

HOW TO DISTINGUISH IDIOPATHIC ACHALASIA FROM PSEUDOACHALASIA?

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received: 5.11.2020;

revised: 23.11.2020;

accepted: 15.1.2021

SUMMARY

Achalasia is a disorder characterized by insufficient relaxation of the lower esophageal sphincter and absent peristalsis. It is usually primary (idiopathic) achalasia, but it can also be secondary achalasia (pseudoachalasia). With a review of the literature, epidemiological data was gathered on achalasia in this paper, and followed up with presented etiopathogenetic mechanisms of achalasia. An optimal diagnostic algorithm along with the therapeutic possibilities in achalasia, from endoscopic to surgical methods of therapy, was analyzed.

The most common causes of pseudoachalasia and the mechanisms of this disorder are reported. In patients with dysphagia and suspected achalasia, it is important to distinguish idiopathic achalasia from pseudoachalasia, since pseudoachalasia most often occurs due to tumor infiltrations of the lower esophageal sphincter. In this paper, the importance of a timely and accurate diagnosis of pseudoachalasia in relation to idiopathic achalasia was shown.

Key words: achalasia - pseudoachalasia - malignant pseudoachalasia - high-resolution esophageal manometry - therapeutic approach

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INTRODUCTION

Achalasia is a disorder characterized by the impaired relaxation of the lower esophageal sphincter (LES) and the absent peristalsis of the esophageal body. It occurs more often as primary (idiopathic), but can also be secondary (pseudoachalasia) (Zaninotto et al. 2018, Oude Nijhuis et al. 2020a).

Although achalasia was reported in the literature as being a rare disease, the incidence and prevalence rates have been higher in recent decades than previously thought. Sadowski et al. 2010 and Gennaro et al. 2011 determined an incidence of 1.6 / 100,000 persons per year. Harvey et al. 2018 and Samo et al. 2017 presented similar results while on the other hand Van Hoeij et al. 2018 reported an incidence of 1.7 to 4.2/100,000 persons per year. The prevalence rate ranged between 5 and 17/100,000 persons per year (Samo et al. 2017, Van Hoeij et al. 2018). Achalasia is rare in childhood, with a frequency of 0.11 cases / 100,000 children, and is mainly associated with genetic mutations or syndromes such as Trisomy 21 and the Allgrove syndrome (Islam 2017, Franklin et al. 2014). In adults, it affects all ages and is equally represented in both sexes (Samo et al. 2017, Van Hoeij et al. 2018).

The etiopathogenesis of achalasia is still not sufficiently clarified. There is a loss of nitrergic innervation

whose damage leads to decreased latency and thus to an impaired relaxation of the LES (Chen 2016). There must be some initial trigger (neurotropic viruses or toxins) that causes an aberrant autoimmune response in genetically predisposed individuals, which leads to chronic inflammation and neuronal loss (Boeckxstaens et al. 2014). On the other hand, some data from the literature related to the familial occurrence of achalasia, support hereditary factors, not only as horizontal but also as vertical inheritance (Gordillo-González et al. 2011, Evsyutina et al. 2014). Furthermore, the Chagas disease, which is infectious and caused by *Trypanosoma cruzi*, can cause an autonomic dysfunction and vagal denervation in the digestive system and lead to the formation of megaesophagus and megacolon (Antinori et al. 2017, Carod-Artal 2018).

PSEUDOACHALASIA

Pseudoachalasia is a secondary achalasia where changes are found in the esophagus, which correspond to achalasia but have a malignant disease or non-malignant obstruction in the background. Of all cases of achalasia, pseudoachalasia accounts for about 2 to 5% (Campo et al. 2013, Ponds et al. 2017, Fabian et al. 2019). The most common is malignant pseudoachalasia, which can occur due to tumor infiltrations of the

esophagus distal part or myenteric plexus, tumor compression or enlarged lymph nodes, or as a part of the paraneoplastic syndrome (Schizas et al. 2020, Shafi 2019). Tumors that cause pseudoachalasia are the most common tumors of an esophago-gastric junction (EGJ) and gastric cardia, followed by small cell lung tumors, other metastatic tumors, and lymphoproliferative diseases. Interestingly, Hirano et al. 2016 in their review of lung tumor cases with pseudoachalasia showed that the etiology was probably caused by a paraneoplastic neurological syndrome, not directly by esophageal invasion. The 2004 Consensus (Graus et al. 2004) proposed diagnostic criteria for paraneoplastic neurological syndromes (PNS) that are defined as definite or possible. This means that if no tumor is identified and / or serologically confirmed onconeural antibodies, there are difficulties in distinguishing a true PNS from neurological syndromes that coincide with tumors. Additionally, amyloidosis and pseudocysts of the pancreas are most mentioned as the cause of obstructive non-malignant diseases, while other causes are the condition after fundoplication and the ligation of gastric varices (Schizas et al. 2020).

According to latest European guidelines (Oude Nijhuis et al. 2020a), it is necessary to exclude pseudoachalasia only in achalasia patients where risk factors can be found, such as in older aged patients (≥ 55 years) with a shorter duration of symptoms (≤ 12 months) and significant weight loss (≥ 10 kg) as well as with endoscopically significantly heavier passage through the LES. Furthermore, Ponds et al. 2017 and Oude Nijhuis et al. 2020a, stated that patients who have ≥ 2 of the risk factors, should have additional diagnostic tests performed such as multislice computed tomography (MSCT) or endoscopic ultrasound (EUS) to exclude pseudoachalasia. Distinguishing idiopathic achalasia from pseudoachalasia can be challenging because of the same clinical features and initial testing results, such as esophagogram findings, endoscopy, and esophageal manometry (Ponds et al. 2017; Schizas et al. 2020). According to literature data, pseudoachalasia was falsely treated as idiopathic achalasia in 24% of all cases (Schizas et al. 2020); as well as 28% of pseudoachalasia cases were only diagnosed during the second or third endoscopic examination with biopsy (Ponds et al. 2017). It should be noted that clinical risk factors, along with numerous diagnostic methods, can contribute to the correct diagnosis of malignant pseudoachalasia in patients with an initial diagnosis of idiopathic achalasia.

Pseudoachalasia and renal cell carcinoma

Our team of researchers (Troškot Perić et al. 2020) recently reported a case of bilateral synchronous renal adenocarcinoma that was clinically manifested by dysphagia, progressive weight loss, and in which the manometric finding indicated achalasia. In the case of our patient, after the achalasia was determined, and

additional examinations were performed, during which tumors were found on both kidneys, a multidisciplinary team was formed to decide on further treatment. As the dominant symptoms were dysphagia and weight loss, and no metastatic kidney tumor diseases were found, achalasia therapy was performed first and followed by renal surgeries. After the first pneumatic balloon dilatation, another dilatation was performed, which achieved an adequate clinical response (Eckardt symptom score < 3). The improvement of this score is the most important clinical parameter for assessing the effect of either endoscopic or surgical therapy in patients with achalasia (Zaninotto et al. 2018). It is important to stress that it was necessary to conduct achalasia therapy, which relieved the patient of symptoms but also improved his nutritional status. This therapy enabled further treatment, i.e. kidney tumor surgeries.

Generally speaking, pseudoachalasia in patients with renal cell carcinoma (RCC) is rare. Cabezas-Camarero et al. 2015 stated that out of 68 cases of RCC with gastric metastases (GM) and esophageal metastases (EM), 64 of them were gastric, and 6 cases were esophageal metastases (in 2 cases both GM and EM were present). Schizas et al. 2020 analyzed the results of 35 studies with a total of 140 patients with pseudoachalasia. The metastatic RCC was reported as the cause of pseudoachalasia in only two patients (1%). In their review, 2/3 of all patients were male who had a shorter duration of symptoms (median time of 5 months). Here, in most published case reports until now, there were metastases of the RCC or in the esophagus, or in the lymph nodes of the EGJ area; in some patients up to 10 years after nephrectomy. Furthermore, Bhalme et al. 2009 described the first case of dysphagia resulting from the paraneoplastic syndrome in a patient with occult RCC, although they failed to demonstrate anti-neuronal antibodies. In recent literature, there are several case reports of an association between RCC and achalasia: Lamm et al. 2018 showed a patient diagnosed with achalasia due to the paraneoplastic syndrome as part of RCC, while Padda & Si 2019 described a patient with dysphagia caused by the metastasis of an undiagnosed RCC. In Padda's report, a detailed upper endoscopy revealed a tumor formation on the EGJ.

DIAGNOSIS OF ACHALASIA

In patients with achalasia, the most common symptoms are dysphagia (90%), heartburn (75%), regurgitation and / or vomiting (45%), non-cardiogenic chest pain (20%), while epigastric pain (15%) and odynophagia ($< 5\%$) are less common. Respiratory symptoms are most often associated, such as cough and asthma (20-40%), chronic aspiration (20-30%), hoarseness or sore throat (33%) and unintended weight loss (10%) (Pandolfino & Gawron 2015). The Eckardt symptom

score (0-12 points, stage 0-3) can be used to assess symptoms, determine the disease stage and therapy effectiveness (Eckardt et al. 1992).

A timed barium esophagram, esophagogastroduodenoscopy (EGD) and esophageal manometry are commonly used in the diagnosis of achalasia (Zaninotto et al. 2018, Oude Nijhuis et al. 2020a, Vaezi et al. 2013, Vaezi et al. 2020). The esophagram with barium showed the dilatation of the esophagus with barium retention in the lumen, a clear air-fluid boundary, and the narrowing of the distal part in the form of a "bird's beak". Thus, this method is used to determine the shape of the esophagus and the degree of the stasis. An enlarged esophagus with retinal contents can be frequently seen endoscopically along with foam and saliva; however, the esophagus may be winding and spiral (like a corkscrew). The esophagogastric junction (EGJ) area may require higher pressure than is usual for the transition to the stomach. All patients with suspected achalasia should have an EGD performed to exclude pseudoachalasia, i.e. in case of changes in the mucosa; biopsies should be taken for a pathohistological diagnosis (PHD). It is important to note that in some patients with achalasia, the endoscopic findings can be normal.

It is widely accepted that the gold standard for the diagnosis of achalasia is high-resolution esophageal manometry (HREM) (Zaninotto et al. 2018, Oude Nijhuis et al. 2020a, Vaezi et al. 2020, Khashab et al. 2020). In patients who cannot endure esophageal manometry, a functional lumen imaging probe (FLIP) can be used as a complementary method (Vaezi et al. 2020, Hirano et al. 2017). In patients with achalasia, the esophageal manometry shows an absent or incomplete relaxation of the LES during swallowing and absent esophageal peristalsis or spasm. According to the Chicago classification v3.0 (Kahrilas et al. 2015), based on the above manometric parameters, achalasia is divided into three subtypes: type I classic (no esophageal contractility, no esophageal pressurization); type II (compartmentalized high pressure in esophageal body), and type III - spastic ($\geq 20\%$ esophageal spasm, distal latency < 4.5 sec). In daily practice, classification into different clinical subtypes of achalasia has prognostic value: type II being the best and type III the worst prognosis (Pandolfino & Gawron 2015). Additionally, there are different therapeutic options that are recommended as first-line therapy depending on which subtype of achalasia is in question (Rohof & Bredenoord 2017).

TREATMENT OF ACHALASIA

The primary goal of treating achalasia is to alleviate its symptoms. Pharmacological therapies such as nitrates, oral calcium channel blockers or phosphodiesterase inhibitors have not shown satisfactory

results. Therefore, the following therapeutic modalities are used in the treatment of achalasia: botulinum toxin injection (BTI), pneumatic dilatation (PD), oral endoscopic myotomy (POEM), laparoscopic Heller myotomy (LHM), and esophagectomy in end-stage achalasia (Vaezi et al. 2013, Zaninotto et al. 2018, Vaezi et al. 2020, Khashab et al. 2020, Oude Nijhuis et al. 2020a). According to the above mentioned guidelines, PD, POEM, and LHM can be used as comparable effective methods for manometric type I and II achalasia, while POEM being the therapy of choice for type III. The endoscopic injection of botulinum toxin has short-term effects and is only used with patients where it is not possible to perform these definitive therapeutic procedures. In addition, choosing a particular therapeutic option depends on the specifics of each patient, his preferences / choices, potential side effects and / or complications, the experience of the specialist and the medical institution where the therapy is performed. According to a meta-analysis by Oude Nijhuis et al. 2020b, age and manometric subtype were reported as predictive factors for therapy selection. In their paper, it is noted that the effect of pneumatic dilatation (PD) was better in the elderly (> 45 years) than in younger individuals, and that manometric subtype III (spastic contractions) generally had a poorer therapeutic outcome.

In a randomized controlled study, Boeckxstaens et al. 2011 (the European Achalasia Trial) showed there were no differences in symptoms, esophageal function, or QoL with achalasia patients who underwent pneumatic dilatation and with those who underwent surgical myotomy. In addition, the results regarding a 5-year follow-up of the European Achalasia Trial confirmed the efficacy of both treatment options (PD 82% vs. LHM 84%) with 25% of patients in the PD group requiring redilatation, and the perforation frequency during PD being 5% (Moonen et al. 2016). In the POEMA trial (Ponds et al. 2019) in which PD and POEM were compared, it was found that after 2 years of follow-up, the therapeutic success of POEM was significantly higher compared to PD (92% vs. 54%), without serious adverse events (SAEs) in the POEM group when compared to the two SAEs in the PD group. It is important to note that an increased risk of reflux was found in the POEM group compared to the PD group. Werner et al. 2019 in a multi-centre randomized study, compared endoscopic and surgical myotomy in patients with idiopathic achalasia, and showed that both POEM and LHM have a high clinical success rate after 2 years of follow-up with a similar safety profile but with a higher gastroesophageal reflux rate in POEM relative to the LHM group.

It can be concluded that symptom improvement is the most important clinical parameter to assess the effect of either endoscopic or surgical treatment in patients with achalasia (Zaninotto et al. 2018).

CONCLUSION

The gold standard for the diagnosis of achalasia is high-resolution esophageal manometry; however, idiopathic achalasia and pseudoachalasia may have manometric features. In patients with dysphagia and suspected achalasia, it is important to distinguish idiopathic achalasia from pseudoachalasia, since pseudoachalasia most often occurs due to tumor infiltrations of the LES. Patients with achalasia who have present risk factors for malignant pseudoachalasia, such as in older aged patients (≥ 55 years) with a shorter duration of symptoms (≤ 12 months) and significant weight loss (≥ 10 kg) as well as with endoscopically significantly heavier passage through the LES, additional diagnostic processing (MSCT or EUS) is recommended. It is important to note that achalasia therapy is tailored to the patient depending on the manometric subtype of achalasia, the patient's age and comorbidity.

Acknowledgements: None.

Conflict of interest: None to declare.

Contribution of individual authors:

Rosana Troskot Perić: conceptualization, literature survey, writing manuscript, supervision.

Danijel Bevanda: writing manuscript, literature survey, conceptualization, methodology.

Sandra Zgodić & Barbara Paušak: data acquisition, literature survey, proof reading.

Marina Madunić & Michael Hasanec: project administration, supervision.

All authors approved the final version.

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