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Acoustic reflex patterns in amyotrophic lateral sclerosis

Andrea Canale[1], Roberto Albera[2], Michelangelo Lacilla[2], Antonio Canosa[3], Andrea Albera[2], Francesca Sacco[2], Adriano Chiò[3], Andrea Calvo[3]

1. ENT Department University of Torino Torino Italy
2. ENT Department University of Torino Torino Italy
3. Rita Levi Montalcini' Department of Neuroscience University of Torino Torino Italy

Abstract

The aim of the study is to investigate acoustic reflex testing in amyotrophic lateral sclerosis patients. Amplitude, latency, and rise time of stapedial reflex were recorded for 500 and 1000 Hz contralateral stimulus. Statistical analysis was performed by the Wilcoxon test and the level of significance was set at 5 %. Fifty-one amyotrophic lateral sclerosis patients and ten sex- and age-matched control subjects were studied. Patients were further divided in two groups: amyotrophic lateral sclerosis—bulbar (38 cases, with bulbar signs at evaluation) and amyotrophic lateral sclerosis—spinal (13 cases, without bulbar signs at evaluation). Stapedial reflex was present in all patients. There was a statistically significant difference in the mean amplitude, latency, and rise time between the amyotrophic lateral sclerosis patients as compared with the controls. Amplitude was lower in both the amyotrophic lateral sclerosis—bulbar and the amyotrophic lateral sclerosis—spinal patients than in the controls ($p < 0.05$) and rise time was longer in both patient groups compared with the controls ($p < 0.05$). These results confirm the presence of abnormal acoustic reflex patterns in amyotrophic lateral sclerosis cases with bulbar signs and, moreover, suggesting a possible subclinical involvement of the stapedial motor neuron even in amyotrophic lateral sclerosis—spinal patients. Amplitude and rise time seem to be good sensitive parameters for investigating subclinical bulbar involvement.

Keywords

Stapedial reflex Amyotrophic lateral sclerosis Bulbar palsy Stapedius motor neuron

Introduction

Amyotrophic lateral sclerosis (ALS) is a rare neurodegenerative disease, characterized by unknown etiology, different phenotypes, and no effective treatment. Ten to 15 % of patients are familial (FALS), while 85–90 % are sporadic (SALS) [1]. About two-thirds of cases have a spinal onset, with signs or symptoms referred on limbs, neck, or trunk, while 30 % of patients have a bulbar onset, characterized by dysarthria, dysphagia, dysphonia, and loss of strength in facial muscles [2].

Several prognostic factors have been identified in ALS, but there is still a lack of clinical prognostic markers useful for care management and for clinical trials [3].

To our knowledge, the only study that analyzed impairment of the stapedius motor neurons in ALS reported that there may be a close relation between bulbar lesions and changes in the acoustic reflex in ALS. [4]. Acoustic reflex testing is a basic part of the audiological test battery for the evaluation of conductive hearing loss and certain otolaryngology (ENT) disorders [5]. This test is not routinely used for neuro-otological examination, though acoustic reflex abnormalities can be associated with brainstem pathologies and facial nerve disorders, including demyelinating (e.g., multiple sclerosis) and neuromuscular (e.g., myasthenia gravis) diseases [6,7].

Because patients with spinal onset frequently develop bulbar signs, the aim of this study was to investigate whether acoustic reflex testing is useful to predict subclinical signs of transition from spinal ALS (ALS-S) to bulbar ALS (ALS-B).

Methods

In this survey, we recruited 51 ALS patients followed-up at the Turin ALS center with a definite, probable, or possible diagnosis of ALS [29 men and 22 women, mean age 63.1 years, ±standard deviation (SD) 11.6] according to the El Escorial Criteria revised [8].

Ten age- and sex-matched healthy controls, without any clinical signs of brainstem, peripheral facial nerve, or cochlear nerve dysfunction, were recruited among the medical staff at our ENT department.

All patients underwent otoscopy, pure-tone audiometry, and tympanometry to exclude middle ear disease. The acoustic reflex was measured using an impedance audiometer (Amplaid A724–A728, Amplifon, Milan, Italy). The acoustic reflex was elicited in each ear by presenting a contralateral pure-tone stimulus at 0.5–1–2–3–4 kHz, broadband noise (BBN) from 0.25 to 4 kHz, and low-pass noise (LPN) from 0.25 to 1.8 kHz. The starting stimulation intensity was 80 dB HL with 5-dB steps up to 120-dB HL; duration 1 s; on/off ratio of 1; steps of 5-dB HL. The acoustic reflex was elicited by contralateral stimulation at the five frequencies and BBN and LPN mentioned above. The amplitude, latency, and rise time were measured only with stimuli at 0.5 and 1 kHz, because of the absence of the reflex in some patients at higher frequencies. Amplitude was defined as the highest value of impedance and expressed in cubic centimeters (cm^3); latency was defined as the time from the presentation of the stimulus to reflex amplitude of 5 % as compared with maximum compliance and expressed in milliseconds (ms). The rise time was defined as the time in msec between 10 and 90 % of contraction as compared with maximum compliance. The acoustic decay test was performed at 0.5 and 1 kHz (duration: 10 s; intensity: +10 dB HL reflex threshold). A reduction of more than 50 % of the maximum amplitude during the stimulation was considered a positive result on the acoustic decay test.

Statistical analysis was performed using the Wilcoxon rank-sum test (WRS) for quantitative variables with a non-normal distribution in two independent samples, considering a p value <0.05.

Results

Of the 51 ALS patients recruited, 21 had a bulbar onset and 30 a spinal onset. 17 cases with spinal onset showed bulbar signs at the moment of the ENT assessment; therefore, we have classified the study population in two groups according to the presence (38 patients, ALS-B) or absence (13 patients, ALS-S) of bulbar signs at the time of the ENT evaluation. The mean duration of disease was 31.9 (SD 14.74) months in those with ALS-S and 37.0 (SD 37.89) months in those with ALS-B type (p = 0.49).

The mean auditory threshold at 0.5, 1, 2, and 4 kHz was 24.41 ± 12.42-dB HL in the ALS group and 21.10 ± 8.50-dB HL in the control group; all subjects had a normal type A tympanogram. Mean auditory threshold values at single frequencies for the ALS-B and ALS-S patients and the controls are shown in Table 1; patients and controls were not significantly different (p > 0.05).

Table 1

Mean auditory threshold at 0.5–1–2–4 kHz in the control group, amyotrophic lateral sclerosis patients (ALS), bulbar type, and spinal type

	0.5 kHz	*p* value	1 kHz	*p* value	2 kHz	*p* value	4 kHz	*p* value
Controls	18.25 (7.55)		18.50 (8.83)		22.25 (9.89)		24.75 (8.20)	
ALS patients	19.41 (8.78)	0.75	18.68 (10.49)	0.82	23.58 (14.52)	0.82	32.84 (19.84)	0.31
ALS-B	20.26 (9.76)	0.61	20.26 (11.07)	0.83	25.46 (15.78)	0.92	35.46 (19.72)	0.13
ALS-S	16.92 (4.35)	0.83	14.04 (7.04)	0.21	18.08 (8.17)	0.33	25.19 (18.89)	0.69

Standard deviation in brackets

The acoustic reflex was present at 0.5 and 1 kHz in all subjects. It was absent at 2 kHz in five ears (all ALS-B with an auditory threshold >55 dB); it was present in three ears (2 ALS-B and 1 ALS-S with an auditory threshold >50 dB). The acoustic reflex at 4 kHz was absent in 19 ears (all ALS-B, 17 of which with an auditory threshold >50 dB and 2 with an auditory threshold between 40 and 45 dB; it was present in 6 ears (4 ALS-B and 2 ALS-S with an auditory threshold >50 dB).

The mean auditory reflex threshold (ART) at 0.5 and 1 kHz in the patients and the controls is reported in Table 2. There were no significant differences between the mean ART at the single frequencies tested in both ALS groups and controls. Among ALS patients, the ART was 88.62 ± 5.12 dB at 0.5 kHz and 88.36 ± 4.87 dB at 1 kHz in patients with ALS-B and 88.65 ± 6.34 dB at 0.5 kHz and 86.54 ± 4.95 dB at 1 kHz in those with ALS-S; there were no differences with respect to controls (87.25 ± 5.95 and 89.75 ± 6.82 dB, respectively).

Table 2

Mean ART elicited by contralateral stimulus, PTS 0.5–1 kHz, BBN, and LPN in the control group, amyotrophic lateral sclerosis patients (ALS), bulbar type (ALS-B), and spinal type (ALS-S)

	0.5 kHz	*p* value	1 kHz	*p* value	Mean 0.5–1 kHz	*p* value	BBN	*p* value	LPN	*p* value
Controls	87.25 (5.95)		89.75 (6.82)		88.50 (6.03)		90.00 (6.01)		90.50 (5.75)	
ALS patients	88.63 (5.39)	0.27	87.89 (4.91)	0.49	88.26 (4.96)	0.87	88.49 (6.14)	0.44	88.51 (5.89)	0.30
ALS-B	88.62 (5.12)	0.28	88.36 (4.87)	0.67	88.49 (4.81)	0.99	88.79 (6.37)	0.56	88.82 (5.85)	0.40
ALS-S	88.65 (6.34)	0.42	86.54 (4.95)	0.25	87.60 (5.51)	0.61	87.69 (5.63)	0.32	87.69 (6.16)	0.24

Standard deviation in brackets

PTS pure-tone stimulus, *BBN* broadband noise, *LPN* low-pass noise

The ART values after presentation of BBN and LPN stimuli were substantially similar to those elicited by the pure-tone stimulation; there was no statistical difference between ALS patients and controls (Table 2).

The values of the auditory reflex variables by group (controls, ALS patients, ALS-B, and ALS-S) at 0.5 and 1 kHz are reported in Fig. 1 (amplitude), Fig. 2, (latency) and Fig. 3 (rise time). There was a significant difference in the mean amplitude, latency, and rise time between ALS patients as compared with controls at 0.5 and 1 kHz. The amplitude was lower in both the ALS-B and the ALS-S patients than in the controls and the difference was significant except for ALS-S at 1 kHz ($p = 0.0002$ and $p = 0.025$ in ALS-B at 0.5 and 1 kHz; $p = 0.0108$ and $p = 0.3038$ in ALS-S at 0.5 and 1 kHz). The latency was longer as compared with the controls in both patients' groups, but the difference was not significant in those with ALS-S. The rise time was longer in both patients' groups, with a significant difference as compared with the controls except for ALS-S at 0.5 kHz ($p = 0.0128$ and $p = 0.0003$ in ALS-B at 0.5 and 1 kHz; $p = 0.072$ and $p = 0.0005$ in ALS-S at 0.5 and 1 kHz). The reflex decay test was positive in only one patient (male, ALS-B type).

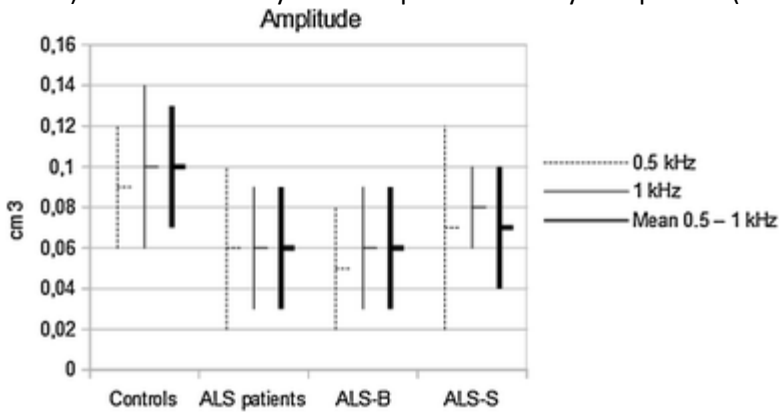

Fig. 1

Amplitude at single 0.5–1 kHz and at mean 0.5–1 kHz in the control group, amyotrophic lateral sclerosis patients (ALS), bulbar type (ALS-B), and spinal type (ALS-S); $p < 0.05$ except the difference at 1 kHz between ALS-S and controls ($p = 0.30$)

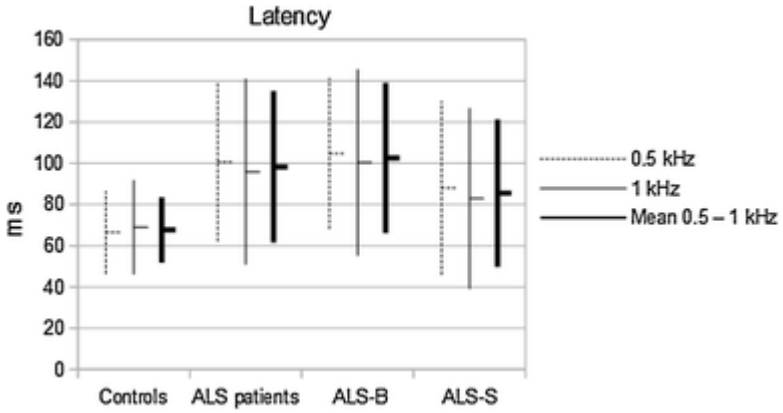

Fig. 2

Latency at single 0.5–1 kHz and at mean 0.5–1 kHz in the control group, amyotrophic lateral sclerosis patients (ALS), bulbar type (ALS-B), and spinal type (ALS-S); $p < 0.05$ except the difference between ALS-S and control at 0.5–1 kHz and mean 0.5–1 ($p = 0.11$; $p = 0.44$; $p = 0.23$)

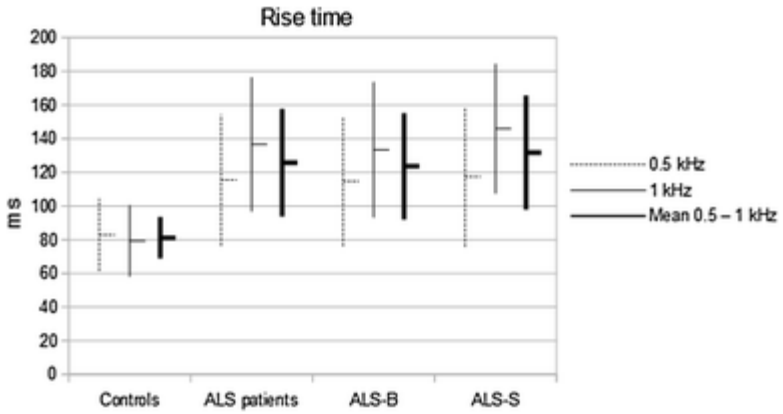

Fig. 3

Rise time at single 0.5–1 kHz and at mean 0.5–1 kHz in the control group, amyotrophic lateral sclerosis patients (ALS), bulbar type (ALS-B), and spinal type (ALS-S); $p < 0.05$ except the difference at 0.5 kHz between ALS-S and controls ($p = 0.07$)

Discussion

In all ALS patients, we have found that the stapedial reflex was present at 0.5 and 1 kHz. In four ALS-B patients, the stapedial reflex elicited by BBN and LPN was absent. Some patients with an auditory threshold >60 dB at 2 and 4 kHz showed no reflex at these frequencies, whereas in others (both ALS-S and ALS-B), the reflex was present, even in those with an auditory threshold of about 50–60 dB. The absence of the stapedial reflex in some cases at 2 and 4 kHz, probably secondary to hearing loss without recruitment, does not allow us to speculate about neurological impairments; therefore, we consider only the parameters of the stapedial reflex at 0.5 and 1 kHz.

Abnormal acoustic reflex patterns of prolonged relaxation, latency times, and reduced amplitude have been associated with various neuromuscular disorders [4,6,9,10,11]. Among these studies, only one investigated the acoustic (stapedial) reflex in ALS patients. In this paper, authors observed a significant reduction in amplitude, a prolonged of latency, and significantly longer contraction and relaxation times in bulbar ALS patients vs. controls, suggesting that the subclinical involvement of the stapedius motor neurons or of the supranuclear stapedius motor system might be responsible for the abnormalities of the stapedial reflex in ALS. [4].

In our study, the ART values of ALS patients were consistently similar to those of controls; in particular, no differences between the two patient subgroups and the controls were found for different stimuli presentation (tonal vs. BBN/LPN). Analysis of the acoustic reflex parameters elicited by tonal stimulation at 0.5 and 1 kHz showed that the amplitude was reduced at both frequencies in all ALS patients as compared with controls; the only non-statistically significant difference was the reduction of the amplitude in the ALS-S group at 1 kHz in the controls (0.077 ± 0.024 vs. 0.095 ± 0.031, respectively). To simplify the results and to strengthen the statistical significance, we considered the mean values of the amplitude at 0.5 and 1 kHz. The reduction was greater in the ALS-B patients, but there was also a significant difference in the ALS overall and even in the ALS-S patients.

Significantly, longer latency values were observed for patients with ALS-B but not for those with ALS-S, even when the latency of the reflex elicited by two tonal stimuli at 0.5 and 1 kHz was analyzed. The reduction in the mean amplitude at 5 and 1 kHz in both the ALS-B and ALS-S patients indicates that, among acoustic reflex variables, amplitude is the most sensitive indicator of neuropathological process. Because latency usually increases as amplitude decreases [12], the prolongation of latency may reflect decreased amplitude. In our sample, the amplitude in the patients with ALS-S was 0.073 ± 0.027, significantly different than that of controls, but higher when compared with those with ALS-B (0.057 ± 0.028). According to

Kimura's model, an explanation for the absence of a difference in the latency between the ALS-S patients could be that the amplitude is not reduced enough to allow a significant prolongation of latency.

As concerns the rise time, a prolonged contraction time was recorded in the ALS patients at 0.5 and at 1 kHz. The prolongation was statistically significant at both frequencies in the ALS-B patients, whereas in ALS-S patients, even though the rise was longer than in controls both at 0.5 kHz than at 1 kHz, the difference was not statistically significant when the stimulus was 0.5 kHz (117.46 ± 41.45 vs. 82.9 ± 21.29). Considering the mean rise time value at both frequencies, the rise was significantly longer in patients with ALS-S than in those with ALS-B and in controls (131.69 ± 33.88 vs. 123.60 ± 31.59 vs. 81.1 ± 12.34, respectively).

The cause of the longer rise time in the ALS patients remains unclear; the acoustic reflex is mediated by interconnected neural pathways in the brainstem. A direct pathway of the reflex involves neurons in the ventral cochlear nucleus with their axons running in the trapezoid body and interneurons in the medial superior olivary complex [13]. Borg also described a multisynaptic indirect pathway of the reflex and proposed the lateral zone of the reticular formation as the responsible region. According to Borg's experiments, a lesion involving the direct pathway may prolong the contraction and the relaxation times. This could explain the longer rise time in the ALS patients.

In their study of the stapedial reflex in ALS, Shimizu et al. found no significant differences between latency, C50 (time from the first increase in acoustic impedance to 50 % of maximum amplitude) or amplitude in the controls and in the patients with ALS. In the patients with ALS-B, both latency and C50 were significantly longer than in the controls, and the amplitude was significantly lower than in the controls [4]. These differences were not present in the ALS-S group.

Our results showed the presence of abnormal acoustic reflex patterns in ALS patients pointing out a relationship between bulbar involvement and impairment in reflex parameters. Moreover, we found significant differences in amplitude and rise time also in patients with ALS-S and a trend toward prolonged latency only in the ALS-S patients. These findings suggest a possible subclinical involvement of the stapedial motor neuron even in such patients. Amplitude and rise time seem to be good sensitive parameters for investigating subclinical bulbar involvement. Further study is needed to demonstrate whether this could be a marker of a possible transition from spinal to bulbar type ALS.

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