International Journal of Community Medicine and Public Health
Aponte R et al. Int J Community Med Public Health. 2022 Jun;9(6):2696-2700
http://www.ijcmph.com
pISSN 2394-6032 | eISSN 2394-6040

DOI: https://dx.doi.org/10.18203/2394-6040.ijcmph20221555

Short Communication

Long COVID-19 and achalasia: a possible relationship?

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Received: 08 April 2022
Accepted: 02 May 2022

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ABSTRACT

Achalasia is a rare esophageal motor disorder with a worldwide prevalence of around 10 cases per 100 000 inhabitants, and an incidence of one new case per 100 000 inhabitants per year. It is characterized by loss or decrease of myenteric plexus neurons in the distal esophagus and lower esophageal sphincter, presenting dysphagia and regurgitation. The objective of this work was to show that the presence of type II achalasia could be a sequela of the COVID-19 infection. Patient histories were reviewed during the 2015-2021 period, the frequencies of achalasia with and without COVID-19 were calculated. Patient profiles were constructed by using cluster analysis based on clinical variables. It was found that frequency of patients with achalasia during the years 2020 and 2021 was higher than that observed in previous years, and by the year 2021, 2/3 of the patients with achalasia had presented COVID-19 infection, in addition, the patients with type I achalasia presented different profiles than patients with type II achalasia according to the cluster analysis, and the frequency of COVID-19 was much lower in patients with type I achalasia. These results seem to indicate type II achalasia could be a sequela of COVID-19 infection. The possible etiopathogenic implications of these results are discussed, as well as their clinical relevance.

Keywords: Esophageal achalasia, COVID-19, SARS-CoV-2 infection

INTRODUCTION

Achalasia is a motor disorder of the esophagus caused by loss or diminution of myenteric plexus neurons in the distal esophagus and lower esophageal sphincter (LES), producing aperistalsis and failure of the sphincter to relax. Symptoms include dysphagia, food regurgitation, chest pain, and weight loss.[1] Worldwide prevalence is 10 cases per 100 000 inhabitants, with an annual incidence of one new case per 100 000 inhabitants.[1]

Esophageal motility is complex, involving extrinsic innervation and local reflex arcs, where in addition to classic excitatory neurotransmitters such as acetylcholine, and inhibitors such as intestinal vasopeptide and nitric oxide, there are several co-transmitters such as the Renin-Angiotensin System (RAS) in the distal esophagus musculature and Angiotensin II (AII) as a powerful stimulator of esophageal contractions through the ATR1 receptor (angiotensin 1 receptor), suggesting AII participates in the control of esophageal motor activity.[2] Angiotensin converting enzyme (ACE) is found in the capillary walls located at the apex of the papillae and in the blood vessel walls of the lamina propria of the distal esophagus.[3]

SARS-CoV-2 virus is a single-stranded virus (β coronavirus). It enters host cells through the angiotensin-converting enzyme-2 (ACE2) receptor. Once inside, it undergoes replication and maturation, causing an inflammatory response with activation and infiltration of immune cells by various cytokines.[3] ACE2 receptor is present on numerous cell types throughout the human body, including oral cavity, nasal cavity, lungs, heart, esophageal epithelial cells, gastric glandular cells, enterocytes, liver, kidneys, spleen, brain, arterial and

venous blood, and endothelial cells. In this way, SARS-CoV-2 can cause damage to multiple organs and its expression varies greatly in relation to the spectrum of symptoms, ranging from asymptomatic, moderate spectrum or severe symptoms that lead to death.[3,4] Although COVID-19 infection mainly affects the respiratory system, it can also manifest with gastrointestinal symptoms that appear more frequently in the acute phase such as hyporexia, ageusia, nausea, vomiting, abdominal pain, diarrhea and lower gastrointestinal bleeding.[3] Although age, sex and comorbidities have been described as the main determinants of severity of COVID-19, there is substantial variability in its presentation that could be due to specific genetic variants in affected patients. Histopathological studies of biopsies collected by endoscopy showed damage to the mucosa of the digestive tract, with numerous plasma cells and lymphocytes infiltrating the lamina propria of the esophagus, stomach, duodenum, and rectum.[5]

This communication intends to show evidence that the increase in the frequency of patients with secondary achalasia diagnosed in the Esophageal Motility Unit of the Clínica Gastro Bariátrica located in Maracay, Aragua state, Venezuela, during the years 2020 and 2021 could be related to prior infection to COVID-19. This coexistence seems higher than expected and we consider its disclosure is important given there is no previous publication on the matter.

METHODS

Subjects and inclusion criteria

Retrospective study. Patients who attended the Esophageal Motility Unit of the Clínica Gastro Bariátrica located in Maracay, Aragua state, Venezuela, for manometric diagnosis due to suspected achalasia due to dysphagia and weight loss as dominant symptoms between January 2015 and November 2021 were included.

The Chicago classification v3.3 (6) was used for manometric diagnosis and definition of achalasia phenotypes. Manometry was performed with a 22-sensor Medical Measurement Systems® (Enschede, NL) water perfusion equipment, advancing the transducer transnasally to the stomach with the patient fasting and in a semi-sitting position (45°). The manometry protocol included 5 drinks of 20 mL of water and a multiple drink test with 200 mL of water to determine the functional reserve of the esophagus. This study was approved by the institution's Medical Ethics Committee.

Medical records, endoscopic and manometric findings corresponding to the study period were reviewed and the number of patients with achalasia was counted. Symptom severity was measured with the Eckardt score. The time of the disease was estimated from the appearance of the first symptoms to the diagnosis of achalasia by manometry. The endoscopic signs used were dilation of the esophagus and retention of fluids or food. For the years 2020 and 2021, patients with achalasia had had a previous COVID-19 infection were counted, either suspected by the presence of symptoms or confirmed by polymerase chain reaction (PCR) test.

Statistical analysis

Exact 95% confidence intervals (95%CI) were calculated for the proportion of patients with achalasia, with and without previous COVID-19 infection. The homogeneity of the annual infection frequency was analyzed with the chi-square (χ^2) test.

Patient profiles for the years 2020 and 2021 were obtained by cluster analysis using quadratic Euclidean distance from the standardized variables and Ward grouping method, considering the variables age (years), peristaltic reserve, degree of achalasia, time elapsed since the first signs and symptoms (months), Eckardt score and endoscopy results. Dendrogram was constructed and individuals belonging to each cluster identifiable by simple inspection were characterized. Data was processed with R 4.1.1 and SPSS 26.0 softwares.

RESULTS

Records prior to the COVID-19 pandemic showed a low frequency for presence of achalasia, ranging between 0.18% (1/561) for the year 2016 and 1.11% (11/994) for the year 2019. Only the year 2015 showed a slightly higher frequency (15/698, 2.15%), so the frequency of patients with achalasia is low, but it was not homogeneous during the study period (χ^2=35.68, p<0.001), although the frequencies were homogeneous during the two years of the pandemic considered (χ^2=0.36, p=0.546). Likewise, out of the 74 patients diagnosed with achalasia during the analyzed period, 20 (20/74, 27.03%, 95%CI=17.35%-38.61%) presented type I achalasia and the rest (54/74, 72.97%, 95%CI=61.39%-82.65%) type II achalasia.

Although, cases of achalasia have been on the rise since 2019, possibly due to the fact that the institution is a specialized center for esophageal motility of national reference, what really makes us suspect there is a relationship between achalasia and COVID-19 can be appreciated for the results of the years 2020 and 2021.

For the year 2020, of 13 patients diagnosed with achalasia, only 3 patients (3/13, 23.08%, 95%CI=5.04%-53.81%) presented symptoms consistent with COVID-19. Unfortunately, these three cases were not confirmed by PCR; however, for the year 2021, during which the cases of COVID-19 increased notably in the country as well as the use of diagnostic tests by PCR, it was found that of 28 cases treated for achalasia, 9 (9/28, 32.14%, 95%CI=15.88%-52.35%) did not have COVID-19, while

of the rest of the patients, 8 had clinical COVID-19 infection without PCR confirmation (8/28, 28.57%, 95%CI=13.22%-48.67%) and 11 COVID-19 infection confirmed by PCR (11/28, 39.29%, 95%CI=21.50%-59.42%); thus, 19 patients (19/28, 67.86%, 95%CI=47.65%-84.12%) showed evidence of COVID-19 infection. In addition, all patients with COVID-19 symptoms or COVID-19 infection confirmed by PCR presented type II achalasia (22/22, 100%, 95%CI=84.56%-100%). Thus, two-thirds of patients with achalasia had previously been infected with COVID-19. Moreover, if we only consider the 9 patients who presented achalasia without COVID-19 (1.19%, 9/758), the percentage obtained adjusts quite well to pre-pandemic results.On the other hand, three clusters can be distinguished (Figure 1) in the cluster analysis dendrogram, it is observed that cluster-1 only included patients who did not present COVID-19 (13/13, 100%), while in clusters 2 and 3 predominated patients who presented COVID-19: (8/8, 100%) in cluster-2, and (11/16, 68.75%) in cluster-3.

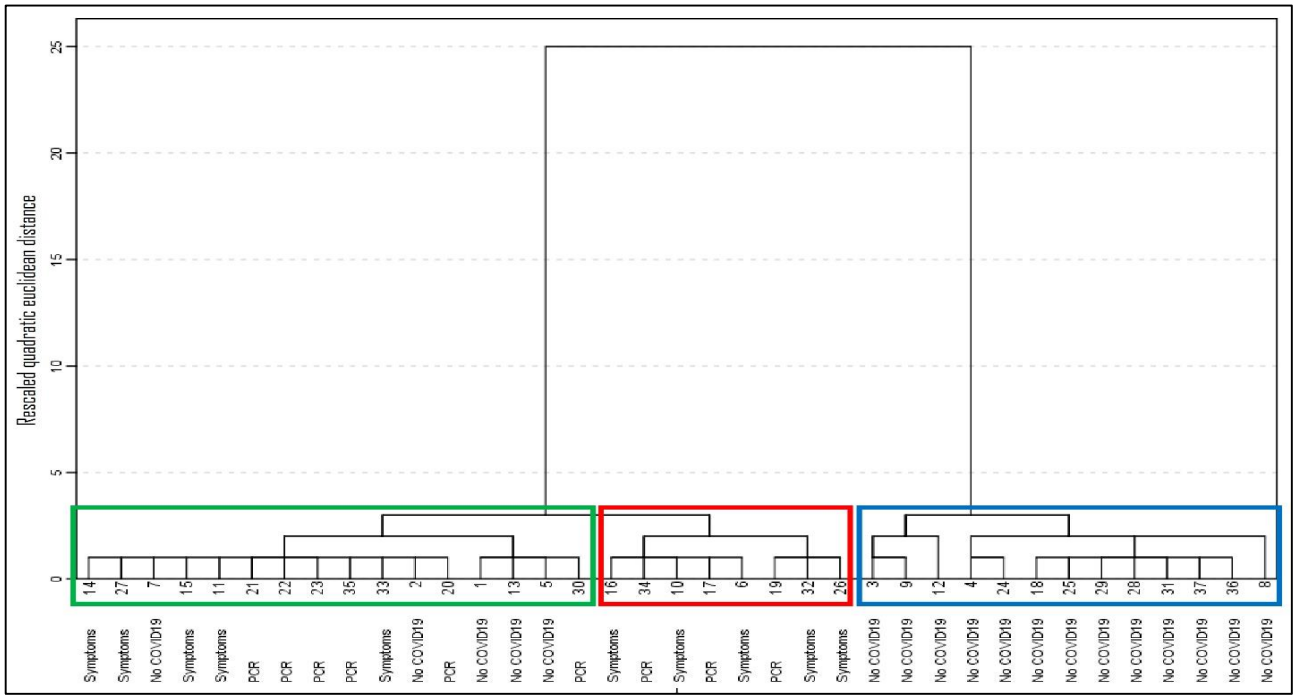

Figure 1. Dendrogram for patients with achalasia. Years 2020 and 2021. Cluster-1: blue color. Cluster-2: red color. Cluster-3: green color. No COVID-19: patients without COVID-19. Symptoms: patients with COVID-19 clinic signs. PCR: patients with COVID-19 infection confirmed by PCR.

Table 1: Profiles of the variables for the patients grouped by cluster.

Variable		Cluster 1	Cluster 2	Cluster 3
Age (mean)		57.85	53.88	37.63
Symptom's time (mean)		34.85	6.88	11.63
Eckardt score (mean)		10.15	5.75	7.44
Peristaltic reserve N (%)	Present	0 (0)	5 (62.5)	16 (100)
	Absent	13 (100)	3 (37.5)	0 (0)
Achalasia type N (%)	I	10 (76.9)	0 (0)	0 (0)
	II	3 (23.1)	8 (100)	16 (100)
Endoscopy results N (%)	Normal	0 (0)	7 (87.5)	9 (56.25)
	Dilatation	3 (23.08)	0 (0)	4 (25)
	Retention	4 (30.77)	1 (12.5)	3 (18.75)
	Dilatation and retention	6 (46.15)	0 (0)	0 (0)
COVID-19 infection N (%)	No	13 (100)	0 (0)	5 (31.25)
	Symptoms and clinic signs	0 (0)	5 (62.5)	5 (31.25)
	Confirmed by PCR	0 (0)	3 (37.5)	6 (37.5)

The patients' profiles grouped by cluster are shown in Table 1. It can be seen that cluster-1 was composed of patients without COVID-19 prior infection, with a high average age, more time elapsed since the appearance of the disease and a higher Eckardt score, without peristaltic reserve, predominance of type I achalasia and was the only cluster that included patients with simultaneous dilatation and retention as endoscopy result; likewise, cluster-2 showed a similar age to cluster-1, but disease time and Eckardt score lower than clusters-1 and cluster-3, in addition, in both cluster-2 and cluster-3 patients with peristaltic reserve predominated, and, all of them presented type II achalasia, with a predominance of normal endoscopies, and none of them with simultaneous dilation and retention as a endoscopy result. Additionally, all the patients in cluster-2 and most of cluster-3 had previously presented COVID-19 infection. The results suggest that patients who did not present COVID-19 infection tended to be patients with long-standing achalasia; while patients who presented COVID-19 infection tended to present more recent achalasia and a lesser degree of progression of the esophageal alteration. These results lead us to suspect that patients who previously had COVID-19 infection may have presented achalasia as a sequel.

DISCUSSION

Achalasia is an esophageal motor disorder characterized by loss or diminution of myenteric plexus neurons in the distal esophagus and LES. From unknown etiology, there is an individual genetic predisposition and autoimmune response to an unknown triggering agent, such as a virus (herpes simplex, herpes zoster, measles).[5] Patients with achalasia are more likely to have concomitant autoimmune diseases than the general population and the prevalence of serum neural autoantibodies is higher, suggesting autoimmune etiology. Gaber et al reported between 6 769 cases of achalasia and 27 076 controls, higher odds ratio (OR) of achalasia with autoimmune conditions (OR=1.26, 95%CI=1.11-1.42).[7] The presence of any of the viral infections studied was also associated with an increased risk of achalasia (OR=1.58, 95%CI=1.23-2.01). Varicella zoster virus (OR=3.84, 95%CI=1.94-7.62) and human papilloma virus (OR=1.77, 95%CI=1.15-2.73) had a close association with achalasia. The inflammatory reaction is associated with an infiltration of T-cell lymphocytes leading to slow destruction of the ganglion cells. The distribution and final results of this plexitis is variable, and can be modified by the response of the host or the etiological stimulus.[7]

High-resolution esophageal manometry is the ideal test for the diagnosis of achalasia, and has made possible to establish several phenotypes. Type I: absence of smooth muscle contractility of the esophageal body represents the late stage with loss of muscle tone and dilation of the esophagus. Type II: with panesophageal pressurization, smooth muscle retains its tone and biophysical properties, and swallows generate increases in panesophageal isobaric pressure. It is considered to represent an early stage of the disease.[5]

Type I achalasia patients tend to present more severe esophageal dilation with almost absent peristalsis, absence of peristaltic reserve, and represent a progression of type II achalasia with decompensation of the esophageal body. Type II achalasia patients correspond to the early stage of the disease without esophageal dilation, with pressurization at each swallow and peristaltic reserve. Studying the histopathological patterns between achalasia subtypes, Sodidkoff et al observed a greater degree of ganglion cell loss in type I achalasia in comparison to type II, suggesting that type I achalasia represents a progression of type II achalasia.[8]

Although the mechanisms of the gastrointestinal manifestations caused by SARS-CoV-2 are still unknown, the role of ACE2 receptors in the esophagus, small intestine and colon is clear. These are highly expressed in the gastro-intestinal tract (GIT) even more abundantly than in the lungs; therefore, it may serve as a viral target site.[4]

AII has been shown to exert potent contractile effects through AT1R on the esophageal body and lower esophageal sphincter. Casselbrant et al reported the presence of a local RAS in the esophageal muscle layer in healthy people and in patients with achalasia using Western blot analysis, immunohistochemistry, and PCR.[9] The results showed differences in the enzymes responsible for AII production and change in physiology from the AT1R receptor to the Mas-receptor in patients with achalasia, suggesting an important role in the pathophysiology of achalasia.[9]

There is very limited information on the nature and prevalence of post-COVID-19 symptoms after the acute event. Halpin et al with 100 surviving COVID-19 patients established an 8-week prevalence of 5% of patients with unexplained dysphagia, although the cause was not investigated.[10]

Given that more than 12 weeks had elapsed since the COVID-19 infection and the presence of dysphagia and the diagnosis of achalasia, this led us to suppose that the alteration of the motor disorder of the esophagus appears as a late manifestation of the viral infection, known as long COVID. This term is used to describe signs and symptoms that continue or develop after an acute outbreak of COVID-19. Includes both: ongoing symptomatic COVID-19 (4 to 12 weeks) and post-COVID-19 syndrome (12 weeks or more). It typically presents with often overlapping groups of symptoms that can fluctuate and change over time, and can affect any system in the body.[11]

This analysis provides a clinical, endoscopic, and manometric view of a group of patients evaluated for

dysphagia as the dominant symptom with a common history of having suffered COVID-19 infection, at least 5 months before the time of the manometric study. The clinical presentation of the infection was mild, none of the patients had to be hospitalized, just being treated at home.

This research has some limitations. First, it is a retrospective study, and since our institution is a national reference center for esophageal manometry, for data collection, we focused on the available reports sent by the treating physicians; consequently, in some cases, interpretation of the data was necessary, which could have caused an information bias, we minimized the latter with telephonic communication to obtain additional information. Second, the sample constitutes a relatively small number of patients with COVID-19 infection, dysphagia, and a manometric diagnosis of type II achalasia. However, the number of achalasia cases was higher than expected, and patients with and without previous COVID-19 infection presented different profiles according to cluster analysis. The limited cases influenced the type of statistical analysis performed. Finally, the objective of this study was not to develop a prediction model for COVID-19 infection and achalasia, but rather to give an idea of causality and the need to take it into account in cases of patients with a history of COVID-19 with a benign course and development of dysphagia in the post-COVID-19 stage, in order to improve the management of these patients,

CONCLUSION

These results seem to indicate type II achalasia could be a sequela of COVID-19 infection.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Aponte R, Daulabani N, Parra R, Pérez-Ybarra L. Long COVID-19 and achalasia: a possible relationship?. Int J Community Med Public Health 2022;9:2696-700.