Abnormal trigeminocervical response in patients with spinal and bulbar muscular atrophy

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Abstract

Objective: To investigate the value of the trigeminocervical response (TCR) for revealing bulbar involvement in patients with spinal and bulbar muscular atrophy (SBMA). *Methods:* Thirty patients with SBMA and 30 healthy male controls were included in this study. In all of the normal controls, stimulation of the infraorbital nerve on one side produced bilateral short latency waves consisting of a positive/negative wave, p19/n31, the mean latency of which was measured. The mean square root of the ratio between the amplitude of p19/n31 and the mean rectified surface electromyography (EMG) activity preceding the stimulus, the A value, was estimated. The parameters of the TCR were compared between the two groups. *Results:* Among the patients with SBMA, 21 (70.0%) had delayed latencies of p19/n31 ($P < 0.01$) and all (100%) had reduced A values ($P < 0.01$) relative to the normal controls.
Conclusions: All parameters of the TCR were significantly different between the patients with SBMA and the normal controls. The TCR is helpful for revealing abnormal lower brainstem reflex integration in patients with SBMA.

INTRODUCTION

Spinal and bulbar muscular atrophy (SBMA), also known as Kennedy's disease, is a late-onset sex-linked genetic disease that was first reported in 1968.[1] SBMA is caused by abnormal expansion of CAG repeats on exon 1 of the androgen receptor (AR) gene, located on the X chromosome.[2-3] This disease is characterized by progressive muscular atrophy and weakness mainly involving proximal limbs. Atrophy and fasciculation of the tongue are also frequent symptoms, indicating that the lower brainstem is usually involved.[4-6] However, besides needle electromyography (EMG) of the sternocleidomastoid (SCM) or tongue muscles, there are few methods available for evaluating the function of the lower brainstem.[7-8] A short latency response can be recorded in the SCM muscle after stimulation of the infraorbital nerve. This response has been named the trigeminocervical response (TCR). Several studies have confirmed that the TCR pathway is confined to the lower brainstem.[9-11] In the present study, we attempt to explore the value of the TCR for evaluating bulbar involvement in patients with SBMA.

METHODS

From September 2006 to July 2009, 85 out-patients were diagnosed with SBMA by genetic analysis at our hospital. The patients were from a total of 35 families. Thirty patients agreed to participate in this study. Our institutional ethics committee approved the study. The study design was fully explained to each participant in written form, and, all participating patients signed an informed consent form.

Neurophysiologic procedures

The TCR was assessed as previously described.[12-13] Before the TCR study, all patients were advised to stop any drugs with a potential of changing nerve excitability for at least one week. Briefly, the responses were recorded symmetrically over the upper half of each SCM muscle, approximately 8 cm above a reference electrode placed over the clavicle. The signal was amplified with a band pass filter of between 30-3000 Hz, and averaged (usually 512 trials) from 20 ms before the stimulus to 100 ms after, using a Keypoint Electromyography apparatus (Medtronic, Skovlunde, Denmark). Electrical stimulus (100 μs in duration) was applied to the infraorbital

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nerve via bipolar surface electrodes fixed near the infraorbital foramina. The intensity was adjusted to three times the perceptual threshold; in all instances it was less than 5 mA and regarded as strong but not painful. The repetition rate was fixed at 3 Hz.

The averaged EMG record produced wave with positive and negative peaks, p19/n31, of which the mean peak latency measured. Lowercase letters indicate polarity. Amplitude was measured from peak to peak of the unrectified averaged waveform but because the size of the EMG response was linearly related to the level of background muscular contractions, it was expressed as a ratio of the mean level of tonic activity measured in the 20 ms preceding the stimulus artifact. The magnitude of the response varied considerably from subject to subject. To transform the distribution of the data into a more Gaussian form, we calculated the square root of the amplitude value before determining the normal limits, which were described using the letter A. Normal limits were defined as mean±2.5 standard deviation (SD) of the values in the normal controls.

Statistical methods

For statistical analysis, we performed SNK (q), paired t tests, and Chi-squared tests with SPSS software version 11.0 (Chicago, IL, U.S.). Values are expressed as the means ± SD, and P values of < 0.05 were considered significant.

RESULTS

All patients in the present study were male. The mean age was 41.6±5.7 years (range, 31-55 years), mean age at onset was 39.2±6.3 years (range, 29-50 years), and mean height was 171.4±5.7 cm (range, 161-180 cm). The diagnosis of SBMA was confirmed by genetic testing of the AR gene, with more than 40 CAG repeats in exon 1, meeting the diagnostic criteria for SBMA. The mean CAG repeat number was 47.6±2.8 (range 42-53). Apparent atrophy and fibrillation of tongue was noted in 56.7% (17/30) patients. None had dysarthria or dysphagia. The normal controls consisted of 30 healthy males whose mean age was 43.2±5.3 years (range 36-53 years) with mean height 170.2±5.4 cm (range, 162-179 cm).

There was no significant difference in age or height between the normal controls and the patients with SBMA. In all normal controls, stimulation of the infraorbital nerve on one side produced bilateral short latency peaks in the unrectified averaged EMG. The responses evoked consisted of a positive and a negative wave, which were described using the mean latencies preceded by letters indicating polarity (p19/n31) (Figure 1). There was no significant difference in the latency or size of the peaks on either side.

Among the patients with SBMA, 21 (70.0%) were noticed with delayed latency and all (100%) with reduced amplitude that was described as A values in TCR (Figure 1). Among the 13 patients without obvious clinical bulbar involvement, 7 (53.8%) were found to have delayed latency but all (100%) showed reduced A values. Bilateral p19/n31 latency and A values were significantly different from those of normal controls (*P* < 0.01) (Table 1).

All patients underwent needle EMG of the SCM muscles. Typical neurogenic changes in EMG of the SCM muscles were noted in 22 (73.3%) patients.
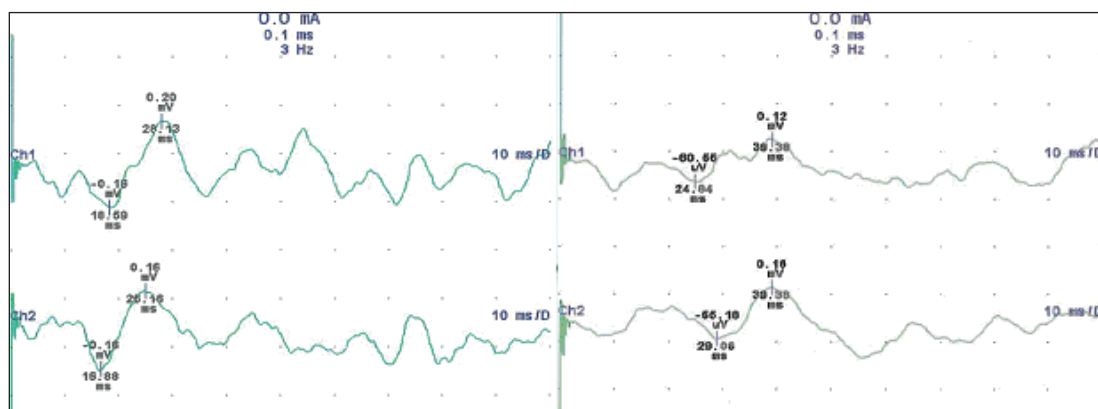

Figure 1. The trigeminocervical reflex: A positive/negative wave (p19/n31) recorded from the sternocleidomastoid muscle following electrical stimuli to the infraorbital nerve in a normal control (left). In a patient with SBMA, the p19/n31 was reduced in amplitude and delayed in latencies (right).

Table 1: Results of the trigeminocervical response (TCR) from the normal controls and the patients with spinal and bulbar muscular atrophy (SBMA)

Group	Ipsilateral			Contralateral		
	p19 (ms)	n31 (ms)	A	p19 (ms)	n31 (ms)	A
SBMA (n=30)	23.91±4.84	35.45±4.76	1.24±0.33	24.34±4.82	36.20±4.91	1.19±0.25
Normal controls (n=30)	18.37±2.16	28.50±1.56	1.90±0.43	18.72±2.18	29.19±1.43	1.84±0.40
t	5.77	8.19	−6.64	5.05	7.62	−7.77
P values	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01

DISCUSSION

Spinal and bulbar muscular atrophy (SBMA) is an X-linked hereditary disease first reported by Kennedy et al in 1968.[1] Although it is not usually the initial symptom, nearly all SBMA patients have bulbar involvement during the course of the illness.[4-6] In the present study, our results showed that the TCR was abnormal in patients with SBMA relative to the normal controls.

After stimulation of the infraorbital nerve, the onset of the short latency response is quite similar to that of the R1 component of the blink reflex, which suggests involvement of a disynaptic or oligosynaptic pathway from the trigeminal input to the cervical motoneurons.[10-11,14] Any involvement in the pathway can result in an abnormal response. In patients with SBMA, sensory nerve action potentials (SNAPs) are always decreased with normal sensory conduction velocities (SCVs).[15-18] The reduced amplitude of TCR in this study may be due to the involvement of the infraorbital nerve. In addition, the SCM muscle atrophy or the disturbance of the accessory nerve itself could play an essential role in the pathophysiology of the abnormal TCR, much like that of the abnormal R1 component in patients with amyotrophic lateral sclerosis (ALS) due to the disturbance of the facial nerve.[19] We found that needle EMG of the SCM muscle revealed chronic denervation potentials in 22 SBMA patients (73.3%). This was close to the abnormal percentage of delayed latency of the TCR (21 patients, 70.0%). Among the patients without obvious clinical bulbar involvement, 53.8% were found to have delayed latencies and all showed reduced amplitude. This indicates that TCR might be useful as a presymptomatic diagnostic test.

Although 70.0% of patients showed delayed latencies upon TCR testing, which seemed no different from the abnormal EMG ratio, the amplitude of TCR was reduced in all patients. The low amplitude suggest that TCR may be even more sensitive than EMG. In addition, EMG is a painful procedure, so TCR would be more easily accepted by patients. Finally, TCR identified abnormalities in 26.7% patients with normal SCM-EMG, which indicates that TCR might be a useful complement to the traditional EMG.

The central pathway for the TCR is presumed to travel to the rostral portion of the spinal trigeminal nucleus (nucleus oralis) and then project medially and ventrally to the spinal nucleus of the accessory nerve on both sides.[11] It is a pathway that may be affected with pathological involvement of the corticobulbar pathways and the brain stem trigeminal nuclei.[20] We have previously reported abnormal TCR in patients with ALS, and the results supported the conclusion that there was involvement of central reflex integration.[13] As in patients with SBMA, the SCM muscle atrophy or disturbance of the accessory nerve itself could be a peripheral cause for abnormal TCR but in ALS patients peripheral sensory nerve involvement cannot be an alternative explanation for this.[21]

In conclusion, our findings indicates that TCR may be helpful as a supplementary electrophysiological test for integration of the lower brainstem reflex, providing some additional objective index of bulbar involvement in patients with SBMA. This was supported by the observation that the TCR seemed to be sufficiently sensitive for revealing lower brainstem involvement in patients with multiple sclerosis and other disorders.[22]

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