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Headache types and characteristics in patients with Amyotrophic Lateral Sclerosis

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Abstract

Background Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder associated with progressive loss of motor neurons, this result in muscle denervation, atrophy and consequently death takes place due to respiratory failure within 3–5 years of onset of symptoms.

Our aim Was to investigate types and frequency of headache in ALS patients.

Methods This is cross sectional hospital based study. Clinically definite 100 ALS Patients (diagnosed according to El Escorial revised criteria) were recruited out of 137 ALS patients presented to the Neuromuscular Clinic in Ain Shams university Hospital from February 2022 to June 2024. Patients were screened for headache types and symptoms diagnosed according to International Headache Society criteria (IHS). Headache severity and impact were assessed using Arabic versions of Headache Impact Test (HIT) and Migraine Disability Assessment (MIDAS). Depression was also assessed via Arabic version of Beck's Depression Inventory (BDI). ALS symptoms severity was assessed via Arabic version of Amyotrophic Lateral Sclerosis Functional Rating Scale Revised (ALSFRS-R). Cognitive functions were assessed via the Egyptian version of the Edinburgh Cognitive and Behavioral Amyotrophic Lateral Sclerosis Screen (ECAS-*EG*). Demographic data and ALS related parameters were collected.

Results Among 100 patients with clinically definite ALS, 79 patients reported headaches, 62 of them had primary headaches; with tension-type headache being the most commonly reported in 46 patients, Migraine in 16 patients. Fifteen ALS patients had secondary headaches; among them 12 had headache secondary to respiratory insufficiency and 3 patients developed headache after the initiation of Riluzole therapy. Two patients had non specific headache. Mean age for the patients at ALS presentation was 43.9 ± 13.8, Mean ALSFRS-R score 33.3 ± 9.04. The relationships between headache and clinical features of ALS were also investigated.

In conclusion ALS patients should be evaluated for Headache; Not only headache secondary to respiratory compromise and hypercapnea, but also primary headaches which can be overlooked in patients with ALS.

Keywords Amyotrophic lateral sclerosis, Headache, Migraine, Tension-type headache, International headache society, Hypercapnea

Introduction

Amyotrophic lateral sclerosis (ALS) is a debilitating neurodegenerative disease that causes muscle weakness, atrophy, and eventually nutritional and respiratory failure leading to a fatal outcome. Both environmental and genetic factors contribute to ALS pathological process. Familial ALS (fALS) accounts for patients with family history of the disease which is 5–10% of ALS cases; while 90–95% of cases are sporadic (sALS) occur

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without genetic risk factors or family history [1]. There is no curative treatment for ALS so far, Riluzole is the first FDA approved drug and the only approved one in Europe [2–4] it works only to prolong the patient's survival for months [5]. Edaravone is the other FDA approved drug for ALS as a treatment to slow the disease progression [6].

Headache is one of the most common and disabling disorders globally that was reported in more than half the studied general population [7]. However, Headache is under-diagnosed and also under-treated in developing countries [8, 9].

In Egypt, available data about headache epidemiology are scarce; one study reported a prevalence of migraine to be 2800/100.000 for those aged more than 8 years in Al Quseir city [10].

Headaches are categorized into primary and secondary, with the Secondary types caused by underlying medical conditions [9]. Along the progression of ALS, patients suffer gradual weakness of respiratory muscles leading to a hypoxia and hypercapnea. "Headache attributed to hypoxia or hypercapnia". Coded [10.1] according to IHS [11]. Early clinical manifestations of respiratory compromise are variable, including sleep disturbances, fatigue, apathy, cognitive impairment, depression and morning headaches [12, 13].

Hence, ALS patients are regularly screened for morning headaches in our neuromuscular clinic. Surprisingly, we noticed a significant number of patients describing different types of headaches not related to respiratory compromise, That's why we conducted this study in order to asses types and frequency of headaches in ALS patients in Egypt.

Methods and patients

This is a hospital-based study conducted in neuromuscular unit in Ain Shams University Hospital; a tertiary hospital serving mainly Greater Cairo. Patients were recruited consecutively between February 2022 and June 2024, ALS was diagnosed according to the El Escorial revised criteria [14]. Demographaic data were collected including age, sex, disease onset and duration.

Disease severity was assessed via Arabic version of Amyotrophic Lateral Sclerosis Functional Rating Scale Revised (ALSFRS-R) [15]; ALSFRS-R is a 12-item scale. Each item is rated from 0 (worse) to 4 (best), corresponding to a total score ranging from 0 to 48, with higher scores indicating greater physical status and function [16].

Stage of the disease was assessed via king's scale [17]; cognitive functions were assessed via the Egyptian version of the Edinburgh Cognitive and Behavioral Amyotrophic Lateral Sclerosis Screen (ECAS-*EG*) [18].

Patients were excluded if they had severe cognitive impairment, respiratory failure, or significant concomitant diseases preventing them from being able to adequately respond to questionnaires.

Patients underwent a semi structured interview. where information on current and previous occurrence of headache, its character, frequency, duration, severity, timing, presence of associated symptoms, aggravation by movement, diet, sun exposure, menstruation in female patients, routine physical activity, presence of autonomic symptoms, and relation to drugs. Patients were asked to recall the above-mentioned features referring to their usual headaches as well as their headache history. Headache severity was assessed by Arabic versions of Migraine Disability Assessment (MIDAS) [19] and Headache Impact Test (HIT) [20], Depression was assessed by Arabic version of Beck's Depression Inventory BDI [21].

Statistical methods

Analysis of data was done using SPSS program version 27. Quantitative data were presented using minimum, maximum, mean and standard deviation (or median and IQR for non-parametric data). Qualitative data were presented using count and percentage. Student t test was used to compare quantitative data between two independent groups (and Mann Whitney test used for non-parametric data). One way ANOVA test was used to compare quantitative data between more than two independent groups (Kruskal Wallis test used for non-parametric data). Pearson and Spearman's correlation tests were used to measure correlation between different quantitative data. Chi square and Fisher exact tests were used to compare qualitative data between different groups. *P* value less than or equal to 0.05 was considered statistically significant.

Results

A total of 137 ALS patients were recruited consecutively in the period between February 2022, and June 2024, 37 patients were excluded due to marked communication difficulty; via both written and spoken responses, severe respiratory compromise and mechanical ventilation; that rendered patients unable to fulfill the interview and the questionnaires, as well as, patients with severe cognitive impairment or FTD because we couldn't truly rely on their self-reporting for headache history.

Thus, only 100 were included in the study, 72 males and 28 females, with M: F ratio = 2.5:1. Mean age for the patients at presentation was 43.9 ± 13.8 years; mean age of onset was 40.03 ± 14.8 years; Median disease duration was 2 ± 1–4 years; 71% of patients had spinal ALS, 74% of patients were sporadic cases. Mean ALSFRS-R

Table 1 Demographic and clinical data

	Min	Max	Mean	SD
Age (years)	18.00	68.00	43.98	13.81
Age of onset	16.00	66.00	40.03	14.82
Duration (years)[a]	.25	20.00	2.00	1.00–4.00
		N		%
Gender	Male	72		72%
	Female	28		28%
Marital status	Married	63		63%
	Single	37		37%
Clinical phenotype	Spinal	71		71%
	Bulbar	29		29%
Cognitive function	Normal	69		69%
	Affected	31		31%
Type S/F	Sporadically	74		74%
	Familial	26		26%
Need for nasogastric tube	No	85		85%
	Yes	15		15%
Need for ventilation support	No	95		95%
	Yes	5		5%
Stage of disease	1	30		30%
	2	34		34%
	3	30		30%
	4	6		6%
Treatment	No	17		17%
	Riluzole	61		61%
	Riluzole and Edaravon	21		21%
	Edaravon	1		1%
Ambulation	No	33		33%
	Yes	67		67%
Currently working	No	36		36%
	Yes	64		64%

[a] Median and IQR

score 33.3 ± 9.04. 36% of patients were unemployed due to illness Table (1).

Amongst 100 ALS patients interviewed 79% reported headaches, 62 patients (78%) suffered primary headache; 46 had tension type headache (58%), 16 patients had migraine (20%); 11 patients had episodic migraine and 5 had chronic migraine.

Fifteen patients (19%) were found to have secondary headache; in which 12 (15%) were attributed to hypoxia and hypercapnia, those patients reported improvement in their symptoms with assisted ventilator support via BiPAP.

In our cohort 82 patients received Riluzole 100 mg daily, 3 of them (~4%) reported headache associated with the treatment 2 patients (3%) had nonspecific headache Table (2) and Fig. (1).

Next, in our examination of the relationship between the onset of ALS and primary headache, 33.8% (21/62) of patients experienced headache associated with ALS which appeared or was exacerbated after they were diagnosed with ALS. Headache worsened in 14 patients, and headache initially appeared in 7 patients after ALS onset, while 42 patients had headaches prior to ALS onset.

The most frequently reported potential triggers for headaches among the patients were stress, lack of sleep, noise, neck muscles spasms as shown in Fig. (2).

Out of 62 patients who had primary headache, 51 (82%) self-medicated with analgesics. With paracetamol being the most commonly used (86%).

Both HIT and MIDAS scores had a significant positive correlation, they showed that 7% of cases had severe headache impact, while BDI showed that 51% and 23% of

Table 2 Prevalence (number and percentage) of headaches in ALS patients

ALS patients	All types of headache *n* (%)	Primary headaches					Secondary headaches			Headache unspecified (3%)
		Tension-type headache *n* (%) 46 (58%)		Migraine 16 (20%)		Total (78%)	Headache after initiation of therapy (4%)	Headache attributed to hypercapnia (15%)	Total	
		Episodic	Chronic	Without aura	With aura					
Males (72)	58 (80%)	34	7	5	1	47	2	7	9	2
Females (28)	21 (75%)	3	2	8	2	15	1	5	6	0
Total (100)	79	37	9	13	3	62	3	12	15	2

our cohort had severe and moderate Depression respectively Tables (3 and 4).

As for ALS related parameters, we found a significant positive correlation between headache severity via MIDAS and ALS severity measured by ALSRFS-R. As well as a significant correlation between MIDAS and ALS stage via king scale, denoting that with ALS advancement, severity of headache increases. There was also a correlation between MIDAS and ALS type; showing significant increased headache severity with Familial ALS. Moreover, Comparing MIDAS scores in different age groups, we found significant correlation between MIDAS severity and patients with youngest age of ALS onset Tables (4 and 5).

As for the HIT scale we couldn't find a correlation initially. But the multivariate analysis of factors affecting headache proved that Female gender and higher ALSFRS R score are independently associated with higher severity of headache via both HIT and MIDAS scales. Additionally, age of onset, and single marital status were associated with increased severity of headache via HIT scale (Tables 6, 7 and 8).

Yet, we couldn't find significant correlation between these parameters and BDI scores Table (9).

Discussion

It seems that certain neurological symptoms can lead to or worsen headache, many studies have claimed the association of primary headaches with major neurological diseases, including Parkinson's disease (PD) [22, 23], multiple sclerosis [24, 25] and myasthenia gravis [26].

Headache is not generally considered a symptom of ALS. The studies delineating the occurrence of headaches in ALS patients have only highlighted secondary headaches as one of the clinical manifestations of respiratory muscle weakness and subsequent respiratory failure which is the leading cause of death in ALS.

In fact, several studies have concluded that ALS isn't restricted to the motor system. Showing that, there is a marked affection of hypothalamus [27] and somatosensory cortex in ALS [28–30]. Moreover, recent studies claims that ALS pathophysiology is affected by the calcitonin gene-related peptide (CGRP) [31]; which is expressed physiologically in the spinal cord [32, 33]. However, it was found to be pathologically accumulated in both the anterior and posterior spinal horns of patients with familial ALS [34]. In addition, CGRP high expression levels were associated with higher levels of motor neuron degeneration [35] which could potentially link ALS and primary headaches.

Our study reveals that Headaches are common in ALS. Not only secondary headache attributed to hypercapnea, which represented 12% of patients, but also Primary headaches, constituting 62% of studied patients; with tension-type headache being the most common (46%), followed by migraine (16%).

As regards the general characteristics of ALS patients, we found a significant correlation between headache severity and severity of ALS symptoms and its stage, as well as with female gender, fALS, and younger age of disease onset. To the best of our knowledge, there are no previous studies describing different types of headaches in ALS patients and their relation with disease parameters. However, there are many studies analyzing headaches in other neurodegenerative diseases as PD [22, 23] a recent meta analysis about primary headaches in PD stated that they commonly occur with PD. However, the correlations between PD parameters and headache have not been verified [36].

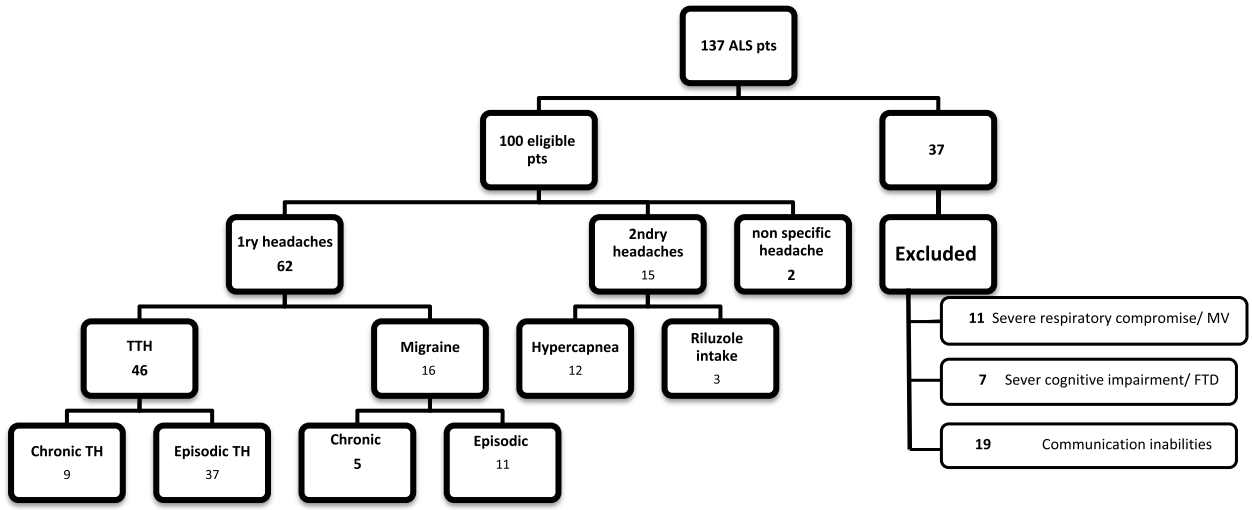

Fig. 1 Showing the frequency of primary and secondary headaches among ALS patients

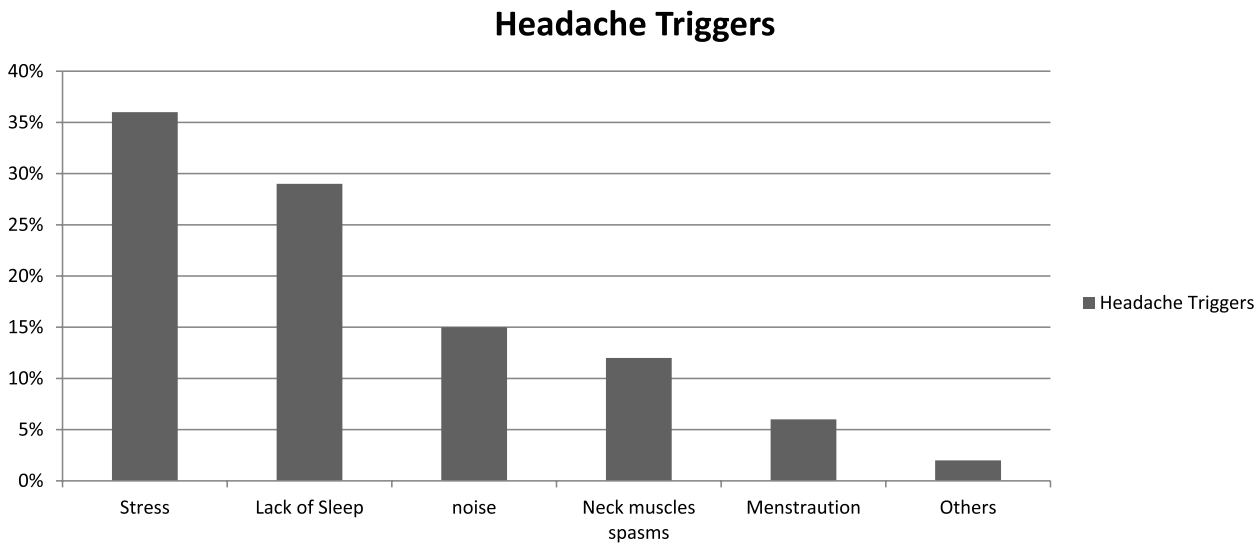

Fig. 2 Showing the most frequently reported potential triggers for headaches among ALS patients

Primary headaches

A systematic review involving over 300 studies found that the global prevalence of migraine was 11.6% worldwide, of which 10.4% in Africa [37]. An Egyptian study showed that the most common headache type was episodic tension type headache (ETTH) (24.5%), followed by migraine (17.3%) [38]. We believe that the high frequency of TTH and Migraine in our cohort is totally imaginable considering their wide prevalence worldwide; the estimated global prevalence of migraine 14% and of TTH 26% [7].

Moreover, the relatively younger age of ALS patients in our cohort; mean age of onset was 40.03 ± (14.8 years) coincides with the timing primary headaches usually peak, as a systemic review stated about migraine being highest during the productive and formative periods of patient's lives, mostly between age 25 and 55 years [39].

As well as an Egyptian study which found that both TTH and migraine peaked in mid-life and dropped to its lowest level above 55 years [38].

Gender

It's widely reported that females remain the most vulnerable population for primary headaches worldwide [6] as well as in the Arab countries [40, 41]. Women in different

Table 3 Headache, depression and severity scores in ALS patients

	Min	Max	Mean	SD
ALS-FRS R	7.00	46.00	33.30	9.04
HIT 6	38.00	78.00	53.52	10.17
BDI	10.00	63.00	35.54	14.39
MIDAS	1.00	20.00	8.19	4.76
Headache and depression Scales			**N**	**%**
BDI	Minimal		15	15%
	Mild		11	11%
	Moderate		23	23%
	Severe		51	51%
MIDAS	No disability		33	33%
	Mild		42	42%
	Moderate		18	18%
	Severe		7	7%
HIT6	Little or no impact		43	43%
	Some impact		33	33%
	Substantial impact		17	17%
	Severe impact		7	7%

Table 4 Correlations between headache and depression scores and ALS related parameters

		BDI	MIDAS
HIT 6	Spearman's correlation	-.097	.686
	P value	.333	**.000**
Diagnostic delay (months)	Spearman's correlation	.187	.121
	P value	.081	.263
ALS-FRS R	Spearman's correlation	.014	.320
	P value	.900	**.003**
Age of onset	Spearman's correlation	.068	.068
	P value	.519	.520
Duration (years)	Spearman's correlation	.126	-.065
	P value	.226	.534

countries were found to be two to three times more prone to migraines [42, 43].

On the other hand, ALS is known to be more predominant in males [44], which was reported in a recent Egyptian study [45].

In our study there is an increased male to female ratio (M: F = 2.5:1); 80% of male ALS patients and 75% of female patients suffered from Headache. Female gender was found to be associated with increased severity of headache in our patients. Moreover, analyzing gender across each type of headache individually further elucidated our findings, As for TTH, it was reported in 17% of female patients (5 out of 28 total female patients) and 57% of male patients (41 out of 72 male patients). Meanwhile, migraine was reported in a total of 16 ALS patients; 35% of female patients (10 out of 28) and 8% of male patients (6 out of 72), which in doubtfully points to increased migraine in our female patients.

Additionally, single marital status correlated with increased headache severity in our cohort; which goes in line with previous studies investigating factors affecting headache intensity [46]. Thus, indicating the role of partner support; which is excessively needed in ALS patients.

Secondary headaches

When we search for ALS-associated headache, the most considered type so far was headache secondary to respiratory insufficiency. Our study showed that 15 patients suffered secondary headaches; 12 of whom had Headache attributed to hypoxia or hypercapnia, and 3 patients had headaches related to their Riluzole treatment; the role of ALS treatments in exacerbating preexisting headaches and triggering de novo headache syndromes hasn't been studied. Headache wasn't among the reported side effect in the Riluzole clinical trial [47].

Also, 2 patients had non specific headache but both of them were suffering from neck muscles weakness and progressive head dropping, which added difficulty to their classification.

On a different note, this should lead us to expand our interview with ALS patients in order to include different disease related parameters that can precipitate headache or aggravate it.

There was a reported case of headache in bed ridden ALS patient secondary to brain abscess [48]. That's why, we shouldn't overlook other causes of secondary headaches that could be related to advanced disease stages and prolonged recumbence.

Headache triggers and impact on ALS patients

ALS is an incurable disease thus management is directed mainly for relieving symptoms in order to improve quality of life (QoL) [49].

The headache triggers most frequently reported among our patients were in accordance with the usually described triggers [50, 51]. However, as regard ALS motor symptoms, neck muscles spasms or pains should be viewed cautiously as a trigger, since it can be related to progressive neck muscle weakness and subsequent head dropping that could be associated with ALS.

Table 5 Factors associated with MIDAS score

		MIDAS								F*	*P* value
		No disability		Mild		Moderate		Severe			
		Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Duration (years)		4.23	4.80	2.97	2.58	2.40	2.17	2.86	1.80	1.33	0.27
ALS-FRS R		30.04	8.38	34.69	8.79	36.07	10.32	35.40	7.50	2.13	0.10
		N	%	N	%	N	%	N	%	X^{2**}	*P* value
Sex	Male	24	72.7%	33	78.6%	12	63.2%	4	57.1%	2.42	0.49
	Female	9	27.3%	9	21.4%	7	36.8%	3	42.9%		
Marital status	Married	19	57.6%	28	68.3%	15	78.9%	2	28.6%	6.25 FE	0.09
	Single	14	42.4%	13	31.7%	4	21.1%	5	71.4%		
Age of onset (years)	< 25	5	16.7%	3	7.7%	3	17.6%	4	57.1%	14.16 FE	**0.02**
	25–45	18	60.0%	18	46.2%	5	29.4%	1	14.3%		
	> 45	7	23.3%	18	46.2%	9	52.9%	2	28.6%		
Site of Onset	Spinal	22	71.0%	25	64.1%	15	83.3%	4	66.7%	2.22 FE	0.53
	Bulbar	9	29.0%	14	35.9%	3	16.7%	2	33.3%		
Type S/F	Sporadic	19	57.6%	36	85.7%	16	84.2%	3	42.9%	11.94	**0.01**
	Familial	14	42.4%	6	14.3%	3	15.8%	4	57.1%		
Need for nasogastric tube	No	23	79.3%	32	84.2%	15	88.2%	5	100.0%	1.10 FE	0.81
	Yes	6	20.7%	6	15.8%	2	11.8%	0	0.0%		
Need for ventilation support	No	29	100.0%	35	92.1%	16	94.1%	5	100.0%	2.64 FE	0.47
	Yes	0	0.0%	3	7.9%	1	5.9%	0	0.0%		
HIT6	Little or no impact	25	75.8%	17	40.5%	1	5.3%	0	0.0%	67.00 FE	**0.001**
	Some impact	6	18.2%	19	45.2%	8	42.1%	0	0.0%		
	Substantial impact	2	6.1%	6	14.3%	9	47.4%	0	0.0%		
	Severe impact	0	0.0%	0	0.0%	1	5.3%	7	100.0%		
Ambulation	No	14	42.4%	11	26.2%	5	26.3%	3	42.9%	2.97 FE	0.41
	Yes	19	57.6%	31	73.8%	14	73.7%	4	57.1%		
Currently working	No	15	45.5%	14	33.3%	5	26.3%	3	42.9%	2.34 FE	0.50
	Yes	18	54.5%	28	66.7%	14	73.7%	4	57.1%		

*One Way ANOVA test

**Chi square test (FE: Fisher Exact)

Table 6 Multivariate analysis for factors affecting MIDAS score

	Unstandardized Coefficients		Standardized Coefficients	Significance	95.0% Confidence Interval for B	
	B	Std. Error	Beta		Lower Bound	Upper Bound
Age of onset	.024	.043	.107	.580	-.061	.109
Duration (years)	-.234	.303	-.126	.443	-.838	.371
Female gender	2.991	1.253	.417	**.020**	.490	5.492
Time from onset to diagnosis	.020	.034	.088	.546	-.047	.087
ALS-FRS R	.141	.059	.510	**.019**	.024	.258
Marital status single	.790	1.370	.117	.566	−1.945	3.525
Site of Onset bulbar	-.172	1.362	-.025	.900	−2.890	2.545
Familial type	−1.509	1.377	-.217	.277	−4.257	1.239

HIT scale showed us that 24% of interviewed ALS patients reported substantial (17 patients) and sever impact of headache (7 patients). Yet, Only 15% (12 out of 79 patients) sought medical help for their headache. Patients attributed their reluctance to seek help for their headache to being in part able to withstand the pain with analgesics, trying not to over burden their caregivers with added physician visits, and finally because they thought

Table 7 Factors associated with HIT 6 score

		HIT 6								F[a]	*P* value
		Little or no impact		Some impact		Substantial impact		Severe impact			
		Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Duration (years)		3.38	4.17	3.27	2.89	2.80	2.75	3.63	2.74	0.13	0.94
ALS-FRS R		33.70	7.99	31.67	10.06	35.20	10.00	36.33	7.09	0.78	0.51
ECAS total score		94.33	17.69	88.97	22.73	97.00	18.21	90.38	21.83	0.78	0.51
		N	%	N	%	N	%	N	%	X^{2b}	*P* value
Sex	Male	32	74.4%	26	78.8%	10	58.8%	5	62.5%	2.86 FE	0.42
	Female	11	25.6%	7	21.2%	7	41.2%	3	37.5%		
Marital status	Married	27	64.3%	24	72.7%	11	64.7%	2	25.0%	6.38	0.10
	Single	15	35.7%	9	27.3%	6	35.3%	6	75.0%		
Age of onset (years)	< 25	4	10.5%	4	12.5%	3	20.0%	4	50.0%	9.53 FE	0.13
	25–45	22	57.9%	12	37.5%	6	40.0%	2	25.0%		
	> 45	12	31.6%	16	50.0%	6	40.0%	2	25.0%		
Site of Onset	Spinal	24	63.2%	25	75.8%	12	75.0%	5	71.4%	1.57 FE	0.69
	Bulbar	14	36.8%	8	24.2%	4	25.0%	2	28.6%		
Type S/F	Sporadic	30	69.8%	26	78.8%	14	82.4%	4	50.0%	3.55 FE	0.32
	Familial	13	30.2%	7	21.2%	3	17.6%	4	50.0%		
Need for nasogastric tube	No	28	77.8%	28	87.5%	13	86.7%	6	100.0%	1.89 FE	0.64
	Yes	8	22.2%	4	12.5%	2	13.3%	0	0.0%		
Need for ventilation support	No	36	100.0%	29	90.6%	14	93.3%	6	100.0%	3.85 FE	0.24
	Yes	0	0.0%	3	9.4%	1	6.7%	0	0.0%		
Ambulation	No	13	30.2%	13	39.4%	4	23.5%	3	37.5%	1.53	0.68
	Yes	30	69.8%	20	60.6%	13	76.5%	5	62.5%		
Currently working	No	15	34.9%	15	45.5%	4	23.5%	3	37.5%	2.42	0.49
	Yes	28	65.1%	18	54.5%	13	76.5%	5	62.5%		

[a] One Way ANOVA test

[b] Chi square test (FE: Fisher Exact)

Table 8 Multivariate analysis for factors affecting HIT-6 score

	Unstandardized Coefficients		Standardized Coefficients	Significance	95.0% Confidence Interval for B	
	B	Std. Error	Beta		Lower Bound	Upper Bound
Age of onset	.301	.085	.247	**.001**	.132	.471
Duration (years)	−1.068	.602	-.105	.080	−2.269	.133
Female gender	8.359	2.489	.212	**.001**	3.393	13.325
Time from onset to diagnosis	.124	.067	.098	.066	-.009	.257
ALS-FRS R	.385	.116	.254	**.002**	.152	.617
Marital status single	8.345	2.721	.226	**.003**	2.915	13.776
Site of Onset bulbar	1.564	2.705	.041	.565	−3.833	6.960
Familial type	2.079	2.735	.055	.450	−3.378	7.536

their headache wouldn't show considerable improvement with medications, as they attributed it to their ALS; believing it's an integral symptom of their condition. Hence, it's critical to consider and screen ALS patients for both primary and secondary headaches and include it in their management plan.

Table 9 Factors associated with BDI score

		BDI								F*	*P* value
		Minimal		Mild		Moderate		Severe			
		Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Duration (years)		3.46	2.79	2.32	1.82	2.68	2.98	3.69	3.96	0.76	0.52
ALS-FRS R		28.64	8.30	32.22	12.97	35.42	9.10	34.00	8.17	1.47	0.23
		N	%	N	%	N	%	N	%	X^{2**}	*P* value
Sex	Male	11	73.3%	9	81.8%	19	82.6%	34	65.4%	2.72 FE	0.44
	Female	4	26.7%	2	18.2%	4	17.4%	18	34.6%		
Marital status	Married	9	60.0%	5	45.5%	15	65.2%	35	68.6%	2.24	0.55
	Single	6	40.0%	6	54.5%	8	34.8%	16	31.4%		
Age of onset (years)	<25	3	23.1%	2	20.0%	1	4.8%	9	18.4%	4.99 FE	0.55
	25–45	6	46.2%	6	60.0%	10	47.6%	20	40.8%		
	>45	4	30.8%	2	20.0%	10	47.6%	20	40.8%		
Site of Onset	Spinal	10	71.4%	5	45.5%	13	61.9%	38	79.2%	5.71 FE	0.12
	Bulbar	4	28.6%	6	54.5%	8	38.1%	10	20.8%		
Type S/F	Sporadic	10	66.7%	10	90.9%	20	87.0%	34	65.4%	5.71 FE	0.12
	Familial	5	33.3%	1	9.1%	3	13.0%	18	34.6%		
Need for nasogastric tube	No	9	81.8%	9	81.8%	16	80.0%	41	87.2%	1.16 FE	0.79
	Yes	2	18.2%	2	18.2%	4	20.0%	6	12.8%		
Need for ventilation support	No	11	100.0%	10	90.9%	18	90.0%	46	97.9%	3.21 FE	0.27
	Yes	0	0.0%	1	9.1%	2	10.0%	1	2.1%		
MIDAS	No disability	7	46.7%	2	18.2%	6	26.1%	18	34.6%	7.80 FE	0.53
	Mild	5	33.3%	6	54.5%	12	52.2%	19	36.5%		
	Moderate	1	6.7%	2	18.2%	5	21.7%	11	21.2%		
	Severe	2	13.3%	1	9.1%	0	0.0%	4	7.7%		
HIT6	Little or no impact	9	60.0%	4	36.4%	9	39.1%	21	40.4%	12.02 FE	0.17
	Some impact	4	26.7%	1	9.1%	9	39.1%	19	36.5%		
	Substantial impact	0	0.0%	5	45.5%	4	17.4%	8	15.4%		
	Severe impact	2	13.3%	1	9.1%	1	4.3%	4	7.7%		
Ambulation	No	5	33.3%	4	36.4%	8	34.8%	16	30.8%	0.38 FE	0.96
	Yes	10	66.7%	7	63.6%	15	65.2%	36	69.2%		
Currently working	No	5	33.3%	4	36.4%	9	39.1%	19	36.5%	0.13	0.99
	Yes	10	66.7%	7	63.6%	14	60.9%	33	63.5%		

*One Way ANOVA test

**Chi square test (FE: Fisher Exact)

Study limitation and future research

Our main limitation would be attributed to recall bias and selection bias. A recall bias may have been present because patients with more severe symptoms may not have paid as much attention to their headache, on the other hand, ALS patients have an average diagnostic delay of one year [45], which means that patients in the very early stages of disease are less represented, as well as those in very advanced stages; who have marked communication limitations, cognitive impairments, and less frequent follow up visits to the clinic, hence the selection bias. Also, the cross-sectional design which hinders the ability to obtain causal relationship, relatively small sample size, younger age of patients, and hospital-based recruitment could limit our results generalization.

That's why; future research is needed with long term studies and larger number of patients; that can help in depth interpretation of headache types and triggers along different ALS stages. As well as, assess patient's response to different lines of headache management. Moreover, it could be beneficial to study MRI brain findings in those patients, and their genotypes to detect whether certain ALS genetic mutations are more prone to headaches.

In conclusion

Headaches could add greatly to the suffering of ALS patients, even when their general conditions are comparatively controlled. Thus, it should be evaluated carefully in patients with ALS. Not only for secondary headaches related to hypercapnea, but also to drugs intake and musculoskeletal factors related to progressive neck muscles weakness and subsequent head dropping. Moreover, primary headaches should be considered based on their wide prevalence worldwide and their usually adequate response to treatment.

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Authors' contributions

Study conception and design: R S; data collection: R S; Analysis and interpretation of results: R S, N F, M S; draft manuscript preparation: R S; prepared figures: R S. All authors reviewed the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

- Our study was approved by the ethical committee and institutional review board of the faculty of medicine, Ain Shams University, Cairo, Egypt with the number FMASUR13/2025, in accordance with the Declaration of Helsinki (WMA, 1964).
- All participants signed informed written consent for participation and publication.

Competing interests

The authors declare no competing interests.

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