

Anaphylaxis versus inducible laryngeal obstruction: a diagnostic dilemma

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SUMMARY

Inducible laryngeal obstruction (ILO) is an under-recognised cause of refractory breathlessness. It presents with an acute onset of difficulty in breathing and is often mistaken for respiratory conditions such as asthma or, in some cases, anaphylaxis. People with ILO often report recurrent Accident & Emergency attendances and have long-term drug treatments initiated and escalated inappropriately. The cornerstone of ILO management is speech and language therapy, and it is essential that cases are identified promptly to ensure they are managed correctly. By doing this, patients can be supported with education and therapeutic strategies, thus reducing associated distress, unnecessary pharmacotherapy and overall healthcare utilisation. In this case study, we describe a patient who was diagnosed and successfully treated for ILO after initially being investigated for recurrent anaphylaxis. She had a significant symptom burden with multiple hospital admissions and relied on epinephrine to manage these episodes. Following specialist assessment and treatment, she was subsequently weaned off potentially dangerous medications that were not clinically indicated, while reporting a marked improvement in her quality of life (see Patient's perspective below).

BACKGROUND

Inducible laryngeal obstruction (ILO) typically presents with breathlessness of sudden onset, caused by paradoxical adduction of the vocal folds at glottic and/or supraglottic level causing laryngeal airflow obstruction¹ (figure 1). Symptoms are distressing for the patient and include dyspnoea, wheeze, stridor, throat tightness and globus. They often mimic conditions like asthma and anaphylaxis, and can be so severe that they require treatment in level 3 critical care facilities.^{2,3} Given this, and the risk to life associated with severe asthma attacks and anaphylaxis, it is extremely important that teams investigating ILO work closely with appropriate specialists to differentiate ILO from severe asthma and allergy.

Asthma + Lung UK estimate that there are currently 5.4 million people living with asthma in the UK.⁴ Several studies suggest that ILO coexists in approximately one-third of severe asthma patients (with approximately 10% of asthma patients being severe), which indicates a population of at least 180 000 patients.^{5,6} The total prevalence is likely to be much higher, however, as a recent registry paper looking at the clinical characteristics and impact of ILO in the UK showed that 32% of ILO patients did not have asthma.⁷ In an attempt to describe

this patient cohort more accurately, Koh *et al*⁸ have recently proposed phenotypes with associated clinical characteristics; (1) classical ILO, (2) lung-associated ILO, (3) exercise-associated ILO and (4) incident-associated ILO. Incident-associated ILO describes the subgroup of patients who are often misdiagnosed as anaphylaxis or allergic reactions, with a key role for allergists in recognising this phenotype.⁸

The prevalence of anaphylaxis misdiagnosis in an ILO population is currently unknown. Misdiagnosis can result in inappropriate treatment escalation, is both time and resource costly, and leads to significant patient morbidity.⁹ To this end, ILO is now recognised as an important differential diagnosis included in the 2023 revision of the Brighton Collaboration case definition for anaphylaxis.¹⁰ We previously developed an infographic to try and help patients and healthcare professionals identify the main differences between ILO and anaphylaxis,³ specifically in relation to symptom onset and treatment.

An added diagnostic challenge in this patient group is that some patients may have both ILO and anaphylaxis, which can be especially difficult to manage. We have also observed ILO alongside spontaneous angioedema and urticaria. This emphasises the importance of close multi-disciplinary working, with comprehensive allergy work-up and careful consideration of laryngeal provocation as part of patient assessment. To safety net more challenging cases with overlapping symptomology, our team conducts laryngeal provocation jointly with allergy colleagues if needed. Joint assessment on the allergy unit allows for closer observation of these patients, with development of a clear and unified management plan. Biofeedback during laryngoscopy here also supports patient understanding, reassurance and buy-in to speech & language therapy treatment should this be indicated.

CASE PRESENTATION

A woman in her 40s presented with severe episodes of throat tightness over a period of approximately 3 years. She had a medical history including rheumatoid arthritis, Sjögren's syndrome, fibromyalgia and hypertension. She reported that these episodes initially started immediately after taking certain medications (specifically daclizumab and rituximab for her autoimmune disease) but had also recently begun happening in response to environmental triggers such as aerosols, smoke or even without apparent external provocation. She had a difficult admission in 2021 following the COVID-19



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Figure 1 Example of inducible laryngeal obstruction as seen via a fibreoptic laryngoscope. Classical paradoxical vocal fold movement with closure of the anterior two-thirds and posterior glottal chink (arrow).

vaccine, where she was initially treated for anaphylaxis. She required treatment in critical care, including a brief period of intubation and invasive ventilation. The patient had subsequent difficulties with extubation and sepsis, resulting in a 5-week stay in the critical care unit.

After this admission, the patient continued to attend her local Accident & Emergency for recurrent throat symptoms. She was subsequently referred to our specialist airways team by her local allergy service as, following their investigations, they did not feel her presentation was typical for anaphylaxis. Nonetheless, the patient continued to have repeated episodes of severe throat tightness and reported 'wheeze' for which she was taking concerning levels of epinephrine; up to 10 EpiPen injections per day, with limited effect. While we suspect it to be the case, it was initially unclear from secondary care documentation whether this 'wheeze' was in fact inspiratory stridor, which is more commonly associated with ILO (and indeed anaphylaxis with laryngeal involvement). During her initial assessment with our service, she reported increasing difficulty in living a normal life, and high levels of stress were exacerbating her overall symptom burden and frequency.

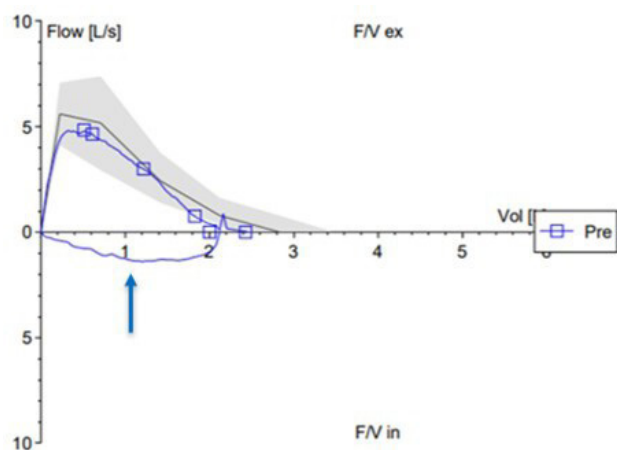


Figure 2 Example of flow-volume loop with flattened inspiratory limb (arrow), which can be suggestive of inducible laryngeal obstruction.

INVESTIGATIONS

At our multidisciplinary clinic, with a speech and language therapist (SLT), physiotherapist, nurse specialist and respiratory consultant physician, we noted a significant breathing pattern disorder (BPD) with no nasal breathing, a thoracic-dominant pattern and forced expiration. There was no clinical evidence of asthma and lung function was essentially normal. While there were no concerns about spirometry in this case, flattening of the inspiratory loop can be suggestive of ILO¹¹ and form part of initial diagnostic hypotheses prior to further investigations or escalations (figure 2). It is important to note that while spirometry is an important part of a diagnostic work-up, it should not be used in isolation to diagnose ILO.¹²

At laryngoscopy, the larynx was structurally normal but excessive tension at rest was noted, with increased lateromedial and anteroposterior squeeze on phonation and evident laryngeal hypersensitivity. The patient was mildly symptomatic at rest but declined provocation with aerosols based on previous experience and trauma. While laryngoscopy with provocation is the gold-standard diagnostic tool for ILO, a 2023 international Delphi consensus study¹² emphasises the importance of identifying concurrent clinical features to provide a clinical perspective and guide judgement. This is particularly relevant in this case, as we know that a normal provocation laryngoscopy does not exclude ILO as a diagnosis. Consequently, we believed that, in the absence of allergy-specific indicators, her symptoms were strongly suggestive of a combination of ILO and BPD, even though we were unable to elicit true paradoxical movement during our assessment.

The working diagnosis of ILO was supported by medical reports from her recurrent acute admissions which documented throat tightness, audible 'upper airway noises' (with no cardiorespiratory compromise or wheeze on the chest) and no observable tongue or mouth angioedema.

DIFFERENTIAL DIAGNOSIS

The main differential diagnoses relevant to this case were anaphylaxis and asthma. Prior to her referral for suspected ILO, the patient had a comprehensive allergy work-up with her local team who felt that they could confidently rule out anaphylaxis based on her clinical presentation and observations from acute admissions (including mast cell tryptase levels which were not elevated during hospital attendances).

To rule out asthma, we obtained a full case history. Here, the patient continued to identify that she felt a restriction at the level of her throat, rather than her chest. The patient completed relevant blood tests including a full blood count, antineutrophil cytoplasmic antibodies, total IgE and common allergy screen. She also completed basic spirometry and fractional exhaled nitric oxide testing. All tests were normal, and the clinical index of suspicion of asthma was not felt to be high enough to warrant bronchial challenge testing. Her case was further discussed in our multidisciplinary meeting, with results reviewed by a specialist respiratory consultant, before we proceeded to provocation laryngoscopy as described above.

TREATMENT

The patient was provided with education and initial advice (specifically ILO-control exercises and laryngeal deconstriction). She was amenable to the ILO diagnosis but understandably reluctant to stop using her EpiPen injections. With further discussion and reassurance from her allergy team, the patient agreed to trial breathing control before reaching

for epinephrine. She was followed up closely by SLT and referred to our team's clinical psychologist. Following her first SLT outpatient appointment, the patient felt more confident and had an increased awareness of the differences between ILO and anaphylaxis. A lot of time was spent reframing her perception of 'allergens' versus upper airway 'triggers' or 'irritants'.

In a short period of time, the patient had reduced her EpiPen use from approximately 10 per day to once a month and was working towards stopping them completely. She began acknowledging a placebo effect with epinephrine and was managing her panic response and anxiety well with the support of our psychologist. Her local allergy team supported our approach by continuing to reiterate that her attacks in response to foods or environmental triggers were not true allergic responses.

OUTCOME AND FOLLOW-UP

Following four sessions of SLT treatment, the patient was controlling her symptoms well but identified some residual laryngeal irritation. She reported benefit to her laryngeal symptoms when she had previously been prescribed morphine for rheumatoid arthritis. As a lot of her attacks of acute throat tightness began with a laryngeal cough, likely exacerbated by the dryness caused by her Sjögren's, the use of low-dose slow-release morphine sulfate (5 mg two times per day) was subsequently discussed as a means of optimising laryngeal hypersensitivity, as is commonly used in refractory cough.¹³ This improved her residual symptoms and was associated with a subsequent complete cessation of epinephrine use.

Within a 12-month period, the patient saw a marked improvement in her overall quality of life and was better able to manage symptoms that had previously been incredibly debilitating. She was able to return to work and even participate in clinical research to support prospective patients.

DISCUSSION

This case study, consistent with similar clinical scenarios described by Stojanovic *et al*,¹⁴ emphasises the importance of multidisciplinary management in complex breathlessness. Once acute episodes have been properly investigated by physicians with allergy-specific expertise, cases refractory to high-dose epinephrine should prompt consideration of ILO and close liaison with SLT.¹⁵ For clinicians outside of specialist centres, resources such as the recent severe asthma toolkit¹⁶ can be considered to support clinical hypotheses and onward referral to specialist teams. However, ILO diagnosis should not be made without tertiary systematic and multidisciplinary assessment.

There remains a limited literature addressing this clinical question and, in response, Stojanovic *et al*¹⁴ have proposed a systematic approach to manage patients with ILO that mimics symptoms in anaphylaxis, with appropriately supervised 'allergen' challenges. Prospective research should continue to focus on collaborative working between clinicians in allergy and laryngeal dysfunction, with a view to develop clear clinical pathways and standardise treatment for these patients.

Patient's perspective

The first time that I experienced my symptoms, they were thought to be due to severe anaphylaxis, after previously being placed in an induced coma for an allergic reaction to the Covid vaccine. The symptoms mimicked an anaphylactic reaction with throat tightening, difficulty breathing, feeling lightheaded, facial and neck redness and choking. Initially ambulance and medical staff in the Emergency Room resuscitation bay treated it as anaphylaxis and couldn't understand why adrenaline wasn't working. No one seemed to know what was happening to me and on occasions it was suggested it could be a panic attack or a mental health problem, which was very frustrating. I felt extremely scared and like I was going to die on a daily basis.

After a year I was referred to the Manchester Airways team. I spent a day discussing symptoms, having diagnostic tests and discussing breathing techniques with speech therapy. I was given a diagnosis of ILO. I was shown breathing techniques and how to respond and cope with an attack. I felt very emotional and relieved to finally understand what was happening to me, but also angry and frustrated that medical professionals that I'd previously seen had misdiagnosed me.

Since having SLT I understand what triggers my ILO episodes off and try to avoid triggers such as strong smells, dust, stress, extreme temperature changes. I can now differentiate between a true anaphylactic reaction and an ILO attack which results in using less Epipens and fewer hospital emergency visits. It has been life changing getting a diagnosis and learning to cope with ILO. I pray that there is wider education about ILO made available for medical professionals.

Learning points

- ▶ Patients who initially present with anaphylactic-type symptoms should always be investigated by a specialist allergy team in the first instance.
- ▶ In cases where allergy/anaphylaxis is ruled out, inducible laryngeal obstruction (ILO) should be considered as part of differential diagnoses.
- ▶ ILO misdiagnosis can result in inappropriate medical escalation, increased time and financial costs, and increased patient morbidity.
- ▶ Collaborative working between allergy and airways teams is key in providing effective assessment and treatment of this patient cohort.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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