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Triple stimulation technique in patients with spinocerebellar ataxia type 6

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Abstract

Objective: To establish further evidence that SCA6 may not be a pure cerebellar syndrome.

Methods: Seven patients with genetically confirmed SCA6 and 9 age-matched normal controls were studied. Recordings of the CMAP were obtained from the right first dorsal interosseus muscle. Transcranial magnetic stimulation of the left motor cortex was applied to the contralateral scalp with a plane figure-of-8 coil. Conventional transcranial magnetic stimulation (TMS), central motor conduction time (CMCT) by F-wave method and the triple stimulation technique (TST) amplitude ratio (TST test/TST control) were investigated.

Results: The mean resting motor threshold and mean CMCT did not show significant differences between normal controls and patients, but the mean TST amplitude ratio was significantly smaller in patients than in controls.

Conclusions: An abnormal TST represents upper motor neuron loss, central axon lesions or conduction blocks, or inexcitability in response to TMS. The lack of pathological changes in the corticospinal tract of patients with SCA6 indicates that this abnormality may be caused by crossed cerebellar diaschisis, or a functional disorder in the brain resulting from CACNA1A mutations.

Significance: TST is a useful method for quantifying corticospinal tract dysfunction.

Keywords: Transcranial magnetic stimulation; Corticospinal tract; Collision technique; Spinocerebellar ataxia type 6; Crossed cerebellar diaschisis; CACNA1A mutation

1. Introduction

Spinocerebellar ataxia type 6 (SCA6) is an inherited ataxic disorder, which is transmitted in an autosomal dominant manner. SCA6 is caused by small expansions of the CAG repeat contained within exon 47 of the calcium-channel gene CACNA1A, located on chromosome 19. Formerly, SCA6 has been described as 'pure' cerebellar ataxia with atrophy limited to the cerebellum on MRI and in post-mortem studies. However, extracerebellar symptoms such as pyramidal signs, Parkinsonism, and mild peripheral neuropathy have been reported.

Central motor conduction time (CMCT) can be measured by subtracting the conduction time in the peripheral nerves from the total latency of motor evoked potentials (MEPs). The conduction time in peripheral nerves is usually measured by F-wave and M-wave latency or by direct stimulation of the cervical nerve roots. Studies of patients with SCA6 have provided controversial results about changes in CMCT (Chen et al., 2004; Lee et al., 2003; Schols et al., 1997, 1998; Schwenkreis et al., 2002). Recently, another method to estimate corticospinal tract dysfunction has been introduced. This sophisticated method, which is called the triple stimulation technique (TST), achieves excitation of the whole motoneuron pool innervating the target muscle, and reflects corticospinal tract dysfunction. In clinical application, this method has

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increased the diagnostic yield of conventional MEPs by a factor of 2.75 in upper limbs (Magistris et al., 1999).

In this study, we obtained additional evidence that SCA6 may not be a pure cerebellar syndrome.

2. Subjects and methods

Seven patients with SCA6 (1 male, 6 females), aged 56–77 years (mean age 68.4±7.0 years) and 9 age-matched normal controls (3 males, 6 females), aged 35–84 years (mean age 66.0±15.8 years) were studied. All patients underwent brain MRI and showed no anatomical abnormalities in relation to corticospinal dysfunction. The clinical characteristics of the patients (age, gender, upper motor neuron sign, CAG repeats) are shown in Table 1. One out of 7 patients had hyperreflexia and none had pathological plantar reflex. Approval was obtained from the local ethics committee. Informed consent was obtained from all subjects before participation in the study.

Blood samples were obtained from all patients and stored in EDTA for molecular genetic analyses. DNA was extracted from blood samples by a standard phenol/chloroform protocol. Detection of the SCA6 mutation was carried out via polymerase chain reaction (PCR) amplifications using S-5-F1 and S-5-R1 primers for SCA6 mutations (Zhuchenko et al., 1997). For an accurate estimation of repeat numbers, a Cy-5-labeled sense primer was used for PCR amplification, then an aliquot of the product was electrophoresed on a 6% denaturing polyacrylamide gel and analyzed with an automated DNA sequencer (ALF express, Pharmacia LKB, Uppsala, Sweden). The data were processed with fragment analysis software (Fragment Manager, Pharmacia). Genetic diagnoses were made by one of the authors (Y.A.).

During the experiment, subjects lay supine with their right hand held in place by a 2 kg sandbag. The 3–5th fingers were bandaged with adhesive tape to avoid generating unnecessary muscle activation, and their palm and forearm were fixed with Velcro tapes on a 10×40 cm board. Recordings of the CMAP were obtained from the right first dorsal interosseus (FDI) muscle through paired Ag–AgCl disk electrodes. Signals were amplified with a band pass of 5 Hz–10 kHz. An epoch of 425 ms duration (25 ms pre- and 400 ms post-stimulus) was collected at a sampling rate of 10 kHz and stored on disk for off-line analysis (micro1401; Cambridge Electronic Design, Cambridge, UK). Transcranial magnetic stimulation (TMS) of the left motor cortex was applied to the contralateral scalp with a plane figure-of-8 coil with each lobe having a diameter of 8 cm (Magstim Co, Dyfed, Wales) . The center of the linear contiguous segment of the coil was placed over a point 5 cm lateral to the vertex on the interaural line. The coil was angled 45 ° to the parasagittal plane about this point so that current in the central segment of the coil flowed toward the midline (Mills et al., 1992). The resting motor threshold (RMT) was defined as the lowest stimulator output intensity capable of inducing MEPs in the target muscle of at least 50 μV peak-to-peak amplitude in at least 5 out of 10 trials (Rossini et al., 1994).

To obtain maximal M-waves, supramaximal electrical stimuli of 0.2 ms duration were delivered through a bar electrode (Nicolet Biomedical) to the ulnar nerve of the right wrist. For Erb's point stimulation, two disposable rectangular Ag/AgCl electrodes (1.5×2.0 cm) were adhered (cathode to Erb's point and anode to the internal region of the suprascapular fossa). Electrical stimuli were given via two isolators (SS-104J and SS-102J, Nihon Koden). Supramaximal stimuli were always used for peripheral nerve stimulation. Timing for the triple

Table 1
Characteristics of subjects, conventional motor evoke potentials and TST results

	Patient No.							Mean±SD		p value
	1	2	3	4	5	6	7	Patients (n=7)	Controls (n=9)	
Sex	F	F	F	F	F	F	M			
Age at onset (years)	47	58	29	50	40	72	42	48.3±13.8		
Present age (years)	66	74	68	73	65	77	56	68.4±7.0	66.0±15.8	0.915
Duration of illness (years)	20	17	40	24	26	6	15	21.1±10.6		
DTR	+/+	+/+	+/+	+/+	++/++	+/+	+/+			
Babinski's sign	-/-	-/-	-/-	-/-	-/-	-/-	-/-			
CAG repeats	14/25	12/22	13/29	13/22	11/23	12/22	7/25			
Resting motor threshold (%)	51	53	49	61	64	41	74†	56.1±11.0	46.1±10.4	0.124
CMCT (ms)	6.48	8.12	8.26	5.29	5.84	5.74	9.99†	7.1±1.7	6.1±1.2	0.368
TST amplitude ratio	0.74	0.54†	0.78	0.66†	0.79	0.94	0.98	0.77±0.15*	0.95±0.11	0.030

†Larger or smaller than mean±2SD of normal controls, *$P<0.05$; TST, triple stimulation technique; DTR, deep tendon reflex; CMCT, central motor conduction time.