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Functional dyspepsia in children

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Abstract

Functional dyspepsia in children is classified as a subset of functional pediatric gastrointestinal disorders. According to ROME II criteria, it is divided into 3 groups including ulcer-like dyspepsia, dysmotility-like dyspepsia and unspecified (non-specific) dyspepsia. Prevalence of functional dyspepsia had been reported around 3/5 of children and adolescents who presented with clinical dyspepsia. Therefore, the appropriated investigations and management should be employed to rule out the possible organic causes of dyspepsia. To date there is no controlled treatment trial in children, however, from adult studies, histamine 2 receptor antagonists or proton pump inhibitor or prokinetic drugs are reasonable to be used as the first line treatment. As there are limited studies on childhood functional dyspepsia, we suggest that the good designed studies from children in all fields of this topic are required to ensure the appropriated recommendation.

Key words: dyspepsia, functional dyspepsia, children, ROME II

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Functional dyspepsia, a childhood functional gastrointestinal disorders (FGIDs), refers to pain or discomfort centered in the upper abdomen. The discomfort can be upper abdominal fullness, early satiety, bloating, bleaching, queasiness, nausea, retching, or vomiting.[1] Since the functional dyspepsia is not rigorously defined in children, the committee on Childhood Functional Gastrointestinal Disorders (Rome II) had adopted the adult diagnostic criteria for use in children (Table 1).[1]

Table 1 Diagnostic criteria for functional dyspepsia in children (ROME II)[1]

In children mature enough to provide an accurate pain history, the pain has to be present at least 12 weeks, which need not be consecutive, within preceding 12 months. The criteria for diagnosis are following.
1. persistent or recurrent pain, or discomfort centered in the upper abdominal (above the umbilicus); and 2. no evidence (including at upper endoscopy) that an organic disease is likely to cause the symptoms; and 3. no evidence that dyspepsia is exclusively relieved by defecation, or associated with the onset of a change in stool frequency or stool form.

Functional dyspepsia is divided into 3 categories based on distinctive features.[1]

1. Ulcer-like dyspepsia

Pain centered in the upper abdomen is the predominant (most bothersome) symptom.

2. Dysmotility-like dyspepsia

An unpleasant or troublesome non-painful sensation (discomfort) centered in the upper abdomen is the predominant symptom. This sensation may be characterized by or associated with upper abdominal fullness, early satiety, bloating, or nausea.

3. Unspecified (non-specific) dyspepsia

Symptomatic patients whose symptoms do not fulfil the criteria for either ulcer-like or dysmotility-like dyspepsia are grouped into non-specific dyspepsia.

Diagnosis

Functional dyspepsia can be diagnosed by exclusion of other organic diseases. Children who have a constellation of sign and/or symptoms shown in Table 2 that include 2 major criteria, one major and 2 minor criteria or 4 minor criteria should be investigated to rule out the organic etiology of dyspepsia.[2] The initial laboratory tests to screen for organic disease include complete blood count (CBC), urinalysis and urine culture, erythrocyte sedimentation rate (ESR), serum electrolytes, liver function tests and stool examination for ova and parasite. In selected cases, upper gastrointestinal series, serum amylase and lipase, or abdominal ultrasound may be required to rule out anatomic abnormalities, pancreatitis and gall bladder diseases, respectively. In patients who are suspected to have carbohydrate malabsorption or parasitic infestation, breath hydrogen test and stool studies for ova and parasite may be required. If the cause of dyspepsia cannot be identified by the initial investigations, an upper endoscopy with biopsies is the procedure of choice. The laboratory investigations in children with dyspepsia are shown in table 3.

Table 2 Criteria to define dyspepsia in children

Major criteria	Minor criteria
Recurrent vomiting (at least 3/ month)	Chronic nausea
Epigastric abdominal pain	Early satiety
	Excessive belching/ hiccups
	Anorexia/ weight loss
	Heartburn
	Periumbilical abdominal pain
	Oral regurgitation
	Positive family history of peptic ulcer disease, dyspepsia, or irritable syndrome

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Table 3 Investigations of childhood dyspepsia

Work up study	Purpose
Complete blood count (CBC), with differential white blood cell count	Evaluate anemia, eosinophilia and infection
Liver function tests	Rule out liver and biliary tract disorders
Stool ova and parasite	Rule out parasitic infection
Sedimentation rate	If increased, rule out inflammatory bowel disease
Serum amylase and lipase	Rule out pancreatitis
Ultrasound of liver	Possibility of gallstones/ right upper quadrant pain
Breath hydrogen test	Evaluate for lactose intolerance and small bowel bacterial overgrowth
Endoscopy	Rule out esophagitis, gastritis, duodenitis or *Helicobacter pylori* infection

Prevalence

Collecting the data from 400 consecutive unselected adult patients with dyspepsia who sought medical attention, Heikkinen and colleague[3] revealed that 135 patients (34%) had functional dyspepsia, in which 22% were ulcer-like, 28% were dysmotility-like and 50% were nonspecific dyspepsia. The study in children and adolescent[4] aged more than 5 years old (n=257) who present with abdominal pain, discomfort and/or nausea for at least 1 month, revealed that 127 patients (49%) fulfill the criteria for dyspepsia. Endoscopy were performed in 56 patients. While 21 children (38%) were found to have mucosal inflammation (10 esophagitis, 12 gastritis and 7 duodenitis), 35 children (62%) were considered to have functional dyspepsia. In children who had normal endoscopic finding, 70% were either asymptomatic or much improve after the 0.5 -1.9 year follow-up period.

Treatment

To date, there is no controlled trial for treatment of functional dyspepsia in children. Therefore, the treatments based on the studies in adults will be discussed.

1. Antacids

In randomized controlled trial (RCT) studies, the absence of benefit of antacids over placebo is shown, neither the pain intensity (4%; 95%CI –12% to 21%) nor the pain index (5%; 95%CI –13% to 23%).[5]

2. Histamine$_2$ receptor antagonists (H2RA)

The treatment outcomes of H_2 receptor antagonists in functional dyspepsia have varied.[6-8] The positive results of H2RA in some studies[9-18] may be due to inclusion of GERD patients. Two large meta-analysis studies showed the effectiveness of H_2 receptor antagonists over placebo, including the improvement of epigastric pain (OR 2.33; 95%CI 1.63 to 3.32), the complete relief of epigastric pain (OR 1.81; 95%CI 1.15 to 2.84) and the probability of treatment success.[19, 20] However, Redstone et al[19] suggested that the study with larger sample size to determine the effective dose are necessary.

3. Proton pump inhibitors (PPI)

A large randomized controlled trial (RCT) study shows the effectiveness of omeprazole in treatment of functional dyspepsia, especially in ulcer-like and reflux-like dyspepsia.[21] One thousand two-hundred and sixty two patients with functional dyspepsia (with normal upper GI endoscopy) were randomly selected to received one of the 3 following regimens, omeprazole 20 mg (O_{20}), omeprazole 10 mg (O_{10}), or placebo (P) for 4 weeks. The patients who had the complete symptom relief were 38% in O_{20}, 36% in O_{10} and 28% in P (P value <0.05 compared with placebo). There was significant benefit of omeprazole over placebo in ulcer-like and reflux-like dyspepsia, but not dysmotility-like dyspepsia. The study showed that the symptom relief in *H. pylori*-positive and negative cases were similar. However, *H. pylori* status may be a confounding factor on the treatment response. Blum et al[22] reported that high dose omeprazole was more likely to have positive effect in *H. pylori* infected patients. They showed that omeprazole (20 mg) has significant

therapeutic effect over placebo in *H. pylori* infected patients (17.6%; 95% CI 4.2 to 31.0), but not in *H. pylori* negative patients (5.5%; 95% CI –8.0 to 19.1). Low dose omeprazole (10mg) or ranitidine (150 mg) has no significant effect over placebo.

4. Prokinetics

The effectiveness of cisapride is generally better than placebo. However, some studies[7, 23] did not shown the statistically difference between cisapride and placebo. Domperidone and metoclopramide have shown a benefit over placebo in an available study.[6] Recently, a meta-analysis study has shown the advantage of both cisapride and domperidone over placebo[24] (OR 2.9; 95%CI 1.5 to 5.8 and OR 7.0; 95%CI 3.6 to 16 for cisapride and domperidone, respectively). Another meta-analysis study[20] also showed the significant effectiveness of gastrokinetics (cisapride, domperidone) over placebo. The difference in proportions of treatment success compared to placebo for gastrokinetics is 0.4029 (95% CI 0.3042 to 0.5069), including 0.3381 (95%CI 0.2127 to 0.4635) for cisapride and 0.5623 (95% CI 0.4828 to 0.6418) for domperidone.

5. *H. pylori* eradication

The prevalence of *H. pylori* in functional dyspepsia varies from 30-70% in adults[25] and 9% in children and adolescents.[4] Therapeutic efficacy of *H. pylori* eradication in functional dyspepsia is varied.[6] In more recent large RCTs, the efficacy is still controversy (Table 4).[26-29]

Table 4 Studies of *Helicobacter pylori* eradication and dyspepsia

Author	Design	Treatment	Results	Comments
Gilvarry et al[26]	RCT	● Bisthmuth based triple therapy (n 50) ● Bismuth+	Triple therapy H.P.negative (n=42): significant response at 8 wk, 6 mo, 1 yr (P<0.01) H.P.- positive: no decrease in symptoms Bismuth-placebo	Eradication of HP*. results in a reduction of symptoms of non-ulcer dyspepsia.

			placebo (n 50)	HP negative (n=7): improvement in symptoms at 8wk, 6 mo, 1 yr HP positive: insignificant improvement	
McColl et al[27]	RCT		• OMA** or OMT (n=160) • O (n=158)	• HP eradication: 88% vs 5% • Resolved symptom at 1 yr: 21% vs 7% (95%CI for difference 7% to 22%, P<0.001)	In HP infected, non-ulcer like dyspepsia, treatment with omeprezole with antibiotics is more likely to resolved symptoms than treatment with omeprazole alone.
Blum et al[28]	RCT, multicenter		• OMC (n=164) • O (n=164)	• HP eradication: 79% vs 2% • Resolved symptom at 1 yr: 27.4% vs 20.7% (95%CI for difference –2.6% to 16.0%, P=0.17)	HP eradication in non-ulcer like dyspepsia is not likely to relieve symptoms.
Talley et al[29]	RCT, multicenter		• OMA (n=135) • P*** (n=143)	• HP eradication: 85% vs 4% • Resolved symptom at 1 yr: 24% vs 22% (95%CI for difference –8% to 12%, P= 0.7)	No evidence was found that eradication of HP relieves the symptoms of functional dyspepsia.

*HP = *Helicobacter pylori* ** O = Omeprazole, M = metronidazole, T = Tetracycline, A = amoxycillin, C = clarithromycin; ***P = placebo

6. Other regimens

6.1 Levosulpiride (levo-enantiomer of sulpiride) is a well-known antiemetic, antidyspeptic and antiphychotic drug. Corazza et al[30] showed the significant effectiveness of levosulpiride (25 mg tid for 4 wk) over domperidone, metoclopramide and placebo (P<0.01) in treatment of functional dyspepsia.

Compared with cisapride in a double-blind crossover study (n=30)[31], the efficacy of levosulpiride was similar in shortening (P<0.001) of gastric emptying time from the baseline. Both cisapride and levosulpiride improve all parameters of dyspeptic symptoms (P<0.001). Levosulpiride was superior to cisapride in the impact of symptoms on patients' everyday activity and some symptoms such as nausea, vomiting and early satiety. However, no significant difference between them in regards to improvements in total symptom scores was observed. The clinical improvement had no significant correlation with gastric emptying acceleration (r=0.1) but another study[32] reported that the effect of levosulpiride in improvement of symptom score correlated with gastric emptying time (r=0.47, P=0.01).

6.2 Fedotozine acts on the kappa receptors located on afferent neurones in the gut wall. Read et al[33] reported the effectiveness of fedotozine (30 mg tid for 6 wk) in functional dyspepsia compared to placebo in RCT multicenter study (P=0.002).

6.3 Simethicone

Holtmann[34] reported that the efficacy of simethicome was better than cisapride after 2-week treatment but not after 4-week treatment in functional dyspepsia. The improvement of symptom scores were 30.7% (P<0.001) at 2 weeks and 10.2% (P=0.11) at 4 weeks.

6.4 Peppermint oil and caraway oil (PCC, Enteroplant)

Madisch et al[35] reported that the efficacy of a fixed combination of peppermint oil and caraway oil (n=60)

was comparable with the efficacy of cisapride (n=58) in functional dyspepsia (RCT study).

7. Placebo

Placebo produced a high symptomatic response rate in functional dyspepsia. In the systemic review trials it varied from 13-73%.[9] In a therapeutic trial with placebo[36] (cellulose) three time daily before meal for 8 wk (n=30), 80% of patients reported improved global health status and markedly decreased symptom index (pre 23.9+/- 1.3 vs post 9.1+/- 1.2, P<0.05). Patients with functional dyspepsia had increased sensitivity to stepwise distension of stomach relative to healthy person and this finding remained unchanged after treatment even though improved clinical status.

Summary

There are a few studies about functional dyspepsia in children. Investigations in all fields of this topic are required. The definition of functional dyspepsia is still not clear especially in children (e.g., etiology, pathology). Therefore, the recruitment of patients for study should be careful. Because of a lot of placebo effects, the study design should be a placebo-controlled trial. Even though bias may occur in studies, the available data of prevalence of dyspepsia in children and adolescents show that around 2/5 of dyspepsia are caused by organic diseases. Therefore, investigations, including gastroscope, should be done especially in children who have signs or symptoms suggestive of organic diseases (weight loss, vomiting), or persistent or recurrent symptoms despite the use of H2RA or PPI, or significant functional disability (extended school absenteeism, unable to participate in age-appropriate activities). There is no controlled treatment trial in children. Referred to the drug treatment in adult studies, H2RA or PPI or prokinetic durgs are reasonable to be used for treatment. The yields of *H. pylori* eradication in resolved symptoms of functional dyspepsia are still equivocally. More studies on other regimens are required before the recommendation.

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