LITERATURE REVIEW

Gastroesophageal Reflux (GER)

by

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Abstract.

Gastroesophageal Reflux (GER) is one of the most frequent congenital gastrointestinal tract anomalies. The anatomy and physiology of lower esophageal sphincter (LES) is adapted to prevent reflux in normal infants and children. Vomiting is the most common symptom with following complications: failure to thrive, aspiration penumonia, esophagitis and strictures.

GER is thought to be associated with other diseases such as Sandifer syndrome, rumination and sudden infant death syndrome (SIDS).

Upper gastro intestinal series (UGI series) is the most common and simple diagnostic test in GER.
Management should start with medical therapy such as positional therapy, dietary consideration, and drugs. For non responders, surgical intervention must be considered.
In the absence of therapy approximately 60 – 65% of cases will be free of symptoms up till 2 years of age. About 5% of cases will die because of pneumonia and severe malnutrition.

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Introduction.

Gastroesophageal reflux is defined as dysfunction of the distal part of esophagus causing frequent regurgitation of stomach contents into the esophagus (Herbst, 1981). Carre (1979) estimated the incidence of GER to be 20 : 10.000 live births. Now, GER may be recognized as one of the most frequent congenital gastrointestinal tract anomalies in children. GER is seen more frequently in England than in the United States. The frequency was approximately 20-fold greater in Great Britain, probably because of differences of diagnostic criteria and radiologic techniques. The terminology of the condition is confusing. In older literature the term chalasia was often used and discribed the free passage of gastric contents into the esophagus without evidence of a functioning sphincter. Carre (1979) used the term partial thoracic stomach (PTS), even though GER might occur without evidence of PTS. The term congenital short esophagus is a misnomer.

Other terms are gastroesophageal incompetence, cardioesophageal relaxation.

This paper presents the clinical manifestation, diagnosis and management of GER.

ANATOMY AND PHYSIOLOGY OF THE DISTAL ESOPHAGUS (Carre, 1979; Herbst, 1981). The esophagus develops from the primitive fore-gut, lenghtening and seprating from the trachea between the 3rd and 6th intrauterine week. The function of the esophagus is to transport fluids and solids to the stomach and to prevent regurgitation. The distal end of the esophagus consists of loose areolar tissue, surrounded by circular smooth muscle, and is called lower esophageal sphincter (LES). Usually the LES is partially in the abdomen. This sphincter is usually connected to the diaphragm by several ligaments, called phrenoesophageal ligament (Fig.1).

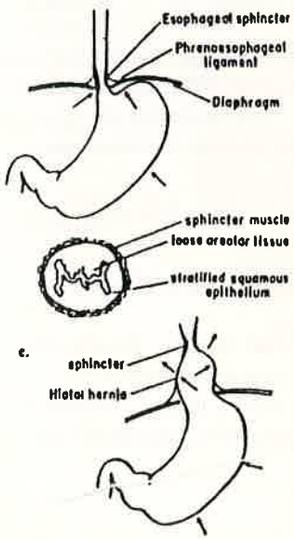

Fig.1.a. A diagram of the normal position of the lower esophageal sphincter.
b. A cross section of the area of the lower esophageal sphincter. c. The posisiton of the sphincter in a patient with hiatal hernia. (Herbst J.J. : Gastroesophageal reflux, J. Pediatr. 98 : 860 1981)

Several factors that may contribute to prevention of reflux are :

1. Pressure generated by the muscles composing the lower esophageal sphincter;
2. Mechanical choke valve. The mechanism is produced by the LES surrounded by circular smooth muscle. The advantage is that small changes in the length of muscle fibres (contraction) can influence the LES, enabling rapid opening and closing of the sphincter;
3. Flap valve mechanism, caused by the esophagus entering the stomach at an angle so that the pressure of gastric contents can help apply pressure on the LES and aids in closing the sphincter;
4. With part of the sphincter in the abdomen, increased abdominal pressure in pushing gastric contents into the esophagus is counteracted.
   This is important because, if there is a hiatal hernia the sphincter is surrounded by negative intra-thoracic pressure, so that with increasing intra abdominal pressure, the sphincter is easier to open. Reflux of food depends upon the difference between intra stomach pressure and intra thoracic pressure. Normally the difference is about 5 – 1 5 mmHg.
5. Anchoring by the phrenoesophageal ligaments.
   These factors are interrelated; the relative importance of each factor may differ from age to age.

Clinical Manifestation.

I. Asymptomatic

II. Symptomatic

a. General : vomiting; failure to thrive: pylorospasm; aspiration and airway diseases; esophagitis; hematemesis and melena; anemia; stricture;
b. Special : Sandifer syndrome; rumination; neuropsychiatric symptoms; sudden infant death syndrome (SIDS);

Less than 10% of cases are without symptoms. In these case GER is found by chance during barium studies undertaken for other reasons (Anderson and Bruke, 1975).
In infants and children, vomiting is the most common symptom and is seen in over 90% of cases. In 80% of patients studied, vomiting started within the first week and in another 10% between the first and sixth week of life.
Only in 1% is the onset of vomiting delayed until after 12 months of age (Carre, 1979). Vomiting is usually projectile in infants. Children always exhibit chronic night vomiting, an occasional brown staining of the vomitus due to blood is a characteristic feature. Dehydration may occur because of frequent vomiting. Loss of ingested calories may result in weight loss or failure to thrive. The vomiting can be associated with pylorospasm. Stimulation of the vagal nerve at the level of the esophageal hiatus causes pyloric contraction in dogs. Vagal stimulation caused by esophageal inflamation may also cause pylorosphasm. Hypertrophic pyloric stenosis and GER may coexist, but their relationship is still unclear (Carre, 1979).

If gastric contents ascend to the pharynx, they may be aspirated and cause respiratory symptoms. The infant and child with chronic night vomiting are more likely to develop

severe respiratory symptoms. The symptoms may mimic those of allergic bronchitis or bronchial asthma. However the finding of airway disease and GER does not confirm a causal relationship. Christie et al. (1978) suggest that GER should always be considered in pediatric patients with recurrent respiratory disease.

Reflux of gastric acid into the esophagus may lead to esophagitis. Blood loss from the inflamed tissue may cause iron deficiency anemia, melena, or hematemesis. Chronic inflamation may lead to formation of esophageal strictures. Strictures and esophageal spasm can make swallowing of food extremely painful or impossible (dysphagia). GER is common in patients with other disorders (Herbst, 1981; Sondheimer and Morris, 1979) such as tracheoesophageal fistula. The incidence of low birth weight among babies with GER is about twice the expected frequency. This increased incidence in low birth weight appears to be unrelated to complications of pregnancy or to the high rate of associated congenital anomalies (Roy et al., 1975).

GER can also cause Sandifer syndrome which consists of head cocking, iron deficiency anemia and severe reflux. This syndrome usually disappears after the GER have been corrected by operation. The mechanism of head cocking is unknown, but it has been suggested that it serves for the relief of pain or to prevent reflux into the esophagus or into the mouth (Herbst, 1981).

Rumination is considered a psychiatric disease of infancy. The hallmarks are thrusting motions of the tongue, arching of the neck, and repetitive reswallowing of refluxed gastric contents as in ruminating animals. According to Boix-Ochoa (1979), however, psychologic factors are not important. Instead he hypothesized that rumination is due to dysfunction of the brain and GER. Pneumonia is a major problem and cause of death in rumination. Correction of GER can cause a dramatic cure.

GER should always be considered in patients suffering from neuropsychiatric syndromes with the symptoms of dysphagia, retardation, irritability, convulsion and other psychiatric symptoms (Bray, 1979).

According to some workers GER is a precipitating factor in SIDS, based on studies of "near miss" SIDS (Herbst et al., 1978; Leape, 1979); the mechanism of SIDS produced by GER is still unexplainded. Apnea can also caused by GER (Ariagno et al., 1982; Herbst et al., 1979; Walsh et al., 1981).

Diagnostic tests.

Many tests have been used to evaluate GER in children such as upper gastro intestinal series (UGI series) lower esophageal sphincter pressure; acid reflux test (Tuttle test); esophagoscopy; radionuclide gastroesophageal scintigraphy; esopphageal biopsy; gastric emptying time.

A careful and detailed history or observation of the child during and after feeding is extremely valuable in assessing the need for diagnostic evaluation (Herbst, 1981).

(1) UGI series is one of the diagnostic test most frequently performed. Reflux of barium from stomach to esophagus is easily seen at fluoroscopy, and at the same time, we can gain information on the swallowing mechanism, PTS/hiatal hernia, esophagitis, stricture and the possible presence of pyloric stenosis or other types of partial intestinal obstruction. Specific protocol and criteria for diagnosis is very necessary (Mc. Cauley, 1979) . Some radiologists are reluctant to make a diagnosis of reflux because occasional reflux can also be seen in normal patients. There are many differences of opinion between radiologists to make the diagnosis, caused by several reasons. A major error in this UGI series test is that insufficient amounts of barium are often used. It is better to use quantities similar to that taken in a normal feed (Herbst, 1981).

Mc. Cauley (1979) put forward the following protocol : before performing this test, fluid or food must be restricted for babies, children should fast; excessive movement of the infants must be prevented by fixing the arms and legs. With the child lying down, barium is given in a quantity similar to that taken in a normal feed for each age; the infant is given barium by bottle and the child by cup; a naso gastric tube can also be used. Fluoroscopy should be performed from the beginning of intake of barium, to observe the larynx and upper part of the esophagus, aspiration from the beginning of swallowing, and thereafter to evaluate esophageal peristalsis and regurgitation during swallowing. After taking one third of the total amount of the barium, the stomach and duodenum X-Rays must be performed to evaluate pyloric stenosis or intestinal malrotation; the child is now instructed to sit and the rest of the barium should be given. The child lies down again. Fluoroscopy is done on the gastroesophageal junction, the left posterior or right anterior oblique position is used; reflux can then be seen in time and if the maximum reflux occurs X-Rays must be performed. If there is no reflux within 2 – 3 minutes, the baby is given a nipple to produce swallowing movements and reflux; if GER is absent, hiatal hernia should be excluded by giving thickened barium. Do not manipulate the abdomen. The last step is clearing the esophagus of the barium (by giving water), wait 3 minutes and repeat X-Rays; the finding of barium in the esophagus can denote the presence of delayed reflux.

With the method GER can be classified into : (1) = reflux of barium reaching distal esophagus only; (2) = reflux extending above the carina but not reaching the neck of the esophagus; (3) = reflux of barium reaching the neck of esophagus; (4) = reflux of barium reaching the neck of esophagus and associated with dilatation of cardia; (5) = reflux of barium and aspiration into the the trachea and lungs; D = delayed reflux.

Grade 1 – 2 is called minor reflux and grade 3 – 5 is called major reflux. This grading is consistent with the severity of the clinical manifestation. GER is abnormal if it occurs frequently.

Jeffery (1983) classified GER based on flouroscopy finding as follows : severe: reflux of barium reaching the pharynx; moderate : reflux of barium reaching the middle or upper of the esophagus; mild : reflux of barium reaching the distal part of the esophagus only.

Usually with a careful and detailed history and the result of UGI series, the diagnosis can be confirmed. Other tests are useful when there are discrepancies between the clinical history

and interpretation of the UGI series or if surgical therapy is considered.

(2) Measurement of the LES pressure is another diagnostic test. This diagnostic test is more difficult to perform. At present, the LES pressure is measured with tiny pressure tranducers in the probe, or the probe is a catheter that is constantly perfused with water and connected to a pressure-sensing device external to the patient. Pressure being measured in the midrespiratory state (Arasu et al., 1980; Herbst, 1981). The value of this test is still in debate. Recent reports indicate a very promising result. Normal LES pressure does not exclude GER. Low or very low pressure can be associated with GER (Herbst, 1981; Worlin et al.,1980).Very low LES pressure is often associated with esophagitis, so that measurement of LES pressure is more useful for adults than for children; this is because esophagitis is rare in children. It seems that LES pressure is not useful in the diagnosis or prognosis of GER in a child (Boix - Ochoa, 1979).

(3) The acid reflux test (Tuttle test) is a simple diagnostic test. At present this test is a reasonable choice, and it has been shown to be sensitive. The principle of the acid reflux test is based on changes of the esophagus pH due to reflux of acid from stomach.Through a nasogastric tube 300 cc/1.73M2 0,1 N HCL is infused into the stomach; the tube is pulled out and a Beckman Cecar electrode positioned in the stomach about 3 cm above LES under flouroscopy control
The esophageal pH is monitored for a minimum of 30 minutes and spontaneous reflux is defined as a drop in pH to less than 4. Two or more episodes of reflux are considered abnormal. Experience indicates this procedure to be sensitive enough and correct in 85% of cases (Arasu et al., 1980; Herbst, 1981).
A better diagnostic test is continuous monitoring of the distal esophageal pH with a similar method during 18 – 24 hours. This establishes the frequency and duration of reflux in the upright and supine position during waking and sleeping in a 24-hour period. Discrimination of normal infants from infants with reflux is best done in the 2 hours post feeding period (Herbst, 1981; Johnson, 1979; Sondheimer, 1980). Reflux can be graded based on its frequency as follows (Jeffrey et al., 1983): mild : 40 – 70 times / 24 hours; moderate : 70 – 100 times / 24 hours; severe : more than 100 times / 24 hours. The disadvantage of this test is that the patient must be hospitalized.

(4) Esophagoscopy provides a direct visual method of detecting gross esophagitis, strictures or large hiatal hernia. The absence of macroscopic changes in the esophageal epithelium at endoscopy can not be used as evidence for the absence of GER; some of the more subtle and early changes can be seen only in histologic sections (Herbst, 1981).

(5) Recently radionuclide gastroesophageal scintigraphy has been performed. A radioactive compound usually Technetium 99m with a cow's milk formula was given to the child. The amount of radioactive reflux could be counted. Radioactivity in the lungs denote that aspiration has occured.

(6) A biopsy of the esophagus is frequently obtained at the time of esophagoscopy. The findings reveal an increase in the basal (proliferative) layer of the stratified squamous epithelium and lengthening of dermal pegs (Herbst, 1981).

(7) Hillemeir et al. (1981) showed that there is a delayed gastric emptying time in infants with GER. They suggest that an inability of the fundus to generate sufficient tone for an adequate gastroduodenal gradient may retard gastric emptying. Further studies are indicated for the diagnostic value of this test (Hillemeir et al., 1981).

In most cases the UGI series will be the first test ordered because it is easily available and can easily confirm the presence or absence of a number of structural disorders that may cause symptoms suggestive of GER. If the history and UGI series are at variance, or if surgical intervention is contemplated, it is reasonable to use one or several of the other tests to confirm the diagnosis. Beside UGI series, the acid reflux test is a reasonable choice, because it is rapid and simple to perform.

Therapy.

I. Medical therapy :
   a. Positional therapy; b. Dietary consideration;
   c. Drugs.

II. Surgical therapy.

(1) Positional therapy is based on the notion that if the esophagus and stomach be kept upright, it will prevent reflux of stomach contents to the esophagus. Many kinds of positions are suggested. However sitting the child upright for a few minutes after feeding or arising the head are both not effective. Carre (1979), advocated the use of special chairs with inclined planes of 60 degrees maintained for 24 hours except during meals or change of napkin. This should be continued for 6 months or 6 weeks if the symptoms disappear. Usually, 50% of cases are cured. If there is no improvement after 3 months surgical therapy is then indicated (Carre, 1979). Strict positional therapy for 24 hours a day in small children is easy to achieve but for those exceeding one year of age, it is more difficult. Herbst (1981), suggested to place the child prone on an inclined plane of 30 degrees with the child astride a padded peg to keep him from slipping. One advantage of the prone position over the supine is that the esophago-gastric junction is then at the most superior part of the stomach (Herbst, 1981).

(2) Dietary consideration is based on the fact that GER can occur if there is an overfilled stomach, so that small, frequent feeding are recommended. Some authors advocate thickened feedings be given. However there is no evidence of the efficacy of both measures. Some foods can increase or decrease the LES pressure. Protein can increase, while fat decreases the LES pressure. This could probably be due to inhibition of phosphodiesterase making cyclic AMP nonactive. Therefore, limitation of fat and chocolate can help decrease GER (Anderson and Bruke, 1975; Byrne and Ament, 1979; Herbst, 1981).

(3) Many drugs such as antacids, cimetidine, metoclopramide and bethanechol are used in the treatment of GER in adults. Antacids can decrease pain due to gastric acid, but the frequency and duration of reflux are not diminished. Side effects of antacids are diarrhea, depression of the central nervous sys-

tem, constipation and osteomalacif. Cimetidine, a histamine H_2 antagonist, reduces gastric acid secretion in peptic ulcer.

Experience of this drug in children is very limited. The dosage is 20 – 40 mg /kg/BW/day. Cimetidine can cause confusion, other central nervous symptoms and bone marrow depression. Methoclopramide is used in adults for reducing symptoms. The doasage for children is : 0,5 – 1 mg/BW/day. Extra pyramidal signs may occur (Byrne and Ament, 1979;Herbst, 1981).

Bethanechol is a cholinergic agent that stimulates the parasympathetic system improving smooth muscle tone. Bethanechol can reduce the frequency and duration of reflux. It may be due to an increase of LES pressure and improvement of peristalsis. It increases the body weight after GER has been corrected. A dosage of 8,7mg/M2/day devided in three doses had been tried (Euler, 1980). Side effects of Bethanechol are abdominal discomfort, flushing of the skin and salivation. This drug should be cautiously used in cases of strictures of the esophagus and in bronchial asthma. This drug can be used in severe cases or if the patient is not responding to other medical therapy. The therapeutic period is about 3 – 4 months, and once the symptoms have been controlled for 4 6 weeks, it in reasonable to decrease the dosage gradually

(4) Surgical therapy is generally agreed upon for patients uncontrolled by medical therapy or indicated for patients who have severe, life-threateneing complications such as choking, aspiration, or recurrent apnea, or in patients with esophagitis and strictures (Herbst, 1981) The most frequent surgical operation in children are gastropexy (Boerma) and fundoplication (Nissen) (Fig.2). A

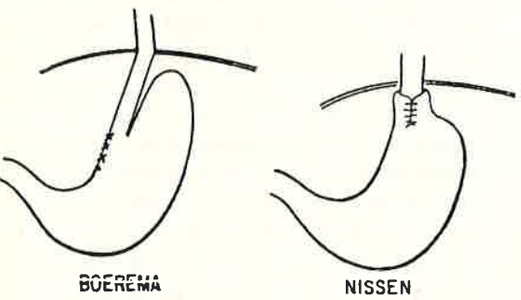

Fig. 2. A diagram of antireflux operations. (Johnson D.G. : Conservative surgical management. of reflux strictures of the esophagus in children.
Report of 76th, Ross conference on Pediatric Research p. 104, Ross Laboratories, Ohio, 1979).

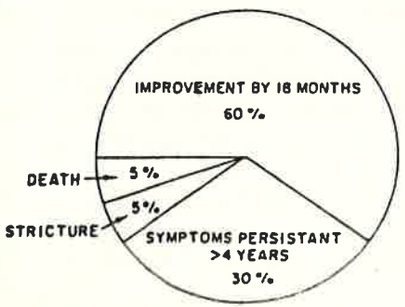

Fig. 3. Natural history of GER in children. (Adapted from data of Carre by Herbst J.J. : Gastroesophageal reflux, J. Pediatr. 98 : 861, 1981).

gastropexy will improve the esophagogastric angle and lengthen the esophageal segment in the abdominal cacity. In fundoplication, the fundus is wrapped around the distal esophagus. A gastropexy will correct 81% of cases, and a fundoplication 96% of cases. A disadvantage of gastropexy is that it is impossible to perform in severe inflammation or shortening of esophagus. The result of Boerma and Nissen operation in children is better than the result in adults (Harnsberger, 1983). The result of operation in mental retardation with GER is worse than without mental retardation, with presistence of respiratory symptoms in 41% of cases (Jolley et al., 1980).

Wilkinson (1981), compared the results of medical and surgical therapy in severe mentally retarded children with GER.

The results of medical therapy in severe mentally retarded children is less than in children without mental retardation. Surgical treatment eventhough with high risk, has shown similar results in both group of children (Wilkinson et al., 1981).

Prognosis.

Without treatment 98% of cases will have symptoms before 3 months of age. Approximately 60–65% of them will improve after starting solid food; the symptoms will disappear at approximately 2 years of age. This group can be expected to follow a relatively benign clinical course. Of the children who experience no clinical improvement at the time of weaning, the majority (or approximately 30% of all patients) are likely to suffer from troublesome symptoms up to 4 years of age without developing esophageal strictures. In a minority (estimated at about 5% of all patients) a stricture is likely to develop in the absence of beneficial therapy (Carre, 1979). In the absence of therapy, approximately 5% will die, usually of pneumonia and severe malnutrition. (Fig.3). Surgical intervention is needed in a small population only.

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