Transient Myoclonic State with Asterixis: Primary Motor Cortex Hyperexcitability is Correlated with Myoclonus

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Abstract

Objective To clarify the clinical features and mechanism of the transience of myoclonus in patients with a transient myoclonic state with asterixis (TMA).

Methods We investigated the clinical and eletrophysiological profiles of 6 patients with TMA (age: 84±3 years). During an asymptomatic period, somatosensory evoked potentials (SEPs) were recorded in all 6 patients and motor evoked potentials (MEPs) were examined in 1 patient. SEPs were recorded and jerk-locked back averaging (JLA) was performed in 2 patients while symptomatic. SEPs were also recorded from 8 aged control subjects (age: 68±5 years).

Results All TMA patients had mild chronic systemic diseases. During an asymptomatic period, SEP amplitudes were not significantly enlarged in comparison with control subjects, and MEPs were normal. Examination of 2 patients during symptomatic period indicated no enlargement of SEP amplitudes and JLA disclosed a positive spike preceding myoclonic jerks. In one of these patients, the amplitude of the positive spike decreased once myoclonus improved.

Conclusion TMA occurred in aged patients with mild chronic systemic diseases. JLA findings and the absence of giant SEPs further support that TMA is a cortical non-reflex myoclonus. In addition, transient hyperexcitability at the primary motor cortex disclosed by JLA correlated well with its transient symptoms.

Key words: transient myoclonic state with asterixis (TMA), generator mechanism of TMA


Introduction

Myoclonus is characterized by sudden, jerky and shock-like movements involving the extremities, face, and trunk, usually without impairment of consciousness. Based on the physiological mechanism, myoclonus is classified into 3 groups: cortical, subcortical, and spinal myoclonus (1). Regardless of the underlying physiological mechanism, myoclonus often persists for many years; it is sometimes intractable to various treatments and thus is frequently regarded as a movement disorder. On the other hand, epileptic myoclonus, i.e., myoclonus of an epileptic nature, often occurs transiently as a seizure disorder (2). As with typical transient myoclonus of adolescent onset, awakening myoclonus is observed in patients with juvenile myoclonic epilepsy.

In aged patients, transient tremulous myoclonus has been reported exclusively from Japan under various designations such as a transient myoclonic state with asterixis (TMA) (3), recurrent myoclonus (4), benign transient shuddering-like involuntary movement (5), and a transient myoclonic state (6). Although the designation may differ, the transient myoclonus in aged patients in those reports shares some common clinical features. It occurs acutely in aged patients with mild chronic diseases, and the myoclonus is predominantly in the trunk, neck, shoulders and upper extremities. It disappears spontaneously within a few days or is markedly ameliorated by benzodiazepines, but it often recurs. Although the etiology of the condition could be heterogeneous, these common characteristics suggest a clinical entity and in Japan

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Received for publication April 1, 2011; Accepted for publication July 22, 2011
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Table 1. Characteristics of Patients with Transient Myoclonic State with Asterixis

<table>
<thead>
<tr>
<th>Pt. No.</th>
<th>Age</th>
<th>Sex</th>
<th>Concomitant diseases</th>
<th>Recurrence</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>86</td>
<td>M</td>
<td>DM</td>
<td>+</td>
<td>CNZ</td>
</tr>
<tr>
<td>2</td>
<td>86</td>
<td>F</td>
<td>HT, Hyperlipidemia</td>
<td>–</td>
<td>CNZ</td>
</tr>
<tr>
<td>3</td>
<td>83</td>
<td>F</td>
<td>CHF, Cerebral infarction, Type C hepatitis, Hyperuricemia</td>
<td>+</td>
<td>CNZ</td>
</tr>
<tr>
<td>4</td>
<td>78</td>
<td>M</td>
<td>DM, HT</td>
<td>–</td>
<td>DZP</td>
</tr>
<tr>
<td>5</td>
<td>82</td>
<td>M</td>
<td>DM, HT, Anemia, CRF</td>
<td>+</td>
<td>CNZ</td>
</tr>
<tr>
<td>6</td>
<td>86</td>
<td>M</td>
<td>CRF</td>
<td>–</td>
<td>CNZ</td>
</tr>
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</table>

DM: diabetes mellitus, HT: hypertension, CRF: chronic renal failure, CHF: chronic heart failure, CNZ: clonazepam, DZP: diazepam,

it is often designated as TMA. Electrophysiological studies in patients with TMA showed cortical spikes preceding myoclonic jerks demonstrated by jerk-locked back averaging (JLA) and the rare incidence of enlarged cortical components of somatosensory evoked potentials (giant SEPs).

Therefore, TMA is not considered as a cortical reflex myoclonus, but rather as a spontaneous cortical myoclonus (3). However, the details of clinical and electrophysiological characteristics, especially related to its transience and the mechanism of the generation of myoclonus, remain unclear. In the present study, our aim was to further investigate the clinical features and mechanism of myoclonus in patients with TMA.

Patients and Methods

Patients with TMA and control subjects

The diagnostic criteria for TMA in this study were as follows: (a) acute onset of tremulous myoclonus in adult patients (>60 years old) without other neurological symptoms, including consciousness impairment and disorientation, and (b) spontaneous recovery or marked improvement within a few days by administration of benzodiazepines. We performed clinical and electrophysiological studies in the 6 patients (4 men and 2 women, mean age of 84±3 years, range 78-86 years) who met the above criteria (Table 1) and received care from 2003 to 2006 at our institute. Control data for this study was on SEPs to median nerve stimulation that had been acquired previously for another purpose in 8 apparently healthy individuals (3 men and 5 women, mean age of 68±5 years, range 61-74 years). Although they were significantly younger than the patients with TMA, we employed their data because of the difficulty in finding completely age-matched apparently healthy control subjects.

The Institutional Review Board (No. E678) approved the recording of SEPs in the control subjects. Informed consent was obtained from all patients with TMA and control subjects.

Electrophysiological studies

A conventional 10-20 system EEG was recorded in 4 patients (Patients 1, 3, 4 and 5) during a symptomatic period.

We examined scalp SEPs to median nerve stimulation during symptomatic and asymptomatic periods in 2 patients (Patients 5 and 6) and only during an asymptomatic period in the remaining 4 patients (Patients 1-4). The electrical stimulus was delivered to the median nerve at the wrist. Stimulus intensity was set to produce a clear twitch of the thenar muscle and the electrical stimulus frequency was set at 0.9 Hz. Scalp electrodes were placed at the contralateral central area; C3, C4, P3 and P4 were used as recording electrodes and the ipsilateral earlobe (A1 or A2) to the stimulated nerve was employed as the reference electrode. The bandpass filter was set at 1-1,500 Hz. Terminology of the peaks (N20, P25 and N35) was adopted from our previous report (7). Amplitudes of P25 and N35 were measured from a peak of the preceding component of the opposite polarity and that of N20 was from the prestimulus baseline level. The definition of giant SEPs was based on results reported in our previous study (7). We had also examined the 8 control subjects using the same settings.

JLA was applied in 2 patients (Patients 5 and 6). Scalp EEGs were recorded from C3, C4, P3 and P4, with the ear lobe electrodes as the reference electrodes (A1 + A2). The recorded muscle was determined by the presence of involuntary electromyogram (EMG) activity in each patient, i.e., the extensor carpi radialis in Patient 5 and pectoralis major and splenius capitus in Patient 6. EMG signals were recorded with a bandpass filter of 20-1,500 Hz and EEG signals were recorded with a bandpass filter of 1-1,500 Hz. Two hundred involuntary myoclonic movements were averaged. JLA was applied before and 30 minutes after oral administration of clonazepam (0.5 mg) in 1 patient (Patient 5). Cortical reflex to median nerve stimulation was also recorded in the same patient.

Motor evoked potentials (MEPs) by transcranial magnetic stimulation were also examined in 1 patient (Patient 6) during an asymptomatic period. Conventional EEG was taken before the MEP study to confirm that there was no epilepti-
form discharge. MEPs were elicited by a magnetic stimulator (Magstim 200, Magstim, Camarthenshire, Wales, UK) and a circular coil with a diameter of 120 mm. Stimuli were delivered at the vertex and MEPs were recorded from the surface electrodes placed on the first dorsal interosseous muscle (FDI) of the hand. After determination of the motor threshold according to the conventional method (8), test stimulus was given with an intensity of 20% above the motor threshold during mild contraction of the FDI.

### Results

#### Clinical profiles

All 6 patients with TMA had mild chronic systemic diseases such as diabetes mellitus, hypertension, mild chronic renal failure, etc (Table 1). The degree of chronic renal dysfunction per se was too mild to elicit myoclonus clinically (Patient 5: Cr 1.5 mg/dL and BUN 33 mg/dL; Patient 5: Cr 1.7 mg/dL and BUN 29 mg/dL). There were no similar clinical events prior to the onset of TMA among the 6 patients, and 1 patient had a preceding infection (Patient 2). All subjects had acutely developed transient generalized tremulous myoclonus predominantly in the trunk, neck, shoulders and upper extremities and asterixis. Myoclonus was enhanced by action and posturing, but it was not exaggerated by other types of sensory stimuli including sound. Consciousness was preserved throughout the clinical course. Benzodiazepines (clonazepam and diazepam) at ordinary dosages were administered to all patients and relieved the myoclonus within 1 to 2 days. Three patients had recurrence (Table 1), with one (Patient 3) having 3 recurrent episodes during the 2-year follow-up period. Recovery from a recurrent episode was spontaneous within a few days in all 3 patients.

#### Electrophysiological studies

In 3 out of the 4 patients who underwent an EEG, there was a mild degree of generalized, intermittent, irregular slow waves (delta to theta range) without epileptiform abnormalities, results that were only mildly abnormal or even normal for the patients’ age. No EEG abnormalities were noted in the other patient. Photoparoxysmal response was not observed in any of the 4 patients.

SEP parameters in the TMA patients and control subjects are shown in Table 2. As for latencies, peaks of SEPs at C3/4 and P3/4 in patients during an asymptomatic period were significantly prolonged in comparison with those of control subjects at C3/4 and P3/4 (Table 2). With regard to amplitudes, early components during an asymptomatic period at C3/4 and P3/4 were not significantly enlarged and the N20 amplitude at C3/4 was significantly smaller compared with that of the control group (Table 2). Comparisons between asymptomatic and symptomatic periods showed no clear differences in SEP parameters (latencies and amplitudes) and in waveforms in Patients 5 and 6 (Fig. 1A, 1B, 1C and 1D). Only 1 patient (Patient 4) had enlargements of P25 and N35 amplitudes according to our previous study's criteria (7). However, the SEP waveforms were less likely to be “giant SEPs” because the N20 amplitude was also enlarged (Fig. 1E), an observation sometimes made in healthy elderly people (3).

In JLA recording, positive-negative-positive triphasic spikes time-locked to the onset of involuntary EMG activities were demonstrated in 2 patients (Patients 5 and 6) (Fig. 2A, 2B, 2C and 2D). The distribution was bilateral but maximal in the central region contralateral to the side of the myoclonus investigated. The positive peak always preceded the onset of EMG discharge from the recorded muscles by 10-15 ms (Fig. 2A, 2B, 2C and 2D). In Patient 5, the amplitude of the preceding spike decreased from the pretreatment amplitude with clinical improvement of myoclonus 30 minutes after oral clonazepam administration (0.5 mg) (Fig. 2A and 2B). Cortical reflex was not observed in that patient. In Patient 6, the latency of the preceding positive spike in the posterior neck muscle (right splenius capitus:

### Table 2. Summary of Somatosensory Evoked Potential Results

<table>
<thead>
<tr>
<th>Patients with TMA (asymptomatic period)</th>
<th>Control subjects (n = 8, Age: 68 ± 5 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 6, Age: 84 ± 3 years)</td>
<td></td>
</tr>
<tr>
<td>C3/4</td>
<td>C3/4</td>
</tr>
<tr>
<td>F3/4</td>
<td>F3/4</td>
</tr>
<tr>
<td>Latency (ms)</td>
<td>Latency (ms)</td>
</tr>
<tr>
<td>N20</td>
<td>N20</td>
</tr>
<tr>
<td>20.4 ± 2.1*</td>
<td>22.0 ± 2.2*</td>
</tr>
<tr>
<td>P25</td>
<td>P25</td>
</tr>
<tr>
<td>26.5 ± 2.1*</td>
<td>25.0 ± 1.8*</td>
</tr>
<tr>
<td>N35</td>
<td>N35</td>
</tr>
<tr>
<td>33.7 ± 2.8*</td>
<td>34.9 ± 3.0*</td>
</tr>
<tr>
<td>Amplitude (μV)</td>
<td>Amplitude (μV)</td>
</tr>
<tr>
<td>N20</td>
<td>N20</td>
</tr>
<tr>
<td>2.3 ± 1.3*</td>
<td>3.5 ± 0.9</td>
</tr>
<tr>
<td>P25</td>
<td>P25</td>
</tr>
<tr>
<td>5.1 ± 1.8</td>
<td>5.6 ± 2.5</td>
</tr>
<tr>
<td>N35</td>
<td>N35</td>
</tr>
<tr>
<td>4.6 ± 3.2</td>
<td>3.8 ± 2.6</td>
</tr>
</tbody>
</table>

* p < 0.05 as compared with control subjects at C3/4 or F3/4 by Mann-Whitney U test.
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Figure 1. Somatosensory evoked potential (SEP) waveforms in response to right median nerve stimulation in 2 patients (Patients 5 and 6) during a symptomatic period (A and C) and an asymptomatic period (B and D), respectively, and in another patient (Patient 4) during an asymptomatic period (E). In Patients 5 and 6, there were no enlarged early cortical components during either the symptomatic (A and C) or asymptomatic period (B and D). In Patient 4, there was an enhanced cortical component during the asymptomatic period, but the waveform was unlikely to represent giant SEPs because the N20 amplitude was also enlarged (E).

Discussion

Clinical profiles

The clinical characteristics of TMA in our patients were as follows: 1) elderly with mild chronic systemic diseases, 2) spontaneous occurrence of myoclonic jerks predominantly in the neck, shoulder girdle and upper extremities and asterixis, both enhanced by action and posturing, 3) no apparent exacerbation of myoclonus by sensory stimuli, 4) acute appearance within 1 day and spontaneous recovery within a few days or well suppressed by benzodiazepines, and 5) no sequelae but rather frequent recurrence. These findings were consistent with those of 4 previous reports of 22 patients in Japan (Table 3) (3-6). In addition, TMA was more frequently observed in men than in women, not only in the present study (4 men and 2 women) but also in previous studies (14 men and 8 women) (Table 3), which suggests that aged men might be more vulnerable to myoclonus under certain conditions.

Acute onset myoclonus other than TMA in aged patients
Figure 2. Waveforms of cortical discharge demonstrated by jerk-locked back averaging time-locked to the involuntary electromyography (EMG) of the right extensor carpi radialis muscle (ECR) in Patient 5 before clonazepam (0.5 mg) administration (A) and 30 minutes after clonazepam administration (B), and EMG of the right pectoralis major muscle (C) and of the right splenius capitus muscle (D) in Patient 6. In Patient 5, the positive spike (arrowhead) preceded the EMG onset by 15 ms (A and B). The amplitude of the preceding spike decreased 30 minutes after clonazepam administration (B) in comparison with that before administration (A). The decreased amplitude of the preceding spike was accompanied by clinical improvement and decreased EMG activity. In Patient 6, the latency of the preceding positive spike for the posterior neck muscle (right splenius capitus: 9.8 ms) was shorter than that for the right pectoralis major muscle (14.2 ms) (C and D).

is caused by toxicity (including adverse effects of drugs), metabolic disturbances (renal failure, hepatic failure, respiratory failure, glycemic disturbances, etc.) and infection (10). As for the etiology of TMA, elevated pyruvate and lactate levels (3) and elevated titer of Epstein-Barr virus (4) were reported in patients with TMA, but these findings were likely to be coincident phenomena. We did not find common concomitant diseases, drug usage or laboratory abnormalities related to TMA. Drug-induced myoclonus is unlikely because the symptoms were resolved through the administration of benzodiazepines or even recovered spontaneously without discontinuing drugs usually taken by the patient. As with adult onset myoclonus in Japan, TMA may share some similarities with benign adult familial myoclonus epilepsy (BAFME). However, TMA is clearly different from BAFME due to lack of family history, continuous tremor-like myoclonus, seizures, and presence of giant SEPs as in cortical reflex myoclonus (11). On the whole, an incontrovertible cause of TMA has not been found but genetic susceptibility to the cortical hyperexcitability resulting in cortical myoclonus may be related to its generator mechanism because TMA has been exclusively reported from Japan. Presumably,
synergic effects, such as aging, chronic diseases, drugs and systemic mild infection combined with a potential genetic susceptibility to cortical myoclonus, could be responsible for the episodic occurrence and recurrence of symptoms, since similar concomitant diseases were also observed in drug-induced myoclonus (12). As for precipitating factors for TMA, infection (7 patients) and a drug (cisplatin) (1 patient) were reported in 8 out of 28 patients in the present and previous studies (Table 3A); however, none of the other patients in these studies experienced any events prior to TMA that might have precipitated an occurrence. Thus, the presence of a particular event preceding TMA is not essential, but could play a supplementary role in an occurrence.

Electrophysiological studies

The electrophysiological findings in the present study are summarized as follows: 1) generalized slow wave without epileptiform abnormalities or normal in the EEG, 2) no giant SEPs during both symptomatic and asymptomatic periods and no cortical reflex, 3) a positive spike in JLA preceding the myoclonus, and 4) a normal MEP finding during an asymptomatic period. Most of these findings were consistent with previous studies (Table 3B) (3-6). The results of an EEG without epileptiform discharges suggest that the epileptic factor is unlikely as a cause of TMA.

As for SEPs in TMA, SEP amplitudes in TMA were not significantly enlarged since SEP amplitudes tend to increase with aging even in normal subjects (13, 14). Since the average age of the patient group was 16 years older than that of the control group in the present study, we may consider that the age-matched normal data on SEP amplitudes at C3/4 was similar or even larger than that of control subjects in the present study. Therefore, it is at least unlikely that patients with TMA had significantly larger SEPs than the age-matched control subjects. In addition, just overall increased amplitude does not necessarily indicate giant SEPs, since increased amplitude of P25 and N35 with a normal N20 component is characteristics of giant SEPs (7). Lack of giant SEPs suggests no hyperexcitability at the primary sensory cortex (SI) in response to somatosensory stimuli even during a symptomatic period and lesser involvement of the SI in the generator mechanism of myoclonus in the present study. Prolongation of latencies in the SEP early components might be explained by an aging effect (14) or a peripheral conduction delay because all of the patients had a chronic illness, including 3 who had diabetes.

In JLA, a spike prior to a myoclonic jerk suggests that hyperexcitability is most likely present at the primary motor cortex (MI) during a symptomatic period. In addition, we demonstrated that the preceding positive spike in JLA had a shorter latency in the proximal muscle and longer latency in the rather distal muscle (Fig. 2C and 2D). We also showed that the decreased amplitude of the preceding spike was accompanied by clinical improvement through administration of benzodiazepines (Fig. 2A and 2B), although an inaccurate EMG trigger could have caused the small difference in amplitude of the preceding spike before and after clonazepam administration. These findings further support the contribution of cortical hyperexcitability selectively at the MI to generating the myoclonus in TMA and that MI hyperexcitability and myoclonus are almost simultaneously suppressed by benzodiazepines.
We also demonstrated a normal MEP threshold during an asymptomatic period, which suggests no clear hyperexcitability at the MI during this period. Therefore, these findings might suggest that cortical hyperexcitability in patients with TMA transiently appeared only at the MI at least during a symptomatic period and that transient MI hyperexcitability temporally correlates well with the transient appearance of myoclonus. However, we could not completely exclude this possibility because MI hyperexcitability had not always been delineated by this method because the motor threshold was shown to be increased in some studies (15, 16) and it was normal in another study (17) in progressive myoclonus epilepsy which usually manifests as cortical reflex myoclonus.

As for the mechanism of the generation of cortical myoclonus, TMA is unlikely to be cortical reflex myoclonus involving both the SI and MI based on the present findings of a lack of giant SEPs and the cortical reflex even during a symptomatic period. These findings provide support that TMA is a spontaneous, non-reflex, cortical myoclonus. However, the polarity of the spike preceding the myoclonus in JLA was positive in cortical reflex myoclonus and negative in spontaneous cortical myoclonus in a magnetoencephalographic study (18). That report mentioned that a surface positive potential may be generated by selective activation of the deep layers of the motor cortex. This activation is usually caused by corticocortical input where corticocortical input from the SI projects to the deep layer of the MI and would produce the surface positive epicortical potential as reported in an animal study (19). It was also discussed that the negative potential in JLA may be generated by a pathologically hyperexcitable cortex, similar to the condition encountered in the epileptic condition. Based on this theory, the positive potential in JLA suggests that TMA is cortical myoclonus and is presumably promoted by cortices other than the SI. This suggestion should be further investigated.

A limitation of this study is that the number of patients was relatively small and not all of those patients were equally assessed by various electrophysiological techniques described herein. In practice, it would be difficult to complete electrophysiological studies within a symptomatic period and the TMA patients were infrequently seen by their physicians. However, most of the clinical and electrophysiological findings in our study were quite consistent with those in previous studies. Therefore, it is reasonable to consider that our findings have a significant role in clarifying the mechanism for the transience of myoclonus.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement
This study was supported by a Research Grant for the Treatment of Intractable Epilepsy (21-1) from the Japan Ministry of Health, Labor and Welfare, and a Research Grant from the Japan Epilepsy Research Foundation.

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