CLINICAL AND DIAGNOSTIC ENDOSCOPIC ASSESSMENT OF GERD AND COMPLICATIONS

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Gastroesophageal reflux (GER) is a process in which gastric contents move spontaneously into the osephagus. This process in itself is for the most part benign in that it occurs in everyone, many times a day and without producing symptoms and signs of tissue injury. Gastroesophageal reflux disease (GERD) is defined as chronic symptoms or mucosal damage produced by the abnormal reflux of gastric contents into the esophagus. GERD denotes abnormality and so should not be confused with the gastroesophageal reflux that occurs in healthy subjects (physiologic reflux), which does not couse symptoms or mucosal injury. Reflux esophagitis refers to a subgroup of GERD patients with histopathologically demonstrated changes in the esophageal mucosa (1,2,3).

Quantitative estimates of the actual prevalence of GERD are difficult to obtain because most of the patients with heartburn have intermittant symptoms which they do not consult their physician and they frequently take over-the counter medications. Those with more persistent symptoms are more likely to see a physician for advice, with a small percentage of symptomatic individuals (probably 10% or less) represents just the tip of the GERD ' iceberg'. In fact, heartburn is a problem affecting approximately 40% of the adult population and the popular concepts that heartburn occurs daily in approximately 10% and monthly in 20% of adult population. Of all ethnic groups, caucasians demonstrate the highest rates of GERD. GERD is less commonly seen in the Asia-Pacific region. Furthermore, erosive esophagitis is usually milder in Asia and complications such as esophageal stricture, Barrett's esophagus and esophageal adenocarcinoma are exceedingly rare.

Fass and Ofman proposed a new concept for reflux disease and postulated that there are three different phenotypes, namely non-erosive reflux disase (NERD), erosive reflux disease (ERD) and Barrett's esophagus (M-GERD, metaplasic GERD) (5). Endoscopy negative reflux disease or nonnerosive reflux disease (NERD) is characterised by the presence of GERD symptoms but without endoscopically visible breaks (erosions or ulcers) in the esophageal mucosa. It is not a mild disease, but is in reality a chronic, relapsing disorder that adversely affects in quality of life of patients (6,7,8). Patients with NERD are more commonly females, usually leaner, report a shorter symptom duration and have a lover incidence of hiatus hernia compared with patients with erosive esophagitis. They are frequently poorly responsive to PPI therapy (9). There are very limited but increasing evidence of progression from NERD to erosive esophagitis in the literature. Some recent data support the concept of a single spectrum disease. Long-therm follow-up by Pace and colleagues of 33 patients with endoscopy-negative patients with pH-metry confirmed reflux disease revealed the chronic nature of the disorder and showed that some patients with NERD undergo progression to erosive esophagitis (10). After 10 years, only 3% of these patients were symptom free, and symptoms were moderate or severe in 67%. Of the 17 patients who underwent repeat endoscopy within 5 years of the initial diagnosis, 16 (94%) were found to have erosive esophagitis. These evidence supports that NERD may be a milder form of histopathologic injury that can evolve into a macroscopic injury. Transition between one stage and another may be dependent on a transition factor which are not present in the majority of patients. These transition factors is likely to revolve around the transforming power of inflammatory process, a process which is highly dependent on host genetics, and that determines who remains with non-erosive disease and who migrates over to

the erosive form of esophagitis (11). In a recent study (UK General Practice Research Databease of GERD diagnosed in general practice), it has been shown that there is a progression from uncomplicated GERD to complicated GERD. Among patients initially diagnosed with uncomlicated GERD, the incidence rate of complicated GERD was 3.5 per 1000 person-years (95% confidence interval 2.8-4.4), compared with 0.3 per 1000 person years (0.2-5.7) in controls. Adjustes relative risk of progression to complications was 13.4 (6.9-26.2) for the GERD cohort compared with controls (12). These findings suggest that GERD is a progressing disease.

Clinical presentation

Clinical presentations of GERD may vary considerably but can be put into three categories; typical symptoms, atypical symptoms and complications.

Typical symptoms

Heartburn is the cardinal symptom of GERD and is believed to be caused primarily by the noxious effects of an acidic refluxate on damaged esophageal epithelium. When the esophagial damage occur by exposure to gastric contents it is typically realised by the development of heartburn. Heartburn can be defined by the presence of substernal discomfort or pain, usually burning in quality, that starts at the epigastrium and radiates towards the mouth. Heartburn generally is worse following meals and with reclining or lying down in bed at night, especially by lying down in bed to the left and is relieved by antacids or other therapies that inhibit gastric acid secretion, such as proton pump inhibitors (PPI). There are some clear relationship between symptoms and certain foods. Heartburn and regurgitation may also be experienced during sexual intercourse (reflux dyspareunia) (13). Heartburn not relieved adequately after at least 4 weeks of therapy with a standart dose PPI is considered refractory heartburn. (14).

Although heartburn is strongly associated with the diagnosis of GERD, many patients with GERD have less spesific presentation, such as epigastric pain or other dyspeptic symptoms with heartburn and the majority of patients will have a normal endoscopy. Almost fifty percent of patient with GERD do not have endoscopic findings of esophagitis and symptom pattern or severity does not predict its the presence or absence (15). Using of an adequate PPI dosage and compliance with therapy are essential for the successful control of symptoms but accurete diagnosis is also important as GERD is not always responsible for symptoms. The development of combined impedance and pH monitoring and prolonged ambulatory pH monitoring systems have made it possible to detect almost all reflux episodes. Data from a multicenter study using multichannel intraluminal impedance and pH (MII-pH) showed that only 20% percent of patients with persistent symptoms on twice daily PPI therapy have symptoms associated with acid reflux. In the remaining 80% , half of these patients had symptoms associated with non-acid reflux while the other half of the patients had no reflux and no relationship between non-acid reflux and sypmtoms, and in such patients PPI therapy in unlikely to be successful (16).

It should be borne in mind that patients with peptic ulcer disease, gastric cancer and delayed gastric emptying may present with heartburn. Furthermore, sudden and isolated heartburn may be caused by pill induced esophagitis or corrosive injury.

Atypical symptoms

GERD is a complex condition presenting with many different symptoms and clinical features. In a recent study designed in a cohort of larger than 6000 patients it has been sown that approximately a third of patients with erosive reflux disease and NERD had extra-esophageal manifestations, namely cough, asthma, laryngeal manifestations or non-cardiac chet pain (17).

Angina like chest pain (Non-cardiac chest pain, NCCP) is an atypical symptom with multifactorial pathogenesis, including GERD, visceral hypresensitivity, motility disorders and psychological factors. Ambulatory ph monitoring studies indicate that previously unrecognised GERD is a major cause of noncardiac chest pain (18,19). Using the PPI test, it is possible to predict with reasonably high specificity (approximately 86%) and sensitivity (approximately 78%) which patients with NCCP will respond to acid-suppressive therapy, avoiding the use of a variety of costly diagnostic evaluations (20). The acccuracy of PPI therapy as a diagnostic test for NCCP has also been confirmed by a meta-analysis (21).

Various pulmonary symptoms may be associated with GERD. Nocturnal episodes of nonallergic asthma are highly suggestive of reflux disease. Intraesophageal pH monitoring studies have showed abnormal amount of reflux in more than 20% of patient with chronic cough and more than 80% of unselected patients with chronic asthma (22,23). Diagnostically it is some times difficult to determine which came first, the cough or the GERD. Clues to think about GERD as a factor in patients with asthma include : 1) Adult onset, 2) nonallergic, 3) poorly responsive to medical therapy, 4) nocturnal cough, and 5) increase in symptoms after meals, in the supine position. Results of meta analysis which were designed to understand the effect of anti-reflux therapy on asthma symptoms are controversial, but subgroups of patient with asthma may benefit , although it is difficult to predict responders. The most cost-effective strategy to assess for GERD as an exacerbating factor in asthma is a trial of a PPI daily for 3 months. (24,25).

Studies have implicated that GERD as an etiologic factor in 20% to 40% of patients with persistent cough, 55% to 80% of patients with difficult to manage hoarseness, up to 60% of patients with chronic laryngitis and sore throat, 25% to 50% of patients with laryngeal cancer. Unfortunately the history is usually not helpful to exclude the contribution of GERD to ENT symptoms , as over 50% of these patients will have no symptoms of GERD(26). The sensitivity and specificity of the direct laryngeal examination is unknown but ENT findings associated with GERD include edema and ertyhema of the vocal cords, edema, erythema and hypertrophy of the interarytenoid region, vocal vord ulcers and vocal cord granulamas. Unfortunately non of these findings is spesific for GERD. Prolonged pH monitoring is abnormal in approximately 54% of these patients irrespective of the location of the probe (27). Patients with a clinical profile highly suggestive of silent GERD as a cause of their cough are characterized by the following findings; 1) normal or nearly normal chest X-ray, 2) no smoking or exposure to environmental irritants, 3) no use of ACE inhibitors, 4) failure of cough to treatment of asthma and, 5) failure of cough to improve with treatment of postnasal drip syndrome (3). There are indications that lansoprazole may provide significant benefit to patients with reflux laryngitis. In general, patients with suspected ENT manifestations of GERD should be given a 3 months trial of a given twice daily.It has been suggested that chronic reflux injury may promote malignant change (28). Protracted hiccup, globus sensation, dental eresion, ear pain, night sweats and intermittant torticollis are another symptoms may be associated with GERD.

Diagnostic evaluation of GERD

The patient who presents with typical heartburn and regurgitation with the usual positional and postprandial relationships requires little additional information for diagnosis and initiate therapy. The patient whose symptoms are less clear or include atypical manifestations usually needs additional diagnostic testing. The critical question often is whether the patient has abnormal reflux, particularly in the patient with an atypical symptom pattern. Despite the fact hat GERD is a common clinical problem, there is no diagnostic gold standart for this disease. Classic symptoms of acid regurgitation and heartburn are spesific but not sensitive for the diagnosis of GERD as determined by abnormal 24-hour pH monitoring.

The variety of test available for patient evaluation may cause diagnostic confusion if not used appropriately. Diagnostic test for gastroesophageal reflux disease include PPI treatment result, endoscopy with and without biopsy, barium upper gastrointestinal series, ambulatory pH monitoring, impedance and pH analysis (MII-pH), esophageal motility evaluation and acid perfusion test (Bernstein).

It is reasonable to consider an empiric trial of antisecretory therapy in a patient with classic symptoms of GERD in the absence of alarm signs. A trial omeprazole (40mg in the morning and 20mg in the evening) has a sensitivity of 80% with a spesificity 57% in patients with GERD as documented either by endoscopy or pH monitoring (29). Further diagnostic testing should be considered in the following settings;

1- Failure ro respond to an empiric course of therapy
2- Alarm signs suggestive of complicated reflux disease such as dysphagia, odynophagia, bleeding, weight loss and choking
3- Chronic symptoms in a patient at risk for Barrett's esophagus
4- Patients requiring chronic therapy

Endoscopy is the technique of choice to evaluate the mucosa in patients with symptoms of GERD. Erosions or ulcerations at the squamocolumnar junction as well as the findings of Barrett's esophagus are diagnostic of GERD. Accurate description of endoscopic findings is essential in GERD. The term esophagitis is nonspesific and should not be used in endoscopy reports without description of the esophageal findings. Although numerous systems for the endoscopic grading of esophagitis are available, none is universally accepted. Examples of two different grading systems are shown below (3). The findings of minor changes of reflux disease such as erythema, friability and edema are so unreliable that these findings are not diagnostic of reflux disease Any patients with these findings should be considered to have endoscopy negative reflux disease (3).

LA classification of esophagitis
Grade A: $\geq$1 mucosal break <5mm long confined to the mucosal folds
Grade B: $\geq$1 mucosal break >5mm long confined to the the mucosal folds but not continious between the tops of 2 folds
Grade C: Mucosal breaks continious between the tops of 2 or more folds involving <75% of the esophageal circumference
Grade D: Mucosal breaks involving $\geq$75% of the esophageal circumference

New Savary-Miller endoscopic grading system
Grade 1: Single erosion or exudate; taking only 1 longidutinal fold
Grade 2: Noncircular multiple erosions or exudative lesions taking more than 1
      longidutinal fold, with or without confluence

Grade 3: Circular erosive or exudative lesion
Grade 4: Chronic lesions; Ulcers, strictures or short esophagus, isolated or
          associated with grades 1-3
Grade 5: Barrett's esophagus alone or associated with lesions grade 1-3

Although presence of a hiatal hernia in endoscopy is not characteristic for GERD, there is a well known fact that the prevalence of hiatus hernia varies between 30% and 90% in patients with GERD and the prevalence is much lower in patients with no reflux symptoms . It has beeen demonstrated that 96% of patients with long-segment (>3cm) Barrett's esophagus, 72% with short-segment (<3cm) Barrett's esophagus, 71% with erosive esophagitis and 29% with NERD have hiatus hernia (30).

Esophageal mucosal biopsy should be a more sensitive test of the presence of reflux injury because histologic abnormalities (presence of polymorphonuclear leucocytes and eosinophiles, bazal zone hyperplasia and increased papillary extension) may be present even when careful endoscopic examination indicates a normal appearing esophagus.

Prolonged ambulatory pH monitoring is considered the procedure of choice to demonstrate the occurence of abnormal acid reflux and define the relationship between spesific symtoms and reflux. This test has long been thought to be the gold standart for the diagnosis of GERD. However, test is normal in 25% of patients with erosive esophagitis and 33% of patients with NERD (31). Clinical indications include diffucult diagnostic problems or atypical reflux symptoms (chest pain, cough, hoarseness), nonresponse to therapy and preoperative and postoperative evaluation of antireflux surgery. Test is limited by the requirement that the patient's symptoms must occur during the test period. A wireless pH system (Bravo) is now available and provides 48 hours of recording instead of 24 hours. It is generally well tolerated with a sensitivity and spesificity of 100% and 85% for patients with endoscopic esophagitis and 57% and 85% for patients without endoscopic esophagitis (32).

Multichannel intraluminal impedance (MII) is a new technique for evaluating esophageal function and gastroesophageal reflux. This technique depends on changes in resistance to alternating current between two metal electrodes produced by the presence of liquid or gas bolus inside the esophageal lumen. Combined MII and pH measuring (MII-pH) allows detection of gastroesophageal reflux episodes irrespective of their pH values (i.e. acid and non-acid reflux) and refluxate clearence time. MII-pH testing brings a shift in the gastroesophageal reflux testing paradigm. It has started to become an important clinical tool, particularly to assess gastroesophageal reflux in the postprandial period and in patients with persistent symptoms on therapy and with atypical symptoms (33),(see atypical symptoms).

In many patients a key question is whether their symptoms are clearly related to acid exposure and sensitiviy of the esophageal mucosa and acide perfusion test (Bernstein) was used for many years with a reported spesificity and sensitivity of 80% in GERD. If the patient's symptoms are reproduced by 0.1N HCL and resolve following saline perfusion, it is appropriate to conclude that acid reflux is the cause of symptoms.

Measurement of LES pressure was previously suggested as a possible way to diagnose reflux disease. A pressure of less than 6mmHg correlates well with abnormal reflux on pH testing and very low LES pressure in this range are predictive of a more severe degree of reflux and worse prognosis. In addition to LES pressure, assessment of peristaltic activity of the esophagus may be informative in the evaluating reflux disease and its prognosis.

The barium esophagram has no role at present in routine evaluatin of GERD. This test demonstrates reflux in 25% to 75% of symptomatic patients and can be falsely positive in 20% of normal controls. However this technique may be useful prior to antireflux surgery to assess the size and reducibility of a hiatal hernia (3).

Complications

GERD can also present with the complications of reflux, such as erosive or ulcerative esophagitis, which may cause bleeding and anemia or peptic stricture which may cause dysphagia or Barrett's esophagus which may cause esophageal cancer. Other complications include involvement of the oropharynx, larynx and respiratory system, resulting in symptoms and signs termed extraesophageal manifestations of GERD (hoarseness, chronic cough, asthma, sleep disturbances, obstructive sleep apnea, etc.).

Peptic strictures may develop in 1% to 23% of patients with GERD symptoms. Uncomplicated acid reflux-related esophageal strictures are typically located at the squamocolumnar mucosal junction and are less than 1cm in lenght. A long history of heartburn with intermittent dysphagia for solids over a period of months to years without weight loss is typical for a benign peptic stricture. These patients are typically older and have long-standing GERD symptoms and severity of reflux symptoms decrease gradually with development of esophageal stricture. Lower esophageal rings (B rings- Schatzki) have a distinc anatomic appearence and similar presentation, but minimal or no heartburn. Barium radiograph is helpful in evaluating a narrow segmet. Once a true stricture has been confirmed, the challenge is to determine the etiology as benign or malignant by endoscopy, biopsy and cytologic examination. Early cases of reflux esophagitis with dysphagia may be due to inflammation and spazm rather than cicatricial narrowing and intermittant dysphagia and odynophagia may be a feature of GERD even when no stricture is present (34,35).

Severe chronic reflux may also induce metaplastic change of the squamous epithelium of the lower esophagus to columnar epithelium, referred to as Barrett's esophagus (BE). It is estimated that BE is found in approximately 6% to 12% undergoing endoscopy for symptoms of GERD and %1 or less of unselected patient populations undergoing endoscopy. The prevalence of long segment BE ($\geq$3cm) is approximately 5% whereas that of short segment BE (<3cm) is approximately 6% to 12% in patients undergoing endoscopy in a variety of settings(36). A study that examined the prevalence of BE in 556 patients without GERD symptoms undergoing screening colonoscopy found a prevalence of 0.36% for long segment BE and 5% for short segment BE (3,37).

Patients with BE are difficult to distinguish clinically from patients with GERD uncomplicated by a columnar lined esophagus. However, observational studies suggest that features such as the development of reflux symptoms at an earlier age, increased duration of reflux symptoms, increased severity of nocturnal reflux sypmtoms and increased complications of GERD, such as esophagitis, ulceration, stricture and bleeding may distinguish BE patients from GERD patients without Barrett's esophagus. Interestingly, similar clinical risk factors have been identified for esophageal carcinoma (1-3).

Endoscopic assesment of Barrett's esophagus

For the endoscopic description of BE, it can be classified as either long segment or short segment, depending on how far the squamocolumnar junction is located from the gastroesophageal junction. The concept of short segment BE makes the diagnosis of BE a bit more problematic. Diagnosing of short segment BE is difficult because the precise junction of the stomach and the esophagus can be difficult to determined endoscopically. An irregular Z-line may appear abnormal to one observer and normal to another. Biopsies from normal gastroesophageal junction may also reveal intestinal metaplasia,which is presumed to represent intestinal metaplasia of cardia. Routine histopathologic techniques are unable to distinguish between intestinal metaplasia orginating in the stomach, a normal

gastroesophageal junction or the cardia. Some studies suggest that chromoendoscopy can help direct biopsies in patients with suspected short segment BE. A variety of endoscopically apllied staining techniques are helpful in highlighting the squamo-columnar junction as well as accentuating patterns of intestinal metaplasia in the distal esophagus. Lugol's iodine, toluidine blue, indigocarmine and methylen blue are all different type of stains used for this purpose. Although not routinely required, their application is spesific circumstances can be useful to diagnose Barrett's esophagus.

Therefore, at the time of endoscopy, landmarks should be carefully defined: the diaphragmatic hiatus, EG junction and squamocolumnar junction. These landmarks document the presence of a columnar lined esophagus. Measurement of the nearest and farthest proximal limits of BE, relative to the distal limit (the gastroesophageal junction, GEJ), is a reasonable assessment of its extent. The proximal limit of linear gastric folds is the most practicable indicator of the GEJ in the presence of suspected BE in routine diagnostic endoscopic practice. The proximal limit of gastric mucosal folds is defined best as the most proximal point at which there is any evidence of lineer fold of gastric mucosa. This is best visualised when the esophagus is distended minimally to the point that the proximal ends of the gastric folds appear. In clinical practice, air must be properly deflated when we observe the gastric fold clearly by endoscopy. Excessive air deflation changes the position of the gastric folds (3).

The longidutinal esophageal palisade vessels, present in the mucosal layer of the lower esophagus, disappear into the submucosal layer at the GEJ and in some endoscopy units, the distal end of palisade vessels is considered to be endoscopic landmark of gastroesophageal junction. The palisade vessels, however, can be difficult to identify endoscopically, pariculary in BE where inflammation or mucosal dysplastic change may obscure them. In addition, the palisade vessels in the lover esophagus may merge with the larger gastric longidutinal vessels of the gastric mucosa in addition to penetrating deeply into the submucosal layer at the more distal level from the GEJ. These factors render the palisade vessels unsuitable as a landmark for the GEJ. Therefore , the gastric folds may be a better landmark of GEJ in the diagnosis of endoscopic BE (38).

If the squamocolumnar junction is above the level of the EG junction, biopsies should be obtained. If intestinal metaplasia is present, defined by goblet cells, the patient is considered to have BE and should be placed in a surveillance program. Columnar-lined esophagus, extending less than 1cm above GEJ, is of uncertain value for the diagnosis of BE (38). Biopsies of the squamocolumnar junction should not be routinely obtained in clinical practice if it is at the level of the EG junction. Goblet cells found at this level should be considered to be diagnostic of intestinal metaplasia of gastric cardia, a condiditon with an unclear cancer risk and cancer surveillance is not yet recommended (3).

BE can be classified as either long segment ($\geq$3cm) or short segment (<3cm) , depending on how far the squamocolumnar junction is located from the gastroesophageal junction. Recently an endoscopic classifications system has been developed by a working group (Working Group for the Classification of Reflux Eesophagitis – IWGCO, C&M Prague criteria) that would be useful for clinical practice, (figure-1). In C&M Prague criteria, upper end of the gastric folds is used as a landmark for defining the GEJ. This is the relatively simple approach of recording both the circumferential extent (the C value) and the maximal extent (the M value) above the GEJ in centimeters and provides easy way to assess the length of BE. True islands of squamous and columnar mucosa should not influence the measurement of extent and that this should be stated in the subtext for the criteria (39).
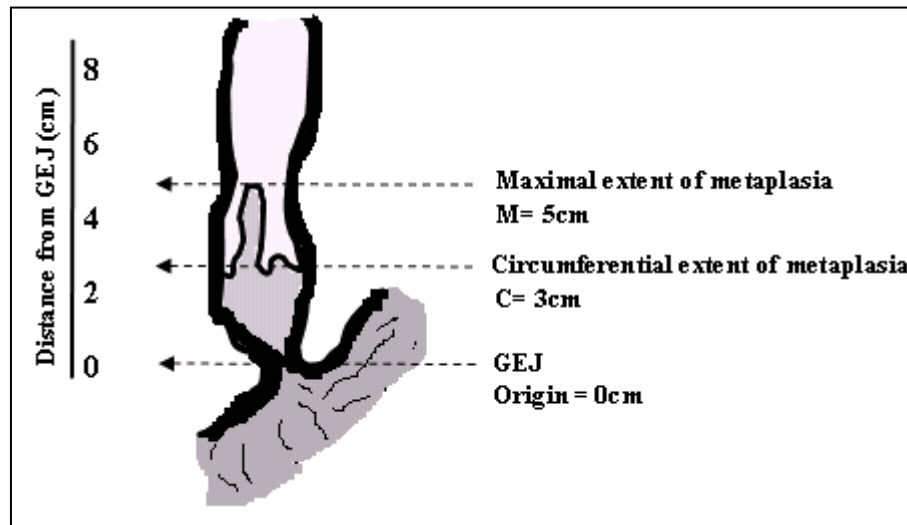
Figure 1. Diagrammatic representation of endoscopic Barrett's esophagus showing an area classified as C2M5. C: extent of circumferential metaplasia;   M: maximal extent of the metaplasia (C plus a distal 'tongue' of 3 cm),   GEJ: gastroesophageal junction (39).

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