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Motor cortical thresholds and cortical silent periods in epilepsy

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Summary We studied motor cortical thresholds (TIs) and cortical silent periods (SPs) evoked by transcranial magnetic stimulation (TMS) in 110 epileptic patients. Sixty-two had primary generalised, 48 had partial type seizures. Fifteen out 110 patients were analysed both before and after anticonvulsant medication. Our aims were to evaluate the TI levels and the duration of SPs in patients with epilepsy and to determine the reliability of TMS in patients with epilepsy. There was no negative effect of TMS on the clinical status and EEG findings in patients with epilepsy. TIs obtained from patients with partial epilepsy were higher than those obtained from both controls and primary epileptics. The duration of SP in patients with primary epileptics was more prolonged than those obtained from controls. There was no correlation between EEG lateralisation and both SP duration and TI values. In de novo patient group, SP duration was significantly prolonged after anticonvulsant medication. We concluded that TMS is a reliable electrophysiological investigation in patients with epilepsy. The analysis of SP duration may be an appropriate investigation in monitoring the effect of anticonvulsant medication on the cortical inhibitory activity.

Introduction

Transcranial magnetic stimulation (TMS) has been rarely used in epilepsy because of the probability the potential risk of inducing seizure. However, there are many reports over the reliability of TMS in patients with epilepsy. Most of them have concluded that TMS is reliable electrophysiological technique in patients with epilepsy.[1—3] Additionally, TMS can be used for the localisation of epileptic focus in presurgical evaluation.[4]

TMS have both excitatory and inhibitory effects on the motor cortex. After the TMS, initially, we can see the excitatory effects of TMS as a muscle response (motor evoked potential—MEP) after the TMS. This excitatory response is followed by a silence (absence of electromyographic activity) at stimulated muscle, lasted about at 150 ms. It's generally agreed that cortical silent period (SP) reflects the activity of intracortical inhibitory interneurons.[5] Whereas, cortical motor thresholds (TIs) reflects excitatory activity of motor cortex. The alterations of the TI have been demonstrated previously in patients with epilepsy.[6] In epilepsy, the balance between cortical excitatory and inhibitory activities changes in favour of excitatory activity. There are many types of seizures and

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different patterns of excitatory and inhibitory neuronal events in epilepsy. Some animal models suggest that the cortical hyperexcitability is the mainly responsible process in idiopathic generalised epilepsy.[7] On the other hand, partially epilepsies are more heterogen conditions. Some nondemonstrable structural lesions and aberrant neuronal connections may be responsible for an epileptogenic irritation in partially epilepsies.[7]

Anticonvulsants can depress the excitability of the motor cortex and motor pathways in epileptic patients. It is supposed that TI is a useful electrophysiological parameter as an index of the adequacy of treatment in patients with epilepsy.[8] Additionally, SP may also be useful parameter to examine the influence of anticonvulsant treatment. Therefore, it is thought that TI and SP can be used as complementary tests in evaluation of patients with epilepsy.

In this study, our aim was to analyse the effects of both epilepsy and anticonvulsant drugs on these electrophysiological parameters. These electrophysiological parameters can be reliable guide in management of epilepsy treatment.

Materials and methods

We studied 110 epileptic patients (48 men, 62 women) aged 16—58 (mean 28.3 ± 10.6) and 35 normal volunteers aged 8—54 (mean 31.6 ± 8.9). Mean disease duration was 12.6 ± 7.1 years (between 1 and 22). Before the electrophysiological assessment, all of the patients were evaluated according to their seizure type, seizure frequency and drugs used for epilepsy. Forty-eight patients were subclassified as partial epilepsy [19 (17.3%) had complex partial epilepsy (CPE), 25 had CPE with secondary generalisation and 4 had simple partial seizures]. On the other hand, 62 patients with primary generalised epilepsy were included to the study. Fifty of them had primary generalised tonic-clonic seizures, 12 had primary myoclonic seizures. All patients had not experienced any seizure for last 48 h.

We classified our patients into three groups according to seizure frequency (disease severity). Fifty-nine out of 110 patients with epilepsy who have 1—12 seizures per month was classified as first group (refractory group). Second group (partially controlled) includes 22 patients who have 1—3 seizures per year. Twenty-nine who have no history about seizure for last year were classified as third group (controlled group). For last month, mean seizure frequency of all patients was 2.15 ± 2.0.[1—12] All patients were prescribed anticonvulsant medication. Thirty-eight out of 110 patients with epilepsy were used CBZ, 24 were used VLP, 10 were used phenytoin, 11 were used both CBZ and VLP, 10 were used three or more anticonvulsants.

Fifteen out of 110 patients were newly diagnosed as epilepsy (nine had primary generalised tonic-clonic, six had CPE). Their electrophysiological assessment were accomplished both before and about 4 weeks after than beginning of antiepileptic treatment. These patients were prescribed CBZ (10 patients) or VLP (5 patients) as anticonvulsant treatment after TMS.

Neurological examination were normal in all patients. Patients who had any cerebral lesion on their CT or MRI examination were excluded. Subjects were informed about the study and their written consents were recruited.

Electrophysiological assessment

All of the patients had initial EEG investigations that had been recorded just before TMS. Ninety-five of them had second EEG, recorded after from TMS to evaluate any effect of TMS on EEG. San-ei A97 18 channelled EEG device was used.

During the TMS, subjects reclined a comfortable armchair. Magstim 200 magnetic stimulator was used. Ninety-millimetre diameter circular coil was used for magnetic stimulation. Maximal magnetic field that made up by this coil was 2.0 T. For recording, Toennies multiliner EMG device was used. Frequency filters were between 10 Hz and 2 kHz, ossiloscope sweep time was 100 ms, gain was adjusted according to the amplitude of muscle response. Initially, motor threshold level was determined for each hemisphere. Motor threshold intensity was defined as the lowest stimulus intensity required to evoke at least three consistent muscle response being at least 50 μV. Coil was located on the vertex. For recordings, we used disc electrodes and muscle responses were recorded from first dorsalis interossei muscle at both sides. With slight contraction of thenar muscle, MEPs were recorded.

For silent period analysis, stimulus intensity was adjusted as 1.5-fold of motor threshold intensity, determined for the same muscle. Osiloscope sweep time was 500 ms, gain was 0.2—0.4 mV and frequency filters were between 10 Hz and 2 kHz. At least, five traces were recorded. The mean duration of SP was analysed by averaging of these potentials in every subject.

The electrophysiological evaluation of de novo group ($n = 15$) was performed before and 4 weeks after anticonvulsant medication.

Statistical methods

To compare the data obtained from electrophysiological investigations from patients and controls, we used Mann–Whitney *U*-test. In de novo group, to compare data, obtained from predrug and postdrug electrophysiological investigations we used Wilcoxon analysis. *P* values smaller than 0.05 were accepted as statistical significance.

Results

EEG analysis of 54 patients accepted as within the normal limits. Twenty-two patients had epileptic activity on the right hemisphere, 11 had epileptic activity on the left side. On the other hand, 9 patients showed bilateral epileptic activity. Seven patients showed slow wave activity on their EEG investigations (three had theta activity on the right side, four had theta activity on the left side). No clinical seizure was encountered in our patients just after TMS. The patients were followed up along the 4 weeks after TMS for their seizure frequency. For the last month, mean seizure frequency of all patients with epilepsy was 2.15 ± 2.0. However, after TMS, mean seizure frequency observed for 1 month was 2.3 ± 2.1. There was no statistical difference in seizure frequencies between after and before TMS ($P > 0.05$).

TI intensities of all epileptic patients ($50.2 \pm 13.0\%$) was higher than those obtained from controls (*P*: 0.3). The threshold intensity of patients with primary epileptics (generalised tonic-clonic) was $48.9 \pm 10.0\%$. There was no significantly difference in TIs between primary generalised epileptics and controls ($45.6 \pm 6.7\%$) (*P*: 0.1). The threshold intensity of patients with partial epilepsy ($56.2 \pm 16.2\%$) was higher than that obtained from controls and generalised epileptics (*P*: 0.01 and 0.02, respectively). On the other hand, the threshold intensity of patients with primary myoclonic epilepsy ($41.4 \pm 10.0\%$) was significantly lower than that obtained from controls and patients with partial epilepsy (*P*: 0.02 and 0.001). The patients who prescribed PHT had higher threshold intensities than those obtained from the patients who used CBZ or VLP (*P*: 0.02 for both groups). Additionally, threshold intensities of patients medicated three or more anticonvulsants (polytherapy) ($59.8 \pm 11.3\%$) was higher than that obtained from patients on monotherapy ($47.1 \pm 10.1\%$) (*P*: 0.0001). Table 1 demonstrates the threshold intensities of patients with epilepsy and controls.

The duration of the SP in patients with epilepsy (134.0 ± 45.4 ms) were more prolonged than those obtained from controls (117.6 ± 26.2 ms) (*P*: 0.0006). SP durations of patients with partial epilepsy (127.4 ± 45.0) was not showed significantly difference from controls (*P*: 0.2). However, the SP durations of patients with primary generalised epileptics (134.8 ± 44.6) and primary myoclonic epilepsy (142.4 ± 46.2) was prolonged (*P*: 0.0008 and 0.0007, respectively). Table 1 shows cortical threshold intensities and SP durations for patients who have different types of epilepsy. The duration of SP was not changed by the number of drugs taken.

There was no significant effect of epileptic focus on SP duration or cortical motor threshold intensity. The SP durations of non-epileptic and epileptic hemisphere were 136.6 ± 44.5 and 131.4 ± 42.4, respectively. Threshold intensities were also not changed between epileptic (49.9 ± 11.6) and non-epileptic side (50.6 ± 12.0) on EEG ($P > 0.05$).

TI levels of de novo patients ($n = 15$) were $48.8 \pm 10.7\%$ before anticonvulsant medication and $50.3 \pm 9.0\%$ 4 weeks after anticonvulsant medication. There was no statistical significantly difference between pre and posttreatment TMS threshold intensities (*P*: 0.2). Their initial SP durations was 122.0 ± 35.5 ms. SP durations (150.4 ± 37.3 ms), obtained after the anticonvulsant treatment was significantly prolonged (*P*: 0.007) (Table 2). De novo patients were used CBZ after initial TMS as anticonvulsant therapy.

Disease severity did not affect the duration of SP (Table 3). However, TI level obtained from

Table 1 Cortical threshold levels and SP durations of patients who have different types of epilepsy.

	Threshold intensities (TI) (%)	*P*	SP duration	*P*
Partial epilepsy	56.2 ± 16.2	0.01	127.4 ± 45.0	0.2
Generalised tonic-clonic	48.9 ± 10.0	0.1	134.8 ± 44.6	0.0008
Generalised myoclonic	41.4 ± 10.0	0.02	142.4 ± 46.2	0.0007
Total (mean)	50.2 ± 13.0	0.03	134.9 ± 45.4	0.01
Controls	45.6 ± 6.7		117.6 ± 25.9	

Table 2 Predrug and postdrug SP durations of newly diagnosed epileptic patients.

	SP durations (ms)	TI (%)
Initial investigation (before medication)	133.6 ± 50.6	48.8 ± 10.7
Second investigation (after medication)	152.0 ± 43.4	50.3 ± 9.0
P value	0.04*	0.2

* Statistical significant at 95% level.

controlled patients was lower than that obtained from both refractory and partially controlled groups (*P*: 0.0008 and 0.001, respectively). There was no significantly difference in TI level between refractory and partially controlled groups.

Discussion

Our results demonstrate that the prolongation of SP was observed in patients with primary epilepsy and TI was higher in patients with partial epilepsy than controls and patients with primary epilepsy. The excitability of both excitatory and inhibitory cortical neurons were increased in patients with myoclonic epilepsy as contrast to other epileptic conditions. The lateralisation of epileptic focus analysed by EEG had no significant effect on these electrophysiological parameters. On the other hand, although anticonvulsant medication had no effect on TI, the duration of SP was significantly prolonged after beginning of anticonvulsant medication.

Initially, we determined the reliability of TMS in patients with epilepsy. Many reports have emphasised that the TMS is a reliable electrophysiological tool in patients with epilepsy.[1–3,9,10] TMS can merely result an increase in seizure frequency in epileptic patients who had any lesion located on cerebral hemisphere.[10,11] Hufnagel et al.[9] applied the TMS in 53 patients with temporal lobe epilepsy. Classen et al. observed an epileptic seizure after TMS in a patient who have a clear focus in left supplementary motor area. In this patient TMS were applied with 8 shaped coil. When they used circular coil for stimulation in same patient, any seizure was not observed. They concluded that focal magnetic stimulation with 8 shaped coil results more localised stimulation on motor cortex so the probability of seizure generation is higher than that of stimulation with circular coil.[12] Our results also indicates that TMS does not cause increased seizure frequency and EEG abnormalities for a period along the 4 weeks.

Table 3 TI levels and the duration of SPs obtained from epilepsy patients classified according to seizure frequency.

	TI (%)	SP duration (ms)
Refractory ($n = 59$)	52.9 ± 15.2	135.0 ± 49.2
Partially controlled ($n = 22$)	49.7 ± 9.3	134.8 ± 40.1
Controlled ($n = 29$)	45.3 ± 8.9*	131.4 ± 41.5

* Statistically significant at the 0.01 level (between controlled and both refractory and partially controlled groups).

In the present study, TI level was increased in only patients with partial epilepsy. Additionally, the patients who used three or more anticonvulsant medication had significantly higher TI than patients on fewer anticonvulsant therapy. On the other hand, anticonvulsant medication has not increased TI levels in de novo epileptic patients. It seems that anticonvulsant medication with monotherapy did not exert the level of TI, although, experimental evidences suggest that anticonvulsant drugs depress the excitability of cortical neurons.[13] Individual anticonvulsant drugs have different mechanisms of action and electrophysiological effects.[14,15] Nevertheless, the drug chosen for anticonvulsant medication had no effect of the level of TI. Some studies have also demonstrated the increased levels of TI in patients with partially epilepsy.[6,9] Hufnagel et al. observed that TI levels was decreased after anticonvulsant medication was reduced.[9] Reutens et al. demonstrated that TI level was increased after anticonvulsant therapy and TI was positively correlated with anticonvulsant blood level in patients with idiopathic generalised epilepsy.[8] Increased TI level may represent protective mechanism due to anticonvulsant drugs against the recurrence of seizures. Nevertheless, our results suggest that the determination of TI levels is not a useful electrophysiological tool for monitoring of the treatment in epilepsy.

In our study, although the duration of SP was prolonged in patients with primary generalised epilepsy, TI was not changed in these patients. This finding has been observed previously.[16] The duration of SP was also prolonged in patients with myoclonic epilepsy. Our findings may suggest that the excitability of cortical inhibitory neurons were also increased as well as excitatory neurons in myoclonic epilepsy. There is a discrepancy between our finding and literature. Manganotti et al. documented impaired functioning of inhibitory interneuronal circuits.[17] Inghilleri et al. has also observed the existence of impaired inhibition of motor cortex in cortical myoclonus.[18] This discrepancy can be

explained by the effect of anticonvulsant medication on the duration of SP.

SP durations was not showed significantly difference in patients with partial epilepsy. Macdonell et al. demonstrated the prolonged SP duration in patients with generalised epilepsy.[19] There are some evidences suggesting enhancement of both excitatory and inhibitory neuronal activities in epilepsy.[20] These findings suggest that SP analysis may be useful in evaluation of cortical excitatory and inhibitory influences in generalised epilepsy. It seems that prolonged duration of SP in patients with primary generalised epilepsy may be caused from enhanced intracortical inhibition.

On the other hand, anticonvulsant medication had more profound effect on SP than TI in our de novo group. Our de novo group was contained a mixed patient population (primary generalised and partial epileptic). This was the limitation of our study. Therefore, this study can be performed in more extensive patient population who have electrophysiological investigations before and after anticonvulsant medication. This analysis can permit the effects of different anticonvulsant drugs on SP and TI.

The lateralisation of epileptic abnormalities on EEG had no effect on the duration of SP and TIs. Similar result has been observed previously.[9] The duration of SP and TI levels were not compared with blood concentrations of anticonvulsant drugs in present study.

Clinical severity of epilepsy had no significant effect on the duration of SP. Ertas et al. observed that the duration of SP was prolonged in resistant epileptics.[21] Clinical severity had effect on the TI level. TI levels can be influenced by the number of anticonvulsant drugs taken due to resistant epileptic seizures. Therefore, we believe that SP durations and TI levels are not reliable indicators of disease severity in epilepsy.

In conclusion, our results suggest that anticonvulsant medication cause different electrophysiological characteristics in patients with epilepsy. The prolongation of SP duration was observed in primary generalised epileptics. On the other hand, TI level was increased in patients with partial epilepsy. Additionally, SP may be more useful electrophysiological parameter than motor cortical TI in expressing the effect of anticonvulsant medication in epilepsy.

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