Journal of the Neurological Sciences 397 (2019) 4–8

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Vestibular dysfunction as cortical damage with amyotrophic lateral sclerosis

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ARTICLE INFO

Keywords:
Amyotrophic lateral sclerosis
Cortical damage
Frontal assessment battery
Vestibular function
Caloric nystagmus
Visual suppression
Frontal eye field
Inferior parietal lobule

ABSTRACT

Background: Cortical damage in areas such as the frontal lobe is reported in amyotrophic lateral sclerosis (ALS). However, aside from executive dysfunction, the pathological significance of this cortical damage has yet to be clarified. The present study investigated the effects of cortical damage on vestibular function in ALS.

Methods: Subjects comprised 18 ALS patients and 18 age- and sex-matched healthy controls. Cold air caloric stimulation was performed in all subjects to induce vestibular nystagmus, which was analysed to evaluate vestibular function. Visual suppression testing to investigate the suppressive effects of visual stimuli on vestibular nystagmus was expressed as suppression rate (SR, %). Executive function was tested using the frontal assessment battery (FAB).

Results: Suppression rate and FAB score were significantly lower in the ALS group than in the control group ($p < 0.01$ each). A positive correlation was also observed between SR and FAB score ($R = 0.65$, $p = 0.023$).

Conclusion: Visual suppression testing showed significant damage to the central nervous system vestibular control mechanisms, which utilize visual information in the ALS group and a positive correlation between SR and FAB score suggest a relationship between frontal lobe damage and impaired vestibular control. A simple vestibular function test may be useful as a tool to objectively monitor the progression of cerebral lesions in ALS.

1. Introduction

Neuropsychological and imaging tests have shown that cortical damage associated with amyotrophic lateral sclerosis (ALS) shows particular involvement of brain regions other than the motor areas [1–9]. TAR DNA-binding protein of 43 kDa (TDP-43) proteinopathy is proposed to constitute a common pathological basis for cortical damage in ALS and frontotemporal lobar degeneration (FTLD) [10–15]. Frontal lobe damage in ALS has therefore been the focus of recent interest. To date, clinical evidence of cortical damage in ALS has been limited to executive dysfunction, leaving many aspects unclear.

We are engaged in research regarding impaired the control of vestibular function resulting from cortical damage. Damage to the vestibular control mechanisms resulting from cortical damage has been shown in Alzheimer's disease and FTLD, and causes balance disorder [16,17]. Impaired vestibular control has been identified in patients with FTLD and motor neurone disease [16]. These findings indicate a common basis for ALS and FTLD. The present study investigated the relationship between cortical damage and vestibular function in ALS.

2. Materials and methods

2.1. Subjects

A total of 18 ALS inpatients and outpatients (8 men, 10 women; mean age, 70.3 ± 8.3 years) attending the University of Tsukuba Hospital Department of Neurology between June 2010 and August 2017 were recruited (Table 1). Patients with clinically defined ALS, clinically probable laboratory ALS, or clinically possible ALS as defined by the revised El Escorial World Federation of Neurology criteria for the diagnosis of ALS were considered to be diagnosed with ALS [18]. We evaluated the daily living activity of these ALS patients using the ALS Functional Rating Scale-Revised (ALSFRS-R) [19].

Although balance disorder is usually evaluated using clinical balance testing, this was not performed in the present subjects in consideration of the effects of decreased muscle strength in ALS patients. Healthy volunteers were recruited in Ibaraki Prefecture in Japan, interviewed, and examined; those scoring ≥24 on the Mini–Mental State Examination (MMSE) were selected as the normal subject group. After undergoing neurological examination to confirm the absence of limb

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https://doi.org/10.1016/j.jns.2018.12.006
Received 31 August 2018; Received in revised form 28 October 2018; Accepted 4 December 2018
Available online 05 December 2018
0022-510X/

Table 1
Comparative analysis of ALS and Control (C) groups.

		ALS (n = 18)	Control (C) (n = 18)	ALS vs (C) *p* value
Age, Year (mean ± SD)		70.3 ± 8.3	70.4 ± 3.8	0.96
Males/Females		8/10	8/10	–
Age at onset, y (mean ± SD)		68.4 ± 8.5	–	–
Years affected (mean ± SD)		1.94 ± 1.1	–	–
FAB (mean ± SD)		11.4 ± 4.2 (n = 12)	15.9 ± 1.2 (n = 18)	0.0001[a]
MMT (mean ± SD)				
Biceps		4.6 ± 0.7	–	–
Triceps		4.4 ± 0.8	–	–
Quad.		4.8 ± 0.4	–	–
Ham.		4.6 ± 0.8	–	–
TA		4.6 ± 1.0	–	–
GC		4.6 ± 1.0	–	–
Pathologic reflex Positive		6/18 (33%)	–	–
Frontal lobe sign Positive		4/18 (22%)	–	–
%FVC (mean ± SD)		87.5 ± 20.9(n = 15)	–	–
ALSFRS-R		35.6 ± 4.7(n = 18)		
Pre-visual fixation test	Rapid Phase of velocity (°/s)	68.3 ± 37.3	88.7 ± 23.8	0.06
	Rapid Phase of amplitude (°)	4.34 ± 3.3	6.02 ± 2.0	0.08
	Slow Phase of velocity (°/s)	13.5 ± 10.9	17.2 ± 6.7	0.23
	Slow Phase of amplitude (°)	4.37 ± 3.2	6.11 ± 2.1	0.07
	Nystagmus frequency (/s)	2.36 ± 0.9	2.54 ± 0.7	0.50
Visual fixation test	SR (%)	20.0 ± 9.1	61.4 ± 9.7	0.0001[a]

FVC, forced vital capacity; ALSFRS-R`ALS Functional Rating Scale-Revised.
[a] Compared using the Mann-Whitney *U* test ($p < 0.01$).

muscle weakness, extrapyramidal symptoms, impaired deep sensation or other sensory disorders, and cerebellar apraxia or other neurological abnormalities, 18 age- and sex-matched controls were selected as a control group (8 men, 10 women; mean age, 70.4 ± 3.8 years) from the normal subject group (30 men, 37 women; age range from 18 to 80 years). Mean MMSE score of the control group was 28.7 ± 1.2. All subjects underwent otolaryngological examination to confirm the absence of previous inner ear disease and individuals with bilateral ear disease were excluded. Informed consent was obtained from all subjects in accordance with the rules of the ethics committee of University of Tsukuba Hospital.

As a test mainly used to evaluate frontal lobe function [20], the frontal assessment battery (FAB), was performed to test executive function in both groups. In the ALS group, the FAB was performed on the 12 subjects with intact arm function and ability to complete the test (mean age, 70.2 ± 5.2 years; mean FAB score, 11.4 ± 4.2).

2.2. Vestibular function tests

Eye movement was recorded using electrodes attached vertically and horizontally to the eyelids. The original waveform (time constant, 3 s) and velocity waveform (time constant, 0.03 s) of eye movements in each direction were recorded using an electronystagmograph and a data collection and analysis device with a sampling frequency of 1 kHz (PowerLab; ADInstruments, Castle Hill, Australia). For caloric testing, subjects wore goggles fitted with an infrared camera (First, Tokyo, Japan) and were visually monitored regarding whether the eyes were open or closed. The caloric stimulus to induce nystagmus was delivered by irrigation with cold air at 24 °C for 1 min from the external auditory canal to the eardrum using an air caloric irrigator with the subject's eyes closed. Forty seconds after the end of stimulation, subjects opened their eyes and visual suppression testing was conducted based on 10-s visual fixation. The induced nystagmus was analysed and the parameters of frequency, amplitude (slow and rapid phase), and mean velocity (slow and rapid phase) were investigated. Mean values of each parameter were calculated for the 10 s before the visual suppression test and the results of stimulation of the bilateral external auditory canals were averaged and investigated. Visual suppression of vestibular nystagmus was expressed as suppression rate (SR; %), calculated using the following equation: SR = 100 × ((pre-VS* slow phase velocity − VS slow phase velocity)/pre-VS slow phase velocity) *VS, visual suppression test [16].

Data were analysed using statistical software (IBM SPSS Statistics base software; IBM, New York, NY) to perform Fisher's exact test or the Mann-Whitney *U* test. Significance was set at $p < 0.05$.

3. Results

Table 1 shows subject characteristics. Mean age at onset and duration of disease in the ALS group were 68.4 ± 8.5 years and 1.94 ± 1.1 years, respectively. In the ALS group, mean muscle strength on manual muscle testing of the arms and legs was 4–5, indicating comparatively mild disease severity. Pathological reflex and frontal lobe signs were present in 33% and 22% of the ALS group, respectively. Mean FAB score was significantly lower in the ALS group (11.4 ± 4.2) compared to the control group (15.9 ± 1.2; $p < 0.01$).

Fig. 1 shows example vestibular stimulation test electronystagmographs for 65-year-old control and ALS patients. Vestibular nystagmus was clearly suppressed during the visual suppression test compared to before the visual suppression test in the control patient (see Fig. 1A). Conversely, decreased suppression of vestibular nystagmus during the visual suppression test indicated impaired visual suppression in the ALS patient (see Fig. 1B). *Z*-score images from single-photon emission computed tomography (SPECT) measurement of cerebral blood flow in the ALS patient showed decreased blood flow in the frontal lobe.

Analysis of vestibular nystagmus revealed no significant differences between the ALS and control groups regarding nystagmus frequency and the velocity and amplitude of the slow and rapid phases (see Table 1). Conversely, SR was significantly lower in the ALS group compared to the control group on visual suppression testing ($p < 0.01$; see Table 1). These findings demonstrated poor visual suppression of vestibular nystagmus in ALS.

A significant positive correlation was observed between FAB score and SR ($R = 0.65$, $p = 0.023$; see Fig. 2). These findings demonstrated that the degree of impairment of visual suppression of vestibular nystagmus increases in proportion to the progression of executive dysfunction. On the other hand, there was no correlation between the ALSFRS-R and SR ($R = 0.12$, $p = 0.650$).

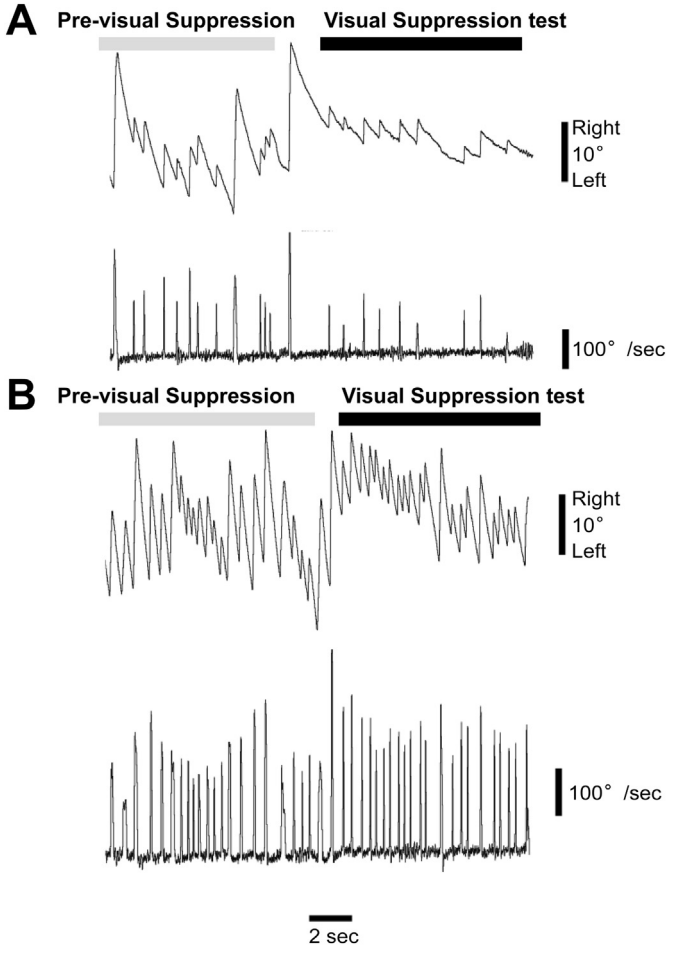

Fig. 1. Electronystagmographs before and during vestibular stimulation in control and ALS subjects.
Electronystagmographs from a 65-year-old female control (A) and an age- and sex-matched ALS patient (B) show horizontal eye movement (upper waveform) and velocity of horizontal eye movement (lower waveform). Vestibular nystagmus is decreased during visual stimulation (visual suppression testing) compared with before visual stimulation in the control. Conversely, no decrease in vestibular nystagmus during testing is seen in the ALS patient, confirming impairment of the suppressive effects of fixed visual stimulation.

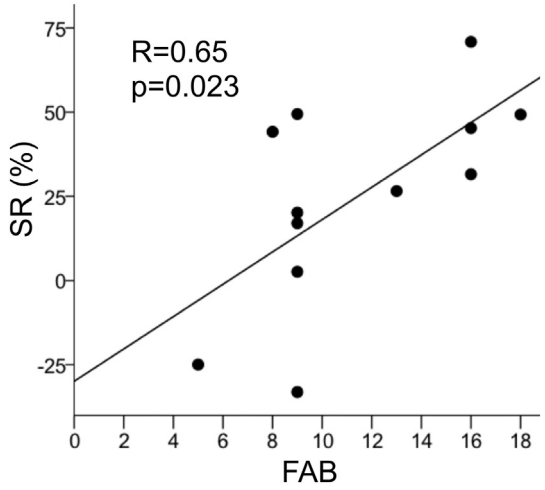

Fig. 2. Correlation between SR and FAB score in the ALS group.
Suppression rate correlates positively with FAB score (R = 0.65, p = 0.023).

4. Discussion

The absence of significant differences between control and ALS groups regarding the analysis parameters of vestibular nystagmus indicate that peripheral vestibular function was intact in the ALS group. The decrease in SR in the ALS group compared to the control group confirmed the existence of damage to central nervous system vestibular control mechanisms, which utilize visual information. One of the few previous studies to report vestibular function testing in ALS found no abnormalities on evoked potential testing using cervical vestibular evoked myogenic potentials to explore lower brainstem function in patients with mild ALS [21]. As in previous studies, peripheral vestibular function was also intact in the present ALS group.

With regard to frontal lobe damage in ALS, SPECT imaging studies and reports using the FAB to evaluate frontal lobe function have been published [1–9]. Frontal lobe damage was also indicated in the present study based on the presence of frontal lobe signs and FAB results. The FAB significantly correlated with the frontal lobe function according to the Wisconsin Card Sorting Test [22] and with the frontal lobe metabolism in positron emission tomography study for patients with frontal lobe damage [23]. The previous studies have shown that the FAB is useful for the evaluation of neurodegenerative disease in patients with varying degrees of frontal lobe dysfunction [24]. The FAB is a good neuropsychological test to evaluate degrees of frontal lobe dysfunction. The present correlation between FAB score and SR was noteworthy, demonstrating that damage to the vestibular control mechanisms becomes more severe with progression of ALS-related damage to the frontal lobe. Furthermore, the SR could represent the normal range in the initial stage of ALS, because ALS lesions might not involve the other cortical areas beyond pyramidal tract. We estimated that the SR might decrease with the progression of ALS. We think it is important to analyze the change in SR in our future study.

In humans, vestibular stimulation activates the vestibular cortex, which comprises the posterior insular region, superior temporal gyrus, inferior parietal lobule (IPL), and anterior cingulate gyrus [25–27]. Known as the parietoinsular vestibular cortex, the posterior insular region is particularly important. During visual suppression testing of vestibular nystagmus, activity in vision-related regions of the brain including the frontal eye field (FEF), temporal pole, inferior temporal gyrus, fusiform gyrus, and lingual gyrus increases while activity in areas of the vestibular cortex such as the IPL tends to decrease with visual stimulation [25–27]. The negative correlation between activation of the vision-related regions and the vestibular cortex suggests that visual input in the cerebral cortex acts to suppress the vestibular system. Histopathologically, efferent projections have been shown to extend from the vestibular cortex to the vestibular nucleus. In other words, in addition to receiving input from the vestibular nucleus, the vestibular cortex may also send outputs to the vestibular nucleus and suppress the vestibulo-ocular reflex [28–30].

The activation of specific regions of the cerebral cortex (vision-related regions) as a result of visual stimulation during the onset of vestibular nystagmus indicate that the lesions responsible for impaired visual control of vestibular nystagmus, in other words, impaired visual suppression, may be found in the cerebral cortex rather than the cerebellum or brainstem. The present ALS patients showed no deficits such as cerebellar ataxia or nystagmus or other eye movement disorders while clinical symptoms and imaging findings also confirmed the absence of cerebellar and brainstem lesions. The relationship between FAB score and SR in the present ALS group thus suggests a role of the frontal lobe in damage to the vestibular control mechanisms. Previous studies have reported the possible contribution of the frontal lobe and specifically the FEF in vestibular control, although these studies were not conducted in ALS patients [28–30].

Conversely, lesions in the IPL are clinically known to damage central nervous system vestibular control mechanisms, which utilize visual information [16,31]. In ALS patients with concomitant IPL lesions,

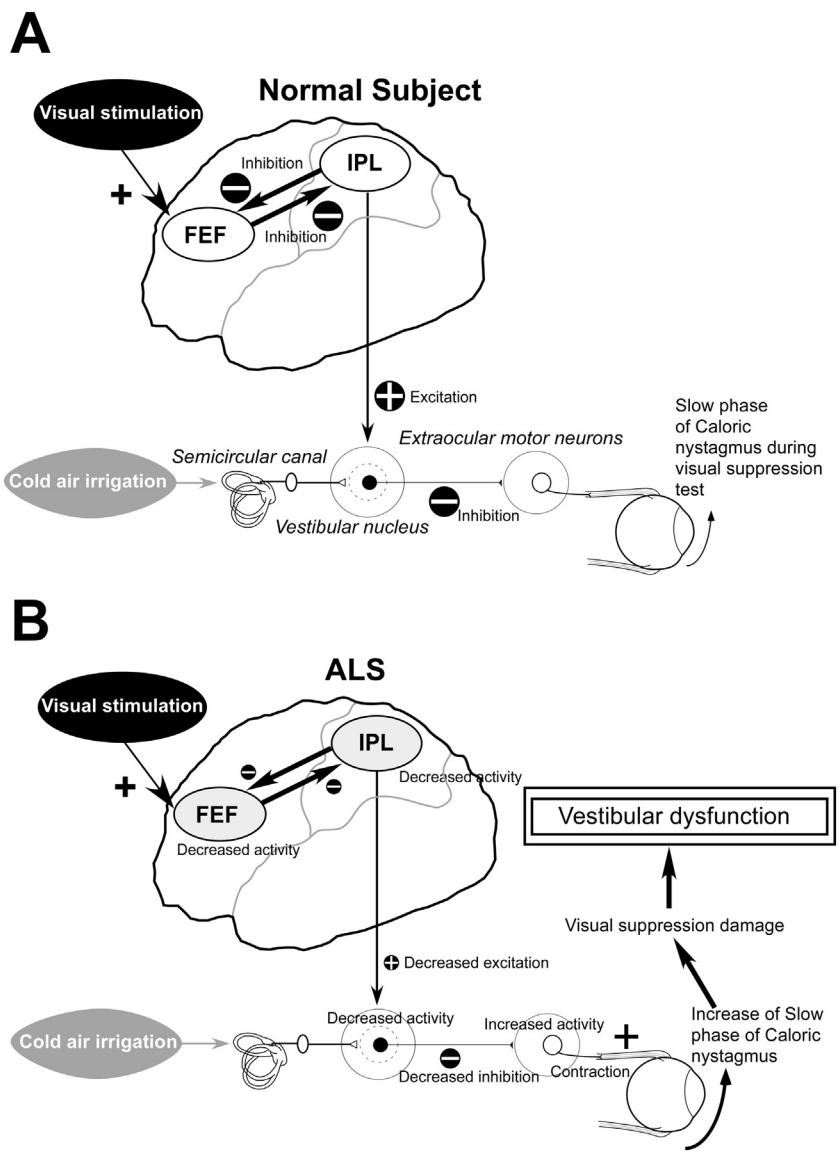

Fig. 3. Theoretical mechanism underlying impairment of visual suppression in ALS.
This diagram shows a theoretical neuronal circuit underlying the vestibulo-ocular reflex in the brainstem based on the literature [16,17,25–30,34,35]. Compared to healthy individuals (A), after vestibular stimulation with fixed visual stimulation during the visual suppression test, the slow phase of vestibular nystagmus in ALS increases due to impaired visual suppression (B). In ALS, vision-related regions of the brain (such as the FEF) and vestibular cortex (such as the IPL) are damaged and neuronal activity is decreased in these areas. This is predicted to lead to decreased excitatory inputs from the vestibular cortex to the inhibitory neurones in the vestibular nucleus. This, in turn, decreases inhibition of the extraocular motor neurone, leading to increased tonus of the abductor muscles on the side of vestibular stimulation. Accordingly, the difference in tonus between abductor and adductor muscles increases. In ALS patients, the velocity of the slow phase of vestibular nystagmus during visual stimulation is increased compared to healthy individuals, decreasing visual suppression. IPL, inferior parietal lobe; FEF, frontal eye field. White circles (○), excitatory neurons; black circles (●), inhibitory neurons; +, excitation; −, suppression. Size of the + and – symbols reflects the amount of neuronal activity.

organic impairment due to cortical thinning has been shown on magnetic resonance imaging (MRI) [32] in addition to functional impairment shown on functional MRI [33]. IPL lesions as well as frontal lobe injury are thus likely to be related to impaired visual suppression of vestibular nystagmus in ALS.

Fig. 3 shows a theoretical mechanism of damage to the central vestibular control mechanisms in ALS from the perspective of cerebral damage in the FEF and IPL. In healthy individuals, the slow phase of vestibular nystagmus is suppressed by visual fixation during the visual suppression test. In ALS patients, damage to the FEF and IPL result in disinhibition of the inhibitory ocular motor neurones via the vestibular nucleus, leading to an increase in the slow phase of vestibular nystagmus rather than suppression.

The finding of a decreased SR by itself could be considered an important indication of the spreading of ALS lesions beyond motor pathways such as the frontal lobe. The role of a specific physiological parameter in the suppression of the vestibular nystagmus, namely the SR, should be identified to give to ALS clinicians as a new additional instrument for clinical assessment of ALS patients.

In summary, the present findings suggest that frontal lobe damage in ALS may be related to the central vestibular dysfunction. A correlation between SR on vestibular function testing and progression of cerebral lesions in ALS was also indicated. Further study is required to investigate the potential utility of a simple vestibular function test as a tool for objectively detecting frontal lobe dysfunction in ALS.

5. Limitations

The present study did not measure cerebrospinal fluid levels of TDP-43 or perform any executive function testing other than the FAB in ALS patients. Additional executive function testing may enable more precise localization or identification of the damaged area.

Some of the present ALS group were receiving oral riluzole (3 of 18 patients). As the relationship between this ALS drug and vestibular function has yet to be reported, the potential effects on visual suppression testing are unclear.

Conflict of interest

The authors report no conflicts of interest.

Authors' roles

1) Research projection:
Dr. Nakamagoe, Conception.
Dr. Nakamagoe, and Dr. Tamaoka, Organization.

Dr. Nakamagoe, Ms. Kawakami, Ms. Yamada, Dr. Miyake, Dr. Tozaka, Dr. Okune, Dr. Takeda, and Dr. Tamaoka, Execution.

2) Statistical Analysis
Dr. Nakamagoe and Dr. Koganezawa Design.
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Dr. Koganezawa, Review and Critique.

3) Manuscription:
Dr. Nakamagoe and Ms. Yamada, Writing of the first draft.
Dr. Koganezawa and Dr. Tamaoka, Review and Crituque.

Acknowledgements

This work was supported by JSPS KAKENHI Grant number JP 26460901.

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