Brief Insight about Psychological Impact of Achalasia

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Abstract

A number of factors may increase the risk for mental health problems in patients with achalasia. Individuals living with a chronic medical condition such as achalasia have been shown to be more likely to develop depression or anxiety. In addition to the psychological burden resulting from symptom load, social and functional impairments may contribute to depressive and anxiety symptoms. Patients with achalasia have reported that their condition conflicted with their social activities, interpersonal relationships, and leisure activities. However, lacking assessment of disorder-specific mental health outcomes such as depression or anxiety limits the clinical relevance of findings and healthcare providers' ability to provide targeted intervention recommendations. Information concerning health-related quality-of-life (HRQoL) in achalasia patients is limited to studies in which non-validated questionnaires were used and to uncontrolled series after Heller myotomy.4–9 Most of these studies report substantially improved HRQoL after Heller myotomy. Data concerning HRQoL after pneumatic dilation is lacking. Besides the limitations of existing data, it is unknown whether remaining achalasia-associated symptoms affect HRQoL or to what extent clinical remission (as defined by symptom scores) is associated with restored HRQoL

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Introduction

Achalasia is a primary esophageal motor disorder of unknown etiology characterized manometrically by insufficient relaxation of the lower esophageal sphincter (LES) and loss of esophageal peristalsis [1].

Idiopathic achalasia is rare, with mean incidences of 0·3–1·63 per 100 000 people per year in adults and 0·18 per 100 000 people per year in children younger than 16 years [2].

In adults, achalasia occurs with equal frequency in men and women and in white and nonwhite people, but incidence increases with age. In most studies, the mean age at diagnosis was over 50 years [3].

Mean incidence in those aged over 80 years is 17 per 100 000 people per year (95% CI 2–61). Mean prevalence was 8·7 per 100 000 people in a study from Iceland, whereas it was 10·8 per 100 000 people in a Canadian population-based study [4].

In both studies, the prevalence increased over time, whereas the incidence remained constant, most likely because achalasia is a chronic disorder with a low disease-related mortality rate. In an attempt to identify potential causative or environmental factors, Farrukh and colleagues studied the epidemiology of achalasia in the immigrant South Asian population in Leicester (UK) [4].

Over 20 years, no changes in frequency of achalasia were reported, arguing against potential environmental factors as triggers of the disease. The finding that autoimmune diseases such as type 1 diabetes mellitus, hypothyroidism, Sjögren's syndrome, and uveitis are more prevalent in patients with achalasia than in the general population suggests that achalasia might have an autoimmune component [5].

Achalasia was divided into primary and secondary Achalasia. In primary Achalasia, the exact etiology is unknown, probably caused by neurotropic virus infection resulting in dorsal vagal nucleus lesion in the brainstem and mesenteric ganglia in the esophagus. A hereditary factor also has a role in this disorder. Otherwise, secondary Achalasia was caused by infection, intraluminal tumor such as cardia tumor, extraluminal pressure from pancreatic pseudocyst, anticholinergic drugs, or post-vagotomy operation [6].

Dysphagia of both solid and liquid food was the most common symptoms of achalasia, followed by regurgitation, chest pain, nausea, vomiting, weight loss, and night cough [7].

In patients with Achalasia, this symptom could be caused by gastric acid retention or toxin produced by fermented lactate by bacteria in the esophagus. Achalasia was divided into three types (Figure 1) based on its motility [8].

Achalasia is a heterogeneous disease categorized into 3 distinct types based on manometric patterns: type I (classic) with minimal contractility in the esophageal body, type II with intermittent periods of panesophageal pressurization, and type III (spastic) with premature or spastic distal esophageal contractions (Figure 1). These subtypes have subtle differences in clinical presentation but have distinct responses to various treatment modalities, including pharmacologic, endoscopic, and surgical [1].

There were several diagnostic modalities to evaluate Achalasia, such as manometry, barium esophagogram, esophagoduodenoscopy, and esophagus CT-scan [9].

Nutrition in patients with achalasia is often overlooked because it is presumed that treatment of LES restrictive physiology should resolve dysphagia and normalize oral intake [1].

Physiologically, a low-fiber diet (defined as a maximum of 10 g of fiber/day) could be considered in these patients, similar to patients who have small bowel strictures. Soluble fiber increases the viscosity of the bolus, which reduces absorption, and insoluble fiber possesses high water-binding capacity and increases the bulk of the bolus [10].

Thus, in the setting of high LES pressure (physiologic obstruction) in patients with achalasia, a low-fiber diet would potentially allow easier passage through a small narrowing. Some patients with significant weight loss and severe malnutrition may need to switch to high-calorie and -protein liquids, which should be coordinated under the guidance of a registered dietitian due to the potential risk of refeeding syndrome [10].

However, it should be noted that despite concerns of significant weight loss in this population, refeeding syndrome has been rarely reported in the literature, with only 1 case report of new-onset Wernicke encephalopathy in a pregnant woman with achalasia. There is also significant overlap between clinical presentations of eating disorders and achalasia, which can often lead to misdiagnosis, especially in young women [7].

Despite achalasia initially being described nearly 300 years ago, the underlying etiology and molecular pathology of why patients develop this disease are still vastly unclear. This lack of clarity is the primary reason that the treatment of achalasia has not evolved significantly over the years from primarily using brute force (pneumatic dilatation (PD), surgical myotomy, or peroral endoscopic myotomy [POEM]) to mechanically disrupting the LES [1].

The primary etiology of achalasia is thought to be selective loss of inhibitory neurons in the myenteric plexus of the distal esophagus and LES, resulting in a neuronal imbalance of excitatory and inhibitory activity. Excitatory neurons release acetylcholine, while inhibitory neurons primarily release vasoactive intestinal peptide (VIP) and nitric oxide (NO) [11].

A localized decrease of VIP and NO with unopposed excitatory activity causes failure of LES relaxation and loss of esophageal peristalsis (Figure 2). Multiple studies have suggested a possible association between achalasia and infections, including parasitic and viral ones [12].

Dysphagia is considered an alarm symptom that mandates the performance of esophagogastro-duodenoscopy (EGD) as an initial diagnostic modality to exclude structural or mucosal lesions in the esophagus or the stomach cardia. Examples of these include tumors, inflammation, esophageal rings, strictures, and other pathologies that can mimic achalasia, a condition traditionally named pseudochalasia [13].

Classic endoscopic findings of achalasia present in about half of the cases include widening of the esophagus, residue in the esophageal lumen, and obstructed EGJ. An additional important diagnosis is eosinophilic esophagitis (EoE), an immune-mediated/allergic disorder involving the esophagus causing dysphagia and diagnosed by eosinophils predominant inflammation [13].

Multiple biopsies are mandatory to confirm the diagnosis. Indicative endoscopic findings of EoE include mucosal thickening and edema, ring formation, and white patchy exudates and fibrosis in the late stage. After the exclusion of anatomical, structural, and inflammatory conditions, HRM

study is necessary to assess the esophageal motor function and the relaxation of the lower sphincter [13].

Oral pharmacologic therapies are the least effective treatment options in achalasia. Calcium channel blockers and long-acting nitrates are the two most common medications used to treat achalasia. They transiently reduce LES pressure by smooth muscle relaxation, facilitating esophageal emptying. The phosphodiesterase-5-inhibitor, sildenafil, has also been shown to lower the LES tone and residual pressure in patients with achalasia [14].

Other less commonly used medications include anticholinergics (atropine, dicyclomine, cimetropium bromide), β-adrenergic agonists (terbutaline), and theophylline. Overall, calcium channel blockers decrease LES pressure by 13–49% and improve patient symptoms by 0–75%. The most commonly employed calcium channel blocker is nifedipine, showing time to maximum effect after ingestion of 20–45 min with a duration of effect ranging from 30 to 120 min [15].

Thus, it should be used (10–30 mg) sublingually 30–45 min before meals for the best response. Sublingual isosorbide dinitrate is also effective in decreasing LES pressure by 30–65%, resulting in symptomatic improvement ranging from 53 to 87%. It has a shorter time to maximum reduction in LES pressure (3–27 min) than sublingual nifedipine but also has a shorter duration of effect (30–90 min) [16].

Hence, sublingual isosorbide dinitrate (5 mg) is commonly administered only 10–15 min before meals. The only comparative study of sublingual nifedipine to sublingual isosorbide dinitrate showed a nonsignificant edge in LES pressure reduction with the latter (65%) than the former (49%) [1].

The clinical response with pharmacologic agents is short-acting, and the side effects, such as headache, hypotension, and pedal edema, are common limiting factors in their use. Furthermore, they do not provide complete relief of symptoms. Thus, these agents are commonly reserved for patients with achalasia who cannot or refuse to undergo more definitive therapies (PD or surgical myotomy) and those who have failed botulinum toxin injections [17].

Although the current treatments for achalasia are effective, PD is associated with a perforation risk of 1.9%, and myotomy still requires laparoscopy and dissection of the EGJ. Thus, there has been interest in developing hybrid techniques that incorporate an endoscopic approach with principles of NOTES (natural orifice transluminal endoscopic surgery) to perform a myotomy. This technique was developed in Japan and is termed POEM (peroral esophageal myotomy) [18].

The procedure requires the creation of a submucosal plane using a forward-viewing endoscope with a distal transparent cap to access the circular muscle fibers for the performance of the myotomy. An endoscopic submucosal dissection knife is used to dissect the plane and also cut the muscle over a minimum length of 6 cm into the esophagus and 2 cm below the squamocolumnar junction onto the cardia [19].

Overall, the success rate, defined by an improvement in symptoms and no requirement of additional medical or surgical treatment, in prospective cohorts have been > 90%, and this does

appear to have promise as an alternative to the laparoscopic approach. Randomized prospective comparison trials with standard laparoscopic myotomy and/or PD are needed, and POEM should only be performed in the context of clinical trials with the understanding that other effective well-studied alternatives are available [20].

A natural evolution of endoscopic technique for the treatment of achalasia would logically lead to the creation of a stent that could be placed across the EGJ to maintain patency without developing severe reflux. The dilation protocol was much less aggressive than the standard technique used in the United States and Europe as the maximal diameter used was 32 mm. These results revealed that the 30 mm stent had an 83% success rate at 10 years, whereas the success rate for the 20 mm stent and dilation protocol was 0% [21].

Long-term management:

As a result of functional obstruction, large amounts of food and saliva can be retained within the esophagus, especially if treatment is suboptimal. Increased bacterial growth and chemical irritation from the continuous decomposition of food and saliva can induce chronic hyperplastic esophagitis, dysplasia, and eventually malignant transformation of esophageal epithelial cells. The risk of esophageal carcinoma varies substantially, ranging from ten to 50 times in patients with achalasia compared with the general population [22].

Because one of the main symptoms of esophageal carcinoma, dysphagia, is frequently attributed to exacerbation or recurrence of achalasia, diagnosis of esophageal carcinoma is often delayed, explaining the poor prognosis in achalasia [23].

This situation raises the question of whether an endoscopic surveillance program should be initiated for early detection of cancer. However, so far no consensus on this topic has been reached for several reasons [22].

First, the death rate from esophageal cancer diagnosed during a surveillance program is not different from that of the normal population. Second, endoscopic surveillance is difficult in patients with achalasia because the whole segment is at risk, the mucosa is often covered with food debris and has a cobblestone appearance, and random biopsies might not be representative. Third, the cost-effectiveness of a surveillance program is dubious because the incidence of cancer is low. However, screening programs undertaken so far used standard white light endoscopy [24].

With the introduction of high-resolution endoscopy and chromoendoscopy with Lugol's staining, the sensitivity to detect premalignant lesions has significantly improved [24].

• Achalasia follow-up

Despite treatment, a proportion of patients will experience ongoing or recurrent symptoms that significantly impair quality of life. In some cases, treatment does not lead to meaningful improvement in the first place (persistent symptoms). In others, a period of initial improvement is followed by subsequent recurrence. In general terms, the former suggests that initial treatment was incomplete, whereas the latter can be due to a variety of causes. There is no universal definition of

what constitutes persistence or recurrence of symptoms. In most trials, an Eckardt score of >3 or a <50% improvement in symptoms is regarded as treatment failure [25].

However, this fails to distinguish between dysphagia and alternative troublesome symptoms such as regurgitation or chest pain. Although dysphagia is the most common ongoing symptom after achalasia treatment, the etiology may be different from that in the treatment-naive setting [25].

Given the wide variety of potential causes of recurrent dysphagia, it is critical to undertake a comprehensive evaluation using objective testing in order to determine the pathophysiology underpinning the recurrent symptoms, and thus select the appropriate treatment. Conversely, in selected cases of persistent dysphagia, where the diagnosis of achalasia is beyond doubt, it may be appropriate to proceed immediately to further treatment without repeat testing (e.g., POEM after failure to improve with PD) [26].

Since the commonest causes of recurrent dysphagia are incomplete myotomy, post-treatment scarring, and esophageal stasis due to aperistalsis and functional dysphagia, objective testing should be targeted at these conditions. Timed barium esophagus (TBO) helps to determine if there is a persistent delay to esophageal emptying, but reports regarding its usefulness as a predictor of long-term treatment success are conflicting. HRM provides additional information on LOS pressure. Impedance planimetry might be a useful complementary tool to assess OGJ distensibility and determine treatment efficacy [27].

Psychological impact of achalasia

A number of factors may increase the risk for mental health problems in patients with achalasia. Individuals living with a chronic medical condition such as achalasia have been shown to be more likely to develop depression or anxiety [28, 29]. In addition to the psychological burden resulting from symptom load, social and functional impairments may contribute to depressive and anxiety symptoms. Patients with achalasia have reported that their condition conflicted with their social activities, interpersonal relationships, and leisure activities [30].

In a study by Ekberg et al., 41% of patients with dysphagia described experiences of panic and anxiety during meals, and over one-third (36%) stated that they avoided eating in the presence of others [31]. Despite the indication of increased psychological burden, information on the prevalence of specific mental health disorders, such as depression and anxiety, in patients with achalasia are scarce. A recent study demonstrated that patients with achalasia are more likely to develop depressive symptoms within one year of diagnosis than patients without achalasia [32].

Other available studies have assessed patients' general mental health status in terms of disease-specific and general quality of life, and few studies have included appropriate population controls [33, 34]. These studies suggest that patients with achalasia who do not respond to therapeutic treatment have worse mental health than the general population, whereas patients who showed reduced symptom load after therapeutic treatment did not report impaired mental health [34].

However, lacking assessment of disorder-specific mental health outcomes such as depression or anxiety limits the clinical relevance of findings and healthcare providers' ability to provide targeted intervention recommendations.

Information concerning health-related quality-of-life (HRQoL) in achalasia patients is limited to studies in which non-validated questionnaires were used and to uncontrolled series after Heller myotomy. Most of these studies report substantially improved HRQoL after Heller myotomy. Data concerning HRQoL after pneumatic dilation is lacking. Besides the limitations of existing data, it is unknown whether remaining achalasia-associated symptoms affect HRQoL or to what extent clinical remission (as defined by symptom scores) is associated with restored HRQoL.

Health-related quality-of-life (HRQoL), referring to the physical, psychological, and social domains of health, influenced by a person's perception of health, has become an important outcome in the treatment of patients with a chronic disease [35]. Disease-specific measures in particular have received much clinical interest in the last 20 years. The advantage of disease-specific measures is their ability to focus on those aspects of HRQoL that are related to specific health problems inherent to a particular disease and monitor changes within patients [36]. In fact, disease-specific HRQoL measures benchmark 'health' or 'clinical state' defined by factors that are relevant to the patient's perception of health. These properties would enable comparisons between groups of achalasia patients (e.g., surgery versus dilation, when used as an outcome measure) to be made. On the other hand, generic measures are more useful for comparisons across conditions and populations [36].

The goal of achalasia treatment is to relieve the symptoms caused by the disorder. Both, surgical (e.g., myotomy and peroral endoscopic myotomy [POEM]) as well as non-surgical procedures are available [37]. However, in some patients, optimal symptom control cannot be achieved, leaving these with long-term distress symptoms. We therefore hypothesized that this distress could be associated with an increased incidence of depression and anxiety disorders in achalasia patients as recently demonstrated for other esophagus-related diseases. Due to the rarity of the disease, such a question can only be answered by analyzing large patient registries [38].

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