Different clinical symptom patterns in patients with reflux micro-micro-aspiration

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Title:

Different clinical symptom patterns in patients with reflux micro-micro-aspiration

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Take home message:
Patients with reflux micro-aspiration most commonly present with a combination of regurgitation and/or heartburn and cough and/or throat clearing.

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Conflict of interest statement:
All authors completed a conflict-of-interest statement summarised as follows:

Oleksandr Khoma – no relevant conflict of interest to declare

Jin-soo Park – no relevant conflict of interest to declare

Felix Michael Lee – no relevant conflict of interest to declare

Hans Van der Wall – no relevant conflict of interest to declare

Gregory L Falk – no relevant conflict of interest to declare
Abstract

Background

Pulmonary manifestation of gastro-oesophageal reflux disease (GORD) is a well-recognised entity, however little primary reported data exists on presenting symptoms of patients in whom reflux micro-aspiration is confirmed. The aim of this study is to report symptoms and presenting patterns of a large group of patients with confirmed reflux micro-aspiration.

Patients and methods

Data was extracted from a prospectively populated database of patients referred to a tertiary specialist centre with severe, refractory, or atypical reflux. Patients with reflux micro-aspiration on scintigraphy were included in this study. Separate group included patients with evidence of proximal reflux to the level of pharynx when supine and/or upright.

Results

Inclusion criteria were met by 243 patients with confirmed reflux micro-aspiration (33% males; mean age 59).

Most common symptoms amongst patients with micro-aspiration were regurgitation (72%), cough (67%), heartburn (66%), throat clearing (65%), and dysphonia (53%). The most common two-symptom combinations were heartburn/regurgitation, cough/throat clearing, regurgitation/throat clearing, cough/regurgitation and dysphonia/regurgitation. The most common three-symptom combinations were cough/heartburn/regurgitation, cough/regurgitation/throat clearing and dysphonia/regurgitation/throat clearing.
Cluster analysis demonstrated two main symptom groupings, one suggestive of proximal volume reflux symptoms and the other with motility/inflammatory bowel syndrome (IBS)-like symptoms (bloat, constipation).

Conclusion

Combination of typical symptoms of GORD such as heartburn or regurgitation and a respiratory or upper aero-digestive complaint such as cough, throat clearing, or voice change should prompt consideration of reflux micro-aspiration.
**Background and aim**

Reflux micro-aspiration is a severe consequence of gastro-oesophageal reflux disease (GORD) (1). Although a well-recognised entity, understanding of the physiology, natural history, or common presentation of patients with reflux micro-aspiration remains limited. Links between typical GORD symptoms such as heartburn and regurgitation and atypical symptoms (e.g. cough, globus pharyngeus) have been made (2, 3). Previously published data shows distinct presenting symptomatology amongst patients with reflux cough (4).

Correlation between reflux micro-aspiration and exacerbation of bronchial disease has been previously shown in a small cohort studies of patients undergoing bronchoscopy (5, 6).

Multiple aero-digestive questionnaires are currently used, such as Reflux Symptom Index (RSI), Supraoesophageal Reflux Questionnaire (SERQ) and Hull Airway Reflux Questionnaire (HARQ), none of which have been validated in patients with proven reflux micro-aspiration largely due to lack of adequate diagnostic test (1, 7-9).

No large-scale studies examining symptoms of patients with proven reflux micro-aspiration have been published so far.

The aim of this study is to analyse patterns of presenting symptoms in a large group of patients with proven pulmonary micro-aspiration by new technology reflux micro-aspiration scintigraphy (RASP). The secondary goal of this study was to analyse symptom patterns in patients with RASP evidence of pharyngeal reflux whilst supine and upright.

**Patients and methods**

Data was extracted from the prospectively maintained database containing records of patients presenting with severe typical or atypical, treatment resistant GORD.
All patients’ clinical symptoms were recorded by a senior consultant at the time of the initial assessment using standardised symptom sheet. Symptoms were recorded as either present or not. Severity of a specific symptom was not graded.

Patients that had evidence of pulmonary micro-aspiration of gastric refluxate on RASP performed between December 2006 and March 2018 were included in this study. We have also included patients with RASP evidence of proximal reflux to the level of pharynx when supine and/or upright were compared as a separate group which excluded patients with reflux micro-aspiration. There was an overlap amongst patients with proximal reflux supine and upright.

Scintigraphy technique included placing fasted overnight patients before Hawkeye 4 gamma camera (General Electric, Milwaukee, United States) with stomach, chest and upper airway in the field of view. Patients were administered 40-60 MBq of 99mTc DTPA diluted in 150 ml of water, followed by a 50ml water to promote clearance of isotope from pharynx and esophagus. Images were obtained for 2 min at 15 seconds per frame into a 64 × 64 matrix, followed by a 30 min dynamic image while supine for 30 seconds per frames. Delayed images were obtained at 2 hours to assess for presence of isotope in the lungs as evidence of reflux aspiration. Isotope time activity curves captured for the pharynx and upper esophagus supine and erect were classified as falling, flat or rising curves, where a falling curve reflected clearance of refluxate and a rising curve accumulation of refluxate. Rising pharyngeal curves have been shown to be strongly associated with reflux aspiration (10). Detailed description of the new modified technique of RASP, as well as validation study, have been previously published (10, 11). It is important to note that this not a standard scintigraphy, but a new, highly specific procedure with improved accuracy and has been instrumental in identifying previously silent micro-aspiration.
Symptoms were analysed for the most common symptom, as well most frequent two and three-symptom combinations in groups of patients with micro-aspiration, pharyngeal contamination supine and pharyngeal contamination upright. Results have been reported in absolute numbers and prevalence.

Cluster analysis of the principal variables (symptoms, micro-micro-aspiration, pharyngeal contamination) was performed using Euclidean distance (root mean squared) and displayed as a vertical icicle plot.

The database was approved by the University of Notre Dame Australia Human Research Ethics Committee (019091S) on 23rd of July 2019, being previously approved by the Concord Hospital Ethics Committee (LNR/12 CRGH/248). This study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. All patients provided informed written consent to participate in research.

**Results**

Inclusion criteria were met by 243 patients with reflux micro-aspiration. Further, 230 patients with pharyngeal contamination when upright and 298 patients with pharyngeal contamination whilst supine were also included. Demographic data summarised in Table 1.

**Table 1. Demographic characteristic of the participants**

<table>
<thead>
<tr>
<th></th>
<th>Micro-aspiration n=243</th>
<th>Pharyngeal contamination supine n=230</th>
<th>Pharyngeal contamination supine n=298</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>67% female</td>
<td>69% female</td>
<td>61% female</td>
</tr>
<tr>
<td>Age</td>
<td>Median 62 (Range 17-88)</td>
<td>Median 61 (range 14-88)</td>
<td>Median 59 (Range 16-87)</td>
</tr>
<tr>
<td>BMI</td>
<td>Mean 27.1 (SD 3.93)</td>
<td>Mean 27.9 (SD 4.01)</td>
<td>Mean 27.3 (SD 2.82)</td>
</tr>
<tr>
<td>PPI use*</td>
<td>68%</td>
<td>66%</td>
<td>66%</td>
</tr>
<tr>
<td>Prokinetic or laxative use</td>
<td>5%</td>
<td>4%</td>
<td>4%</td>
</tr>
</tbody>
</table>

*Appropriateness of prescription could not be assessed as vast majority presented on PPI therapy*
Rate of reflux micro-aspiration detection following referral for RASP was 26% (946 referred, 243 positives studies).

Reflux micro-aspiration

The most common symptom in patients with reflux micro-aspiration was regurgitation (72%), followed by cough (67%) and heartburn (66%). The most common two-symptom combination was heartburn and regurgitation, followed by cough and throat clearing. The most common three symptom combination was cough, heartburn, regurgitation followed by cough, regurgitation and throat clearing. Summary of symptoms of patients with reflux micro-aspiration can be found in table 2.

Table 2. Symptom prevalence in patients with reflux micro-aspiration (N = 243)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regurgitation</td>
<td>72.43%</td>
</tr>
<tr>
<td>Cough</td>
<td>67.49%</td>
</tr>
<tr>
<td>Heartburn</td>
<td>66.67%</td>
</tr>
<tr>
<td>Throat clearing</td>
<td>66.26%</td>
</tr>
<tr>
<td>Dysphonia</td>
<td>53.09%</td>
</tr>
<tr>
<td>Dyspnoea all</td>
<td>43.62%</td>
</tr>
<tr>
<td>Sore throat</td>
<td>42.39%</td>
</tr>
<tr>
<td>Regurgitation (throat)</td>
<td>25.10%</td>
</tr>
<tr>
<td>Laryngospasm</td>
<td>23.87%</td>
</tr>
<tr>
<td>Chest pain atypical</td>
<td>22.63%</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>21.81%</td>
</tr>
<tr>
<td>Dysphagia (slow)</td>
<td>20.99%</td>
</tr>
<tr>
<td>Dyspnoea (exercise induced)</td>
<td>18.93%</td>
</tr>
<tr>
<td>Bloating</td>
<td>17.70%</td>
</tr>
<tr>
<td>Dyspnoea (post prandial)</td>
<td>5.35%</td>
</tr>
<tr>
<td>Flatus</td>
<td>4.94%</td>
</tr>
<tr>
<td>Voice change</td>
<td>3.70%</td>
</tr>
<tr>
<td>Regurgitation (low)</td>
<td>3.29%</td>
</tr>
<tr>
<td>Odynophagia</td>
<td>1.23%</td>
</tr>
</tbody>
</table>
Patients self-reported medical diagnosis as “symptoms” including asthma as a child (4.53%), as an adult (5.35%), pneumonia (5.76%), and bronchitis (18.52%). Accuracy of these diagnosis as well as criteria on which they were based were unable to be verified.

Pharyngeal reflux contamination

Patients with pharyngeal contamination most commonly presented with regurgitation (71%), heartburn (68%) and throat clearing 67%. Most common two-symptom combination was heartburn/regurgitation, followed by regurgitation/throat clearing and cough/throat clearing. Top three symptom combination included heartburn/regurgitation/throat clearing, cough/regurgitation/throat clearing and dysphonia/regurgitation/throat clearing.

Summary of symptoms of patients with pharyngeal contamination supine and upright is presented in table 3.

Table 3. Symptoms prevalence amongst patients with pharyngeal contamination whilst supine and upright

<table>
<thead>
<tr>
<th>Symptom</th>
<th>patients with supine pharyngeal contamination n=230</th>
<th>patients with upright pharyngeal contamination n=298</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regurgitation</td>
<td>71.81%</td>
<td>70.87%</td>
</tr>
<tr>
<td>Heartburn</td>
<td>68.46%</td>
<td>67.39%</td>
</tr>
<tr>
<td>Throat clearing</td>
<td>67.79%</td>
<td>66.09%</td>
</tr>
<tr>
<td>Cough</td>
<td>62.75%</td>
<td>64.35%</td>
</tr>
<tr>
<td>Dysphonia</td>
<td>57.05%</td>
<td>54.35%</td>
</tr>
<tr>
<td>Sore throat</td>
<td>47.32%</td>
<td>46.09%</td>
</tr>
<tr>
<td>Mucous</td>
<td>41.61%</td>
<td>44.78%</td>
</tr>
<tr>
<td>Globus sensation</td>
<td>38.26%</td>
<td>42.17%</td>
</tr>
<tr>
<td>Dysphagia (typical)</td>
<td>36.24%</td>
<td>36.96%</td>
</tr>
<tr>
<td>Laryngospasm</td>
<td>28.52%</td>
<td>28.70%</td>
</tr>
<tr>
<td>Bloating</td>
<td>23.15%</td>
<td>28.26%</td>
</tr>
<tr>
<td>Chest pain atypical</td>
<td>22.82%</td>
<td>25.22%</td>
</tr>
<tr>
<td>Regurgitation (throat)</td>
<td>22.15%</td>
<td>23.04%</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>21.81%</td>
<td>22.17%</td>
</tr>
<tr>
<td>Dysphagia (slow)</td>
<td>18.79%</td>
<td>21.74%</td>
</tr>
</tbody>
</table>
Cluster analysis

Whist no specific symptom clustering was observed in relationship to aspiration, two distinct symptom clusters emerged demonstrated in figures 1 and 2 [insert figure 1 and 2]. The first cluster was of laryngospasm, voice change, aspiration, and atypical chest pain and second cluster of nausea, vomiting, early satiety, bloating, flatus, pneumonia, asthma, diarrhoea, dyspepsia, and lethargy.

Discussion

Aspiration of gastric refluxate has been long recognised as a less common form of GORD (12-15). It can lead to pulmonary complications including adult-onset asthma, chronic cough, and pulmonary fibrosis (16-20).

Reflux micro aspiration has been suspected in adults and children with chronic unexplained respiratory symptoms. However, no current recommendations exist in whom possibility of GORD should be interrogated early for fear of pulmonary disease (21-25).

The diagnosis of atypical or extra-oesophageal manifestations of GORD can be challenging. For example, patients presenting with laryngo-pharyngeal reflux (LRP) to this

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Exercise Induced</th>
<th>Post Prandial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnoea</td>
<td>14.09%</td>
<td>16.52%</td>
</tr>
<tr>
<td>Early satiety</td>
<td>10.07%</td>
<td>13.48%</td>
</tr>
<tr>
<td>Flatus</td>
<td>6.71%</td>
<td>6.52%</td>
</tr>
<tr>
<td>Voice change</td>
<td>4.70%</td>
<td>5.22%</td>
</tr>
<tr>
<td>Regurgitation (low)</td>
<td>3.69%</td>
<td>3.91%</td>
</tr>
<tr>
<td>Odynophagia</td>
<td>2.68%</td>
<td>3.91%</td>
</tr>
</tbody>
</table>
service tend to be 8 years older than those presenting with typical GORD, many of whom spent years between subspeciality medical services without diagnosis (10).

The aim of this study was to examine common clinical symptom patterns amongst patients with proven reflux aspiration. We have discovered that commonly patients with reflux aspiration would present with a combination of typical GORD symptoms (most commonly regurgitation and heartburn) and respiratory symptoms such as cough or throat clearing.

Cluster analysis revealed two distinct patterns of symptoms clustering. The first cluster included aspiration associated with laryngospasm, voice change, and atypical chest pain, most suggestive of volume proximal reflux and possibly impaired pharyngeal guarding and/or clearance. The second cluster included symptoms of nausea, vomiting, early satiety, bloating, flatus, pneumonia, asthma, diarrhoea, dyspepsia, and lethargy suggestive of motility related irritable bowel syndrome-like symptoms which were associated with pulmonary complications of the reflux aspiration. This raises the question of reflux aspiration being associated with IBS in a group of patients. Global gut dysmotility has been proposed as one of the pathophysiological explanation for IBS (26). Furthermore, bloating and constipation has been associated with refractory GORD and LPR (27). Can two of the diseases (IBS and reflux aspiration) be related? We have previously demonstrated a link between dysmotility and aspiration (10), in this study have demonstrated clustering of IBS symptoms in patients with proven reflux aspiration. The connection seems plausible, however specific studies in patients with confirmed IBS are needed to test for a possible relationship.

Typical GORD symptoms such as regurgitation can be overlooked by clinicians and not presented by patients as both concentrate on heartburn. The results of this study demonstrated this to be the most common symptom in patients with reflux aspiration and
made apparent by experienced questioning. We therefore suggest taking focused GORD symptom history in patients presenting with chronic cough unexplained by most common causes such as smoking, ACE inhibitor use and post-nasal drip. The use of validated questionnaires such as Hull Airways Reflux Questionnaire can be helpful to further select patients requiring a confirmatory test to demonstrate aspiration or proximal pharyngeal reflux.

Patients with reflux micro-aspiration can present with isolated respiratory complaints, usually cough, with little-to-no typical symptoms of GORD such as heartburn or retrosternal chest pain. Multiple hypothesis have been proposed to explain this including aerosolised refluxate (airway reflux) producing little irritation to the digestive system (12). Amongst these patients eliciting symptoms related to the oesophageal dysmotility (such as slow transit dysphagia, globus, bloating and early satiety) can increase the index of suspicion of airway reflux as ineffective oesophageal motility is strongly associated with reflux micro-aspiration (10).

Proton pump inhibitors (PPI) which were prescribed in close to 70% of patients in this study can mask some of the typical GORD symptoms by reducing the acidity of the refluxate. Whist reducing the acidity of the refluxate, PPI have not shown to reduce the rate of reflux events, and possibly increase aspiration risk as the rates of community acquired pneumonia are increased amongst PPI users (28, 29).

Conventional GORD investigations such as endoscopy, impedance and pH monitoring have limited sensitivity in detecting proximal reflux and are unable to demonstrate reflux aspiration. Use of invasive tests such as salivary or bronchial lavage testing for pepsin has had conflicting evidence (5, 6, 30). Patients with suspected reflux aspiration should therefore
proceed onto confirmatory tests such as the modern precise reflux scintigraphy, which is inexpensive, non-invasive with excellent specificity (1, 11).

Multiple hypotheses of causative relationships between cough and reflux have been proposed including esophago-bronchial reflex hypersensitivity, laryngeal irritation by LPR and micro-aspiration (9, 31). The results of our study where participants were confirmed to have pulmonary reflux micro-aspiration and proximal (LPR) reflux would support both above-mentioned hypotheses.

A limitation of this study was in significant pre-selection bias as the decision to refer patients for RASP was based on the clinical judgement of a senior treating clinician. Generally, patients with combination of typical GORD symptoms and presence of extra-oesophageal symptoms or discordant findings of clinical history and impedance or manometry would prompt RASP study. Since RASP is not used to investigate all patients referred to this service, selection bias was introduced when patients were referred for scintigraphy. It was therefore difficult to perform comparison with patients in whom RASP study was negative for micro-aspiration, as the pre-test probability was very high by the virtue of referral to tertiary reflux institution and further pre-test selection by clinical suspicion based on history. Therefore, results cannot be generalised to all patients with typical or atypical GORD. Another limitation was lack of a control group to assess the specificity of the symptom patterns.

Another limitation of this study is a lack of use of validated questionnaires limiting ability to assess the sensitivity of such questionnaires.

Possible bias may have been introduced by the modification of the RASP technique, most significantly by addition of SPECT/CT in 2017. This is thought to increase sensitivity and specificity of the study, however to date has not shown to increase micro-aspiration detection rates.
The strength of this study is robust symptom recording and the use of validated RASP study to confirm reflux micro-aspiration and pharyngeal contamination.

**Conclusion**

The results of this study demonstrated that patients with reflux micro-aspiration most commonly present with a combination of a typical symptom or reflux such as heartburn and regurgitation and a throat, voice or respiratory symptoms such as cough, voice change or throat clearing. Presence of an unexplained cough in settings of regurgitation or heartburn should prompt clinicians to interrogate for presence of reflux micro-aspiration for the risk of chronic pulmonary disease.
Reference:

Figure 1.
Cluster analysis of the principal variables demonstrating clustering of symptoms of laryngospasm, voice change, aspiration, and atypical chest pain
Figure 2

Cluster analysis of the principal variables demonstrating clustering of symptoms of nausea, vomiting, early satiety, bloating, flatus, pneumonia, asthma, diarrhoea, dyspepsia, and lethargy.