

## GASTROESOPHAGEAL REFLUX IN INFANTS AND CHILDREN

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يعتبر الجزر المعدي المريئي اضطراباً مألوفاً لدى الولدان والرُضع في سائر أنحاء العالم. يهدف هذا المقال إلى توفير المعلومات المستجدة ذات العلاقة بمختلف أنماط هذا الداء. نأمل أن تؤدي هذه الدراسة إلى زيادة الوعي وإلى تنشيط الأبحاث في هذا المجال.

Gastroesophageal reflux is a common disorder in infants and children worldwide. This paper is intended to provide updated information on various aspects of the disease. It is hoped that this review will increase awareness and stimulate research in this field.

Gastroesophageal reflux (GER) is a common condition in infants and children. The availability of more sensitive diagnostic techniques has increased awareness and recognition of reflux. Consequently, better understanding of its pathogenesis, clinical manifestations, and complications has improved patient care.

Despite worldwide interest in GER, no reports have originated concerning its pattern in Saudi Arabia though the problem does exist here. In a five-year retrospective survey, we documented 22 cases of GER, of which six (27%) had peptic esophagitis [1]. This incidence of four to five cases per year is a conservative figure, considering the limited diagnostic facilities at our institution. Nevertheless, these data strongly suggest that GER is not uncommon in the pediatric population of Saudi Arabia. We will discuss the various aspects of GER in children that may contribute to early recognition and management of this disorder.

In 1959, Carre [2] estimated an incidence of gastroesophageal reflux (GER) of 1000 live births, but has since revised this estimate to approximately 1 in 300 live births [2]. A similar increase has been noted for many centers in Europe and North America, but this is attributed to increased

awareness and recognition of the disease as a result of the availability of more sensitive diagnostic techniques, rather than to a true increase in the incidence of GER [3]. A male preponderance of about 60% has also been reported in most studies. There is also a higher incidence of GER in patients with certain disorders. These include congenital disorders of the nervous system, mental retardation, and Down's syndrome [4]. Similarly, recurrent respiratory symptoms and anastomotic strictures commonly develop in infants who have been operated on for esophageal atresia and tracheoesophageal fistula. These problems result from GER and associated motility disorders of the esophagus [5].

Knowledge of the natural history of any condition is essential. The indications and different approaches to treatment must be weighed against the outcome if no therapy is used. In England, Carre reported that most infants have symptoms by two months of age, and that 60% of the patients will be symptom-free by 18 months of age, with the greatest improvement occurring by eight to ten months when most infants assume an upright posture. However, the same author pointed out that, if untreated, about 30% of the patients will continue to have symptoms up to four years of age, 5% will die, and esophageal strictures will develop in another 5% of the patients, requiring extensive medical and surgical treatment [6].

### Pathogenesis

Although the mechanism of GER is not fully

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understood, several anatomic and physiological features appear to be important in the prevention of reflux. These include the supportive role of the phrenoesophageal ligament, the acute esophageal angle contributing to a flap valve mechanism, and the role of the basal lower esophageal sphincter (LES) pressure.

The LES, which is an extension of the esophageal muscle, has no anatomic identity. However, the sphincter muscle differs from the esophageal muscle in its greater response to cholinergic stimulation. In addition, the LES (with its positive resting pressure of 15 to 60 mm Hg) is located between the stomach (with its positive pressure of 6 to 10 mm Hg) and the intrathoracic esophagus (with its negative pressure of -6 to -10 mm Hg) and constitutes a true barrier that gastric contents must overcome in order to reflux into the esophagus [7]. However, it is well known that the LES pressure is variable, as the sphincter undergoes spontaneous relaxations that are independent of relaxations triggered by deglutition [8].

Earlier reports suggested that most patients with reflux have reduced basal LES pressure as compared with normal subjects [9,10]. However, overlaps between normal subjects and patients with GER have been seen. Furthermore, recent studies using simultaneous and continuous esophageal manometry with pH monitoring have shown that, in patients with GER, only 12% of the reflux episodes occurred while the resting LES pressure was reduced, and the majority of reflux episodes (54%) occurred during transient increases in intraabdominal pressure associated with physiological activities such as coughing, crying, defecating, and moving about of patients who were awake [8,11]. It would appear that the role of reduced resting LES pressure has been overestimated in earlier reports, and the role of other factors in the genesis of GER should be studied. Finally, the delayed gastric emptying commonly seen in patients with GER and which is most marked in infants with pulmonary disease, makes it a potentially important factor in the pathogenesis of reflux [12].

Regardless of its mechanism, the reflux of gastric contents (hydrochloric acid, bile acids, pepsin) into the esophagus has severe pathological consequences. These substances damage esophageal mucosa, resulting in peptic

esophagitis. The incidence and severity of esophagitis depends on the criteria of diagnosis, the type of refluxed material, and the efficiency of esophageal clearance. Delayed acid clearance with or without abnormal esophageal peristalsis has been found more commonly in patients with GER and esophagitis than in normal controls [13,14].

Respiratory manifestations of GER may result from aspiration or from the reflex mechanism. Recurrent pneumonia [15], chronic bronchitis [16], and near-miss infant death syndrome [17] have been associated with GER and repeated aspiration. However, the presence of acid in the lower esophagus, without evidence of inhalation, has been implicated in the genesis of reflex laryngospastic disorders such as obstructive apnea, sudden infant death syndrome, and stridor [18-20]. Similarly, bronchospastic episodes such as nocturnal asthma and cough in patients with GER have been linked to a reflex mechanism, rather than to aspiration [15,21]. Although there is strong evidence implicating GER in the genesis of respiratory distress, this relationship is more complex. Conditions associated with increased positive intraabdominal pressure, such as coughing and wheezing, may themselves induce GER. Other disorders causing increased negative intrathoracic pressure, such as hiccups and stridor, may also potentiate GER. Furthermore, therapeutic modalities such as bronchodilators, nasogastric tubes, and chest physiotherapy, which are frequently used in patients with respiratory disease, may induce reflux by a variety of mechanisms. The interrelationship between GER and respiratory disorders therefore remains obscure and needs further investigation.

### Clinical Manifestations

The clinical presentation of patients with GER has been described in the literature. Vomiting is the most common symptom in infants and children, occurring in about 90% of cases. The projectile type is not uncommon, and may be confused with pyloric stenosis or pylorospasm. When vomiting is severe, it leads to loss of water, electrolytes, and calories, causing dehydration with electrolyte imbalance, failure to thrive, and malnutrition. Respiratory manifestations have already

been mentioned. Patients with recurrent pneumonia, reactive airway disease, chronic nocturnal cough, recurrent stridor, bronchopulmonary dysplasia, and apnea, as well as those with near-miss sudden infant death syndrome, may have GER and should be investigated for this possibility, even if there is no history of vomiting. Irritability in infants, heartburn in older children, melena or hematemesis, and iron-deficiency anemia are well-known manifestations of peptic esophagitis complicating GER. Unusual clinical features include Sandifer syndrome, abnormal posturing, and movements simulating convulsions, rumination, and protein-losing enteropathy. All of these manifestations disappear once appropriate therapy for GER is introduced.

### Diagnostic Methods

The number of diagnostic tests have been increasing, which indicates that no single test is able to distinguish all patients with significant GER from those with physiological reflux. The fact that reflux of gastric content into the esophagus occurs in nearly all normal subjects [22] and the scarcity of data on patterns of physiological reflux in healthy pediatric patients have made it difficult to define clinically significant GER. Nevertheless, the development of newer techniques, such as prolonged esophageal pH monitoring, has not only increased the ability to diagnose significant reflux but also to relate reflux episodes to a variety of clinical conditions.

#### *Barium swallow*

Barium swallow is one of the oldest methods used to diagnose GER. Its most important advantages are availability, technical simplicity, and the ability to detect swallowing and structural abnormalities, as well as esophagitis with strictures that may be associated with reflux. Disadvantages include a high incidence of false-positive and false-negative results. However, recently developed radiological techniques may enhance the radiologist's skill in detecting significant reflux [23]. Although there are no clear-cut criteria for the diagnosis of reflux in barium studies, it is generally accepted that small, brief wisps of barium reflux are insignificant and should not be over-

interpreted. By contrast, reflux occurring more than twice during brief fluoroscopy, or reflux with clear delay in esophageal clearing, is strongly suggestive of GER.

#### *Scintigraphy*

Scintigraphy involves the administration of a meal labeled with a radionuclide agent (technetium 99m), given either orally or by nasogastric tube, and scanning of the esophagus for evidence of reflux. The ability of this study to detect the immediate postprandial reflux, bile reflux, and pulmonary aspiration is one of its most important advantages. However, the presence of radioactive material in the lung fields does not necessarily prove aspiration caused by GER; it can also have occurred during swallowing. Other advantages of the scintiscan include the ability to diagnose and treat delayed gastric emptying [24].

#### *Esophageal pH studies*

These tests directly measure esophageal pH and therefore can detect acid and, more rarely, alkaline reflux into the lower esophagus. The duration of monitoring is variable according to the information required.

The Tuttle test (acid reflux test) was originally used in adults and has been modified for pediatric patients [25]. It involves the instillation of 300 ml of 0.1 N HCl/1.73 m<sup>2</sup> into the stomach to ensure a low gastric pH. A pH probe placed about 3 cm above the LES measures changes in esophageal pH, which is monitored for about 30 minutes. The test is positive when more than one episode of reflux (pH < 4) occurs in 30 minutes, or when a single episode lasts for more than 30% of the monitoring time. Unsweetened apple juice may be used instead of HCl. The test is simple, and accuracy may reach 85% [25]. As with any test, false negative and false positive results can occur.

The Tuttle test monitors esophageal pH for brief periods and produces high false-negative results. Monitoring esophageal pH for three to six hours has therefore been suggested. The variables that are usually analyzed are: the number of reflux episodes (pH < 4.0), their duration, the number of episodes more than five minutes long, the duration of the longest episode, and the percentage of time the pH is less than 4.0. The method remains relatively simple, and when performed on fasting,

supine, sedated patients, it is sufficiently accurate to diagnose reflux in most cases [26].

Extended or prolonged monitoring of esophageal pH is usually performed continuously for 18 to 24 hours [27]. The pH probe is placed in the same way as for the acid reflux test, and the variables analyzed are the same as those for the shorter tests. The more prolonged study time also permits recording of other events, such as the position of the patient, sleep or waking state, meals and administration of drugs, all of which may affect the number and duration of reflux episodes [28,29]. Furthermore, the relationship between reflux and other disorders, such as apneic and bradycardic episodes and sleep disturbances, may be defined by this method, in conjunction with other polysomnographic studies [30,31]. The need to hospitalize patients for performing extended pH studies has been obviated by the recent development of portable pH recorders that are programmed to measure pH levels every one to sixty seconds with a built-in event marker. Recent studies have indicated age-related differences in the variables obtained from the test. Younger infants tended to have fewer and shorter episodes of reflux, with a gradual increase with increasing age [28]. Other studies have shown that the frequency and duration of reflux episodes when patients are upright or awake are similar for patients with GER and controls. During sleep (recumbent position), significant differences are demonstrable [32]. Further studies on portable pH monitoring are needed to define the normal range of pH parameters for ambulatory infants and children, and the relationship of GER to associated disorders.

Esophageal manometry measures the pressures generated by the esophageal musculature using perfused catheters that are introduced into the stomach and pulled out slowly. Despite earlier technical difficulties, this test, especially when coupled with pharyngeal electromyography, gives valuable information on the function of both the lower and upper esophageal sphincters, as well as the motility of the esophagus. The position and pressure of the LES can be defined in the resting state and during deglutition. However, motility disorders may be the cause or the result of GER. Therefore, esophageal manometry, though not considered a diagnostic test for reflux, is a useful

adjunct in the evaluation of these patients [33].

Endoscopy and biopsy are also used in the diagnosis of GER. The principal advantage of endoscopy is the demonstration of esophagitis that frequently complicates GER. The fact that peptic esophagitis can occur without gross endoscopic findings indicates the necessity for biopsies, even though the mucosa may appear normal [34].

In the Bernstein test, saline and 0.1 NHC1 are alternately administered to the esophagus by drip through a nasogastric tube. The patient, who does not know which solution is being infused, is asked whether he or she feels any symptoms, usually heartburn. The study is of limited value in infants and children who are unable to describe symptoms. Its greatest value, in older children and adults, is the ability to demonstrate the association of atypical symptoms and GER and to differentiate esophageal pain from other causes of chest pain.

#### Therapeutic Methods

Although LES pressure is not clearly modified by positioning, esophageal pH studies have demonstrated significant variation with position. The number of episodes and the percent time of the episode are more important in the wakeful than in the sleeping state. Furthermore, in the awake state, the number of reflux episodes was found to be less frequent in the upright than in the recumbent position [32]. Moreover, it is generally accepted that the prone position is more effective than the dorsal position, probably because it facilitates gastric emptying. Therefore, positioning in ventral decubitus (prone position) with a 30- to 45-degree inclination angle, 24 hours a day, is recommended for the success of postural therapy [35].

With regard to the dietary measures, recent studies have indicated that the efficacy of adding a thickening agent, such as rice cereal, to infant feeds varies from unpredictable to beneficial. However, it is generally accepted that thickening the infant's liquid meals with cereal is not only harmless but also provides more calories in the diet. Small, frequent feedings avoid overfilling of the stomach. In older children, reduced intake of fat and chocolates and avoidance of exposure to tobacco smoke are based on the adverse effects of these factors on the LES pressure.

Drug therapy represents an additional approach to the medical treatment of GER. Antacids neutralize hydrogen ions in the stomach and protect the esophageal mucosa from the effects of acid reflux. These drugs are effective in the treatment of esophagitis and relief of heartburn. The presence of simethicone, dimethicone, or alginates may be additionally protective [36,37]. The usual dose of aluminum and magnesium compounds is 30 to 60 ml/1.73 m<sup>2</sup>/day.

H<sub>2</sub> antagonists, such as cimetidine inhibit gastric acid secretion and therefore may help in the treatment of esophagitis [38]. The usual dosage is 30 to 40 mg/kg/day. The drug has potentially serious side effects, however, and should not be considered for prolonged use in children. Newer, more potent H<sub>2</sub> blockers, such as ranitidine and famotidine, with reportedly fewer side effects, might replace cimetidine in the treatment of esophagitis.

Prokinetic agents are also used in the treatment of GER. Metoclopramide is a dopamine antagonist. It increases the LES pressure, increases the amplitudes of smooth muscle contractions, and coordinates gastric, pyloric, and duodenal muscle activity [39,40]. The usual dosage is 0.3 to 0.5 mg/kg/day. However, the drug has been associated with serious side effects such as methemoglobinemia in young infants, extrapyramidal syndromes, sedation, dizziness, and restlessness.

Unlike metoclopramide, domperidone does not readily penetrate the central nervous system and therefore is less likely to cause extrapyramidal side effects. The prokinetic actions of domperidone are, however, similar to those of metoclopramide. Domperidone is considered more potent but with fewer side effects [41,42]. The usual dosage to achieve a prokinetic effect is 0.3 to 1 mg/kg/day.

Bethanechol is a stable choline that is not hydrolyzed by acetylcholinesterase. It increases the LES pressure, but its action appears to be related more to improved esophageal motor activity and clearance, rather than increased LES or gastric emptying [43]. Studies in patients with reflux indicate that this drug is effective in decreasing the frequency and duration of reflux episodes. However, a recent study comparing bethanechol and aluminum hydroxide found that

both drugs are equally effective in reducing the number of reflux episodes and clinical symptoms [44]. The average oral dosage is 0.6 mg/kg/day, divided into three doses. Side effects may include headache, abdominal pain, and increased blood pressure.

Cisapride is believed to affect gastrointestinal function through indirect cholinergic mechanisms without interfering with dopamine receptors [42]. When used in patients with GER, the drug was observed to not only decrease all esophageal pH monitoring parameters but also improved esophageal peristalsis, leading to improved clinical symptoms [42]. The usual oral dosage is 0.2 mg/kg, given three to four times daily. Side effects include abdominal cramps, diarrhea, disorders of appetite, and somnolence.

### Surgical Therapy

The most commonly used surgical technique is the Nissen fundoplication, followed by Thal fundoplication and gastropexy. Pyloroplasty alone or in combination with fundoplication may be required in some patients who have marked delay in gastric emptying [45]. The outcome of surgical therapy is excellent. Reflux is cured in about 95% of cases, and mortality varies from 0 to 0.5%. Surgery is less effective in mentally retarded patients with GER, however, and most deaths occur in patients who have additional high-risk factors such as prematurity or congenital heart disease [46,47]. In addition, the complications of surgery, including the gas bloat syndrome, are very rare.

### General Approach To Treatment

Although the natural history of GER indicates that the condition of most infants improves with age, spontaneous recovery is impossible to predict. Therefore, all patients with significant GER should be treated. Except in the event of life-threatening manifestations, an adequate trial of medical treatment should be given, consisting of postural therapy with the patient in the prone position at a 30-degree caudal inclination for 24 hours a day, thickening of liquid feeds with dry rice cereal, and the use of a prokinetic agent. This regimen should be followed for six to eight weeks. Antacids and H<sub>2</sub>

blockers should be reserved for patients with esophagitis, although some practitioners routinely prescribe antacids. The duration of treatment in patients who respond is controversial. We recommend continuing the same regimen for an additional two months, then decreasing the intensity of treatment, especially postural therapy, which is difficult to enforce as infants grow. If there is no improvement after an adequate trial of medical therapy, the patient should be re-evaluated and surgical therapy considered.

Surgery, without a prior trial of medical therapy, is indicated in patients with hiatal hernia and reflux. It is also recommended for infants with acute life-threatening complications, once the causal relationship between GER and such complications (apnea, near-miss sudden infant death syndrome) is established. In addition, surgical repair should be performed in patients with esophageal strictures, older infants with peptic esophagitis, patients with neuropsychiatric manifestations, and all patients who do not respond to medical therapy.

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