Neurophysiology of Brain Gliomas

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Abstract: We have evaluated central motor pathways involvement and central inhibition in patients with brain gliomas. TMS (single-pulse protocol) was used; MEP amplitudes, latency, central motor conduction time (CMCT), CMCT asymmetry and silent period were evaluated. 12 glioma patients and 16 controls were enrolled.

Key words: Glioma · Neurophysiology · TMS · Silent period · MEP

INTRODUCTION

Gliomas are the most frequent brain malignancies [1]. It was demonstrated that psycho-emotional condition plays significant role in carcinogenesis, tumor growth and metastasis [2]. One of the main stress-protective reactions of the brain are the central inhibition, with GABA system being a keystone of this reaction [3]. In most of the models GABA acts as an anti-tumor agent [4, 5]. Gliomas tend to excrete glutamate and GABA suppresses their invasion and migration abilities [6, 7]. GABA receptors expression is maximal in low-proliferative glioma fractions and almost absent in high-proliferative gliomas [3].

Transcranial magnetic stimulation (TMS) are one of the main methods for central inhibition evaluation in human. Length of the silent period (SP), measured by EMG on flexed muscle after the magnetic discharge over the motor cortex reflects the central inhibition [8]. In conditions with high GABA content in brain SP lengthens and in diseases such as epilepsy SP duration shortens [9]. TMS itself lengthens SP duration, as well as GABA-ergic preparations intake [10].

To our knowledge, there are no works evaluating conduction parameters and SP duration in relatively big groups of brain glioma patients. Aim of our study was to study central motor pathways and central inhibition in patients with brain glioma.

MATERIALS AND METHODS

28 patients were enrolled: 16 controls and 12 glioma patients. Control group consisted of patients without neurologic symptoms and signs, average age 42 years, 11 males, 5 females. Glioma group consisted of 11 males and 5 females; average age 49.5 years. All patients had established diagnosis of hemisphere glioma: 8 anaplastic astrocytomes, 1 anaplastic olygodendroglioma and 2 glioblastomes. Right hemisphere localization was seen in 5 cases and in 7 cases gliomas were left-hemispheric. Average time of the investigation from the first symptoms onset was 108 days, range 60-163 days. All patients underwent surgery, total glioma removal was not achieved in all cases; average time from the surgery until the investigation was 30 days, range 22-45 days.

Clinical signs in glioma group were brain hypertension syndrome (in 11 cases), hemiparesis in 4 cases and pyramidal signs in 3 cases. There were no severe hemiparesis in any case. All patients were right-handed.

TMS was performed according to currently accepted standard procedures [11]. Patients were seated comfortably in a chair in a well-lit room. We used circular coil 90 mm in diameter and Neiro-MS-D monophasic current pulse magnetic stimulator. Single-pulse TMS protocol was used. Coil was positioned over the optimal scalp site: over the vertex for the hand motor cortex
stimulation and 5 cm in front for the leg motor cortex stimulation. Cortical motor areas, cervical and lumbar parts of the spine were stimulated to obtain motor evoked potentials (MEPs) and to calculate central motor conduction times (CMCTs). For the conduction studies target muscles were at rest. The onset of the MEP was determined by measuring the shortest latency of at least 5 single stimulation responses. For each site at least 5 MEPs were collected, averaged and analyzed. MEPs amplitude, duration and onset latency were measured. MEP amplitude was calculated by the area under the curve. The measurements were performed for the hands and legs. Recording surface skin-mounted EMG electrodes (diameter 8 mm) were placed on both hands on m. Abductor pollicis brevis. Surface EMG signal was recorded using a Neiro-MVP apparatus. In silent period investigation average (controlled by the surface EMG monitoring) voluntary muscle contraction was made, after which single-pulse EMG was performed according to the procedures described above. At least 5 silent period recordings were made, averaged and analyzed.

Study was approved by the local ethical committee according to the Helsinki declaration. The purpose of the study was fully explained to the participants, their parents or legal representatives, written informed consent was obtained from all patients’ parents or legal representatives.

Obtained values were compared between groups. Statistical analysis was performed by using statistical analysis software for Windows. For the demographic features of the cohort descriptive statistics were used. For group comparisons chi-squared test was used, the student t-test was used for normally distributed parameters. For not normally distributed values Mann-Whitney U-test was used. A p value of <0.05 was considered statistically significant.

RESULTS AND DISCUSSION

No patient in both groups presented complaints. No adverse reaction in both groups were seen. TMS parameters (MEPs latencies, amplitudes, CMCT) of the patients and the control group are presented in Table 1. Variability of the MEP latencies and CMCT in controls was small.

In the average over all glioma patients CMCTs was comparable on both sides. CMCTs of individual patients sometimes were asymmetrical. In general there were no significant average asymmetries between MS group and controls.

As it can be seen from the obtained data, in control group average results had tendency towards medical normative. In glioma patients in all cases lower MEP amplitudes were seen, which can reflect general lowering of the motor neurons functional activity. Also in glioma group tendency towards longer CMCT in right hemisphere stimulation was seen. This can be explained by the frequent right-hemisphere tumor localization in this group (70% of the cases).

On the individual level severe abnormalities (polyphasic MEP, CMCT asymmetry more than 3 ms, cortical MEP latency lengthening) were seen in 2 cases (20%). Moderate abnormalities (polyphasic MEP, CMCT asymmetry 2 ms) were seen in 3 cases (30%). Mild dysfunctions, namely 1 ms CMCT asymmetry, slightly polyphasic MEP were seen in 4 patients (40%). In controls MEP shape was polyphasic in 2 cases (13%), but in glioma patients it was changed in 80% of the cases. Absolutely normal TMS parameters were seen in glioma group only in 1 case (10%).

Thus TMS was informative in about 50% of the cases in glioma patients; signs of motor conduction dysfunction of all grades were seen in 90% of the cases.

Silent period parameters in gliomas and control groups are presented in Table 2.

In normal conditions dominant hemisphere silent period is longer on 30-40 ms. In both groups on average level asymmetry between hemispheres was normal. Average duration of silent period in glioma patients in hemisphere affected by the tumor was 151±47 ms and in unaffected hemisphere it was 113±29 ms.

On individual level in 4 cases in glioma patients (40%) asymmetry between affected and unaffected hemispheres were more than 40 ms. In all cases in affected hemisphere

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<th>Table 1: Distribution of TMS parameters among patients and controls</th>
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<td>TMS parameters</td>
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<tr>
<td></td>
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<tr>
<td>Right arm</td>
</tr>
<tr>
<td>Left arm</td>
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<tr>
<td>CMCT, right arm (ms)</td>
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<tr>
<td>CMCT, left arm (ms)</td>
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<tr>
<td>Average CMCT asymmetry (ms)</td>
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Table 2: Distribution of silent period parameters among patients and controls (M±SD)

<table>
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<tr>
<th>Parameters</th>
<th>Controls (n=16)</th>
<th>Glioma patients (n=10)</th>
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<tr>
<td>Silent period, right hemisphere, ms</td>
<td>151.71±38.21</td>
<td>135.43±49.21</td>
</tr>
<tr>
<td>Silent period, left hemisphere, ms</td>
<td>126.71±27.4</td>
<td>129.65±39.61</td>
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<tr>
<td>Silent period asymmetry, ms</td>
<td>37.85±31.06</td>
<td>40.17±28.06</td>
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silent period was longer (in one case 80 ms asymmetry was seen). In controls such asymmetry was seen only in 2 cases (12%).

Thus, in glioma patients in 40% of the cases in hemisphere, affected by tumor, central inhibition activation was seen. As it was shown in several reports, silent period duration reflects GABA system activity [12, 13]. It is known that glioma secretes glutamate [6, 7], which seems to affect central inhibition and may possibly activate GABA system. Also one of the reasons for the central inhibition asymmetry in glioma patients may be the GABA interneurons activation in affected brain tissue.

In our study all patients before TMS evaluation underwent partial surgery for the tumor. Unresolved question is what central inhibition looks like in patients before the surgical removal of the tumor tissue. Also the future investigation may be focused on changes of central motor conduction and central inhibition in patients before and after the tumor therapy (radiology and chemotherapy).

**CONCLUSIONS**

- TMS are well tolerated by the patients with gliomas of the brain (hemispheric localization).
- TMS are sensitive in 90% of the cases of hemisphere gliomas of the brain. One of the most prominent changes is the motor neurons functional activity lowering, presumably unspecific.
- In 40% of the cases in glioma patients central inhibition asymmetry is seen, with central inhibition prevalence in tumor-affected hemisphere.

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**REFERENCES**