



Symptoms of GER

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Abstract

Gastroesophageal reflux (GER) is defined by the passage of gastric contents into the esophagus. GER is a normal physiologic process occurring several times per day in healthy infants, children, and adults. Most episodes of GER in healthy individuals last <3 min, occur in the postprandial period, and cause few or no symptoms. Conversely, gastroesophageal reflux disease (GERD) is present when the reflux of gastric contents into the esophagus causes troublesome symptoms and/or complications. Distinguishing physiologic GER from GERD may often be tricky, especially in infants. Indeed, in the first months of life, GER usually underlies recurrent regurgitation and vomiting, mainly due to anatomic features and liquid feeding. These symptoms, along with persisting crying and irritability, are often a source of anxiety for parents. Clinicians should be aware that the vast majority of these spitting infants does not deserve diagnostic test, and GERD should be suspected only when alarm signs arise.

Unlike infants, children and adolescents do not usually experience any relevant symptom related to physiologic GER. Therefore, in these age groups symptoms such as vomiting, heartburn, and chest pain should not be overlooked, and a diagnostic work-up is advisable. Only in older children and adolescents, an empiric acid-suppressive trial may be recommended. Respiratory symptoms,

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such as cough, wheezing, and hoarseness, may also be associated with GERD, being sometimes the only “atypical” presentation of the disease.

Keywords

Gastroesophageal reflux · Gastroesophageal reflux disease · Regurgitation
Vomiting · Irritability · Heartburn · Chest pain · Typical GERD presentation
Atypical GERD presentation · Respiratory symptoms

Introduction

Gastroesophageal reflux (GER) is a normal physiologic process occurring several times per day in healthy infants, children, and adults. It is defined as the passage of gastric contents into the esophagus, with most episodes lasting <3 min, occurring in the postprandial period, and causing few or no symptoms [1]. Conversely, gastroesophageal reflux disease (GERD) is diagnosed when the reflux of gastric contents into the esophagus causes troublesome symptoms and/or complications [2].

A proper diagnosis of these two conditions, besides other possible conditions mimicking GER, is crucial in order to target the treatment, avoiding the overuse of acid-suppressive drugs which currently represents a major source of concern. Reflux symptoms may vary widely according to age and distinguishing physiologic GER from GERD may often be tricky. The clinical picture alone is frequently nonspecific and does not allow, except in older children and adolescents, to settle the actual need for acid-suppressive medications. Therefore, instrumental diagnostic tests, such as combined esophageal multiple intraluminal impedance and pH monitoring and upper gastrointestinal endoscopy, are often requested.

The typical presentation of GERD includes the following symptoms: recurrent regurgitation, vomiting, weight loss or poor weight gain, excessive crying and irritability in infants, ruminative behavior, heartburn or chest pain, hematemesis, and dysphagia. Besides these esophageal symptoms, there is a set of extra-esophageal symptoms, mainly respiratory, which may occur along with typical symptoms or may represent the only clinical picture of GERD: odynophagia, wheezing, stridor, cough, hoarseness, dental erosions and apnea/apparent life-threatening events. Moreover, GERD may underlie other signs or conditions, such as impaired quality of life, food refusal, persisting hiccups, abnormal posturing/Sandifer’s syndrome, anemia, and bradycardia. Finally, esophagitis, Barrett’s esophagus, and esophageal adenocarcinoma are possible acknowledged and worrisome long-term outcomes, especially when GERD is undiagnosed or untreated.

As already reported, all the abovementioned signs and symptoms are variously prevalent and relevant in the different pediatric age groups. Therefore, GERD clinical pictures of infants, children, and adolescents will be treated in separate paragraphs.

Clinical Picture of Physiologic GER and GERD in Infants

Physiologic GER is very common in infants, especially during the first 6 months of life. About 70% of healthy infants show regurgitation, vomiting, and irritability several times per day, and in about 95% of them these symptoms disappear without intervention by 12–14 months of age [3, 4]. The term “happy spitter” has been used to identify these subjects, in order to emphasize the benignity of such condition. Regurgitation occurs more frequently in infants than in adults because of the large liquid volume intake, the limited capacity of the stomach and esophagus, and the prolonged horizontal position of infants [5, 6]. Reflux episodes sometimes trigger vomiting, a coordinated autonomic and voluntary motor response, causing forceful expulsion of gastric contents through the mouth. Vomiting associated with reflux is probably a result of the stimulation of pharyngeal sensory afferents by refluxed gastric contents.

Unlike physiologic GER, GERD is very rare in infants and should be suspected only in the presence of warning signals (Table 3.1). A proper diagnosis of GERD should rely on instrumental testing, such as combined esophageal multiple intraluminal impedance and pH monitoring and upper gastrointestinal endoscopy. Indeed, no symptom or cluster of symptoms has been shown to reliably predict complications of reflux or to predict those infants likely to respond to therapy. Therefore, the major role of history and physical examination in the evaluation of purported GERD is to rule out other more worrisome disorders that present with similar symptoms

Table 3.1 Warning signals requiring investigation in infants with regurgitation or vomiting

Bilious vomiting
Gastrointestinal bleeding
Hematemesis
Hematochezia
Consistently forceful vomiting
Onset of vomiting after 6 months of life
Failure to thrive
Diarrhea
Constipation
Fever
Lethargy
Hepatosplenomegaly
Bulging fontanelle
Macro-/microcephaly
Seizures
Abdominal tenderness or distension
Documented or suspected genetic/metabolic syndrome

(especially vomiting) and to identify possible complications of GERD. Parent-reported questionnaires based on clusters of symptoms have been developed in the last decades. *Orenstein* et al. developed a diagnostic questionnaire for GERD in infants, in which a score >7 (of possible 25) demonstrated a sensitivity of 0.74 and a specificity of 0.94 during primary validation [7]. The questionnaire has undergone several revisions [8]. The questionnaire has been shown to be reliable for documentation and monitoring of reported symptoms. However, when applied to a population in India, it had a sensitivity and specificity of only 43% and 79%, respectively, compared with pH monitoring results [9]. In another study of infants referred for symptoms of reflux disease and controls, the questionnaire had a sensitivity and specificity of 47 and 81% for a RI $>10\%$ and 65 and 63% for a reflux index $>5\%$. The questionnaire score failed to identify 26% of the infants with GERD. The score was positive in 17 of 22 infants with normal biopsies and pH studies and in 14 of 47 infants with normal pH studies. No single symptom was significantly associated with esophagitis [10]. In another study, the questionnaire was unable to identify a group of infants responsive to proton pump inhibitor (PPI) therapy [2].

The concept that infant irritability and sleep disturbances are manifestations of reflux is largely extrapolated from adult descriptions of heartburn and sleep disturbances that improve with antacid therapy [11–14]. Although one study in infants showed a correlation between infant grimacing and episodes of reflux [15], multiple other studies have shown no relationship between crying and GERD determined by esophageal pH testing [16–19] or the presence of esophagitis [17, 20]. Therefore, neither regurgitation and vomiting nor irritability and excessive crying, regardless of their extent and their severity, are sufficient to diagnose GERD. GERD should be suspected in infants with these symptoms but none of the symptoms are specific to GERD alone.

Although reflux does occur physiologically in most infants, clinicians should be aware that there is a continuum between physiologic GER and GERD leading to significant symptoms, signs and complications. The vast majority of these spitting and crying infants suffer from physiologic GER (also called infant regurgitation), a benign condition with a good prognosis, needing no other intervention than parental education and anticipatory guidance, and possible changes in feeding composition. Overfeeding exacerbates recurrent regurgitation [5]. Thickened or anti-regurgitation formulas decrease overt regurgitation [21]. Only a small proportion of symptomatic infants may deserve an instrumental diagnostic assessment for GERD or other GERD-mimicking diseases.

Clinical Picture of GERD in Young Children

Whether of new onset or persisting from infancy, physiologic regurgitation, episodic vomiting, or regurgitation followed by swallowing of refluxate in the mouth is less common in children older than 18 months of age and deserves an instrumental evaluation to diagnose possible GERD and to rule out alternative diagnosis [2]. Besides regurgitation and vomiting, GERD may present in children with many other signs or

symptoms, the most frequent of which are heartburn, food refusal, dysphagia, persisting hiccups, feeding or sleeping disturbances, impaired quality of life, failure to thrive and dental erosions. Respiratory symptoms, such as chronic cough, wheezing, hoarseness, laryngitis, ear problems, aspiration pneumonia, chronic asthma, and sinusitis, are atypical symptoms possibly associated with GERD. Nevertheless, the paucity of clinical studies, small sample sizes, and varying disease definitions do not allow firm conclusions about their association with reflux to be drawn [22].

According to the latest NASPGHAN-ESPGHAN pediatric GER guidelines, subjective symptom descriptions are unreliable in children younger than 8–12 years of age, and many of the purported symptoms of GERD in children are nonspecific. A five-item questionnaire developed for children showed a sensitivity of 75% and a specificity of 96% compared with pH monitoring during primary validation [23]. No subsequent independent confirmatory validation has been performed. Other diagnostic questionnaires, such as the GERD symptom questionnaire [24], have not been compared with objective standards like endoscopy, pH monitoring, or esophageal multiple intraluminal impedance monitoring. Some researchers have used questionnaires to monitor symptoms of children during GERD therapy [16]. Whether this method is preferable to monitoring, individual symptoms are uncertain. Although daily symptom diaries are frequently used in adults to monitor the effects of therapy, these have not been validated in children.

Therefore, a clinical diagnosis based on a history of heartburn cannot be used because these individuals cannot reliably communicate the quality and quantity of their symptoms. According to expert opinions, although the verbal child can communicate pain, the description of quality, intensity, location, and severity is generally unreliable until at least 8 and possibly 12 years of age [25–29]. GERD testing may include upper GI endoscopy and/or esophageal pH/MII and/or barium upper GI series. The diagnosis of GERD should be inferred when tests show excessive frequency or duration of reflux events, esophagitis or a clear association of symptoms and signs with reflux events in the absence of alternative diagnoses (Table 3.2).

Clinical Picture of GERD in Older Children and Adolescents

In older children and adolescents heartburn, chest pain, and regurgitation are the typical symptoms of GERD. According to expert opinion, the description and localization of these symptoms are a reliable indicator of GERD in this age group, and an empiric acid-suppressive trial may be indicated regardless of an objective assessment of reflux. This approach is mainly driven by adult studies. One study found that dominant heartburn had a positive predictive value of 81% for GERD determined by pH study [30], even if other studies have not confirmed this close association between history and test results [31]. Esophageal pH probe results are normal in one-third of adults with chronic heartburn, even those whose heartburn is reproduced by esophageal acid perfusion and those who respond favorably to antacids. Nevertheless, some adults with heartburn and normal pH studies have endoscopically proven esophagitis [31].

Table 3.2 Differential diagnosis of vomiting in infants and children

<i>Gastrointestinal obstruction</i>
Pyloric stenosis
Malrotation with intermittent volvulus
Intestinal duplication
Hirschsprung disease
Antral/duodenal web
Foreign body
Incarcerated hernia
<i>Other gastrointestinal disorders</i>
Achalasia
Gastroparesis
Gastroenteritis
Peptic ulcer
Eosinophilic esophagitis/gastroenteritis
Food allergy
Inflammatory bowel disease
Pancreatitis
Appendicitis
<i>Infectious</i>
Sepsis
Meningitis
Urinary tract infection
Pneumonia
Otitis media
Hepatitis
<i>Metabolic/endocrine</i>
Galactosemia
Hereditary fructose intolerance
Urea cycle defects
Amino and organic acidemias
Congenital adrenal hyperplasia
<i>Renal</i>
Obstructive uropathy
Renal insufficiency
<i>Toxic</i>
Lead
Iron
Vitamins A and D
Medications—Ipecac, digoxin, theophylline, etc.
<i>Cardiac</i>
Congestive heart failure
Vascular ring
<i>Others</i>
Pediatric falsification disorder (Munchausen syndrome by proxy)
Child neglect or abuse
Self-induced vomiting
Cyclic vomiting syndrome
Autonomic dysfunction

Along with heartburn and chest pain, many other signs and symptoms may occur in older children and adolescents, such as epigastric pain, regurgitation, dysphagia, impaired quality of life, food refusal, anorexia, sleeping disturbances, and dental erosions. Moreover, likewise, infants and younger children, even older children, and adolescents may experience respiratory symptoms as the only manifestation of GERD. Among these, the most relevant symptoms complained are chronic cough, wheezing, and hoarseness.

Several studies indicate a significant degree of overlap between GERD and functional dyspepsia (FD) [32, 33]. According to the latest Rome diagnostic criteria for pediatric functional gastrointestinal disorders, FD is defined as “a feeling of persistent or recurrent pain or discomfort in the upper abdomen, most often aggravated by meal ingestion, not relieved by defecation or associated with the onset of a change in stool frequency or stool form (i.e., not irritable bowel syndrome) when no physical or organic cause for the symptom is identified with conventional testing” [34]. A defective accommodation reflex leading to a reduced postprandial relaxation of the fundus has been suggested as an underlying mechanism for FD in adults [35]. In FD, there is an abnormal intragastric distribution of food, with preferential accumulation in the distal stomach 6–8. It is unclear whether the symptoms are generated by distension-induced activation of the mechanoreceptors in the fundus or in the antrum.

However, clinicians should carefully approach upper GI symptoms, being aware that the current scientific literature on the overlap between GERD and FD is affected by considerable heterogeneity in terms of the criteria and diagnostic procedures used to assess both conditions. To exclude GERD, patients must undergo upper digestive endoscopy and/or pH monitoring and/or an empiric acid-suppressive trial. A lack of correspondence between symptoms and reflux episodes, together with normal acid exposure in the distal esophagus, would suggest a diagnosis of FD.

Finally, clinicians should be aware that other causes of heartburn-like chest pain including cardiac, respiratory, musculoskeletal, medication-induced, or infectious etiologies should be considered besides GERD.

Overview on GERD and Respiratory Symptoms

As abovementioned, GERD may also underlie respiratory symptoms, such as chronic cough, odynophagia, wheezing, stridor, and hoarseness. Although the role of GERD in the pathogenesis of respiratory symptoms in adults is widely accepted [36], in children there is less evidence to support this relationship [37, 38]. Several pathogenetic mechanisms have been proposed to explain the link between GERD and respiratory symptoms, including aspiration of acid gastric contents into the upper airways, vagal reflex induced by the presence of acid in the esophageal lumen, and sensitization of the central cough reflex [2, 39].

Recent advances in the pathogenesis of reflux-induced respiratory symptoms have followed the introduction in clinical practice of MII-pH, which is available for pediatric use since 2002 [40]. Combined esophageal pH and impedance

monitoring offers several advantages over a standard pH assessment, such as the ability of detecting nonacid reflux events, recognizing swallows from authentic reflux episodes, determining the height and composition of the refluxate (liquid, gas, or mixed), assessing the bolus clearance time, and measuring symptom association with reflux (symptoms association probability, SAP) even while the patient is taking acid-suppressive medication [41]. Thanks to pH-impedance studies, several authors have recently emphasized the role of nonacid and weakly acid reflux [42–49]. Furthermore, a recent systematic review by Chang et al. showed that a significant number of patients with GERD-related respiratory symptoms do not report improvement despite aggressive acid-suppressive therapy [50] thus supporting the hypothesis that respiratory symptoms are less related to acidity than GI symptoms.

In conclusion, the analysis of the medical literature concerning the relationship between GERD and respiratory symptoms highlights a large body of evidence often discordant and conflicting, which almost never allows to draw firm conclusions to be used in clinical practice. The reason for this variability of the study results is probably linked to the poor methodological quality of the clinical trials that often lack a perspective design, a rigorous sampling, a comparison group, and accurate diagnostic criteria of the different analyzed conditions. In addition, the use of relatively recent diagnostic methods, such as esophageal impedance, allowed to investigate for the first time the alkaline or weakly acid reflux, downsizing the role of acidity in the genesis of lung problems and contradicting the results of numerous studies solely based on the finding of acid reflux pH-metric.

Over the next years the use of pH-impedance, combined with manometry or with cardiorespiratory monitoring, in longitudinal, double-blind, placebo-controlled, clinical trials will help clarify the main pathophysiological aspects that link, with currently still little known modalities, GER and respiratory system, providing the clinician with a fundamental scientific basis for diagnostic and therapeutic choices.

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