Size variance of motor evoked potential at initiation of voluntary contraction in palsy of conversion disorder

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Abstract

Aim: To investigate the efficacy of transcranial magnetic stimulation (TMS) with a cue signal for the objective diagnosis of palsy of conversion disorder (CD).

Methods: Ten patients with palsy of CD, 9 with amyotrophic lateral sclerosis (ALS), and 8 control subjects were examined. Motor evoked potential (MEP) was recorded from the abductor digiti minimi (ADM) muscle under three conditions: at rest, during tonic contraction, and with an audio cue signal. In the cue signal paradigm, subjects were asked to perform ramp-and-hold contraction in response to a cue signal.

Results: MEP size increased in the cue signal paradigm in both controls and patients with ALS, but was not obvious in some CD patients. This was likely due to variance among trials in the cue signal paradigm in each CD patient. The coefficients of variance (CV) among trials in the cue signal paradigm were 15±4.3 in controls, 25±11 in ALS, and 70±40 in CD.

Conclusions: CV of MEP size with cue signal was larger in CD than in controls ($P<0.005$) and ALS patients ($P<0.01$). The size variance among MEP trials with the cue signal is a supportive parameter for the diagnosis of CD.

Introduction

Patients with psychogenic motor and sensory disturbance show various motor or sensory symptoms, such as motor palsy, paroxysmal or continuous involuntary movement, seizure, loss of sensation, or dysesthesia, with motor palsy and weakness being the most common symptoms[1]. The diagnosis of psychogenic motor and sensory disturbance is based on the judgment of well-trained physicians after excluding the possibility of organic disorder. However, patients sometimes have difficulty accepting a diagnosis of conversion disorder (CD) without any underlying organic disorder. During neurological examination, patients are sometimes able to contract the paretic limbs voluntarily or perform strange voluntary movements that require great muscle strength, even though they cannot perform proper muscle contraction as requested. Patients are not aware of these discrepancies and believe they are not able to contract the paralyzed muscles. An objective laboratory investigation capable of diagnosing palsy of CD would be very useful in daily clinical practice for both psychiatrists and neurologists.

Motor evoked potential (MEP) evoked by transcranial magnetic stimulation (TMS) is one possibility, which widely used in clinical practice for evaluation of pyramidal tract disorders. In palsy of CD, the latency of TMS-MEP remains normal[2-5]. However, the size and latency of TMS-MEP differ among test conditions. During voluntary contraction, the size and latency of MEP become larger and shorter than those at rest, respectively, while MEP becomes smaller during contraction of antagonistic muscles. Thus, MEP reflects the intentional condition of voluntary effort during contraction[6].

On the other hand, recent functional imaging studies suggested that the pathognomonic mechanism of CD involves inappropriate functional disconnection among higher motor components of volition[7-9]. If pathognomonic mechanism of palsy in CD involves functional disconnection, such inappropriate modulations may be reflected in the size and latency of MEP, and such changes should be obvious at the initiation of voluntary contraction rather than that at rest. Therefore, we examined such processes in patients with palsy of CD using an audio cue signal and TMS, and evaluated the usefulness of TMS-MEP with a cue signal as an objective method of diagnosing palsy in patients with CD.

Methods

The subjects consisted of 10 patients with palsy of CD without any underlying organic disorders, 8 healthy control subjects, and 9 patients with amyotrophic lateral sclerosis (ALS). Diagnosis of CD was in accordance with DSM-IV (Diagnostic and Statistical Manual of

Mental Disorders, 4th Edition) published by the American Psychiatric Association. All of the participating patients with ALS showed weakness due to both upper and lower motor disturbances in the examined limb. All subjects consented to participation in the study after being fully informed about the aims and protocol of the study, and the local ethics committee approved the study design. Although the mean age of healthy control subjects (28±8y) was the same as that of CD patients (29±9y), patients with ALS were older (66±13y) than those in the other two groups.

Each subject sat on a reclining chair or lay on a bed during the test. MEP was recorded from the abductor digiti minimi (ADM) muscle using a pair of surface Ag-AgCl electrodes placed on the muscle belly and proximal part of the fifth finger, which was fixed to the other fingers with adhesive tape. Signals were amplified with an NEC-Sanei type 4124 (NEC-Sanei, Tokyo, Japan) or MEB-2200 (Nihon Kohden, Tokyo, Japan) biological amplifier using bandwidths between 3 and 1kHz. The size of the response was measured as the area of the negative part, and was expressed as a percentage of the maximal M-response (Mmax) in each subject. The size of Mmax was measured with supramaximal electrical stimulation of the ulnar nerve at the wrist in the same manner as in a routine laboratory examination of motor conduction. The maximal contraction strength was determined from the amplitude of rectified and integrated electromyography (EMG) during isometric voluntary contraction. To measure the maximal contraction strength, the subjects were asked to perform maximal contraction for several seconds. This was repeated at least 3 times, and the maximal amplitude during contractions was expressed as the maximal contraction strength for that subject.

For TMS, a Magstim 200 (Magstim, Carmarthenshire, UK) with a figure-of-eight coil was used. The coil was held in place at the appropriate position to obtain the lowest motor threshold for MEP on ADM. As contraction strength and effort of contraction change motor threshold, the size and latency can fluctuate easily with weak stimulation. When stimulus intensity was sufficiently stronger than the threshold, the size and latency became constant at the maximal and shortest values, respectively. To minimize the effect of stimulus intensity among conditions or situations, especially in patients showing weakness or palsy, we used a constant strong intensity for all situations. TMS intensity was therefore set to 80% of the maximal output. Because this stimulus intensity was more than 1.6 times motor threshold in all the three situations described below, we were constantly able to record the maximal MEP[10]. We thus minimized the contribution of stimulus intensity to the size and latency of MEP without causing the subjects any discomfort.

TMS-MEP was recorded under three conditions: at rest (rest-MEP), during tonic

contraction (tonic-MEP), and in response to an audio cue signal (cue-MEP). The TMS-MEP was recorded 10 times under each condition. For the tonic contraction paradigm, subjects were asked to perform tonic voluntary contraction of 10% of their maximal strength. The contraction level was displayed as a line of amplitude of rectified and integrated EMG of ADM in front of the subject with a line indicating the target level.

A simple ramp-and-hold contraction task, as commonly used for the reaction time paradigm, was used for the audio cue signal paradigm. Subjects were asked to begin contraction when they heard the cue sound. They were asked to achieve 10% of their maximal contraction level within 200 ms, and then maintain the contraction for around 1 s. A warning (ready) signal preceded each cue signal by about 1 s (Figure 1). To support proper contraction, the sweep of the beam of EMG level was displayed with a line indicating the target contraction strength. The beam indicated that contraction strength began to sweep at the same time as the cue signal. Four of 10 patients with CD were not able to perform any voluntary contraction. In these patients, tonic-MEP was not recorded and they were asked to make a strong effort to perform voluntary contraction in response to the cue signal and maintain the same effort in each trial. Five of 9 patients with ALS also claimed difficulty in maintaining the proper tonic contraction level and performing the ramp-and-hold paradigm correctly. We did not record tonic-MEP and requested the patients perform the same contraction effort in each trial in the cue-MEP paradigm, even if the contraction was stronger than the target level. Therefore, the contraction strength was more than 10% of the maximal contraction in some patients with CD or ALS.

The MEP size in each situation in each subject was expressed as the mean of 10 trials. The MEP size in each situation and group was calculated as the mean and standard deviation from the mean of each subject. We measured the fastest MEP among the trials in each situation to determine the latency.

For quantitative determination of inter-trial fluctuations in size of MEP, we calculated the coefficient of variance (CV) and the size difference between the maximal and minimal response [Difference index, DI = (maximal MEP-minimal MEP)/maximal MEP (%)] from 10 trials for each subject for cue-MEP.

We compared differences among the three groups and situations with Student's *t*-test using commercial software (Sigmastat 3.0; SPSS, Chicago, IL, USA). *P*<0.05 was taken to indicate significance.

Results

Some patients with CD or ALS showed muscle atrophy. On average, the size of Mmax in patients with ALS was significantly smaller than that in healthy control subjects (control 16.2±2.4 mV, ALS 11.2±5.5 mV, $P<0.01$). The size of Mmax was slightly smaller in CD subjects than in healthy controls, but the difference was not significant (12.9±4.4 mV, $P=0.06$).

The sizes of TMS-MEP under these three conditions are summarized in Table 1. In all three groups, the size of cue-MEP was maximal under all three conditions, but the size of cue-MEP in CD showed larger variability among subjects than in either of the other two groups.

The minimal latencies among the trials under the three conditions are summarized in Table 2. In healthy control subjects, the latencies of tonic- and cue-MEP were shorter than that of rest-MEP as shown Fig. 1. Although the latencies in patients with ALS were longer than those in control subjects, especially for rest-TMS and cue-TMS, the latencies were reduced with voluntary contraction. However, this was not true for the patients with CD; the latencies of both tonic- and cue-MEP were same as rest-MEP in CD. Thus, when comparing the results as averages of groups, the lack of reductions in latency with contraction seemed to be specific to patients with CD. However, this was not useful as a diagnostic parameter of CD because of its low specificity.

The unique finding of MEP in CD was the large intra-subject variance among trials within the same sequence, which was especially obvious during the cue signal paradigm. Figure 2 shows the raw traces of cue-MEP in two patients with CD; there was no MEP in some trials, but the size was very large in other trials. Figure 3 shows size variations of cue-MEP in each subject within a single session. Although size differences within the sequence were evident in both patients with CD and those with ALS, the variance in CD seemed larger than that in ALS.

The variances among trials were quantified as DI and CV (Fig. 4). The values of both parameters in CD were larger than the maximal values in control subjects. The mean values for both DI and CV in ALS were smaller than those in CD. Therefore, DI and CV show clear specificity for differentiating CD from both control and ALS. Neither of these indices showed any correlation with the size of Mmax, the maximal contraction strength, or the mean size of MEP in control subjects or patients with CD or ALS.

Discussion

CD is associated with a variety of symptoms, including sensory and motor disturbance. Diagnosis depends on careful clinical observation and laboratory examination to exclude other organic disturbances[11,12]. Normal findings on routine neurophysiological study support the diagnosis. We attempted to identify a disease-specific objective abnormality associated with palsy of CD using MEP. Patients with palsy of CD showed marked variability in the size of MEP recorded at the cue signal.

The size and latency of MEP clearly increased and shortened, respectively, in control subjects and patients with ALS. The increase in MEP size was more obvious in subjects with ALS, which was probably because it was necessary for ALS patients to try harder to perform contraction using stronger effort because it was difficult for them to perform a weak contraction. The variance among trials expressed as CV and DI in ALS was larger than that in controls. As patients with ALS could not control their voluntary movement precisely, the contraction strength was not as stable as that in the controls. If the contraction strength was variable among trials, variance in MEP among trials increased. These observations indicated that the presence of organic motor disorder affected the variance among trials.

This was also true for patients with CD. Some patients could not perform voluntary contraction and many CD patients had difficulty in performing proper contraction. This difficulty should cause an increase in variance among trials, especially in the cue-MEP paradigm. However, the variance in CD was more obvious than that in ALS. These findings will support the diagnosis and be useful in daily clinical practice.

Recent studies indicated brain dysfunction in palsy of CD. The left dorsolateral prefrontal cortex (DLPFC) was hypoactive only in patients with palsy but not in those with feigned palsy[13]. Another report demonstrated increased activity of the orbitofrontal and anterior cingulated cortex, which was speculated to be a reflection of the inhibitory effect to promote voluntary contraction[14]. Experiments using the reaction time paradigm also suggested that dissociation of implicit and explicit motor processes among the information processes was the cause of motor disturbance in CD[15].

In control subjects, voluntary effort to achieve contraction affected the size and latency of TMS-MEP, as shown in Fig. 1. If the commands for motor initiation are "disconnected" in processing linkages of higher motor function due to "implicit negative intention", MEP may become smaller or disappear with "explicit volitional effort" to contract the target muscle. The variation among trials should reflect these balances between implicit and explicit processes. Therefore, we recorded MEP at the beginning of voluntary effort to contract the muscle.

The small MEP in the cue paradigm may reflect implicit negative intension. In addition, cue-MEP should become larger if volitional effort becomes stronger than implicit inhibition. We may be able to explain the large variance among trials in palsy with CD based on this factor.

Another problem for cue-MEP as a diagnostic tool for CD is whether cue-MEP is able to differentiate CD from feigning subjects. As mentioned above, the size and latency of MEP are functions of voluntary effort. It is not difficult for a subject to inhibit voluntary effort intentionally if trying to act like a patient with palsy. We simulated this variance among trials in control subjects. Figure 5 shows a representative result in a subject who was one of the authors and knew the physiological properties of TMS very well, and who tried to perform contraction while feigning disorder. The size and latency varied among trials, as seen in CD patients, indicating that this protocol could not differentiate between feigned disorder and CD.

In conclusion, the large variance in MEP size among trials in the cue paradigm and normal MEP at rest are available as objective findings of CD. Although we recorded cue-MEP with computer-controlled beep signals, the simple conditioning voice of an examiner indicating "ready" and "go" with a manual magnetic stimulation also showed a large degree of variance among trials in patients with CD (data not shown). Although strict calculation of indices is difficult in trials conducted in this manner, physicians can perform manual cue-MEP recording during routine clinical examination without any additional equipment to confirm a diagnosis of CD.

Acknowledgments

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Table 1. Size of MEP under each condition

	Rest	Tonic	Cue
Normal		$p<0.001$	
		$p<0.005$	n.s.
mean	6.1	15.6	17.4
sd	4.5	5.9	3.4
CD		$p<0.1$	
		n.s.	n.s.
mean	4.7	16.4	18.8
sd	6.6	22.7	21.5
ALS		$p<0.005$	
		n.s	$p<0.05$
mean	7.4	11.8	32.3*
sd	7.7	10.0	20.1

(% of Mmax)

*Larger than that in normal subjects $p<0.05$

Table 2. Latency of MEP under each condition

		Rest	Tonic	Cue
Normal			p<0.005	
			p<0.05	n.s.
	mean	21.4	19.3	18.3
	sd	2.2	1.4	1.3
CD			n.s.	
			n.s.	n.s.
	mean	20.8	22.7**	21.8*
	sd	4.0	1.5	3.9
ALS			p<0.05	
			p<0.1	n.s.
	mean	24.1*	21.6^{+}	20.6*
	sd	2.9	3.2	2.3

(ms)

Longer than that in normal subjects *p<0.05,

**p<0.005, ($^{+}$p<0.1)

Figure legends

Figure 1

Experimental paradigm and TMS-MEP under each condition in a normal subject.

A: Experimental paradigm of cue-MEP. Subjects were asked to begin contraction in response

to a cue signal.

B: The raw traces of MEPs under each condition. The size of MEP at rest (rest-MEP) was

smaller than that under the other two conditions and latency was longer. During tonic

contraction of 10%, the size increased and latency became shorter. The MEP increased in the

cue paradigm, and variance in size and latency increased.

Figure 2

Cue-MEP in two patients with palsy of CD

The large variance in MEP among trials was a peculiarity of palsy of CD. In the case shown

in the lower trace, there was no MEP evoked in some trials.

Figure 3

Variance in the size of cue-MEP in each subject

Circles indicate the maximal and minimal MEP and bars indicate the mean ± 1 standard

deviation. Variance among trials in CD and ALS seemed larger than that in normal subjects.

Figure 4

Calculated indices of variance among trials in cue-MEP

Both the difference index (DI) and coefficient of variation (CV) in CD patients were larger

than those in either normal subjects or ALS patients. Horizontal dashed lines indicate the

upper normal limit (mean + 2sd) of normal subjects. The values of both indices in CD patients

were larger than the normal limit except for CV in one patient.

Figure 5

Cue-MEP in a normal subject who tried to perform feigned illness

Upper trace indicates cue-MEP in a normal subject making a true effort. In the lower trace,

the subject sometimes performed a true contraction effort and sometimes feigned effort. With

feigned effort, the variance became as large as that in CD.