High Resolution Manometry and pH step-up method on the localisation of the lower esophageal sphincter

To the Editor,

Ambulatory pH-recording is one of the key diagnostic studies in gastroesophageal reflux disease. It is recommended that the pH-probe is inserted 5 cm above the proximal border of the lower esophageal sphincter (LES) and the latter should be determined optimally with manometry [1]. However, some studies have shown that the pH step-up especially done in the supine position could be almost as accurate as manometry to locate the LES [2, 3]. Also the pH step-up method has been used in the positioning of the pH sensor in daily practise. On the other hand, it has been also shown that the location of LES with the pH step-up method in the supine position is equally inaccurate as the location in the upright position [4]. The pH step-up method is considered to have an acceptable accuracy if the location of the LES is within ± 3 cm compared to the location detected with manometry [5]. Nowadays, high resolution manometry (HRM) has replaced conventional manometry at least in many industrial countries. To the best of our knowledge, the accuracy of the LES location with the pH step-up method in comparison to HRM has not been previously reported. Therefore, the aim of the present study was to compare performance of these methods in the localisation of the LES in patients with clinically indicated HRM and pH recording.

We analysed retrospectively 525 patients who had pH-step or pH-impedance study with pH-step and HRM available from September of 2013 to November of 2016 in the Tampere University Hospital in Finland. Solid state HRM was performed with MMS Solar GI and pH step-up was measured with MMS Ohmega (Medical Measurements Systems B.V., The Netherlands). pH step-up was done in a sitting position and HRM in a supine position. Pearson correlation was used to calculate the relation between the HRM and pH step-up on the LES location; ± 3 cm was considered as the normal margin of error between the two methods on the LES location and the data was later divided by that limit. The χ2 test or ANOVA test was used to calculate the difference between these groups.

In this cohort, 61 % of the patients were women and the mean age of the cohort was 49 years (range 15 – 87 years). There was a strong correlation on the LES location between the HRM and pH step-up (Fig. 1, Pearson correlation 0.808, p<0.001). The mean difference between these two methods was only -1.49 cm (SD 2.02 cm). However, in 16 % (n=84) of the patients the difference was over ± 3 cm. The patients in the group where the difference was over ± 3 cm were significantly taller than the patients with a smaller difference between measurements (mean heights 170.9 cm and 162.9 cm, respectively, p=0.037). Age, sex or use of gastric medications was not significantly different between these groups.

In conclusion, using the pH step-up method in LES localisation would have led to an unacceptable position of the distal pH-probe in up to 16 % of the patients when compared...
with the HRM-based method. This seems to be related at least partly to the patients' height. These results support the current recommendation to use manometry for accurate localisation of the LES.

Atte Haarala¹, Juli-Anna Linjamäki², Heikki Tuominen², Mika Kähönen¹,²
1) Department of Clinical Physiology and Nuclear Medicine, Tampere University Hospital, Tampere; 2) University of Tampere, Faculty of Medicine and Life Sciences, Tampere, Finland.

Correspondence: Atte Haarala, atte.haarala@pshp.fi

Conflicts of interest: None.

DOI: 10.15403/jgld.2014.1121.264.haa

REFERENCES


Gallstone ileus - a rare finding in the era of laparoscopic cholecystectomy

To the Editor,

Gallstone ileus (GI) is a mechanical intestinal obstruction caused by the impaction of gallstones within the gastrointestinal tract. It is usually the complication of a cholecysto-duodenal fistula allowing the passage of a large stone that blocks the lumen of the terminal ileum. We retrospectively reviewed the data of 27 patients operated for GI in our tertiary hospital between 1997-2017. During this period, strangulated hernias and large bowel malignancy were the main causes for obstruction [1, 2]. With only 27 out of a total of 6,523 operated obstructions, GI was indeed a rare cause (0.041%). A nationwide American study [3] conducted between 2005-2009 on 3,452,536 cases found GI in 0.095% of the cases. Like most spheroidal intraluminal foreign bodies, gallstones rarely produce perforation with peritonitis [4].

The rarity of GI is better defined by its frequency as a complication of cholelithiasis. In series operated before the laparoscopic era, GI developed in 0.3%-0.5% of patients with cholelithiasis [5, 6]. It is worth mentioning that the largest series before 1990 reached a number of 37 patients [5], while more recent papers mention no more than 14 patients with GI [7]. This fact suggests a trend of GI occurring more rarely. The explanation may lie in the wide acceptance rate of laparoscopic cholecystectomy by patients who previously may have been reluctant to accept an open procedure. As a consequence, fewer patients postponed surgery for decades, thus leading to a reduced number of complicated cases.

Laparoscopic cholecystectomy was started in our hospital in 1992, with a total of over 30,000 operations performed between 1997 and 2017. Considering the 27 cases of GI operated in the same period, only 0.09% of the patients with symptomatic cholelithiasis developed GI. If divided between decades, 17 cases were recorded between 1997-2007 and only 9 in the decade 2007-2017. These figures may confirm the aforementioned presumed trend. Our patients met the classical features, being females, older than 50 years, with a prolonged history of gallbladder lithiasis. The preoperative work-up consisted mostly of an ultrasound and a plain abdominal X-ray.

Patients with symptoms of high obstruction due to a Bouveret syndrome were less numerous (6) than those with an impacted stone in the ileum (21). In one situation the Bouveret syndrome was diagnosed by gastroscopy and in a patient with ileum impaction a CT-scan identified a large stone as the cause of the obstruction (Fig.1). All other cases were diagnosed intraoperatively. The size of the obstructing gallstones ranged from 2 to 9 cm.

Fig.1. CT scan with contrast showing an ectopic stone in the ileum (arrow).

The technique of choice for duodenal impaction was duodeno-jejunal Roux-en-Y anastomosis (5 cases) or suture (1 case) and enterotomy (18 cases) or enterectomy (9 cases) for ileal obstruction. Only one death, caused by pulmonary thromboembolism, was recorded. A review on 176 cases published in Japan between 1985 and 2005 considers simple enterolithotomy appropriate in most patients. However, one-stage enterolithotomy, cholecystectomy and fistula management are advisable if the general status of the patient allows it because recurrent gallstone obstructions can arise due to the persistence
Letters to the Editor

We read with great interest the recent paper by Radoi et al. in your journal, addressing the frequencies of UGT1A1 genotypes in a Romanian cohort of Gilbert subjects and controls [1]. In addition to the common polymorphisms, UGT1A1*1 (TA)6, and UGT1A1*28 (TA)7, they also reported allele frequencies of 0.61% and 0.72% for UGT1A1*33 (TA)5 and UGT1A1*34 (TA)8 alleles respectively. All subjects with the UGT1A1*33 allele were found in the control group, which is in line with studies showing that the promoter activity increases with a decreasing number of TA repeats [2].

Previously, UGT1A1*33 and UGT1A1*34 have been described to be common in African populations, but very rare among Europeans [3, 4]. In three small-size studies, occasional subjects with these genotypes have been found in European populations [5]. In a retrospective Croatian study, the allele frequency for UGT1A1*33 allele was 0.18% and for UGT1A1*34, 0.13% [6].

We pooled the UGT1A1 genotyping data from three prospective studies within the Northern Sweden Health and Disease Study [7], comprising cases who later developed a stroke [8], myocardial infarction [9], or breast cancer (unpublished), and their matched referents. All subjects were healthy at inclusion as samples and data for the cohort were obtained through the Västerbotten Intervention Program, the Northern Sweden MONICA Study, and the mammary screening program of Västerbotten. The Department of Biobank Research, Umeå University, aided in acquisition of samples and data. The genotyping procedure of the UGT1A1 promoter TATA box has been described in detail elsewhere [9].

We found 15 out of 3,292 genotyped subjects with the UGT1A1*33 allele and two subjects with the UGT1A1*34 allele in our ethnically homogeneous cohort from Northern Sweden (Table I). The allele frequency of the UGT1A1*33 allele was 0.23%, which is approximately 1/3 of the allele frequency in European populations [3, 4]. In three small-size studies, occasional subjects with these genotypes have been found in European populations [5]. In a retrospective Croatian study, the allele frequency for UGT1A1*33 allele was 0.18% and for UGT1A1*34, 0.13% [6].

We found 15 out of 3,292 genotyped subjects with the UGT1A1*33 allele and two subjects with the UGT1A1*34 allele in our ethnically homogeneous cohort from Northern Sweden (Table I). The allele frequency of the UGT1A1*33 allele was 0.23%, which is approximately 1/3 of the allele frequency in the total study group described by Radoi et al. The findings in the study of Radoi et al. and in our material suggest that UGT1A1*33 is not a very rare allele, neither in Romania, nor in Northern Sweden.

Kim Ekkblom, Johan Hultdin
Department of Medical Biosciences, Clinical Chemistry, Umeå University, Umeå, Sweden

Correspondence: Kim Ekkblom, kim.ekkblom@umu.se

Conflicts of interest: None.
DOI: 10.15403/jgld.2014.1121.264.ugt

<table>
<thead>
<tr>
<th>UGT1A1 genotype</th>
<th>Cases (n=1249)</th>
<th>Referents (n=2043)</th>
<th>Women (n=1661)</th>
<th>Men (n=1631)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5TA/6TA</td>
<td>1 (0.08)</td>
<td>5 (0.24)</td>
<td>3 (0.18)</td>
<td>3 (0.18)</td>
</tr>
<tr>
<td>7TA/7TA</td>
<td>6 (0.48)</td>
<td>3 (0.15)</td>
<td>7 (0.42)</td>
<td>2 (0.12)</td>
</tr>
<tr>
<td>6TA/6TA</td>
<td>577 (46.2)</td>
<td>996 (48.8)</td>
<td>781 (46.8)</td>
<td>792 (48.6)</td>
</tr>
<tr>
<td>6TA/7TA</td>
<td>534 (42.8)</td>
<td>843 (41.3)</td>
<td>698 (42.0)</td>
<td>679 (41.6)</td>
</tr>
<tr>
<td>7TA/7TA</td>
<td>131 (10.5)</td>
<td>194 (9.50)</td>
<td>171 (10.3)</td>
<td>154 (9.4)</td>
</tr>
<tr>
<td>7TA/8TA</td>
<td>0 (0)</td>
<td>2 (9.79)</td>
<td>1 (0.06)</td>
<td>1 (0.06)</td>
</tr>
</tbody>
</table>

Table I. Genotype frequencies of the UGT1A1 in subjects from the Northern Sweden Health and Disease Cohorts [no. (%)]. Stratification has been made both for case/referent status and for sex.

UGT1A1*33 (TA)5 is more common in Romania and Northern Sweden than previously believed

To the Editor,

We read with great interest the recent paper by Radoi et al. in your journal, addressing the frequencies of UGT1A1 genotypes in a Romanian cohort of Gilbert subjects and controls [1]. In addition to the common polymorphisms, UGT1A1*1 (TA)6, and UGT1A1*28 (TA)7, they also reported allele frequencies of 0.61% and 0.72% for UGT1A1*33 (TA)5 and UGT1A1*34 (TA)8 alleles respectively. All subjects with the UGT1A1*33 allele were found in the control group, which is in line with studies showing that the promoter activity increases with a decreasing number of TA repeats [2].

Previously, UGT1A1*33 and UGT1A1*34 have been described to be common in African populations, but very rare among Europeans [3, 4]. In three small-size studies, occasional subjects with these genotypes have been found in European populations [5]. In a retrospective Croatian study, the allele frequency for UGT1A1*33 allele was 0.18% and for UGT1A1*34, 0.13% [6].

We pooled the UGT1A1 genotyping data from three prospective studies within the Northern Sweden Health and Disease Study [7], comprising cases who later developed a stroke [8], myocardial infarction [9], or breast cancer (unpublished), and their matched referents. All subjects were healthy at inclusion as samples and data for the cohort were obtained through the Västerbotten Intervention Program, the Northern Sweden MONICA Study, and the mammary screening program of Västerbotten. The Department of Biobank Research, Umeå University, aided in acquisition of samples and data. The genotyping procedure of the UGT1A1 promoter TATA box has been described in detail elsewhere [9].

We found 15 out of 3,292 genotyped subjects with the UGT1A1*33 allele and two subjects with the UGT1A1*34 allele in our ethnically homogeneous cohort from Northern Sweden (Table I). The allele frequency of the UGT1A1*33 allele was 0.23%, which is approximately 1/3 of the allele frequency in the total study group described by Radoi et al. The findings in the study of Radoi et al. and in our material suggest that UGT1A1*33 is not a very rare allele, neither in Romania, nor in Northern Sweden.

Kim Ekkblom, Johan Hultdin
Department of Medical Biosciences, Clinical Chemistry, Umeå University, Umeå, Sweden

Correspondence: Kim Ekkblom, kim.ekkblom@umu.se

Conflicts of interest: None.
DOI: 10.15403/jgld.2014.1121.264.ugt
REFERENCES


Uses and limitations of IgG4 positive plasma cells in evaluating ulcerative colitis

To the Editor,

Ulcerative colitis (UC) is an inflammatory bowel disease (IBD) manifesting flares frequently alternating with periods of remission. The development of UC has been associated with an exaggerated Th2 response, which involves immunoglobulin G, subclass 4 (IgG4) [1]. In fact, IBD frequently coexists with IgG4 related diseases such as autoimmune pancreatitis [2]. Patients with UC and elevated serum IgG4 levels have been found to be younger at diagnosis, more likely to have backwash ileitis and flares, and often proceed to colectomy [3]. High levels of IgG4 identified by immunohistochemistry of plasma cells in the colon mucosa have also been linked to disease activity, and are found significantly more frequently in patients with active UC [4]. In addition, these patients tend to progress to colectomy or azathioprine treatment [5]. While immunohistochemical staining for IgG4 positive plasma cells has become a key tool in the diagnosis of IgG4-related disease, it is still not clear how to interpret these positive results in UC specimens or whether mucosal IgG4 will be established as an independent predictor of disease course in UC.

We conducted a retrospective study on rectal mucosal biopsies from patients with UC in order to assess the reproducibility of IgG4 count using immunohistochemistry and to evaluate the role of IgG4 count as an independent risk

Table I. Analysis for predictors of unfavorable clinical outcomes in the cohort of 134 cases.

<table>
<thead>
<tr>
<th></th>
<th>Unfavorable (n=60)</th>
<th>Favorable (n=74)</th>
<th>P</th>
<th>OR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>29 (48)</td>
<td>39 (53)</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>31 (52)</td>
<td>35 (47)</td>
<td>1.19 (0.6, 2.35)</td>
<td>0.615</td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis*, mean (SD)</td>
<td>23 (14)</td>
<td>32 (16)</td>
<td>0.001</td>
<td>0.96 (0.93, 0.98)</td>
<td>0.002</td>
</tr>
<tr>
<td>Duration of disease, mean (SD)</td>
<td>12 (76)</td>
<td>24 (103)</td>
<td>0.035</td>
<td>0.996 (0.99, 1.0)</td>
<td>0.041</td>
</tr>
<tr>
<td>Ulcerative colitis extent, n (%)</td>
<td></td>
<td></td>
<td>0.069</td>
<td>0.079</td>
<td></td>
</tr>
<tr>
<td>Proctitis</td>
<td>6 (10)</td>
<td>18 (25)</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>18 (30)</td>
<td>23 (31)</td>
<td>2.35 (1.16, 9.26)</td>
<td>0.132</td>
<td></td>
</tr>
<tr>
<td>Pancolitis</td>
<td>36 (60)</td>
<td>33 (45)</td>
<td>3.26 (0.77, 7.14)</td>
<td>0.025</td>
<td></td>
</tr>
<tr>
<td>Mayo score*, mean (SD)</td>
<td>6.8 (2.8)</td>
<td>4.9 (2.6)</td>
<td>&lt;0.001</td>
<td>1.32 (1.14-1.53)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Endoscopic score, mean (SD)</td>
<td>1.9 (0.7)</td>
<td>1.5 (0.8)</td>
<td>0.0007</td>
<td>2.14 (1.28, 3.57)</td>
<td>0.004</td>
</tr>
<tr>
<td>Endoscopic category, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>14 (23)</td>
<td>38 (51)</td>
<td>0.002</td>
<td>Reference</td>
<td>0.003</td>
</tr>
<tr>
<td>Moderate</td>
<td>37 (62)</td>
<td>32 (44)</td>
<td>3.13 (1.44, 6.88)</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>9 (15)</td>
<td>4 (5)</td>
<td>6.1 (1.62, 2.33)</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>Histologic activity grading, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>27 (45)</td>
<td>50 (67)</td>
<td>0.004</td>
<td>Reference</td>
<td>0.149</td>
</tr>
<tr>
<td>Moderate</td>
<td>23 (38)</td>
<td>22 (30)</td>
<td>1.93 (0.93, 4.08)</td>
<td>0.089</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>10 (18)</td>
<td>2 (3)</td>
<td>9.25 (2.181, 43.63)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>IgG4 positive cells/HPF, mean (SD)</td>
<td>12 (11.76)</td>
<td>10 (12.37)</td>
<td>0.56</td>
<td>1.35 (0.64, 2.61)</td>
<td>0.386</td>
</tr>
</tbody>
</table>

SD: standard deviation; HPF: high power fields; *Significant predictors at multivariable logistic regression analysis: age at diagnosis, OR= 0.96 (95% IC 0.93-0.99), p=0.036; Mayo score, OR=1.27 (95% IC, 1.03-1.57), p=0.007
factor for poor prognosis as well as its potential function as an early predictor of unfavorable outcome in UC. All biopsy specimens (174) were collected as part of routine endoscopic/surgical procedures. The exclusion of 40 patients already taking anti-TNF or thiopurine at the time of biopsy resulted in a remaining cohort of 134 study subjects which was then divided into Group A (n= 69), those originally diagnosed within one year or less prior to evaluation in this study, and Group B, those originally diagnosed more than one year earlier. In this series there was an excellent agreement among the two trained observers when counting IgG4 positive plasma cells, validating the reliability of the staining. In accordance with Kuwata et al. [5], we confirmed a strong correlation between the histologic assessment of the severity of disease and a high number of IgG4 positive plasma cells infiltrating the colonic mucosa (Kruskal-Wallis test, p= 0.001). As the interobserver agreement was higher for IgG4 counts than for activity grading, IgG4 immunohistochemistry could strengthen the information given by classical H&E based grading alone.

Younger age at diagnosis, shorter duration of disease, and higher clinical severity (Mayo score, endoscopic score) as well as moderate to severe histologic grading were predictors of poor outcome at univariable analysis, while only younger age at diagnosis and Mayo score were significant for poor outcomes at multivariable analysis (Table I). However, when looking for an early predictor of an unfavorable outcome (Group A was compared with group B, patients with a disease course of over one year before evaluation), only a high Mayo score retained statistical significance in the multivariate analysis. This study has confirmed several clinical predictors of outcomes in UC but IgG4 counts were not independently significantly associated with any differences in outcome.

Kian Keyashian1, Eleonora Duregon2, Brian T. Brinkerhoff3, Laura Bradley1,6, Benjamin Larson1,7, Jeong Lim1, Nir Modiano1, Judy Collins4, Terry K. Morgan1, Jody E. Hooper2 (*equally contributed to the study)

1) Department of Internal Medicine, Division of Gastroenterology, Oregon Health & Science University, Portland, Oregon; 2) Department of Pathology, The Johns Hopkins University, Baltimore, Maryland; 3) Department of Pathology, OHSU, Portland, Oregon; 4) Biostatistics and Design Program, School of Public Health, OHSU, Portland, Oregon; 5) Chinook Regional Hospital, Alberta Health Services, Alberta; 6) Department of Internal Medicine, University of California, Davis, California; 7) Department of Internal Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA

Correspondence: Jody E. Hooper, jhooper9@jhmi.edu

Conflicts of interest: None.

DOI: 10.15403/jgld.2014.1121.264.igg

REFERENCES