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Vestibular evoked myogenic potentials and their clinical utility in patients with amyotrophic lateral sclerosis

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HIGHLIGHTS

- A high rate of cervical vestibular evoked myogenic potential (VEMP) abnormalities (67%) was observed in patients with ALS.
- The main change in VEMPs of ALS patients was delayed latency rather than alteration in amplitude.
- VEMP abnormalities may provide important localizing information for understanding the underlying pathogenesis of ALS.

ABSTRACT

Objective: To evaluate the diagnostic value of vestibular evoked myogenic potentials (VEMPs) in the assessment of brainstem function integrity in patients with amyotrophic lateral sclerosis (ALS).
Methods: This was a prospective case-control study including 30 definite or probable ALS patients divided into two groups (with or without brainstem involvement) and 30 healthy controls. Cervical (c-), masseter (m-) and ocular VEMP (o-VEMP) measurements were obtained for all the participants.
Results: The c-VEMP mean p13 and n23 were significantly prolonged in the ALS patients. The interside peak differences in p13 and n23 of c-VEMP and in n10 and p15 of o-VEMP were significantly prolonged. The rates of alteration in c-VEMP, m-VEMP and o-VEMP in the ALS patients were 67%, 40%, and 45%, respectively. The ALS patients with brainstem involvement had a significantly higher percentage of VEMP abnormalities than did those without brainstem involvement ($p = 0.027$).
Conclusions: c-VEMP is a sensitive tool to detect lower levels of brainstem involvement. Impairments in o-VEMP and m-VEMP indicate involvement of the upper brainstem. The use of combined VEMPs may provide useful insights into the pathophysiological mechanism of ALS.
Significance: VEMPs may be useful in the evaluation of brainstem dysfunction in ALS patients.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease sharing common characteristics of neuronal loss and degeneration of upper motor neurons (UMNs) and lower motor neurons (LMNs) (Chen et al., 2015; Robberecht and Philips, 2013). Together with the lack of diagnostic biomarkers for ALS, the varied phenotypes and progression rates all contribute to delayed diagnosis. Electrophysiological studies, especially needle electromyography (EMG) of the tongue and sternocleidomastoid muscle (SCMM), can help detect the presence of subclinical bulbar LMN (Kilic et al., 2012) involvement. The trigeminocervical reflex (TCR) (Xu et al., 2005) and other brainstem reflexes (Cengiz et al., 2017) have also been identified as useful tools for detecting bulbar involvement in patients with ALS. However, these tests only reflect lower brain stem involvement, and their current

Abbreviations: ALSFRS, ALS functional rating scale; AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; IOM, inferior oblique muscle; LMN, lower motor neuron; PD, Parkinson's disease; MRC, Medical Research Council; SCMM, sternocleidomastoid muscle; TCR, trigeminal cervical reflex; UMN, upper motor neuron; VEMPs, vestibular evoked myogenic potentials.

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use in detecting UMN impairment and upper brainstem involvement is limited.

Vestibular evoked myogenic potentials (VEMPs) are evoked by short, intense auditory stimuli, bone-conducted vibrations, or forehead taps (Oh et al., 2018). Three VEMP tests exist. Cervical VEMP (c-VEMP), masseter VEMP (m-VEMP) and ocular VEMP (o-VEMP) correspond to the vestibulo-collic reflex, vestibulo-masseteric reflex (VMR) and vestibulo-ocular reflex, respectively (Colebatch et al., 1994). The c-VEMP test evokes ipsilateral inhibitory responses in the sternocleidomastoid muscle (SCMM) (p13/n23 wave), the m-VEMP test induces a bilateral and symmetric biphasic potential (p11/n15 wave), and the o-VEMP test evokes excitatory responses in the contralateral inferior oblique muscle (IOM) (n10/p15 wave) (Deriu et al., 2003). The 3 types of VEMPs can reflect the integrity of the reflexes from different segments of the brainstem, and combined VEMPs can theoretically reflect the functional integrity of the whole brainstem.

VEMPs have been used for decades to assess peripheral neurovestibular diseases. In recent years, an increasing number of studies have focused on evaluating brainstem involvement in central neurological disorders, including multiple sclerosis, cerebral vascular disease and neurodegenerative diseases, such as Parkinson's disease (PD) and Alzheimer's disease (AD) (de Natale et al., 2015; Deriu et al., 2016; Gazioglu and Boz, 2012). VEMPs have shown potential for good sensitivity for the detection of disease in otherwise clinically normal patients, although they usually cannot indicate the etiology of the disease. Therefore, VEMPs have often been used as an important localizing assessment (Deriu et al., 2016). Considering the significance of brainstem involvement in ALS, the objectives of this study were to evaluate the diagnostic value of c-VEMP in the assessment of bulbar involvement in patients with ALS. We also combined c-VEMP with m-VEMP and o-VEMP to explore whether VEMPs can serve as possible markers of brainstem involvement in ALS patients.

2. Methods

2.1. Subjects

A total of 60 subjects (30 definite and probable ALS patients and 30 healthy controls) participated in the study. Patients were diagnosed and classified according to the Airlie House diagnostic criteria (Brooks et al., 2000). None of the subjects had hearing problems, and they all were examined by audiometric testing and otoscopy before inclusion. The exclusion criteria were a diagnosis of cervical spondylosis with impaired neck movements, mild or severe dizziness with ear disease or cerebrovascular disease, and use of medications that might influence VEMP results, such as diazepam or clonazepam. The study protocol was approved by the institutional ethics committee of Peking University Third Hospital (PUTH IRB 00006761-2016141), and all the subjects provided written informed consent prior to inclusion in the study.

2.2. Clinical examinations

All the patients with ALS were examined by experienced neurologists for motor neuron dysfunction, with at least two neurologists for each patient. All the patients underwent a thorough physical and neurological examination, specifically for the presence of the brainstem reflexes and eye movement impairment, including saccades, smooth pursuit, ophthalmoplegia and nystagmus. The following data were also obtained: total Medical Research Council (MRC) manual muscle testing score, ALS functional rating scale (ALSFRS) score and electrophysiological data, including nerve conduction velocity and EMG data of the SCMMs and the trigeminal cervical reflex (TCR). TCR testing was performed using a standard method (Di Lazzaro et al.,1996).

According to the presence of upper motor neuron (UMN) and lower motor neuron (LMN) signs in the bulbar region, the patients were subdivided into 2 groups: ALS patients with bulbar involvement (group 1) and ALS patients without bulbar involvement (group 2). LMN signs included weakness, atrophy or fasciculation of bulbar motor neuron-innervated muscle, which also includes the affected muscles defined by EMG criteria. UMN signs include the presence of the clonic jaw jerk, exaggerated gag reflex, exaggerated snout reflex and pseudobulbar features (Brooks et al., 2000).

2.3. VEMP analysis

VEMP tests were performed by a different experienced technician who was blinded to the clinical examination.

VEMPs were elicited using the Keypoint G4 (9031A070, Alpine biomed Aps, Denmark) with the following settings and equipment: scanning velocity 10 ms/D; sensitivity 0.2 mV/D; filter 5 Hz–5 kHz; 2 channels; click sound (300–500 stimuli of 0.1 ms, 5 Hz frequency each); a single channel calibrated stereophonic earphone and an electrode for the Ag/AgCl surface electrode. (1) c-VEMP test: the patient assumed the supine position. The recording electrode was positioned on the muscular belly of the sternocleidomastoid muscle, and the reference electrode was placed at the junction of the sternum and ribs. First, we measured the hearing threshold and then asked the subject to lift off the bed approximately 10 cm. At this time, the examiner placed a finger on the subject's forehead to exert a certain resistance and recorded the baseline amplitude before stimulation. Next, the examiner adjusted the headphone stimulation to 135 dB SPL, approximately 300–500 times on average, until a stable waveform was obtained and marked as P13, N23. This procedure was repeated 2–3 times (Colebatch et al., 1994; de Natale et al., 2015). (2) m-VEMP test: the recording electrode was positioned on the belly of the masseter muscle, the reference electrode was positioned on the mandibular angle, the ground line was located on the forehead, the subjects' teeth were occluded at a strength of approximately 30–50% of the maximum bite force, and the waveform of the bilateral P11 was recorded; (Deriu et al., 2003). (3) o-VEMP test: the recording electrode was positioned on the lower oblique muscle at a position approximately 1 cm under the lower eyelid. The electrode was placed 1.5 cm under the recording electrode, and the patient was asked to gaze at the wall at an angle of 30–50° in the indicated direction and a height above 2 m. N10 and P15 could be recorded on the contralateral inferior oblique muscle.

All waveforms were measured by latency (P13, N23, P11, N10, P15), interpeak latency (P13-N23, N10-P15), interside peak latency (P13, N23, P11, N10, P15), peak to peak amplitude (P13-N23, N10-P15), and amplitude ratio before and after stimulation and then converted to log form of the ratio for c-VEMP. The amplitude asymmetry ratio (AR) was calculated for c-VEMP and o-VEMP as reported by Rosengren et al. (2005, 2010) AR was calculated as follows: (larger response − smaller response)/(larger response + smaller response) 100%. The latency asymmetry ratio was calculated as follows: (longer latency − shorter latency)/(longer latency + shorter latency) 100%.

2.4. Other electrophysiological studies

EMG of SCMM and TCR were performed in all the patients with ALS. EMG of SCMM were performed in each patient bilaterally using standard methodology. The presence of acute and chronic denervation in the SCM EMG were considered indications of a neurogenic abnormal EMG. Acute denervation includes the presence of

a large number of fibrillation and positive sharp waves in at least 3 points in the SCMM. Chronic denervation includes increased MUP with a duration and amplitude above the boundary of the mean plus 2.5 × SD, as well as reduced recruitment.

The method for TCR is similar to that of c-VEMP. The recording electrode was positioned on the muscular belly of the sternocleidomastoid muscle, and the reference electrode was located at the junction of the sternum and ribs. The stimulating electrode was applied to the infraorbital foramen. The response of P19, N31 could be elicited bilaterally after adequate activation.

2.5. Statistical analysis

Statistical analysis was performed with SPSS 16.0 for Windows (Chicago, IL). The baseline demographic and clinical characteristics of the ALS patients and each VEMP parameter of all the subjects were compared using *t*-tests for continuous variables and x^2 tests for categorical variables. Mann-Whitney U two-sample tests were used if the assumption of normal distribution was not reasonable. Comparison of two diagnostic methods for ALS patients was performed using paired McNemar's test. Correlations between the ALSFRS or disease duration and VEMP alterations were evaluating using Spearman's correlation coefficients. A p value of less than 0.05 was required for statistical significance.

3. Results

3.1. Participants and clinical findings

The ALS patients consisted of 20 males and 10 females (aged 29–70; mean age 53.40 ± 10.49 years) and the control group of 19 males and 11 females (aged 27–78; mean age 53.07 ± 11.59 years). There were no significant differences in age or sex between the two groups. For the ALS patients, the mean age at symptom onset was 52.2 ± 10.8 years, and 66.7% of patients (20/30) were between 40 and 59 years old. The median disease duration was 14.8 months (ranging from 4 months to 6 years). Five patients had bulbar-onset ALS, 19 patients had upper-limb-onset ALS, and 6 had lower-limb-onset ALS. Thirteen patients had past or present bulbar symptoms upon examination and were classified as ALS patients with bulbar symptoms. The mean ALSFRS score was 39.1 ± 3.32. The demographic features and clinical characteristics of the study subjects are shown in Table 1.

3.2. VEMP findings

3.2.1. Comparison of VEMPs between ALS patients and control subjects

c-VEMP, m-VEMP and o-VEMP responses were obtained from both sides in all control subjects, except for o-VEMP in 1 control subject. c-VEMPs could be recorded from both sides in 24 ALS patients, from one side in 3 patients, and 3 patients were absent bilaterally. m-VEMPs could be elicited from both sides in 29 patients but were absent bilaterally in 1 patient; o-VEMPs could be elicited from both sides in 27 patients, from one side in 1 patient, and 2 patients were absent bilaterally. c-VEMP, m-VEMP and o-VEMP recordings in a representative control subject and ALS patients with and without bulbar involvement are shown in Fig. 1.

Three types of latencies in VEMP were compared between the ALS patients and controls subjects: mean response latency (P13, N23, P11, N10, P15), interpeak latency (P13-N23, N10-P15) and interside peak latency. The c-VEMP mean p13 and n23 latencies were 15.41 ± 3.28 ms and 25.79 ± 5.05 ms, respectively, which were significantly prolonged in ALS patients ($p < 0.01$). The o-VEMP mean p15 was also significantly prolonged (15.84 ± 2.35 ms), while the mean interpeak latency for n10-p15 in the o-VEMP and p13-n23 in the c-VEMP showed no significant differences between the 2 groups. The mean interside peak latency differences for the p13, n23, n10 and p15 latencies were significantly prolonged in the ALS patients ($p < 0.01$). However, there was no significant difference in the mean interside peak difference for the p11 latency. Though the corrected amplitude of c-VEMP showed a mild reduction compared to controls (0.36 ± 0.21 vs 0.44 ± 0.14), there was no significant difference between the 2 groups. The amplitude ARs of o-VEMP showed an elevation in ALS patients, but no significant differences were observed. The comparisons of each VEMP parameter for the ALS patients and control group are summarized in Table 2.

3.2.2. VEMP abnormality rate

There are 3 types of abnormalities in VEMP in patients with ALS: (1) prolonged latency with normal amplitude (the abnormality of latency is defined as above the boundary of the mean plus 2.5 × SD); (2) decreased amplitude or altered waveform morphology; (3) absence of response.

A significantly higher frequency of abnormalities in VEMPs were observed in patients than in controls (Table 3).

c-VEMP abnormalities were observed in 6.7% of the control subjects and in 63.3% (19/30) of the ALS patients. There was a significant difference in the percentage of subjects who exhibited c-VEMP abnormalities between the controls and ALS patients ($p < 0.001$). The c-VEMP was abnormal in 84.6% of the ALS patients with bulbar involvement and in 47.1% of the ALS patients without bulbar involvement, and there was a significant difference between the groups ($p = 0.016$). The observed TCR and SCMM EMG abnormality rates were 53.3% (16/30) and 43.3% (13/30) in ALS patients, respectively (Supplementary Tables 1 and 2). Though the detection rate seems higher in VEMPs, there were no significant differences between the 3 detection methods or between the two categories of ALS patients. The sensitivities among the VEMP, SCMM EMG and TCR methods were not significantly different (Table 4, Fig. 2).

The percentages of subjects with abnormalities in the m-VEMP were 6.7%, 33.3% and 38.5% for the control subjects and the group 1 and group 2 ALS patients, respectively. There was a significant difference between the controls and ALS patients ($p = 0.01$) but not between group 1 and group 2 ($p = 0.602$).

Finally, o-VEMP abnormalities were detected in 43.3% (13/30) of the ALS patients, with a significant difference between the controls and ALS patients ($p = 0.001$) but not between group 1 and group 2 ($p = 0.310$). Combined assessment of all VEMP responses resulted in a 65% abnormality rate in the ALS patients. A prolonged

Table 1
Demographic and clinical features of control subjects and patients with ALS.

	Control subjects (n = 30)	ALS patients with bulbar involvement (n = 13)	ALS patients without bulbar involvement (n = 17)	p value
Mean age (years)	53.07 ± 11.59	55.69 ± 10.42	51.65 ± 10.5	0.609
Gender (male/female)	19:11	8:5	11:6	0.984
Disease duration (month)	–	16.08 ± 13.02	19.59 ± 18.68	0.568
ALSFRS score	–	37.62 ± 4.43	40.24 ± 1.48	0.06

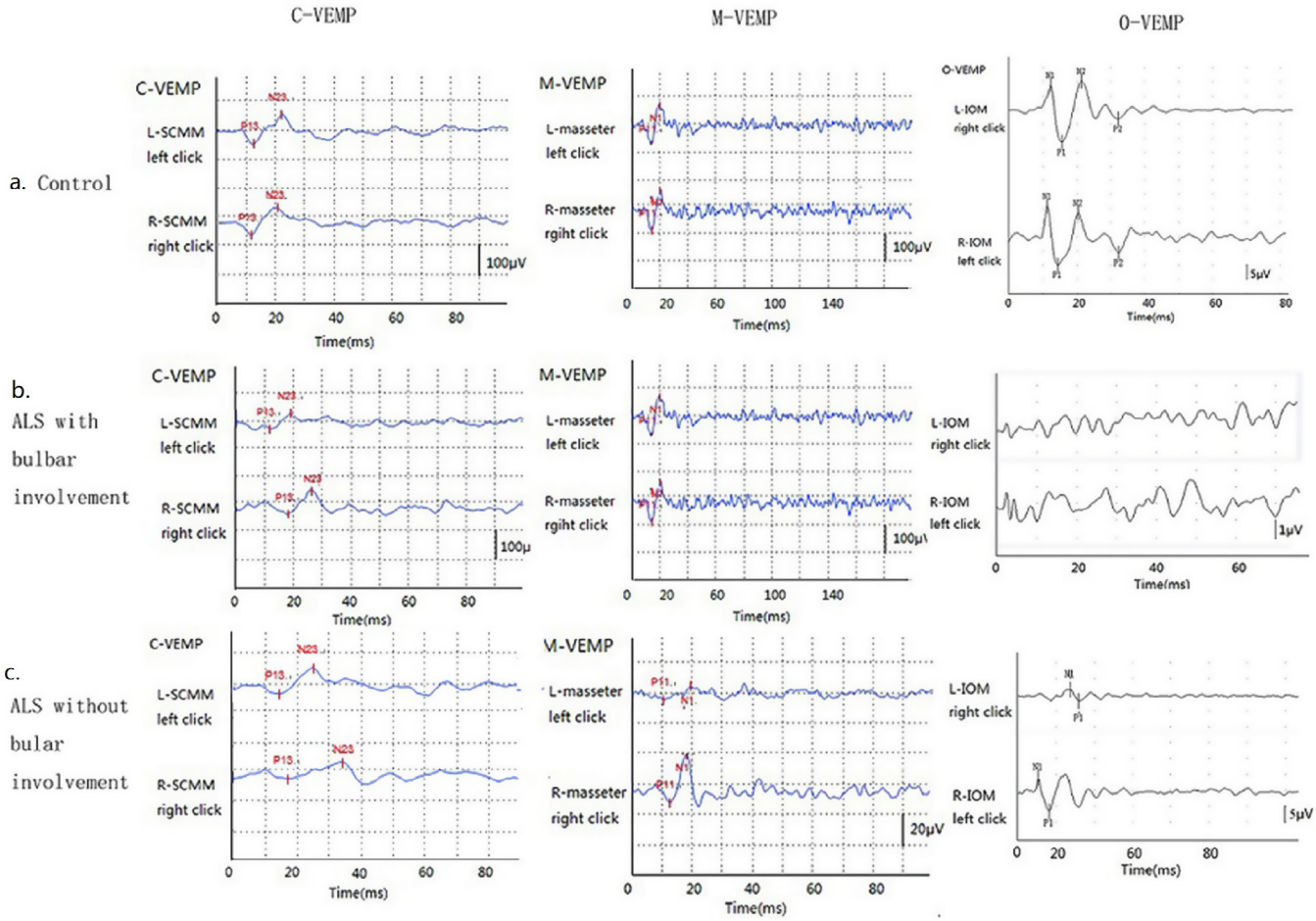

Fig. 1. c-VEMP, m-VEMP and o-VEMP recordings in a representative control subject and ALS patients with and without bulbar involvement. Cervical (c-VEMP), masseter (m-VEMP) and ocular (o-VEMP) VEMPs recorded in a representative control subject (a), in an ALS patient with bulbar involvement (b) and in an ALS patient without bulbar involvement (c). In the control subject, c-VEMP appears as an ipsilateral p13/n23 wave, m-VEMP appears as a bilateral and symmetric p11 wave and o-VEMP as a contralateral n10/p15 wave. a. A representative control subject: a 45-year-old healthy man; b. (patient 4): a 56-year-old man with bulbar-onset ALS with a disease duration of 16 months. Mean response latency of P13, N23 of the right side and interside peak latency of P13, N23 were prolonged in c-VEMP, and no responses were elicited bilaterally in o-VEMP. c. (patient 19): a 32-year-old woman with lower-limb-onset ALS, a disease duration of 6 years, SOD1 H46R mutation with a positive family history. Alterations in this patient include prolonged latency of P13, N23 bilaterally, low amplitude of P11 in the left side and prolonged latency and low amplitude in N10, P15 in the left side.

Table 2
VEMP results of the ALS patients and control subjects.

Parameter		Control subjects	ALS patients	p value
c-VEMP	Latency p13 peak (ms)	12.7 ± 1.57	15.41 ± 3.28	<0.01
	Latency n23 peak (ms)	21.7 ± 2.61	25.79 ± 5.05	<0.01
	p13-n23 interpeak latency (ms)	9.02 ± 1.89	10.33 ± 3.47	0.11
	p13 interside peak difference (ms)	1.23 ± 1.05	2.42 ± 1.73	0.003
	n23 interside peak difference (ms)	1.72 ± 1.90	3.35 ± 2.95	0.017
	P13/n23 amplitude (range, μV)	128.86 ± 52.89 (37–187)	90.05 ± 38.23 (47.6–239)	0.105
	p13/n23 corrected amplitude	0.44 ± 0.14	0.36 ± 0.21	0.138
	Amplitude ratio asymmetry	20.58 ± 12.3	25.4 ± 16.55	0.258
m-VEMP	p11 peak (ms)	11.9 ± 2.0	13.2 ± 2.62	0.058
	p11 interside peak difference (ms)	1.55 ± 1.24	1.56 ± 1.52	0.965
	p11 corrected amplitude	0.37 ± 0.17	0.33 ± 0.19	0.453
	Amplitude ratio asymmetry	15.47 ± 11.13	19.81 ± 21.00	0.358
o-VEMP	Latency n10 peak (ms)	9.8 ± 1.0	10.7 ± 3.43	0.181
	Latency p15 peak (ms)	14.3 ± 1.69	15.84 ± 2.35	0.011
	n10-p15 interpeak latency (ms)	4.91 ± 1.33	5.67 ± 1.83	0.107
	n10 interside peak difference (ms)	1.1 ± 1.02	2.35 ± 2.52	0.028
	p15 interside peak difference (ms)	1.4 ± 0.9	2.60 ± 2.39	0.026
	Amplitude ratio asymmetry	24.01 ± 16.99	26.04 ± 19.59	0.701

Comparison between ALS and controls group in c-, m-, o-VEMP abnormalities rate were used t-test, p value from t-test, significant if <0.05; The number of control subjects included in c, m, o-VEMP is 30, 30, 29; The number of ALS patients included in c, m, o-VEMP is 27, 29, 28. The mean ± SD values were obtained from subjects with preserved VEMPs. The abnormality of latency and amplitude is defined as above the boundary of the mean plus 2.5 × SD.

Table 3
Distribution of VEMP abnormality and asymmetric index in the control subjects and ALS patients.

VEMP	Subjects	Number (%) of subjects with abnormal VEMPs	Pattern of VEMP abnormalities, no. (%) of patients			p value	Asymmetric index (%)
			Delay	Amplitude change	Absence		
c-VEMP	Controls	2/30 (6.7%)	1 (3.3%)	2 (6.7%)	–	<0.01	1 (3.3%)
	ALS patients	19/30 (63.3%)	13 (43.3%)	4 (13.3%)	6 (20%)		12 (40%)
	Group 1	11/13 (84.6%)	7 (53.8%)	2 (15.4%)	4 (30.8%)	0.016	7 (53.8%)
	Group 2	8/17 (47.1%)	6 (35.3%)	2 (11.8%)	2 (11.8%)		5 (29.4%)
m-VEMP	Controls	2/30 (6.7%)	1 (3.3%)	2 (6.7%)	–	0.01	1 (3.3%)
	ALS patients	10/30 (33.3%)	8 (26.7%)	4 (13.3%)	1 (3.3%)		5 (16.7%)
	Group 1	5/13 (38.5%)	4 (30.8%)	2 (15.4%)	1 (7.7%)	0.602	3 (23.1%)
	Group 2	5/17 (29.4%)	4 (23.5%)	2 (11.8%)	–		2 (11.8%)
o-VEMP	Controls	2/30 (6.7%)	–	1 (3.3%)	1 (3.3%)	0.001	0
	ALS patients	13/30 (43.3%)	10 (33.3%)	2 (6.7%)	3 (10%)		6 (20%)
	Group 1	7/13 (46.2%)	5 (38.5%)	–	2 (15.4%)	0.310	4 (30.8%)
	Group 2	6/17 (41.2%)	5 (29.4%)	2 (11.8%)	1 (5.9%)		2 (11.8%)

Comparison of abnormality rate between control subjects and ALS patients or Group 1 and Group 2 in ALS patients in c-, m-, o-VEMP abnormalities rate were used chi-square test, p value from chi-square test, significant if <0.05.

Table 4
TCR and SCMM EMG results in control subjects and ALS patients.

	TCR						EMG of SCMM		
	P19 (ms)		N31 (ms)		Ratio of amplitude (A)		Fibrillation, PSW (n, %)	Duration (ms)	Amplitude (μV)
	Ipsilateral	Contralateral	Ipsilateral	Contralateral	Ipsilateral	Contralateral			
ALS (n = 30)	22.3 ± 3.4	23.4 ± 3.1	33.3 ± 4.7	32.6 ± 4.1	1.5 ± 0.4	1.4 ± 0.4	9 (69.2%)	12.0 ± 1.5	989.8 ± 404.2
Control (n = 30)	18.6 ± 1.4	19.6 ± 1.5	28.6 ± 2.8	28.3 ± 2.9	1.7 ± 0.5	1.8 ± 0.5	1 (5.8%)	10.5 ± 1.1	738.4 ± 251.5

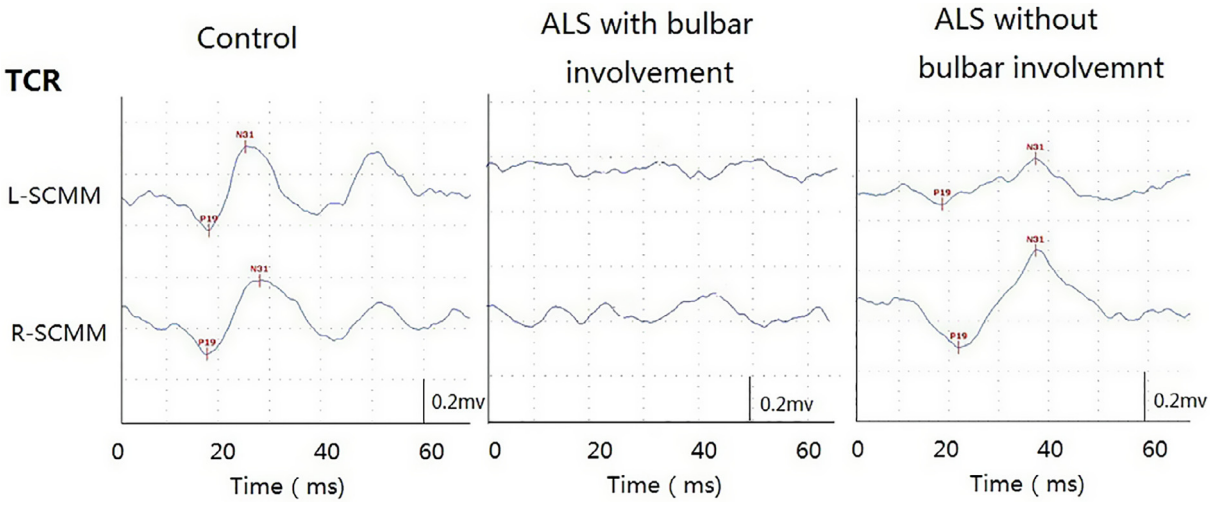

Fig. 2. TCR of p19-n31 in a representative control subject and ALS patients with and without bulbar involvement. In the control subject, TCR appears as bilateral p19/n31 waves. No responses were elicited in the ALS patient with bulbar involvement. Prolonged latency of n31 and reduced amplitude of p19/n31 in the left side were observed in the patient without bulbar involvement.

latency was more prevalent in the patients with UMN symptoms in our study ($p < 0.01$).

3.2.3. Correlation with ALSFRS and disease duration

Fig. 3 illustrates the correlations among c-, m- and o-VEMP latencies, ALSFRS score and disease duration. There was no significant correlation among any of the VEMP latencies and the ALSFRS score or duration of the disease (Supplementary Table 3).

4. Discussion

In our study, higher abnormality frequencies were observed in c-VEMP, m-VEMP and o-VEMP in 30 ALS patients. It has been thought that age-related effects could impact VEMP results (de Natale et al., 2015; Rosengren et al., 2011). As the ages of the controls and patients did not significantly differ, the age-related factor may be negligible in our study.

Studies on brainstem reflexes in ALS are very rare, and the results are controversial. Shimoda demonstrated a significant increase in the latency and a decrease in the amplitude of R2 responses in the blink reflex (BR) in ALS patients (Shimoda et al., 1995), and as the only study of VEMP in ALS to our knowledge, Kilic et al. (2012) did not find any significant differences from controls in the p13 or n23 latencies. The small patient series or the inclusion and exclusion criteria of the design could be potential reasons for the negative results. Moreover, the m-VEMP and

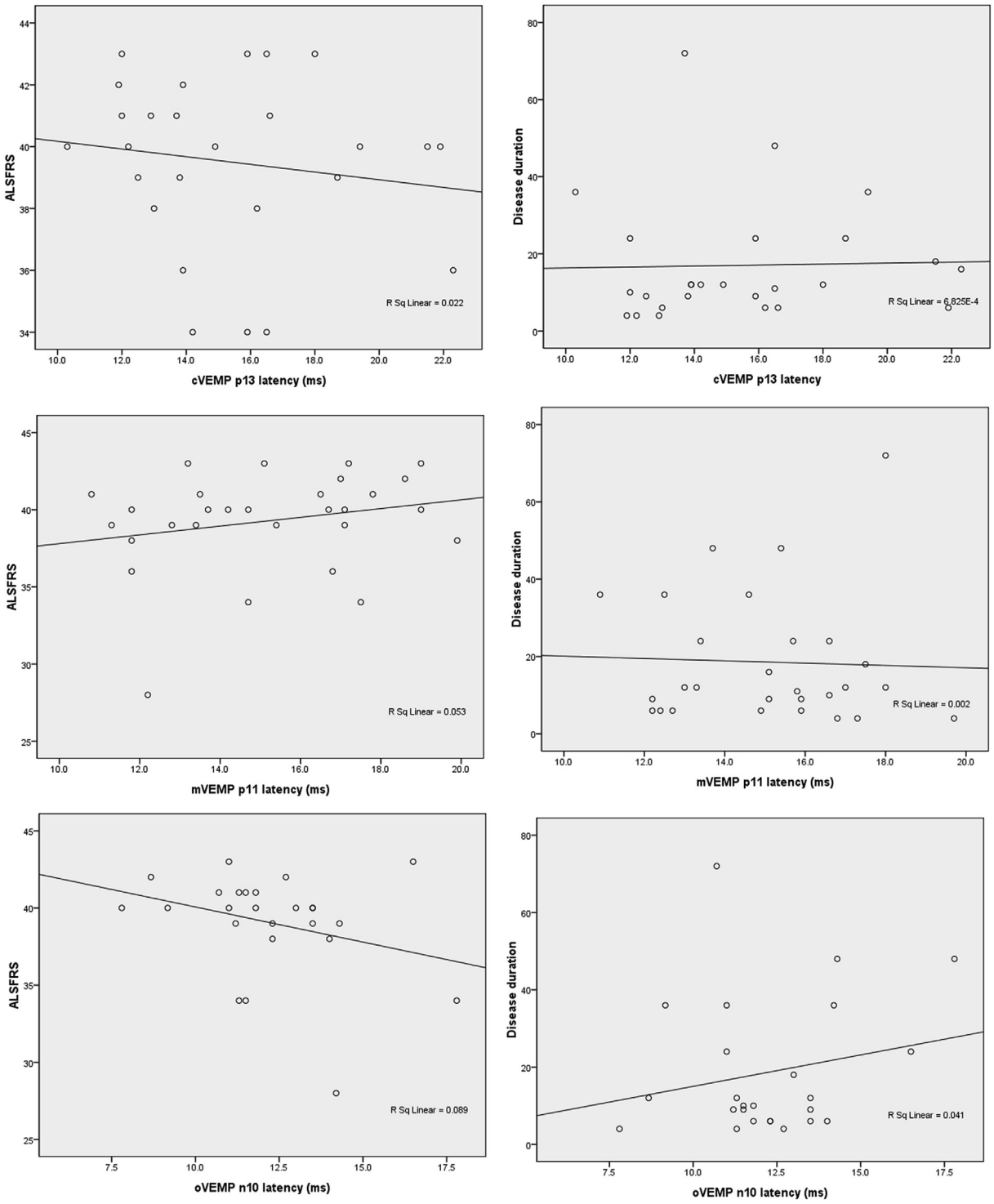

Fig. 3. The correlation of cervical, masseter and ocular VEMP latencies with ALSFRS and disease duration.

o-VEMP changes in ALS remain unclear. Therefore, the aim of our study was to evaluate the diagnostic value of VEMPs in the early stage of ALS and explore the potential of using VEMP to assess the integrity of brainstem function in patients with ALS.

The c-VEMP abnormalities mainly presented as changes in latency, i.e., delayed p13 and n23 waves in combination with increased p13-n23 interpeak latencies and p13 interside peak differences. The rate of abnormalities was very high (84.5%) in ALS patients with bulbar involvement (group 1). As the EMG of the SCMM has important diagnostic value in detecting the presence of clinical and subclinical LMN involvement, we compared the abnormality rate between the c-VEMP and SCMM EMG and found that the c-VEMP abnormality rate was slightly higher but not significantly different. To verify these results, we chose the TCR as our positive control (Xu et al., 2005). Because the TCR and c-VEMP share the same efferent pathway, the only difference is that instead of stimulating the vestibular nerve as the afferent pathway, we stimulated the trigeminal nerve to evoke a bilateral response in

the SCMM in the TCR. The TCR results in the paired group also showed a high detection rate. Therefore, c-VEMP, along with SCMM EMG and TCR, are sensitive tools to detect the impairment of the lower brain stem in patients with ALS.

In contrast to our expectation, no significant differences were observed in the corrected amplitude in c-VEMP or the amplitude ARs in m- or o-VEMPs, despite the corrected amplitude showing a mild reduction in c-VEMP and the amplitude ARs of m- and o-VEMP showing an elevation in ALS patients. This indicates that the change of amplitude may be a later alteration, with disease progression, partial denervation and reinnervation causing the CMAP to become prolonged and thereby delaying the responses (Liu et al., 2009; Shefner, 2001). The evidence of LMN loss in bulbar region may partially explain the especially high prevalence of abnormalities in c-VEMP group 1.

The higher abnormality rate in o-VEMP (40%) compared to the normal group was unexpected in our study, as previous reports suggested the eye movement was spared in patients with ALS. The o-VEMP alteration patterns included prolonged latency, low amplitude and absent responses. The changes did not significantly correlate with disease duration ($P > 0.05$). In the patients with altered o-VEMP, the majority (8/12, 66.7%) had upper motor neuron signs, and half of the patients (6/12, 50%) had no clinical bulbar involvement.

Changes in o-VEMP are likely due to dysfunction of the ocular muscles and the vestibulo-ocular pathway in the brainstem. Although the clinical examinations of eye movement were normal in patients with changes in o-VEMP, an increasing number of studies in recent years have shown slowed saccades, smooth pursuit and fixation disturbances in ALS using thorough video analysis (Donaghy et al., 2010, 2011; Moss et al., 2012). The paramedian pontine reticular formation is responsible for horizontal saccades, and the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF) in the midbrain is responsible for vertical and torsional saccades. Lesions in pontine reticular formation and riMLF and omnipause neurons in ALS may cause the delayed saccades, indicating brainstem involvement in ALS. Gorges et al. (2015) showed that eye movement dysfunction is consistent with a staging model of pTDP-43 pathology in ALS and can be classified by executive deficits in Stage 1 and additional impaired infratentorial oculomotor control pathways in Stage 2. Changes in o-VEMP may be caused by disturbances of burst and suppression neurons in the brainstem pathway and may serve as an early marker of neuropathological spreading.

Another possible explanation is the dopaminergic neuron decrease and astrocytosis observed in ALS. Reduced dopaminergic neurons in the substantia nigra and subsequent astrocytosis have been described pathologically and functionally in many previous studies in sporadic ALS (Chiò et al., 2014; Fathinia et al., 2013). The medial and lateral vestibular nuclei are thought to contain dopamine D2 receptors (de Natale et al., 2015), and any disconnect between the vestibular nuclei and nearby regions may cause altered o-VEMPs. Moreover, as most patients with abnormal o-VEMPs exhibited upper motor neuron signs, decreased serotonin levels and subsequently increased glutamate levels may affect the saculo-ocular reflex arc as a result of o-VEMP alterations, as indicated by the dying back hypothesis. However, the interneuron is not as important as the R2 response in the blink reflex in influencing the o-VEMP results, and an imbalanced environment of excitation and inhibition in the neuropool in the midbrain may have less impact on the VEMP due to tonic activation; therefore, the underlying pathophysiology changes in the ALS brainstem must be further explored. To our knowledge, this is the first study to investigate o-VEMP alterations in ALS. As this study has been performed on a small series of patients and due to the lack of data of a follow-up study, these results need to be supported by future studies.

There were no significant correlations between any of the VEMP latencies and the ALSFRS score or disease duration. This finding is different from that of PD patients, who showed a delayed latency in early PD as well as a low amplitude and absence of response in late PD (de Natale et al., 2015). Though ALS and PD share some similar pathophysiological mechanisms (Vermeiren et al., 2018), the rapid progression of ALS patients may obscure the correlation between VEMP and disease severity. VEMP observation in patients with a more advanced stage of ALS needs to be performed in the future.

In conclusion, VEMP can be easily performed by well-trained technicians, and the method is well tolerated by patients. Prolonged latency, rather than a decrease in amplitude, is the main manifestation of the VEMP in patients with ALS. c-VEMP, as well as EMG of the SCMM, is a sensitive tool to detect lesions in the lower brainstem. LMN lesions in ALS are primarily responsible for the c-VEMP abnormality, while the o-VEMP alterations are likely due to dysfunction of the brainstem. As VEMPs may provide important localizing information, the combined use of VEMPs may provide useful insights into the pathophysiological mechanism of ALS.

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Author contributions

DS Fan and XX Liu conceived and designed the study. X Huang, S Zhang and YS Zhang performed the experiments. XX Liu wrote the paper. DS Fan reviewed and edited the manuscript. All authors read and approved the manuscript.

Conflict of interest

None.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2019.01.023.

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