Gastro-oesophageal reflux disease in paediatric patients

Terblanche AJ, MMed(Paeds), FCP, DipAllerg, CertGastroenterology(Paeds)
Paediatric gastroenterologist
Department of Paediatrics and Child Health, University of Pretoria
Correspondence to: Dr Alta Terblanche, e-mail: alta.terblanche@up.ac.za

Introduction

Gastro-oesophageal reflux (GOR) is one of the most common and frequently occurring phenomena in humans, in both normal children and adults. It may affect up to 50% of infants from birth to three months of age. It is usually self-limiting and the majority of infants outgrow their reflux by 12 months of age.[1] In this article the difference between GOR and gastro-oesophageal reflux disease (GORD), the clinical presentation, special investigations required, complications and treatment will be discussed.

Definitions

GOR involves the involuntary regurgitation of gastric contents into the oesophagus. This is a physiological event that may occur several times a day, particularly after meals, and most episodes are brief, limited to the distal oesophagus and unaccompanied by symptoms. Physiological GOR is reflux associated with absence of symptoms, or during the first few months of life, only with occasional vomiting. It is a normal function that serves a protective role during meals or in the immediate postprandial period.

Healthy and sick individuals differ in the frequency, duration and intensity of the episodes and in the association with symptoms or complications. Pathological reflux means frequent reflux episodes, with poor clearance of the refluxate, accompanied by symptoms other than regurgitation. Gastro-oesophageal reflux disease (GORD) can be defined as GOR which causes subjective troublesome symptoms and impairment of quality of life, or reflux-associated complications like oesophagitis, strictures, Barrett's oesophagus or failure to thrive.

Regurgitation is the passive passage of gastric contents into the oral pharynx and mouth, normally accompanied by gastric contents drooling out of the mouth, as opposed to vomiting where stomach contents are expelled with force. In healthy, thriving babies regurgitation is almost always physiological. It occurs more frequently in infants, as a result of transient immaturity of the developing oesophagus and stomach, higher fluid intake and the small capacity of the oesophagus (10 ml). Many infants with GORD present with frequent regurgitation, and this diagnosis should be suspected if regurgitation is accompanied by excessive crying, refusal to feed, failure to thrive or haematemesis.

Primary GOR results from a functional disorder of the upper gastrointestinal tract or poor function of the lower oesophageal sphincter. Secondary GOR has a cause outside the gastrointestinal tract, e.g. cow's milk protein allergy, mechanical factors such as chronic upper airway obstruction, systemic or local infection, food allergy, metabolic disorders, or raised intracranial pressure etc. Management of these conditions will improve the GOR. Children at risk of more severe GOR include those with neurological impairment, cystic fibrosis and oesophageal atresia repair.[2] Obesity, certain genetic syndromes and a history of prematurity also increase the risk of reflux in children.

Furthermore, there is significant clustering of reflux symptoms, erosive oesophagitis, hiatus hernia, Barrett's oesophagus and adenocarcinoma in families, suggesting a component of heredity in GORD and its complications. A higher concordance for reflux in monozygotic twins than dizygotic twins was also found in a large Swedish Twin Registry Study. Susceptible genes were identified on chromosomes 9 and 13.[3-6]

Clinical presentation

The symptoms, signs and disorders commonly associated with GORD in children are shown in Table I. It is a spectrum of disease that can be best described by manifestations of oesophageal or adjacent organ injury secondary to the reflux of gastric contents into the oesophagus, mouth or airways.

The symptoms vary according to age. The most common presentation of infant GORD is regurgitation, with

Table I: Symptoms, signs and disorders associated with gastro-oesophageal reflux disease in children (adapted from Rudolph and Hassall[3])

Well documented	Poorly documented
Recurrent regurgitation ("spitting up")	Infant irritability
Poor weight gain	Infant feeding refusal
Heartburn, chest pain, abdominal pain	Infant sleep apnoea
Oesophagitis	Hoarseness
Sandifer syndrome	Sinusitus
Vomiting	Otitis media
Haematemesis	Dental erosions
Anaemia	
Barrett's oesophagus	
Asthma or wheezing	
Chronic cough	
Globus sensation	
Acute life-threatening events	
Recurrent pneumonia	

occasional projectile vomiting. Infants and young children cannot express symptoms verbally, and therefore they present with persistent crying, irritability, back-arching, and feeding and sleeping difficulties, symptoms that are proposed to be the equivalent of heartburn in adults. As a result of the discomfort associated with eating, an aversion to food may develop. Severe regurgitation may cause caloric insufficiency and failure to thrive in a minority of infants.

Older children report regurgitation and vomiting rather than heartburn, chest pain or dysphagia. They find it difficult to describe these unpleasant sensations. They may present with abnormal posturing (Sandifer syndrome), abdominal pain, feeding difficulties, irritability, chronic respiratory infections or failure to thrive. GORD in the adolescent presents more adult-like, with heartburn as the predominant symptom. Atypical symptoms such as epigastric pain, nausea, flatulence, hiccups, chronic cough, asthma, chest pain, hoarseness and earache account for 30-60 % of GORD complaints.

Alarm symptoms include weight loss, anaemia, bleeding, chest pain, choking, failure to thrive, irritability, feeding or sleeping difficulties, apnoea, and apparent life-threatening events. Quality of life is impaired in both adults and children (and their parents) with GOR. The infant oesophagus exposed to acid seems to be hypersensitive to pain stimuli, even with no tissue damage, similar to nonerosive reflux disease (NERD) in adults.

GORD may be associated with severe complications such as oesophagitis, Barrett's oesophagus, strictures and adenocarcinoma, although the last three are rare in children. An undesirable endpoint of GORD is strictures that can lead to dysphagia. Barrett's oesophagus is not uncommon in adolescents, especially if *Helicobacter pylori* is present.

Diagnosis

There is no "gold-standard" diagnostic technique and each investigation focuses on different aspects of the disease. The role of diagnostic testing is to prove whether GOR causes disease. Each test answers a specific question. History is important to exclude other causes of vomiting. Often history alone is adequate to diagnose GORD in older children and initiate treatment. Owing to the nonspecific nature of symptoms and the inability of children less than eight years of age to describe these subjectively, diagnosis is challenging in this population.

Contrast radiography like a barium meal would have value to exclude any anatomical abnormalities such as malrotation, duodenal webs, stenosis or achalasia. However, it is unsuitable to diagnose reflux, as the frequent nature of reflux episodes may give a false positive result, and the short time of exposure when the film is taken, may give a false negative result. Scintigraphy has low sensitivity and specificity, and is sometimes used to identify pulmonary aspiration. Endoscopy and biopsy may reveal anatomical abnormalities, for example a sliding hernia or oesophagitis and may be helpful by excluding other causes of oesophagitis. Ambulatory 24-hour pH-metry measures the incidence and duration of acid reflux in a 24-hour period. It is the best method to demonstrate the presence of acid in the oesophagus although not all reflux episodes are associated with acidity. It is a helpful tool to monitor the effect of treatment. Similarly, oesophageal impedance monitoring, a method where electrical potential differences are measured, is of value to indicate both acid and non-acid reflux episodes and to differentiate between liquid and gas reflux episodes. Evaluation of the efficacy of treatment is another asset of this method. However, this is a costly investigation and interpretation is laborious. There is no universally accepted optimal investigation, and the therapeutic approach should be adapted to the spectrum of symptoms in the given patient.

Treatment

Symptoms of GORD are frequent and nonspecific during infancy, and owing to the lack of a "gold standard" diagnostic technique, many infants receive anti-reflux treatments empirically. Physiological GOR does not need treatment and "frequent regurgitation" may respond to dietary treatment such as thickened feeds. Established GORD, on the other hand, necessitates treatment with proton-pump inhibitors. Failed medical therapy would make surgical therapy, such as Nissen fundoplication, a consideration. A stepwise treatment approach is summarised in Table II.[2]

Nonpharmacological treatment options include positional changes, formula thickening, a trial of hypoallergenic milk formula, altered mode of feeding (increased frequency or

Table II: Schematic therapeutic approach to gastro-oesophageal reflux disease (adapted from Vandenplas[2])

Phase	Treatment
1	Parental reassurance, observation, lifestyle changes, exclude overfeeding
2	Dietary treatment (decrease regurgitation, no decrease in GOR) Thickened formula, thickening agents, hydrolysates in cow's milk protein allergy
3	Alginate (some efficacy in moderate GORD, relatively safe)
4	Prokinetics (products available vary from country to country) Treats pathophysiological mechanism of GORD but no commercialised drug can be recommended
5	Proton-pump inhibitors (drug of choice in severe GORD) H_2-receptor blockers are less effective than proton-pump inhibitors
6	Laparoscopic surgery (endoscopic procedures under evaluation)

energy density of feeds) and weight loss in case of obesity. Although reflux episodes occur less frequently in the prone and left lateral position, there is an increased risk of sudden infant death syndrome and these are therefore not advocated. Thickening of feeds or specialised anti-reflux formulas do not decrease the time of acid exposure to the oesophagus, but they do decrease the frequency of overt regurgitation. Because a subset of infants with allergy to cow's milk protein experience symptoms of reflux, it is justified to initiate a two-week trial of hypoallergenic formula and then evaluate symptom improvement.

Pharmacological treatment is aimed at reducing oesophageal acid exposure, either by buffering the already secreted gastric acid or by decreasing further gastric acid secretion. Possible agents include antacids, surface agents, motility agents, H_2-receptor blockers and proton-pump inhibitors.

Oral antacids, like magnesium hydroxide and aluminium hydroxide, in high doses are as effective as H_2-receptor blockers in treating reflux oesophagitis. The raised serum aluminium levels associated with these high dosages and the adverse effects thereof, i.e. osteopenia, rickets, microcytic anaemia and neurotoxicity, make these agents unsuitable for chronic use in children. For the same reason the chronic use of surface agents is also not recommended.

Of the prokinetic agents, cisapride was the most effective, but it was withdrawn as it caused QT prolongation in susceptible individuals. Metoclopramide, domperidone and baclofen are the remaining alternatives. Side-effects, like dystonia associated with metoclopramide, limit their use in children.

H_2-receptor blockers limit acid secretion by blocking the histamine receptors in the parietal cells. Effective agents tested in children include ranitidine, cimetidine, nizatidine and famotidine. They have a quicker onset of effect than proton-pump inhibitors but studies have demonstrated that proton-pump inhibitors are superior in both symptom relief and healing of erosive oesophagitis. Further drawbacks that limit chronic use of these agents are tachyphylaxis and tolerance.

Proton-pump inhibitors bind and inactivate the H^+K^+-ATPase pumps in the parietal cells, thereby inhibiting acid secretion. These agents are highly efficacious and safe in treating GORD and reflux oesophagitis, and available agents for children include omeprazole, esomeprazole and pantoprazole. However, it is important to remember that in children between one and 10 years of age the drug is metabolised much faster, and a greater dosage on kilogram basis may be necessary. Furthermore, the timing of dosing, 30 minutes before breakfast, is essential for optimal efficacy. As a result of the acid-rebound effect, it is necessary to taper these drugs on discontinuation. The side-effect profile is low and may include headache, vomiting, diarrhoea or constipation.

Anti-reflux surgery (Nissen fundoplication) may be of value in a selected group of patients where optimal medical therapy has failed, non-adherence or long-term treatment is a problem, or life-threatening complications have arisen. Children in whom GORD is associated with respiratory complications are most likely to benefit, although children with neurological impairment as a group have a worse outcome. Appropriate education of the family, specifically with regard to the complications and high symptom recurrence risk, is essential.

Conclusion

GOR and GORD commonly occur in children. Symptomatology varies with age and also in severity. Appropriate application of the diagnostic techniques available will aid in judicious use of the available treatment modalities. Proton-pump inhibitors remain the treatment of choice in severe GORD.

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