Prevalence of Gastrointestinal Symptoms, Severity of Dysphagia, and Their Correlation with Severity of Amyotrophic Lateral Sclerosis in a Mexican Cohort

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Keywords

Amyotrophic lateral sclerosis · Cohort study · Neurodegenerative disease · Gastrointestinal symptoms · Prevalence

Abstract

Objectives: Our study aimed to identify the prevalence and severity of gastrointestinal (GI) symptoms and dysphagia in patients with amyotrophic lateral sclerosis (ALS) and to assess whether a correlation exists between these symptoms and the severity of ALS progression. **Methods:** The presence and severity of GI symptoms and dysphagia were identified by means of the Gastrointestinal Symptom Rating Scale (GSRS) and the Functional Outcome Swallowing Scale (FOSS). The Revised ALS Functional Rating Scale (ALSFRS-R) was utilized to determine the severity of ALS. Analysis of data was performed with Spearman correlations in semi-qualitative variables of clinical scales. ALSFRS-R scores were divided into 2 categories: those with mild to moderate ALS (≥ 40 –30 points) and patients with moderate to advanced ALS (29– ≤ 20 points). **Results:** We studied 43 patients with definite ALS. The most frequent GI symptoms were constipation (60.5%), rectal tenesmus (57.5%), hard stools (55.0%), and borborygmus (42.5%). The moderate to advanced ALS stage

was correlated with constipation ($r = 0.334$; $p = 0.028$), acid regurgitation ($r = 0.384$; $p = 0.013$), eructation ($r = 0.334$; $p = 0.032$), rectal tenesmus ($r = 0.498$; $p = 0.001$), and functional dysphagia ($r = 0.656$; $p < 0.001$). **Conclusions:** Early detection of these GI symptoms can guide timely therapeutic decisions to avoid weight loss, a predictor for worse prognosis. This study highlights the relevance of the detection of these symptoms in ALS patients who score ≤ 29 points in the ALSFRS-R scale to establish an appropriate treatment, prevent systemic complications, provide more comfort, and improve quality of life.

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Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder characterized by the selective death of motor neurons in the cerebral cortex, brainstem, and spinal cord [1]. ALS has traditionally been considered a predominantly motor disease. The existence of additional neurological manifestations or other organ involvement suggests an alternative diagnosis [1, 2]. However, it is increasingly recognized that nonmotor manifestations can occur. The sympathetic nervous system, parasympa-

Table 1. Functional Outcome Swallowing Scale

FOSS	Characteristics
Stage 0	Asymptomatic
Stage 1	Episodic or daily symptoms of dysphagia with normal mealtime
Stage 2	Dysphagia requiring significant dietary modification or prolonged mealtime
Stage 3	Dysphagia with weight loss $\leq 10\%$ of body weight with daily symptoms
Stage 4	Dysphagia with weight loss $\geq 10\%$ of body weight or severe aspiration or requiring intermittent non-oral feeding for nutrition
Stage 5	Non-oral feeding for all nutrition

FOSS, Functional Outcome Swallowing Scale.

thetic nervous system, and enteric nervous system control the gastrointestinal (GI) system's peristalsis through neurotransmitters along with the electrical and contractile properties of smooth muscle cells [3, 4]. Autonomic nervous system participation as well as presence of pain, urinary dysfunction, heart rate variability, and arterial hypotension further support the concept of ALS as a multisystem disease. ALS with progressive bulbar involvement may also present with prominent weakness of the muscles supplied by the glossopharyngeal and vagus nerves [4, 5]. Therefore, dysphagia is a frequent complaint in ALS, and patients may have bronchial aspiration or respiratory muscle fatigue [6]. In addition, patients with nerve dysfunction may present with symptoms of pseudo-intestinal obstruction syndrome [7]. Furthermore, ALS-associated mutations are believed to cause defects not only in neurons, muscles, and bones but also in the intestine [8].

Despite this, there is not enough research on GI symptomatology in ALS. Identifying their prevalence allows for a more accurate assessment of ALS patients' complaints and also establishing an appropriate treatment. Hence, the aims of our study were to identify the prevalence of GI symptoms in patients with definite ALS using the Gastrointestinal Symptom Rating Scale (GSRS), along with the Functional Outcome Swallowing Scale (FOSS), and to assess whether a correlation exists between the severity of ALS determined by the Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised (ALSFRS-R).

Materials and Methods

Participants

A cross-sectional design study was performed in the ALS multidisciplinary clinic at Zambrano Hellion Hospital. The Ethical Review Board of Instituto Tecnológico in Monterrey, Nuevo Leon, Mexico, approved the protocol (reference number P000435-P.S.G.I.E.L.A-CEIC-CR002).

All procedures were conducted in accordance with the principles in the Declaration of Helsinki. All the participating patients or their guardians signed an informed consent form. The inclusion criteria were as follows: (1) patients older than 18 years with confirmed diagnosis of definite ALS according to the clinical and neurophysiological criteria of the El Escorial and Awaji-Shima; (2) cervical and cranial magnetic resonance imaging, excluding structural damage to the brain and spinal cord; (3) a functional respiratory test showing the forced vital capacity; and (4) cognitive evaluation showing ability to understand questionnaires and accept to participate in the study. The exclusion criteria included patients with (1) possible or probable ALS and (2) concomitant cardiovascular, neoplastic, infectious, or autoimmune disease.

Measurement of GI Symptoms, Dysphagia, and ALS Progression

We identified 43 Mexican patients with definite ALS who were included in this study. Data were obtained by the medical records and patient self-reporting. The tools adopted in this study were (1) GSRS, (2) FOSS, and (3) ALSFRS-R.

The prevalence and severity of GI symptoms were assessed by the GSRS. The GSRS is a self-administered questionnaire developed to measure GI symptoms that is highly reliable and validated [9]. It is composed of a seven-point graded Likert-type scale in which 1 represents absence of symptoms and 7 represents very troublesome symptoms [10]. FOSS was utilized to assess the functional severity of dysphagia (Table 1) [11]. FOSS was calculated from detailed notes of primary care physicians and documented during evaluation at the ALS multidisciplinary clinic. ALS severity was determined by means of the ALSFRS-R score [12]. The questionnaire is structured on a 5-point scale from 4 to 0, where 4 represents no loss of function and 0 represents a total loss of function. In patients included in this study, ALSFRS-R scores were divided into 2 categories: those with mild to moderate ALS (≥ 40 –30 points) and patients with moderate to advanced ALS (29– ≤ 20 points).

Statistical Methods

Data analyses were performed by Stata 16 software. Data entry was verified by different researchers. Patient demographic and clinical data were analyzed according to the descriptive statistics. Descriptive statistics were summarized as absolute frequencies and percentages in categorical variables and median, mean, and standard deviation in continuous variables. The relationships between the ALSFRS-R score and prevalence of GI symptoms as well as dysphagia

Table 2. Demographic and clinical characteristics of patients (*n* = 43)

Characteristic	Patients with ALS, <i>n</i> (%)
Gender	
Male	26 (60.5)
Female	17 (39.5)
Age, years	
<65	30 (69.8)
>65	13 (30.2)
ALSFRS-R by stage	
Mild to moderate (≥ 40 –30 points)	19 (44.2)
Moderate to advanced (29– ≤ 20 points)	24 (55.8)
FOSS stage	
0	7 (16.3)
1	2 (4.7)
2	6 (13.9)
3	8 (18.6)
4	11 (25.6)
5	9 (20.9)

ALS, amyotrophic lateral sclerosis; ALSFRS-R, Revised Amyotrophic Lateral Sclerosis Functional Rating Scale; FOSS, Functional Outcome Swallowing Scale.

severity were explored by correlation analyses. Analysis of data was performed with Spearman correlations in semi-qualitative variables (scales grading symptoms/presence or absence of symptom). The approach utilized for correction multiple correlations was the false discovery rate (FDR) of Benjamini and Yekutieli [13]. The correlations were grouped by the 5 dimensions assessed in the GSRS [14].

Results

We studied 43 patients with diagnosis of definite ALS. The mean age was 59.33 (SD = 9.93) years. Most ALS patients were male (60.5%) and <65 years (69.8%). The average ALSFRS-R score was of 26.09 (SD = 13.9) points, and the median score was 25 (2–48) points. There were 19 patients with mild to moderate ALS (≥ 40 –30 points) and 24 (55.8%) patients with moderate to advanced ALS (29– ≤ 20 points). The FOSS stage among patients was from stage 0 to 5; there were 7 patients (16.3%) in stage 0, 2 patients (4.7%) in stage 1, 6 patients (13.9%) in stage 2, 8 patients (18.6%) in stage 3, 11 patients (25.6%) in stage 4, and 9 patients (20.9%) in stage 5 (Table 2).

The most frequent GI symptoms were constipation (60.5%), rectal tenesmus (53.5%), hard stools (51.2%), and borborygmus (39.5%) (Table 3). The median was 3 $\pm$ 2.7 symptoms for each case. The majority of them were not especially distressing for patients (the mean score was

Table 3. Frequency of GI symptoms in 43 patients with ALS

Symptom	Frequency	Percentage	Missing values, <i>n</i> (%)
Constipation	26	60.5	0
Tenesmus	23	57.5	3 (6.97)
Hard stools	22	55.0	3 (6.97)
Borborygmus	17	42.5	3 (6.97)
Urgent need for defecation	11	27.5	3 (6.97)
Increased flatus	11	27.5	3 (6.97)
Loose stools	10	25.0	3 (6.97)
Heartburn	10	25.0	3 (6.97)
Hunger pain	9	22.5	3 (6.97)
Satiety	9	22.5	3 (6.97)
Eructation	8	19.5	2 (4.65)
Nausea	7	16.3	0
Acid regurgitation	6	14.6	2 (4.65)
Epigastric pain	5	11.6	0
Diarrhea	2	4.7	0

GI, gastrointestinal; ALS, amyotrophic lateral sclerosis.

2 in the GSRS for minor discomfort), except constipation, hard stools, and rectal tenesmus (the mean score was 3 in the GSRS for mild discomfort). In addition, sex was associated with incontinence (46% women/16% men; $p = 0.042$), and older patients (>65 years) frequently had increased flatus (50% vs. 17% in young; $p = 0.047$). Furthermore, moderate to advanced ALS was correlated with constipation ($r = 0.334$; $p = 0.028$), acid regurgitation ($r = 0.384$; $p = 0.013$), eructation ($r = 0.334$; $p = 0.032$), rectal tenesmus ($r = 0.498$; $p = 0.001$), and functional dysphagia ($r = 0.656$; $p = <0.001$) (Table 4).

Discussion

The prevalence of GI symptoms in patients with definite ALS has scarcely been evaluated. These GI complaints have been attributed to autonomic involvement including constipation, diffuse abdominal pain, and a feeling of fullness or nausea [15]. In our study, the most frequent GI symptoms were constipation (60.5%), rectal tenesmus (57.5%), hard stools (55.0%), and borborygmus (42.5%). Interestingly, Toepfer et al. [4] have also previously reported markedly delayed colonic transit times in 11 out of 18 studied ALS patients. Factors contributing to a delayed colonic transit in ALS may be the lack of physical activity, inadequate fiber intake due to dysphagia, and dehydration [4]. However, patients included in the study by Toepfer et al. [4] could swallow a regular solid diet and

Table 4. Correlation of moderate to advanced ALSFRS-R stage and GI symptoms

Variable	Correlation with moderate to advanced ALSFRS-R stage	FDR (adjusted <i>p</i> value)	Null hypothesis after <i>p</i> value correction
Reflux			
Acid regurgitation	$r = 0.384; p = 0.013^*$	0.025	Rejected
Heartburn	$r = 0.157; p = 0.313$	0.050	Accepted
Abdominal pain			
Epigastric pain	$r = 0.176; p = 0.257$	0.016	Accepted
Nausea	$r = 0.138; p = 0.375$	0.033	Accepted
Hunger pain	$r = -0.086; p = 0.593$	0.050	Accepted
Indigestion			
Eructation	$r = 0.334; p = 0.032^*$	0.012	Accepted
Borborygmus	$r = 0.210; p = 0.193$	0.025	Accepted
Increased flatus	$r = 0.137; p = 0.398$	0.037	Accepted
Satiety	$r = -0.002; p = 0.986$	0.050	Accepted
Diarrhea			
Loose stools	$r = 0.202; p = 0.210$	0.016	Accepted
Diarrhea	$r = -0.025; p = 0.869$	0.033	Accepted
Urgent need for defecation	$r = 0.025; p = 0.877$	0.050	Accepted
Constipation			
Tenesmus	$r = 0.498; p = 0.001^*$	0.016	Rejected
Constipation	$r = 0.334; p = 0.028^*$	0.033	Rejected
Hard stools	$r = 0.145; p = 0.369$	0.050	Accepted
Dysphagia			
FOSS stage	$r = 0.656; p = <0.001^*$	0.050	Rejected

Correlation and significance levels are specified. Moderate to advanced ALSFRS-R stage (29–≤20 points). ALSFRS-R, Revised Amyotrophic Lateral Sclerosis Functional Rating Scale; GI, gastrointestinal; FDR, false discovery rate; FOSS, Functional Outcome Swallowing Scale. * Significant correlations.

did not show clinical symptoms of dehydration. It has also been demonstrated that a sedentary lifestyle alone does not always necessarily influence colonic transit times significantly [16, 17]. Therefore, one plausible explanation for our findings is that the autonomic nervous system may be affected in several ways in patients with ALS.

Additionally, several ALS patients in our cohort (25.6%) were classified as FOSS stage 4 with a loss of 10% or more of their body weight. Hirsch et al. [18] also reported dysphagia as an important cause of malnutrition in a cohort of ALS patients. Timely detection of these GI symptoms can help guide therapeutic decisions to avoid early and marked weight loss, which has previously been shown to significantly predict a worse prognosis for ALS patients [19]. It is also important to mention that no significant correlations were found between constipation and early satiety or hunger pain in our cohort.

In our study, the moderate to advanced ALS stage was correlated with constipation ($p = 0.028$), acid regurgitation ($p = 0.013$), eructation ($p = 0.032$), rectal tenesmus ($p = 0.001$), and functional dysphagia ($p = <0.001$). All

correlations remained significant after correction with FDR-adjusted p values, except for eructation. We additionally grouped patients according to sites of ALS symptom onset to evaluate if a correlation exists with GI symptoms, but no significant correlation was found in our cohort. Results can differ if patients are in hospital or at home; variations can also occur if questionnaires are answered by the patient or by their families, by mail, or by an interview with a doctor or a nurse. It is also relevant to mention that the majority of GI symptoms in our study were not especially distressing for ALS patients (the mean score was 2 in the GSRS for minor discomfort), except for constipation, hard stools, and rectal tenesmus (the mean score was 3 in the GSRS for mild discomfort).

Moreover, no correlation was found between urgent need for defecation and the severity of ALS; this observation goes in accordance with previous reports. Although pathological findings have been described in Onuf's nucleus that are consistent with denervation of the external anal sphincter, this may be insufficient to cause incontinence in longer surviving patients [20–23]. Nübling et al. [24] also found a

high prevalence of constipation (46%) in their cohort of ALS patients, while stool incontinence was a rare finding (9%). However, in our cohort, sex was associated with urgent need for defecation (46% women/16% men; $p = 0.042$). This could be explained by the fact that some women may undergo episiotomy after labor, which might predispose them to develop problems with fecal continence later in life [25]. This was not further corroborated in our cohort.

Some important correlations between the prevalence of several GI symptoms, severity of dysphagia, and severity of ALS are described (Table 4). One of the limitations of our study is that it did not consider changes in the diets of the patients included in this cohort. Moreover, results must be interpreted with caution because while the statistical significance is strong, they have low r values. More studies are needed to establish the clinical importance of these associations. The correlation between GI symptoms and severity of ALS could potentially help discriminate different disease stages and improve the management of these symptoms.

Conclusions

The results in this Mexican cohort of ALS patients showed that the moderate to advanced ALS stage was correlated with constipation, acid regurgitation, eructation, rectal tenesmus, and functional dysphagia. Identification of GI symptoms is essential to give an appropriate treatment and provide more comfort for the final phases of life.

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Statement of Ethics

Published research complies with the guidelines for human studies and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The study protocol was approved by the Ethical Review Board of Tecnológico de Monterrey, School of Medicine and Health Sciences. The protocol reference number is P000435-P.S.G.I.E.L.A-CEIC-CR002. A written informed consent was obtained from all individual participants included in this study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

C.P.-C. and M.M.-V. conceived the presented idea. C.P.-C. implemented the research and wrote the manuscript. A.Z.-R. performed the calculations and analysis of the results. C.P.-C., M.M.-V., and H.R.M. contributed to the interpretation of results. H.R.M. was in charge of overall direction and planning. All authors provided critical feedback, discussed results, and commented on the manuscript.

Data Availability Statement

The data that support the findings of this study are openly available in Figshare at <https://doi.org/10.6084/m9.figshare.14707329.v1> [26]. Further inquiries can be directed to the corresponding author.

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