Electroencephalographic Activity of Wakefulness and Sleep Associated with Primary Brain Tumors in Human: A Pilot Study

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Abstract

The primary brain tumors usually cause cognitive impairment and sleep disturbances. Furthermore, it is unknown how these impairments depend on tumor value, and how patients with different tumor value recover after surgical intervention. The present research showed mild cognitive impairment in the second group patients before and on the seventh day after surgical intervention. The first group patients showed sleep disturbances on the seventh day after surgery. The second group patients had sleep disturbances with delta-sleep recovery on the seventh day after surgery. Patients of the first and second groups had low delta- and alpha-power density over site of tumor. On the seventh day after surgery patients of the first group had delta power increasing for the rest wakefulness and sleep over uninjured brain regions. Patients with big tumor showed decreasing delta power for the rest wakefulness and increasing for sleep over uninjured brain regions.

Thus, brain tumor has an essential influence on bioelectrical activity of the brain; the extend of cognitive impairment, sleep disturbances and recover after surgery intervention depend on the tumor volume. But further studies with larger series are needed.

ABBREVIATIONS

EEG: Electroencephalography; FAB: Frontal Assessment Battery; MMSE: Mental State Examination; TST: Total Time of Sleep; REM stage: Rapid Eye Movement Sleep; FFT: Fast Fourier Transform; NREM: Nonrapid Eye Movement Sleep

INTRODUCTION

Brain tumor is an abnormal and uncontrolled cells division inside the brain or the skull. Primary brain tumors appear from cells of the brain itself (neurons, cells, blood vessels and etc.) [1]. Primary brain tumors are more electrically active. Electroencephalography (EEG) is a reliable tool for brain tumor diagnosis [2,3]. EEG shows changes in the brain physiology and patient’s condition. These changes depend on the volume of the brain tumor and its localization. EEG abnormalities in patients with brain tumor are caused by pathological growth of tumor due to which the intracranial pressure in the brain increases, and the healthy cells and tissues of the brain are displaced and damaged. Functional changes of cerebral tissues occur in tumor site and cause a focal excitation or focal attenuation there. This may be seen in focal (near to tumor site), distant (second abnormalities, on distance to tumor site), and cerebral changes [4]. At the early stages of disease symptomatic epilepsy in EEG, epileptiform discharges may appear, focal slow waves, localized attenuation of background activity, asymmetric beta-activity may be registered near the tumor [5,6]. The polymorphic delta wave in all brain regions, sharpened alpha rhythm, beta-activity increase may be seen at the time of diagnosis at later stages of brain tumor when cerebral disturbances occur as a result of cerebral edema, hypoxia, increasing intracranial pressure in the brain. [7]. Depending on the stage of the brain tumor, light, pronounced and deep cerebral disturbances are marked out. Light cerebral disturbances appear as dysrhythmia in the activity of the brain, attenuation of alpha-activity, focal slow wave in tumor site, epileptiform discharges. Pronounced cerebral
disturbances are characterized with polymorphic delta wave activity in all brain regions and attenuation of alpha activity. Asymmetry of amplitude is registered only under functional tests. Deep cerebral disturbances produce slow waves (1.0 – 2.5 oscillation per second) in all regions of the brain, while alpha and beta rhythms are destroyed [7]. Therefore, brain tumor has an essential influence on bioelectrical activity of the brain. Most studies are reasonably focused on wakefulness-related EEG abnormalities associated with brain tumor, as patients suffer headache, epilepsy, and cognitive impairment etc [8-10].

The present research was aimed to study the extent of cognitive impairment and night sleep disturbances as well as to analyze the bioelectrical activity of brain in the primary tumor before and on the seventh day after surgical intervention.

**MATERIALS AND METHODS**

Data were collected from the Rostov Scientific Research Institute of Oncology. All the procedures were approved by the ethic committee at the institute and were in accordance with ethical standards of the Declaration of Helsinki (1964). Patients gave informed consent for the study. Six patients aged 48.6 ± 4.2 yr. with right hemisphere primary astrocytic tumors participated in the present study. Patients did not exhibit epileptic discharges. Tumor length (L), weight (W), heights (H) were measured using MRI and then tumor volume was calculated using formula:

\[ V = \frac{\pi}{6} \cdot L \cdot W \cdot H \]

The method consisted of testing, EEG recording at the rest with eyes closed and sleep registration before surgical intervention and on the seventh day after intervention. A physician tested patients in the morning in separate room. Frontal assessment batteries (FAB) [15], Mini-Mental State Examination (MMSE) [16] were used. Nineteen-channel scalp EEG records, in the standard 10-20 electrode system, at the rest with eyes closed were obtained using electroencephalograph “Encephalan EEGR-19/26” (Medicom MTD, Russia). Unipolar registration of EEG signals was in pass band of 0.5 and 30 Hz at a sampling rate of 250 Hz. A 50 Hz notch filter was attenuated electrical noise. Artifacts were detected automatically and were eliminated from analysis. Night sleep was recorded with the electroencephalograph "Encephalan EEGR-19/26" (Medicom MTD, Russia) in accordance with international criteria [17,18].

Electroencephalogram bilateral central (C3 and C4), parietal (P3 and P4), and occipital (O1 and O2) sites to A1+A2, bilateral electromyogram of the sublingual muscle, electrocardiogram, and respiratory rate were recorded. Unipolar registration of EEG signals was in pass band of 0.5 and 30 Hz with sample rate of 500 Hz. A 50 Hz notch filter was attenuated electrical noise. Sleep was visually staged by three experts in accordance with standard criteria [17,18]. Artifacts were detected automatically and were eliminated from analysis. The total time of sleep (TST), sleep latency (as a time from light-out and initial presence of stage 2), time awake after sleep onset (as the total minutes from sleep onset to wake-up), total minutes of 2nd stage, delta-sleep and REM were measured. Percentages of 2nd stage, delta-sleep and REM were determined by dividing the total amount of time in each of these stages by the total sleep time. These parameters were calculated for all period of night sleep. EEG power spectral density was performed using Fast Fourier Transform (FFT). Power spectral density was computed for frequencies 0.5-4.0 Hz for delta and 8.0-12.0 Hz for alpha. FFT was computed for 5-sec segments of relaxed wakefulness period in which subjects had his/her eyes closed, for night sleep periods of 2nd stage and delta-sleep, and REM. Consequent analyses with natural logarithm transformed spectral power were performed. The asymmetry index was derived from subtracting the natural logarithm of the left hemisphere power value from the natural logarithm of the right hemisphere [19].

The patients with small brain tumor (volumes were 17.8 cm, 3.2 cm and 1.9 cm) were combined in the first group, and patients with big brain tumor (volumes were 46.8 cm, 60.57 cm and 60.3 cm) were combined in the second group. In current study the results of analyses were presented as mean (SD) for patients of the first and second groups. The statistical analyses were not performed.

**RESULTS AND DISCUSSION**

The means of scales of tests in the first and second group’s patients are presented in Table (1). The present research showed mild cognitive impairment in the second group patients with a big brain tumor before surgical intervention and on the seventh day after it.

Comparing sleep parameters in the primary tumor patients with healthy people of the same age range published by Kryger and others was performed. Kryger and others [20] showed sleep latency varied from 5 to 15 min, total minutes of 2nd stage were 40-50%, total minutes of delta-sleep were 20-27%, REM was 17-25%, and total minutes of awake after sleep onset were 5% in healthy people of the same age range. Thus, the first group patients had drawn-out sleep latency previous to surgical intervention. On the seventh day after surgery, they had drawn-out sleep latency, shorter 2nd stage, and more delta-sleep than healthy people had. The second group patients had more awake after sleep onset, shorter 2nd stage, and more delta-sleep and REM previous to surgical intervention. On the seventh day after surgery, they showed more awake after sleep onset, shorter 2nd stage, and more REM. On the seventh day after surgery second group patients showed shorter sleep latency, less awake after sleep onset, more 2nd stage and REM than they had previous to surgery. The sleep parameters of first and second group patients are presented in Table (1).
Table 1: Means of scales of test and sleep measures in first and second group’s patients previous and on the seventh day after surgical intervention.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>First group</th>
<th>Second group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before surgery</td>
<td>7th days after surgery</td>
</tr>
<tr>
<td>FAB scores, mean (SD)</td>
<td>18.0 (1.2)</td>
<td>17.33 (0.6)</td>
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<tr>
<td>MMSE scores, mean (SD)</td>
<td>29.7 (0.3)</td>
<td>30.0 (3.1)</td>
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<td>TST, min, mean (SD)</td>
<td>493.7 (65.8)</td>
<td>556.3 (93.1)</td>
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<tr>
<td>Sleep latency, min, mean (SD)</td>
<td>21.3 (4.7)</td>
<td>23.0 (6.0)</td>
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<tr>
<td>Awake after sleep onset, min, mean (SD)</td>
<td>26.3 (15.6)</td>
<td>32.7 (12.5)</td>
</tr>
<tr>
<td>% of TST</td>
<td>5.3</td>
<td>5.9</td>
</tr>
<tr>
<td>Z stage NREM, min, mean (SD)</td>
<td>200.7 (94.9)</td>
<td>215.7 (96.1)</td>
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<tr>
<td>% of TST</td>
<td>40.7</td>
<td>38.8</td>
</tr>
<tr>
<td>Delta-sleep, min, mean (SD), % of TST</td>
<td>126.3 (50.6)</td>
<td>190.3 (54.2)</td>
</tr>
<tr>
<td></td>
<td>25.6</td>
<td>34.2</td>
</tr>
<tr>
<td>REM, min, mean (SD), % of TST</td>
<td>119.0 (63.5)</td>
<td>94.7 (35.3)</td>
</tr>
<tr>
<td></td>
<td>24.1</td>
<td>17.02</td>
</tr>
</tbody>
</table>

Abbreviations: FAB: Frontal Assessment Battery; MMSE: Mini-Mental State Examination; TST: Total Sleep Time; NREM: Nonrapid Eye Movement Sleep; REM: Rapid Eye Movement Sleep

The Figure (1) shows power spectral density of first (Figure1A) and second (Figure1B) group patients being wakeful with closed eyes previous and on the seventh day after surgery. Before surgery, the first group patients had low power density of delta- and alpha-activity in the T3T4 sites. Power density of alpha-activity dominated in all the brain areas with the exception of F7F8 sites. On the seventh day after surgery, besides the EEG changes noted before surgery, in the first group patients the increasing power of alpha-activity in all the brain areas and increasing delta-activity in Fp1Fp2FzF3F4F8C4 were registered. The asymmetry of delta-power appeared in the frontal (F8>F7, 53.6%; F4>F3, 91.2%) and central (C4>C3, 51.9%) areas. Previous to surgery, in the second group patients low power density of delta- and alpha-activity in the T3T5T6 sites were observed. The asymmetry of delta-power was observed in some areas (F4>F3, 42.2%; F3>F7, 48.3%; T3>T4, 42.2%). Delta-power dominated in all the brain areas both before surgery, and on the seventh day after surgery. On the seventh day after surgery, besides the EEG changes noted before surgery, the second group patients registered the decreasing power of delta- and alpha-activity in all brain areas. The amplitude asymmetry of delta-activity in temporal (T6>T5, 50.6%), central (C4>C3, 67.5%) and parietal (P4>P3, 58.5%) areas were registered.

The power spectral density of the first and second group patients being sleep before and on the seventh day after surgery is presented in Figures (2-4). On the seventh day after surgery, the first group patients showed the increasing delta power of F4C4 sites and decreasing alpha power of F3F4C3C4 during 2nd stage of sleep (Figure 2A). Increasing delta power in all areas and decreasing alpha power in F4C4 sites were noted in the delta-sleep (Figure 3A). Increasing delta power in all areas with exception O1 site in REM was noted. Amplitude asymmetry of delta power in the frontal area (F4>F3, 47.8%) appeared (Figure 4A).
The second group patients on the seventh day after surgery had increasing delta power in all areas and decreasing alpha power in F4C4 sites during 2nd stage of sleep (Figure 2B). The decreasing power in all areas and decreasing alpha power in all areas with exception of O2 site in the delta-sleep were observed (Figure 3B). Amplitude asymmetry of delta power in the central (C4>C3, 36.3%) and occipital (O2>O1, 44.1%) areas appeared. The decreasing alpha power in F3C3 sites in the REM were noted (Figure 4B).

DISCUSSION

The primary brain tumors and tumor treatment usually cause deficits of cognitive function, changes in psychological well-being [8,21]. The type of changes in cognitive function depends on site of lesion and treatment [10]. Thus, the patients with frontal tumors have impairments of frontal lobe function such as impairment of cognitive flexibility, abstraction, personality changes and memory loss [22]. The present research showed cognitive impairment in the second group patients with a big brain tumor. These findings illustrate that the mass effect on site of lesion and adjacent brain region play important role in cognitive impairment in primary brain-tumor patients.

Wakefulness functioning impairment mostly related to night sleep disturbances in primary brain-tumor patients [13]. Insomnia, hypersomnia and nightmares are common for these patients. Sleeping problems become persistent and chronic in some patients even after therapy completion [12].

Figure 2 Power spectral density of the 2 stage of sleep in first (A) and second (B) group patients.

Figure 3 Power spectral density of the delta-sleep in first (A) and second (B) group patients.

Figure 4 Power spectral density of the REM in first (A) and second (B) group patients.
Comparing sleep parameters in the primary tumor patients with healthy people of the same age range [20] showed that the sleep disturbance value before surgical intervention depended on the tumor volume, and these disturbances were similar to hypersomnia. The sleep disturbances on the seventh day after intervention in the first and second group patients were, more likely, the result of the cerebral edema that extended the compression area. The physiological estimate of changes of the bioelectrical activity of the brain under the brain tumor is traditionally used in clinic in order to localize the tumor and measure the general brain changes [2,6]. The brain tumor patients get pathological changes of the bioelectrical activity that appear and increase as the tumor grows. These changes may become apparent in the tumor site and extend, as the tumor grows, to symmetric areas of the other hemisphere or over all the areas of the hemispheres. The main typical EEG-sign of the brain tumor is believed to be delta-waves that appear in the tumor site. The presence of delta-activity, as reduced alpha- and beta-oscillations last, reflects displacement and compression of the cortical tissue [23]. Some authors believe that focal delta-waves appearing in EEG under the brain tumor are caused by development of the perifocal edema of the brain tissue [23]. The work by Rusinov [24] showed the patients with low-grade tumors had slow waves called forth by a progressive increasing influence of the tumor upon the underlying cortical tissue and by disorders of the local vascularization in this area. Marecek et al., found correlation hemodynamic fluctuation in brain regions known to be involved in active processing [25].Registrations of the cortex biopotentials from the open brain showed that local slow waves are drawn off not from the tumor itself but from the cortex area that surrounds the tumor and is influenced by it for a long time [26]. The present study observed domination of delta-power in all the brain areas both before surgery, and on the seventh day after surgery in the first and second group patients being wakeful with closed eyes. Besides these EEG changes before surgery, the second group patients were revealed to have an amplitude asymmetry of delta-activity, the most amplitude being observed in the tumor site and in the area symmetric to it.

On the seventh day after surgery, besides the EEG changes noted before surgery, the first group patients registered the increasing power of delta- and alpha-activity in the tumor site, in the area symmetric to it and in the nearest areas. The asymmetry of delta-power appeared in the tumor area and in the areas next to it, while the tumor site hemisphere presented its highest value. The second group patients, besides the above changes before surgery, also registered the amplitude asymmetry of delta-activity in remote cortex areas, with major amplitude in the damaged hemisphere.

Besides the above EEG changes in wakeful patients of the first and second group, the decreasing power of delta- and alpha-activity in the tumor site and in the areas next to it was registered. The cause of these changes was explained in a work by Promyslov and others [27]. Promyslov and his colleagues showed, on an experimental tumor model, that as the tumor was growing, it was observed to infiltrate the surrounding brain structures, which was leading to breaching the intracerebral synaptic bonds, to degeneration of conduction tracts and to a partial death of cell elements of the cortex and sub cortex. This study showed an EEG where the area of the maximum changes of the cortical tissue due to infiltration was revealed in decrease of amplitude and deceleration of the oscillations period of delta-waves, as well as no alpha- and beta-oscillations exist at all.

The comparative analysis of change of the sleep EEG on the seventh day after surgery showed that on the seventh day after surgery the first group patients were revealed to have an increase of delta-power and a decrease of alpha-power in the tumor site. The delta-sleep and paradoxical sleep stage registered an increase of delta-power in all the cortex areas. At the second sleep stage, the second group patients revealed an increase of power in all the areas, while the delta-power contrarily decreased during the delta-sleep and paradoxical sleep. It is interesting to know that the decrease of alpha-power at the second sleep stage was noted in the tumor site, it was noted in all areas during the delta-sleep and in its contralateral area during the paradoxical stage.

CONCLUSION

The current article presents the results of a pilot study of the primary brain tumor’s influence on the organization of the wakefulness - sleep cycle. According to the obtained data, the mass effect on site of lesion and adjacent brain region play important role in cognitive impairment and sleep disturbances in primary brain-tumor patients. The patients with big brain tumor showed mild cognitive impairment and sleep disturbances before and on the seventh day after surgical intervention. At the same time, the EEG of wakefulness and sleep stages is of great importance for diagnostics of the cortical tissue damage area. So, all patients had low power density on site of lesion. Patients with small tumor showed less tissue damage area. On the seventh day after surgery, the next changes of EEG wakefulness and EEG sleep in patients with small tumor were registered: increasing alpha power in all regions in wakefulness, increase delta power on the site of lesion in sleep stages. The patients with big tumor showed decrease delta power in all brain regions in state of wakefulness, increase delta power in all regions during 2nd stage and decrease delta power in all brain regions during delta-sleep. Thus, the patients with different tumor volume illustrated different changes after surgical intervention both wakefulness and sleep.

We suppose the EEG analysis at the wakefulness and sleep stages may allow estimating the damage level of afferent and efferent connection frontal lobes with all the other brain structures. Studies in this direction may favor specific measures that will contribute to recover after surgery intervention in the brain tumor patients.

REFERENCES


