The 18th Annual Congress of the Lebanese Society of GASTROENTEROLOGY

November 2019
Beirut

Diagnosis of Motility disorders
Conflict of Interest

• Symposium sponsorship, paid invitation to lecture:
  • Diagmed/Given Imaging/Covidien/Medtronic
    • Dr Falk Pharma
Oesophageal function

- Transport food from mouth to stomach
- Prevent gastro-oesophageal reflux

- Dysfunction leads to
  - Dysphagia
  - Reflux and Aspiration
  - Pain
• Endoscopy and/or barium first...always

- Varadarajulu S Gastrointest Endosc. 2005
- Arora AS. Et al CGH 2005 3
- Levine, M. S. Applied Radiology 2006
- Ott DJ. Dysphagia. 1990
- Jalil S, Castell DO. J Clin Gastroenterol 2002
Endoscopy

- Patients with dysphagia should be investigated with endoscopy & biopsy to exclude mucosal/structural structure:
  - Malignancy
  - reflux oesophagitis
  - Eosinophilic oesophagitis
  - Peptic stricture
  - Schatzki ring
  - etc.

- Varadarajulu S Gastrointest Endosc. 2005
- Arora AS. et al CGH 2005 3
- ASGE Standards of Practice Committee. Pasha et al. GI Endosc 2014
Endoscopy & Functional Disorders

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Endoscopic Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reflux Disease</td>
<td>Esophagitis (Sensitivity &lt;50%)</td>
</tr>
<tr>
<td>Achalasia</td>
<td>Difficulty passing LES, food bolus, Candida</td>
</tr>
<tr>
<td>Diffuse Esophageal Spasm</td>
<td>Spasm (<em>subjective</em>)</td>
</tr>
<tr>
<td>Eosinophilic esophagitis</td>
<td>Exudates, Rings, Furrows, Schatziki, stricture</td>
</tr>
<tr>
<td>Obstruction</td>
<td>Food residue</td>
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</tbody>
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• Most patients with ‘esophageal symptoms’ have normal endoscopy
• Endoscopy visualizes the empty, fasted bowel
• Endoscopy detects primarily only complications of functional disease
• Very limited role in assessing function
• Rarely enough to define disorder
Barium Swallow

- Exclude structural diagnoses, especially if no Endoscopy
  Levine, M. S. Applied Radiology 2006
  Ott DJ. Dysphagia. 1990
  Jalil S, Castell DO. J Clin Gastroenterol 2002
  Malagelada JR et al. J Clin Gastroenterol. 2015

- Failure to clear Ba = severe dysmotility or obstruction
  - Defines abnormal bolus transport but not underlying cause
  - Requires manometry to diagnose motility disorder
    Nelleman H et al. Acta Radiologica 2000

<table>
<thead>
<tr>
<th>Manometry Diagnosis</th>
<th>Abnormal Radiology</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Achalasia</td>
<td>80-95%</td>
<td>Confident</td>
</tr>
<tr>
<td>Diffuse Esophageal Spasm</td>
<td>~60%</td>
<td>Non-specific (Corkscrew)</td>
</tr>
<tr>
<td>Non-specific Motor Disorder/Ineffective Esophageal Motility</td>
<td>~50%</td>
<td>Non-specific</td>
</tr>
</tbody>
</table>

- Everything else is non-specific
- Radiology is not sensitive or specific to diagnose GORD
  Saleh et al NGM 2015
Routine testing do not adequately define functional oesophageal disorders
Esophagus: Muscles and Plexus

- Meissner's plexus (submucosal)
- Circular muscle
- Auerbach's plexus (myenteric)
- Longitudinal muscle
- Vagus nerve

Neuromuscular anatomy of the esophagus

- Upper esophageal sphincter
- Striated Polymyositis
- Myasthenia gravis
- Smooth Scleroderma
- Achalasia
- Lower esophageal sphincter

18-22 cm long
Investigation for Dysphagia

- Clinical History and Exam
- Endoscopy
- Histology
- Radiology
- Endoscopic USS
  - Stationary Manometry
    - Conventional manometry ± Impedance
    - High Resolution Manometry ± Impedance
  - Ambulatory Reflux Studies
    - pH/Impedance-pH monitoring
High Resolution Manometry
Spatiotemporal (Clouse) Plot

- Display method can improve accuracy and speed of recognition of motility disorders even in manometry-naive individuals

Grubel et al. CGH 2008

Water perfused

Solid state
(Sierra systems)

HRM demonstrates segmental character of oesophageal motor function
Conventional Manometry

Pharynx
(Deglutination)

UOS

LOS

Gastric
(Reference)
From line plots to Spatiotemporal plots
Spatiotemporal (Clouse) Plot

Single small volume (5-10ml) Water Swallows

- Display method can improve accuracy and speed of recognition of motility disorders even in manometry-naive individuals

Grubel et al CGH 2008

HRM demonstrates segmental character of oesophageal motor function
Chicago Classification 3.0

Major Motor Disorder
- Hyper-Contraction
- Absent peristalsis

Minor Motor Disorder
- Frequent Failed Swallows
- Fragmented

OGJ Pathology + Spasm

Treat Disorder

Kahrilas et al Chicago Classification 3.0. NGM 2015
EGJ relaxation = Integrated Relaxation Pressure (IRP)

Normal <15 mmHg

Amenable to automated calculation

Courtesy PJKahrilas
Non-Functional causes of obstruction

- Tight Fundoplication
- Slipped wrap
- Peptic/benign stricture
- Post-gastric band
- Submucosal lesion
Eosinophilic Oesophagitis

- T-cell mediated hypersensitivity response to a food antigen → eosinophil activation and the consequences of this cytokine cascade
- Solid food dysphagia
- 4% patients with refractory GERD have EoE

Poh et al Gastrointest Endo 2010
Garcia-Compean Dig Liv Dis 2011

Kumar, Khan, Wong, Sweis. PMJ 2014
Histology

- Eosinophil-predominant inflammation
- ≥15 eos/HPF

- Macroscopic & microscopic patchy inflammation
- Eosinophilic microabscesses
- Intercellular edema/'moth-eaten’
- Lamina propria papillae elongation
- Basal zone hyperplasia
- Lamina propria fibrosis

- Straumann A et al. *SMW* 1994
- Furuta GE et al. *GASTRO* 2007
- Gonsalves et al. Gastrointestinal Endosc 2006

![Histological image with eosinophils and fibrosis]
Endoscopic findings

- **Acute**
  - exudates
  - oedema
  - Furrows

- **Chronic**
  - rings
  - strictures
  - combination

Progression of EoE from inflammation to fibrosis

*1
Barium swallow in EoE
Achalasia subtypes

- loss of the postganglionic inhibitory neurons of the myenteric plexus
- Incidence 1 in 100,000 adults
- M=F

Achalasia I

Achalasia II

Achalasia III

Lumen-obliterating Spastic contractions
Pathology within the Oesophageal Body

Major Motor Vs. Minor Motor
Absent Contractility

- 100% of the wet swallows with *NO* peristalsis = DCI < 100
- IRP not raised

_Xiao Y et al, Am J Gastroenterol 2012;107:1647-54_
Distal Contractile Integral (mmHg.cm.s)

• Measure of Contractile Vigour (amplitude x length x time of contraction)
Hypertensive Dysmotility

- Hypertensive dysmotility does not disrupt function.
- High contractile pressures *can be associated* with pain
- Extreme contractile pressures *can cause* pain
- Normal 450-8000 mmHg.cm.sec
Distal Latency (DL)
(measure for spasm)

**CDP (Contractile Deceleration Point)**
- Inflection point along the 30 mmHg isobaric contour where propagation velocity slows demarcating the tubular oesophagus from the phrenic ampulla

**DL (Distal Latency)**
- Interval between UOS relaxation and the CDP
  - $DL \geq 4.5 \text{ sec} = \text{normal}$
  - $DL < 4.5 \text{ sec} = \text{premature contraction}$
Type III Achalasia vs. 
Diffuse Oesophageal Spasm (\(DL<4.5s\))

Type III Achalasia

- Premature contraction
- Resistance to flow

Diffuse Oesophageal Spasm

- Premature contraction
- No Resistance to flow

Diagnosis requires at least 2 swallows with DL<4.5
Adjunctive Testing

- 5ml water
  - Supine vs. Upright

- 1cc bread/marshmallow/viscous

- Meal

- MRS

- RDC

- Post-prandial

- More complex pressure activity more difficult to analyse
Rapid Drink Challenge
Rapid Drink Challenge (RDC)

- Pressure gradient across the OGJ (aka IRP) – direct assessment of resistance to flow
  - rate of drinking > rate of clearance into the stomach = resistance to flow (e.g. achalasia)

- Abnormal IRP during MWS improves sensitivity of HRM for diagnosing achalasia in patients with low baseline LES pressure and those with equivocal findings during SWS.
  - Ang et al 2016 (submitted to CGH)
  - Ang et al DDW 2015
  - Fox MR, Bredenoord AJ. Gut. 2008
  - Sweis R, et al. NGM 2014
  - Fox et al NGM 2004

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Sweis, Anggiansah, Wong, Brady, Fox. NGM 2014
Outcome measurement

Objective

Timed barium swallow

- Objective measure of oesophageal emptying
  - Simple, easy to perform, reproducible
  - Ingestion of 150-200ml barium in the upright position
    → spot films at 1, 2 and 5 min

De Oliviera JMA. Am J Roentgen 1997
Timed Barium swallow (TBS)

• TBS - important tool in objective evaluation of achalasia post therapy (dilation).
• >73% concordance between degree of symptom improvement and degree of oesophageal emptying.
• Poor oesophageal emptying is present in ≈30% achalasia with complete relief post dilation.
  • 90% of these fail within 1 year of treatment  
    Vaezi et al AJG 1999
    Vaezi et al Gut 2002

• High Sensitivity (88%) to predict the need of retreatment with oesophageal stasis
  Rohof & Boeckxstaens. AMJ 2013
Failure to respond to physiologic challenge characterizes esophageal motility in erosive gastro-esophageal reflux disease

- Not all patients with ineffective oesophageal motility (water) have dysphagia
- Erosive oesophagitis (n=20) vs. ENRD (n=20) vs. Healthy Controls (n=23)
- 5ml water - dysmotility common in GORD
  - no significant difference between NERD and ERD.
- Solid swallows - # ineffective swallows of solids (1cc bread) reduced in healthy controls & ENRD
  But Not in ERD
HRM while eating
HRM can aid diagnosis

- Asymptomatic healthy volunteer
  5 nonpropagating pharyngeal swallows
  5 effective, clearing contractions

- Gastro-oesophageal reflux disease
  7 nonpropagating pharyngeal swallows
  3 hypotensive contractions (DCI<450)

Pouderoux et al AJG 1999
Sweis, Anggiansah, Wong, Brady Fox. NGM 2014
5ml water
• Absent motility on 10 water swallows
  • (DCI<100 x 10)
  • i.e. Major Motor Disorder

Eating
• Normal peristaltic contractions with a solid meal
  • reflects the “functional reserve” that can be recruited when esophageal workload is increased

Sweis, Anggiansah, Wong, Brady, Fox. NGM 2014
Meal post anti-reflux surgery
Wang, Tai, Yazaki, Jafari, Sweis, Tucker, Knowles, Wright, Hamlett, Fox, Sifrim.
CGH 2015

• Double High Pressure Zone (DHPZ) can be observed:
  i. with dehiscence of the wrap and (re-)formation of HH
  ii. twisting/slipping of wrap with outlet obstruction.

• DHPZ present Only in patients with symptoms after fundoplication surgery
  • More often in patients with final Dx of oesophageal outlet obstruction (40%) than other patients (13%) p=0.03
Consecutive patients referred for physiological investigation of oesophageal symptoms between Jan 2010 and Dec 2013 University Hospitals of Nottingham

All had:
- 5x10ml water
- 200ml water (free drinking)
- Cheese and onion pasty (195g, 500kcal, 34g fat)

805 patients referred for tests/750 patients completed HRM

Primary symptoms:
- Reflux n=329
- Dysphagia n=360
- Other n=61
• **Meal doubled diagnostic yield of NEW Major Motor Disorder**

• **22% re-classified to another major motor disorder with solids**

10 patients with absent peristalsis on WS had peristalsis activity seen only during meal (Peristalsis recovery)

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**Major Motor Disorders in Single water vs. Meal**

N=750

New Major Motor Disorder

<table>
<thead>
<tr>
<th></th>
<th>Water swallow</th>
<th>Meal</th>
<th>P&lt;0.0001</th>
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<tbody>
<tr>
<td></td>
<td>163 (21.7%)</td>
<td>321 (42.8%)</td>
<td></td>
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</table>

- **Water Swallow**
  - Normal: 33.6%
  - Ineffective: 40.9%
  - Spasm/Jackhammer: 5.7%
  - Aperistalsis: 4.4%
  - EGJ Obstruction: 7.5%
  - Achalasia: 4.1%
  - Nutcracker: 3.7%

- **Meal**
  - Normal: 36.9%
  - Ineffective: 17.6%
  - Spasm/Jackhammer: 24.8%
  - Aperistalsis: 2.1%
  - EGJ Obstruction: 10%
  - Achalasia: 2.7%
  - Nutcracker: 2.1%
In those with major motor disorders, typical symptoms were reproduced:
- 9 (1.2%) with single water swallows vs.
- 461/750 (61.5%) with solid test meal (p < 0.001)
High Resolution Impedance Manometry
Complete vs Incomplete Bolus transit

Incomplete bolus transit

Complete bolus transit

7cm

2cm

2cm
Summary

• Endoscopy does not measure function
• Barium study measures function over only a few swallows
• High Resolution Manometry measures oesophageal function
  – Can reproduce normal eating and drinking behavior by varying volume and consistency
  – Allows for symptoms to be reproduced
  – Identify disorders that are relevant and exclude normal
- 53 year old female
- Achalasia 13 years ago
- Heller's myotomy and fundoplication - 2007
- Botox injections 2011 and 2016
- Pneumatic dilatation July 2018 - 30 mm + 35mm

Plan – for proximal POEM
Case

- 55 year old male
- 7 year history of food sticking in upper esophagus + chest pain 2-3/wk
- Endoscopy non-diagnostic.

- Aperistalsis
- Normal LOS basal tone
- No symptoms.
- IRP – normal (12).

5ml water

- Non-relaxing LOS + pan-oesophageal pressurisation
- IRP 19
- Dysphagia reproduced

200ml water swallow

- Non-relaxing LES
  - (IRP 26.6mmHg)
- Pan-oesophageal pressurisation
- Dysphagia reproduced from mid-meal with every swallow thereafter

Meal
Case

- 75 year old female
- Intermittent dysphagia/pain to solids and tablets
- Endoscopy – proximal benign leiomyoma after repeated biopsies
- Barium swallow (liquid) – entirely normal
- Reflux symptoms improved with twice daily lansoprazole but not dysphagia/pain

- Normal peristalsis
- Normal contractile pressures
- Normal OGJ

- Repeated, hypercontractions
- DCI > 15000 mmHg.cm.sec = Jackhammer oesophagus
- Normal OGJ function / Normal IRP
  - Hypercontractions reproduced symptoms
Regurgitation – something else

• Solid swallows + free drinking a 200ml milkshake
  – reproduced typical symptoms of regurgitation

  • short, sharp increases of intra-gastric pressure + concurrent relaxation of UOS
    → Rumination

Sweis. 2008 (http://moodle.bsg.org.uk/)
HRM and Rumination/SGB

Classical Rumination

- Short, sharp increases of intra-gastric pressure + concurrent relaxation of UOS

Reflex related Rumination

- Clinical utility of HRM studies during a test meal identifies 3 groups with distinct mechanisms of disease

Supragastric Rumination

- Vivid, visual demonstration of oesophageal function provided by HRM can help patients (and their doctors)
  - understand the cause of their symptoms
  - enhance patient acceptance of the diagnosis and the effectiveness of behavioural therapy.

Tucker et al. Rumination variations: Aetiology and classification of abnormal behavioural responses to digestive symptoms based on HRM studies 2013
**Chicago Classification 3.0**

**Major Motor Disorder**
- Hyper-contraction
- Absent peristalsis

**Spasm**

**Minor Motor Disorder**
- Hypo-contraction
- Frequent Failed Swallows
- Fragmented

**Treat Disorder**

**Treat Symptoms**

Kahrilas et al Chicago Classification 3.0. NGM 2015
Eosinophil numbers typically increase as you go down the gut\(^1\)

- Eosinophils - typically present throughout the GI tract - continuously exposed to foods, environmental allergens, toxins, and pathogens\(^2\)
- Healthy individuals - unique in that eosinophils are generally absent in the oesophagus\(^2\)

Upper normal limits for eosinophil numbers within the GI tract\(^1\)

- Oesophagus < 15/hpf
  - Usually none at all
- Stomach < 30/hpf
  - Usually a few are seen in normals
- Ileum < 50/hpf
- Colon < 50-100/hpf

Eosinophilic esophagitis (EoE)

- chronic disorder - eosinophils infiltrate oesophageal epithelium
  - Characterised:
    - clinically - symptoms related to oesophageal dysfunction
    - histologically - eosinophil-predominant inflammation
  - Since its recognition as a clinical entity in 1989, EoE has evolved from sporadic case reports to become a widely recognised cause of oesophageal morbidity

European consensus group has recommended that 
≥15 eosinophils per hpf as the threshold for diagnosis
- because microscopes vary in regard to HPF size, this definition is for a standard size hpf of ~0.3 mm²
Histologically the oesophagus has four layers:

**The mucosa**
The inner layer, which creates a protective barrier, it is arranged in folds that allow for expansion when food passes through.

**The submucosa**
This contains glands that produce mucus, important in clearance and protecting oesophageal tissue from acid.

**The muscularis propria**
The muscle layer, which pushes food down to the stomach, it is composed of an inner circular and outer longitudinal layer.

**The adventitia**
The outer layer, which attaches the oesophagus to nearby parts of the body.

Epidemiology of EoE

- Meta-analysis of 13 population-based studies from North America, Europe and Australia

EoE prevalence†

28.1 cases / 100,000 inhabitants

EoE incidence*

7.2 new cases / 100,000 / year

These rates are similar to those described for inflammatory bowel disease in Europe, underscoring the burden of EoE on health systems in the region

†from studies with a low risk of bias

*from post-2008 research

Clinical Features

- **Children**
  - Feeding intolerance
  - Failure to Thrive
  - Heartburn
  - Emesis
  - Dysphagia/Food impaction
  - Refractory GERD

- **Adults**
  - Intermittent dysphagia
  - Food impaction
  - Chest pain
  - Refractory GORD
Endoscopy

• Endoscopic abnormalities often unremarkable or misleading
  – Neither consistent nor disease specific.


• Up to 17% of patients have normal endoscopy or have subtle features which are easily missed

  Kim HP et al. CGH 2012
Debate whether the aim for treatment should be symptomatic remission, histological remission, or both. Although the most common endpoint is a reduced number of eosinophils in biopsies, changes in symptoms and endoscopic features are becoming important targets of therapy.
Achalasia diagnosed despite normal integrated relaxation pressure responds favorably to therapy
Sanagapalli, Roman, Hastier, Emmanuel, Patel, Raeburn, Banks, Haidry, Lovat, Graham, Sami, Sweis
NGM 2019

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panesophageal pressurization with RDC, n (%)</td>
<td>22/28</td>
<td>79%</td>
</tr>
<tr>
<td>Panesophageal pressurization with solid swallows, n (%)</td>
<td>7/14</td>
<td>50%</td>
</tr>
<tr>
<td>Stasis on barium esophagogram, n (%)</td>
<td>23/29</td>
<td>79%</td>
</tr>
</tbody>
</table>