 69 children aged 10 years and under with 54.5±40.4 pg/mL than in 51 children aged over 10 with 79.1±59.8 pg/mL, which showed a significant difference ($p=0.01$) between the two age groups. In children aged 10 and under, plasma cholecystokinin levels included 69.6±48.1 pg/mL in colonic inertia, 52.5±33.3 pg/mL in hindgut dysfunction, 49.5±42.8 pg/mL in pelvic outlet obstruction, and 58.9±40.2 pg/mL in normal transit, which showed no significant difference ($p>0.05$) among the four groups. In children aged over 10, plasma cholecystokinin levels were 87.0±69.8, 107.1±52.0, 69.7±65.6, 77.2±54.7 pg/mL in each group respectively, which also showed no significant difference ($p>0.05$) among the four groups (Table 3).

Table 2. Serum CCK Levels and the Colonic Transit Patterns

	No. of patients	Serum CCK (pg/ml) (mean±SD)
Colonic inertia	11	79.2±58.7
Hindgut dysfunction	18	70.7±47.1
Pelvic outlet obstruction	49	57.4±53.1
Normal	42	67.7±47.9
Total	120	65.0±50.8

There were no significant differences among the groups for the variable.

Plasma cholecystokinin levels and defecation frequency per week

The plasma cholecystokinin level was 34.5±33.7 pg/mL in 7 children with less than three defecations per week, 66.0±51.4 pg/mL in 107 children with 3 to 21 defecations per week, and 82.2±50.3 pg/mL in 6 children with more than 21 defecations per week. There was no significant difference ($p>0.05$) among the three groups based on defecation frequency (Table 4).

Plasma cholecystokinin levels and defecation pain

The plasma cholecystokinin level was 53.7±41.2 pg/mL in 26 children with defecation pain, and was

Table 3. Serum CCK Levels and Colonic Transit Pattern by Age Group

Age (year)	Group	No. of patients	Serum CCK (pg/ml) (mean±SD)
≤10	Colonic inertia	5	69.9±48.1
	Hindgut dysfunction	12	52.5±33.3
	Pelvic outlet obstruction	30	49.5±42.8
	Normal	22	58.9±40.2
	Total	69	54.5±40.4*
>10	Colonic inertia	6	87.0±70.0
	Hindgut dysfunction	6	107.1±52.0
	Pelvic outlet obstruction	19	69.7±65.6
	Normal	20	77.2±54.7
	Total	51	79.1±59.8*

*$p=0.01$.

Table 4. Serum CCK Levels and Defecation Frequency per Week

Defecation frequency/week	No. of patients	Serum CCK (pg/ml) (mean±SD)
<3	7	34.5±33.7
3−21	107	66.0±51.4
>21	6	82.2±50.3
Total	120	65.0±50.8

There were no significant differences among the groups for the variable.

Table 5. Serum CCK Levels and Defecation Pain, Milk Intolerance or Emotional Stress

	No. of patients (n=120)	Serum CCK (pg/ml) (mean±SD)
Defecation pain		
Yes	26	53.7±41.2
No	94	68.1±53.0
Milk intolerance		
Yes	43	61.1±52.6
No	77	67.1±50.1
Emotional stress		
Yes	46	70.8±57.0
No	74	61.3±46.3

There were no significant differences among the groups for the variables.

68.1±53.0 pg/mL in 94 children without defecation pain. There was no significant difference (p=0.15) between the two groups (Table 5).

Plasma cholecystokinin levels and milk intolerance

Milk intolerance defines that ingestion of milk (milk challenge test) induces gastrointestinal symptoms. The plasma cholecystokinin level was 61.1±52.6 pg/mL in 43 children with milk intolerance, and was 67.1± 50.1 pg/mL in 77 children without milk intolerance. There was no significant difference (p>0.05) between the two groups (Table 5).

Plasma cholecystokinin levels and emotional stress

Some children have emotional stress induced by various stressful environments including death or separation from a significant family member, physical illness, handicap in relationship between patient and parents, sibling or peer pressure, school problems, poverty, and the patient's personality or character. The plasma cholecystokinin level was 70.8±57.0 pg/mL in 46 children with emotional stress, and was 61.3± 46.3 pg/mL in 74 without emotional stress. There was no significant difference (p>0.05) between the two groups (Table 5).

DISCUSSION

The gastrointestinal motility, the secretion of its digestive enzymes, and the intestinal absorption of nutrients are largely modulated by the gut hormones, originating from neurons of the enteric nervous system (ENS) and endocrine cells of intestinal mucosal epithelium.[10] Most of the gut hormones are also present in the central nervous system (CNS) and play a role as neurotransmitters. Both ENS and CNS participate in the exchange of physiologic information in our body and also affect each other significantly. This relationship has been called 'the brain gut axis'.[10]

Cholecystokinin, the gut peptide belonging to the gastrin family, is released by the stimulation of food, especially fat and amino acid, entering the duodenum.[11] Its release is inhibited by somatostatin and by intraduodenal bile acid.[12] Cholecystokinin is released from an I cell, the endocrine cells presenting in the duodenal and jejunal mucosa,[13] and its secretion is mediated by trypsin-sensitive duodenal peptide termed cholecystokinin-releasing factor (CCK-RF). Pancreatic enzymes secreted into the duodenal lumen degrade CCK-RF. This negative feedback mechanism inhibits further cholecystokinin release.[10]

The main actions of cholecystokinin are stimulation of gallbladder contraction and secretion of exocrine pancreatic enzymes.[14] As well, cholecystokinin has a function of contracting the pyloric muscle, resulting in the inhibition of gastric emptying, a satiety effect and enhancing migrating motor complexes.[10,15]

In a report by Heinlid and Malver which analyzed plain abdominal roentgenograms of children with recurrent abdominal pain, gastroduodenal motilities were increased compared to normal children.[16] Dimson reported delayed intestinal transit of carmine red dye in children with functional abdominal pain triggered by emotional factors.[17] Pineiro-Carrero et al.

described that the specific motility patterns associated with recurrent abdominal pain included high amplitude duodenal contractions and activity of the migrating motor complex (MMC) indicating a temporal relationship between altered gastroduodenal motility and the presence of abdominal pain.[6] The children with recurrent abdominal pain had more frequent migrating motor complexes, but these were shorter in duration and moved more slowly down the intestine.

In children with recurrent abdominal pain, the pain has been reported to occur frequently after meals, and therefore a relationship between disordered gastrointestinal motilities and gut hormones could be assumed.[7,18]

Alfven and Moberg reported that plasma cholecystokinin levels were increased in children with chronic recurrent abdominal pain, but plasma gastrin and somatostatin levels were not increased.[7] Harvey and Read reported that intravenous injection of cholecystokinin in patients with irritable bowel syndrome resulted in increased colonic motor activity, and the increase was especially pronounced in patients with postprandial abdominal pain.[19]

In our study, there was no significant difference of plasma cholecystokinin levels ($p > 0.05$) among four groups including colonic inertia, hindgut dysfunction, pelvic outlet obstruction and a normal transit group based on colonic transit time. However, there was a tendency that the more delayed transit occurred in the proximal colon and that higher cholecystokinin concentrations were noted. Alfven et al. investigated the relationship between age and plasma levels of cholecystokinin. Plasma cholecystokinin levels in children aged 1−2 years were twice as high as children older than 10 years.[20] As well, children aged under 7 had significantly higher cholecystokinin levels than children older than 7, but there was no significant difference in this hormone levels between boys and girls. The high cholecystokinin levels in infancy can be explained by the high energy consumption per kilogram of body weight, and therefore a high food intake causes the high hormone levels. In our study, the plasma cholecystokinin levels were lower in 69 children aged 10 years and under (54.5 ± 40.4 pg/mL) than in 51 children aged over 10 (79.1 ± 59.8 pg/mL), which showed a significant difference ($p=0.01$) between the two age groups. But there was no significant difference between sexes. This age related increase of plasma cholecystokinin levels is contrary to the results reported by Alfven et al.[20] It is assumed that further studies are needed to clarify the relationship between this plasma hormone level and age.

No significant difference was noted between plasma cholecystokinin levels and colonic transit patterns in our study. It can be explained by the fact that other gut hormones besides cholecystokinin could affect the colonic transit patterns. As well, various ingested foods and the individual habits of defecation could affect colonic transit.

As recurrent abdominal pain may be associated with altered gastrointestinal motility, we have thought that defecation habits, defecation pain and milk intolerance may affect plasma cholecystokinin levels. But in our study, there was no significant difference in plasma cholecystokinin levels between groups based on defecation frequency per week, the presence of defecation pain, or symptoms of milk intolerance.

Emotional stress causes disturbance of gastrointrstinal motility and invites one to gorge. Once one has overeaten, the cholecystokinin released from CNS and ENS causes a physiologic satiety effect through the inhibitory neural pathway.[21] In our study, there was no significant difference in plasma cholecystokinin levels between children with emotional stress and children without stress. This result may be due to the effect of midnight fasting.

Clinical studies in regard to the gut hormones associated with intestinal dysmotility in children are hardly found in the literature as yet. The reason for this may be due to the difficulty of blood sampling in children, the annoying method of handling these blood samples, the decrease of gut hormone levels in blood samples over time, and the sophisticated detection method of plasma cholecystokinin concentration.

In conclusion, there was a tendency of increasing plasma cholecystokinin levels in children with proximal colon transit delay, although there was no significant difference of plasma cholecystokinin levels among four groups including colonic inertia, hindgut dysfunction, pelvic outlet obstruction and a normal transit group based on colonic transit time. Plasma cholecystokinin levels in children aged 10 years and under 10 were significantly lower than in children over 10 years. There was no significant difference in plasma cholecystokinin levels between groups based on defecation frequency per week, presence of defecation pain, symptoms of milk intolerance, or the presence of emotional stress. Further study is necessary in rela-

tion to plasma cholecystokinin levels based on colonic transit patterns in a large number of patients.

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