Usefulness of Transcranial Magnetic Stimulation in Diagnosis of Acute Bell’s Palsy

Jeong-Hoon Lim, M.D., Ph.D., In-Sik Lee, M.D., Ph.D., Seong-Eun Koh, M.D., Ph.D., Se-Won Kim, M.D., Shin Kyoung Kim, M.D., Jongmin Lee, M.D., Ph.D.

Department of Rehabilitation Medicine, Konkuk University Medical Center, Seoul 143-701, Korea

Objective  To investigate the diagnostic significance of transcranial magnetic stimulation (TMS) compared with electro-neurography (ENoG) in very early period of Bell’s palsy.

Method  Thirty-six Bell’s palsy patients within four days of disease onset were recruited and disease severity was assessed using the House-Brackmann grading system on the first visit, on the second visit (14 days later) and one year later. TMS at the labyrinthine segment was performed only on the first visit, while ENoG was done on the first and second visit.

Results  The amplitude ratio of magnetically evoked muscle responses between the affected side and the healthy side was correlated significantly with the clinical course and the final outcome which were documented using the House-Brackmann grade, whereas ENoG was not on the first visit. On the other hand, ENoG on the second visit was correlated significantly with the final outcome.

Conclusion  In the early period of Bell’s palsy, magnetically evoked muscle responses by TMS reflect neural insult more accurately than ENoG. TMS could be a useful measuring tool for the diagnosis and prognosis of Bell’s palsy in the acute stage.

Key Words  Bell’s palsy, Diagnosis, Prognosis, Transcranial magnetic stimulation

INTRODUCTION

Bell’s palsy, the most common form of facial neuropathy, is acute, idiopathic, unilateral paralysis of the facial nerve. The causes of Bell’s palsy are unknown, but the possibilities include viral infection, heredity, autoimmune or vascular ischemia, of which the most likely cause is viral. Bell’s palsy is characterized by a combination of varying degrees of demyelination and axonal damage to the facial nerve fiber. Also, the most common pathogenesis of Bell’s palsy is thought to be an acute conduction block in the Fallopian channel.

Within five days after disease onset, the majority cases of Bell’s palsy experience the maximum paralysis. The Copenhagen facial nerve study on 1,701 cases of Bell’s palsy showed that all Bell’s palsy patients recovered to some extent: 83% of all patients recovered with fair result; 4% of patients were left with an unacceptably high degree of sequelae. Normal function was regained within three months in about two-thirds of all patients; after six months no additional patient regained normal function.
Hitherto, electroneurography (ENoG) of the facial nerve has been most widely used to evaluate the neural damage and predict the recovery. ENoG has the advantage of enabling quantitative evaluation of the various degrees of axonal regeneration. ENoG can stimulate only the distal part of the facial nerve located outside of the temporal bone, so it cannot reflect properly the proximal segment such as canalicular portion which is thought to be the most vulnerable site of neural insult in Bell’s palsy. To stimulate the intracranial part of the facial nerve, intraoperative electrical stimulation was the only method before the advent of transcranial magnetic stimulation (TMS). In the beginning, TMS was introduced to extracranially stimulate cerebral cortex, but later it enabled noninvasive stimulation of various parts of nervous system. Successful methods for magnetic stimulation of intracranial portion of facial nerve have been demonstrated, and the clinical application of them is under discussion. Time course of electrophysiological parameters of TMS was reported, and the elicitation of TMS responses was used to predict good prognosis of Bell’s palsy. On the other hand, there was a negative opinion that TMS does not provide any prognostic data on the clinical evolution of the lesion. To thoroughly verify the merits of TMS in the diagnosis and prognosis of Bell’s palsy, it is needed to refine the quantification of magnetically evoked muscle response in detail, not confined to the elicitation, and correlate them with clinical index of disease severity.

The purpose of this study was to investigate the diagnostic and prognostic value of TMS in a novel methodology and compare it with ENoG in the acute stage of Bell’s palsy.

**MATERIALS AND METHODS**

**Participants**

Diagnosis of Bell’s palsy was confirmed by a clinical examination, blood laboratory tests and radiological studies including magnetic resonance imaging or computed tomography. Among the patients of facial paralysis, those with following conditions were excluded: traumatic facial nerve injury, skull base tumor, a previous history of head surgery, epilepsy, pregnancy, breast feeding, uncontrolled diabetes mellitus, suppurrative otitis media, multiple sclerosis, sarcoidosis, Guillain–Barré Syndrome and bilateral facial palsy. We included only those patients whose disease onset was within four days of the first hospital visit (mean 3.3±0.7 days). In the beginning, 45 patients with acute Bell’s palsy (25 males, 20 females) were recruited from the outpatient clinic of the Department of Rehabilitation Medicine between January 2006 and June 2008, but only 36 patients (19 males, 17 females; age, 14-64 years, mean 42.2±15.3 years) were included in this study because of the follow-up loss. The study protocol was approved by the Institutional Review Board of Konkuk University Medical Center.

**House-Brackmann grading**

On the first hospital visit, the severity of the facial palsy was evaluated using the House-Brackmann grading system. Fourteen days later (mean 17.7±1.9 days from disease onset), we checked the House-Brackmann grade again to assess the clinical change of facial nerve function. High-dose steroid pulse therapy was done to all patients with Bell’s palsy during the interim period. The final clinical outcome of the patients was evaluated using the same grading system one year later (mean 381.3±40.4 days from disease onset). Patients were classified into complete recovery group (grade 1) and incomplete recovery group (grade 2 and above).

**Electrophysiological studies**

ENoG for facial nerve was done on the first and second hospital visit. For ENoG, compound muscle action potential (CMAP) was recorded from the nasalis muscles. Two surface electrodes were placed symmetrically over the bilateral nasalis muscles and a ground electrode was placed over the glabella. All recordings were performed bilaterally to make side-to-side comparisons. Filter was set to 2 Hz-10 kHz and a supramaximal electrical stimulation was given at the stylomastoid foramen. Latency was defined as the interval from the stimulus artifact to the onset of the initial deflection of CMAP from the baseline level. Amplitude was measured from baseline to the negative peak of the CMAP. The percentage of CMAP amplitude of the affected side divided by that of healthy side, which was marked as %ENoG. We labeled %ENoG1 for the value of %ENoG on the first visit and %ENoG2 for that on the second visit.

TMS was performed only on the first visit using a MagStim 200 (The Magstim Company Limited, Wales, UK) connected to a circular stimulation coil 90 mm in diameter. The coil was positioned parieto-occipitally on the skull (6-10 cm laterally from Cz point) with a clockwise current orientation for the right side and vice
versa. Stimulation intensity was set at a level of about 30% of maximum output of TMS and increased stepwise by 10% until a maximal response was obtained. The healthy side was stimulated first to determine the intensity to obtain a maximal response of TMS on facial nerve. For magnetically evoked compound muscle action potential (MEP) obtained by TMS, the latency and the amplitude were measured in the same way as in the electrical stimulation. The percentage of MEP amplitude of the affected side divided by that of the healthy side was marked as %MEP.

Statistical analysis
Data were analyzed by SPSS statistical software (SPSS for Windows version 16.0; SPSS Inc., Chicago, USA). The differences between the means of study parameters were evaluated using t-test. Linear regression analysis was performed to determine the correlation coefficients between the clinical index of facial palsy (House-Brackmann Grade) with %ENoG or %MEP. To analyze the correlation between %ENoG or %MEP and final clinical outcome (classified into complete recovery or not), binary logistic regression was performed. Statistical significance was given when a P value was less than 0.05.

RESULTS
Electrophysiological parameters
On the first hospital visit within four days from disease onset, the latency and the amplitude of CMAP and MEP of the affected side were compared with those of the healthy side. The mean latency of CMAP was 3.17±0.60 msec (affected side) and 3.07±0.53 msec (healthy side), and that of MEP was 3.21±0.75 msec (affected side) and 3.20±0.76 msec (healthy side). As shown in Fig. 1-A, there was no significant difference of the latency between the affected side and the healthy side in both electrical stimulation and TMS. The mean amplitude of CMAP was 1.07±0.48 mV (affected side) and 1.55±0.55 mV (healthy side), and that of MEP was 0.68±0.54 mV (affected side) and 1.72±0.67 mV (healthy side). The amplitude of CMAP and MEP was significantly higher in the healthy side compared with the affected side as illustrated in Fig. 1-B. The amplitude reduction in the affected side was more prominent in MEP than ENoG as depicted in Fig. 2.
Correlation between MEP and the House-Brackmann grade

As described in the methods section, TMS was performed solely on the first hospital visit. The percentage of MEP amplitude of the affected side divided by that of the healthy side (%MEP) was measured and correlated with the clinical index of disease severity represented as the House-Brackmann grade on the first visit. Logistic regression method was used to analyze the relation between the %ENoG and House-Brackmann grade. Fig. 3-A demonstrates that %MEP was correlated significantly with the House-Brackmann grade on the first visit ($p < 0.01$). The %MEP was also correlated well to the House-Brackmann grade on the second visit as shown in Fig. 3-B ($p < 0.01$). The final outcome was classified into complete recovery (grade 1) and incomplete recovery (grade 2 and above). Among 36 patients, 27 (75%) showed complete recovery. Binary logistic regression analysis revealed that %MEP and the final outcome were correlated significantly as indicated in Fig. 4-A ($p < 0.05$).

Correlation between ENoG and the House-Brackmann grade

The percentage of CMAP amplitude of the affected side divided by that of the healthy side on the first hospital visit (%ENoG1) was calculated and correlated with the House-Brackmann grade. Logistic regression analysis was used to assess the relation between %ENoG1 and the House-Brackmann grade. As shown in Fig. 3-C, there was no significant correlation between the two. On the second visit, which was 14 days after the first, the relationship between %ENoG2 (%ENoG measured on the second visit) and the House-Brackmann grade was evaluated. %ENoG2 was correlated significantly with the clinical index of facial palsy on the second visit as depicted in Fig. 3-D ($p < 0.01$). To evaluate the prognostic
value of ENoG, the correlation between %ENoG and the final clinical outcome (complete recovery or not) measured one year later was analyzed using binary logistic regression (Fig. 4-B, 4-C). %ENoG2 was correlated significantly with the final outcome whether the recovery is complete or not (p < 0.01), whereas %ENoG1 was not correlated with it (p > 0.1).

DISCUSSION

In the viewpoint of electrophysiological parameters of ENoG and MEP, the latency did not reflect the neural insult in the canalicular segment on the first visit (Fig. 1-A). On the other hand, the amplitude of the affected side decreased significantly in both ENoG and MEP (Fig. 2-B).

Especially, in acute stage, the amplitude reduction in the affected side was more prominent in MEP than ENoG (Fig. 2) and this result is well matched with previous studies.9,12 The peculiar point of our study is to compare electrodiagnostic values measured by TMS and ENoG with the clinical outcomes prospectively over one year as well as cross-sectionally. To detect the conduction block of the proximal segment of the facial nerve located intracranially, TMS is considered more appropriate than ENoG. Taking into account the fact that it takes time for the damage of proximal part of a nerve to be reflected in the distal end, ENoG is not supposed to sufficiently indicate the neural damage of proximal segment in very early period. However, TMS stimulating intracranial part of the facial nerve can figure out any lesion along the long pathway of it even at the very moment of neural injury. As presented in Fig. 3-A and Fig. 3-C, on the first visit, the number of cases with the amplitude reduction to be less than 20% compared with the healthy side was 13 among 36 (including two cases without any amplitude reduction) in ENoG while...
2 among 36 in MEP. In addition, %MEP was notably correlated with the House-Brackmann grade measured on the same day of the first visit as opposed to the %ENoG1. These facts suggest that MEP reflects neural damage sensitively in very early days of Bell’s palsy when ENoG cannot give any useful information.

On the second visit following the acute stage (about 17 days after disease onset), ENoG represented well the clinical picture of facial palsy as shown in Fig. 3-D. In the context of Wallerian degeneration, this phenomenon is understandable. As time progresses, neural damage of the canalicular segment affects the extracranial portion of facial nerve so markedly that ENoG can detect the progress of nerve degeneration down to the stylomastoid foramen accordingly.

Concerning the prognostic value of TMS for the clinical course and final recovery in Bell’s palsy, some studies indicated that the elicitability of MEP in the early period can be useful for the prediction of the clinical outcome.\textsuperscript{11-13} One of those studies presented that 5 out of 15 patients did not elicit TMS responses on the affected side during the first four days after disease onset.\textsuperscript{12} However, our data in this study showed that there were no absolute non-responders to TMS among 36 patients during the same period. Though there might be some differences in stimulation protocol and measurement method between two studies, this reveals that the elicitability only of TMS response could be inadequate as a reliable prognostic indicator of Bell’s palsy.

This is the reason why we started to investigate %MEP, the percentage of MEP amplitude of the affected side divided by that of the healthy side, as a novel index of TMS response for the prediction of prognosis. It is inspiring that %MEP measured on the first visit was well correlated with the clinical course on the second visit and the final outcome (Fig. 3-B, 4-A). At this point, because of the limited subject number (n=36), it would be impetuous to present cut-off values for prediction of prognosis in MEP study. Therefore, a multi-center study is needed to confirm the diagnostic usefulness of MEP and establish the clinical application. We also remind that some patients in whom clinical recovery had been complete still were not responsive to TMS on the affected side.\textsuperscript{8} This finding suggests that the response to TMS reflects axonal excitability rather than axonal function.\textsuperscript{16}

When it comes to the prognostic value of ENoG, only %ENoG2 measured on the second visit was correlated with the final recovery (Fig. 4-C). The prognostic value of ENoG has been a contradictory issue. Some investigators insisted that ENoG performed between day 7 and 10 from disease onset is not a precise prognostic indicator.\textsuperscript{17} However, the mainstream consensus seems to recognize the worth of ENoG as an index for the prediction of the final outcome. According to our data, ENoG measured within four days from disease onset (%ENoG1) was irrelevant with the final recovery, while ENoG around 17 days from disease onset (%ENoG2) was correlated significantly. There are at least seven days difference for the measurement of ENoG between aforementioned study and ours (%ENoG2). We think that time point of ENoG measurement should be also taken into account before judging its prognostic value. In addition, it should be noted that TMS is similar to ENoG performed two weeks later in its statistical significance to diagnose and predict the prognosis of Bell’s palsy.

This study has some limitations. First of all, the number of cases was small because of the strict application of the exclusion criteria and follow up loss. Considering the natural course of Bell’s palsy, the majority of drop-out patients must be due to complete resolution. In this context, our data were not free from the selection bias and might be inclined to exaggerate poor outcome of the disease. Therefore these data should be supplemented to give an established statistical meaning. On top of that, there could be some confusion about the notion of Bell’s palsy because it should exclude all possible etiologies by definition. Though we performed a comprehensive diagnostic work up to find the specific etiology causing facial nerve palsy, we could not cover all categories especially of rare ones such as borreliosis etc. It is also taken into account that even the negative result of laboratory test does not completely rule out the assumed etiology. Finally, due to the wide variety of settings and protocols for the facial nerve stimulation in each laboratory, the standard value for this method should be tailored according to the situation. We tried to present the possible application of TMS in the acute stage of Bell’s palsy for the prediction of the outcome and introduced its methodology available in our laboratory.

**CONCLUSION**

In conclusion, MEP obtained by TMS detects the neural damage properly even in very early period of Bell’s
palsy when ENoG is useless in detection of the insult of proximal segment of facial nerve. The percentage of MEP amplitude of the affected side divided by that of the healthy side is correlated significantly with the clinical course and final outcome. TMS might be a useful tool for the early diagnosis and prognosis of Bell’s palsy in the acute stage.

ACKNOWLEDGEMENTS

This work was supported by the Konkuk University Medical Center Research Grant 2008-11. We thank Jeong Kim of the electrophysiological laboratory in Konkuk University Medical Center for her assistance in the preparation of the data.

REFERENCES

4) Petersen E. Bell’s palsy: the spontaneous course of 2,500 peripheral facial nerve palsies of different etiologies. Acta Otolaryngol Suppl 2002; 549: 4-30