Tumor location and IDH1 mutation may predict intraoperative seizures during awake craniotomy

Clinical article

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Object. Intraoperative seizures during awake craniotomy may interfere with patients’ ability to cooperate throughout the procedure, and it may affect their outcome. The authors have assessed the occurrence of intraoperative seizures during awake craniotomy in regard to tumor location and the isocitrate dehydrogenase 1 (IDH1) status of the tumor.

Methods. Data were collected in 137 consecutive patients who underwent awake craniotomy for removal of a brain tumor. The authors performed a retrospective analysis of the incidence of seizures based on the tumor location and its IDH1 mutation status, and then compared the groups for clinical variables and surgical outcome parameters.

Results. Tumor location was strongly associated with the occurrence of intraoperative seizures. Eleven patients (73%) with tumor located in the supplementary motor area (SMA) experienced intraoperative seizures, compared with 17 (13.9%) with tumors in the other three non-SMA brain regions (p < 0.0001). Interestingly, there was no significant association between history of seizures and tumor location (p = 0.44). Most of the patients (63.6%) with tumor in the SMA region harbored an IDH1 mutation compared with those who had tumors in non-SMA regions. Thirty-one of 52 patients (60%) with a preoperative history of seizures had an IDH1 mutation (p = 0.02), and 15 of 22 patients (68.2%) who experienced intraoperative seizures had an IDH1 mutation (p = 0.03). In a multivariate analysis, tumor location was found as a significant predictor of intraoperative seizures (p = 0.002), and a trend toward IDH1 mutation as such a predictor was found as well (p = 0.06). Intraoperative seizures were not associated with worse outcome.

Conclusions. Patients with tumors located in the SMA are more prone to develop intraoperative seizures during awake craniotomy compared with patients who have a tumor in non-SMA frontal areas and other brain regions. The IDH1 mutation was more common in SMA region tumors compared with other brain regions, and may be an additional risk factor for the occurrence of intraoperative seizures.

(http://thejns.org/doi/abs/10.3171/2014.7.JNS132657)

Key Words • awake craniotomy • seizures • brain tumors • supplementary motor area • isocitrate dehydrogenase 1 mutation • oncology

A wake craniotomy with intraoperative mapping and monitoring is a well-established surgical technique to achieve maximal tumor resection when the tumor is located within or adjacent to eloquent brain regions. Awake craniotomy has been shown to minimize the risk of permanent postoperative neurologic deficits and to better preserve the patient’s quality of life.1,2,6,18,20,22,23 Seizures are a common presenting symptom in patients with brain tumors. Previous studies have reported that 30%–50% of patients with brain tumors experience a seizure prior to tumor diagnosis.8,13,14,24 Both tumor histological features and location have been shown to be highly predictive of seizure occurrence, with a higher incidence of seizures in patients with low-grade gliomas (LGGs), compared with high-grade gliomas (HGGs),19 and in patients with tumors located in the temporal or frontal lobes, compared with other brain regions.4,21 Importantly, no distinction has been made between the vari-
ous intrafrontal regions (i.e., the supplementary motor area [SMA] vs other frontal regions) regarding seizure prevalence. Preliminary observations in our patients have suggested a high occurrence of intraoperative seizures in patients with tumors located in the SMA region, and this was further investigated in this study.

Interestingly, an association between seizures as a presenting symptom in patients with diffuse LGGs and the isocitrate dehydrogenase 1 (IDH1) mutation has recently been reported, with the IDH1 mutation occurring mostly in tumors located in the insula and in frontal regions. In this study, we have evaluated the association between tumor location, specifically in the SMA region, IDH1 mutation status, and the occurrence of intraoperative seizures during awake craniotomy.

Methods

This retrospective study was based on prospectively collected data in consecutive patients undergoing awake craniotomy at the Tel Aviv Medical Center between January 2010 and May 2012. The study was approved by the Tel Aviv Medical Center Institutional Review Board committee.

Patient Selection

We reviewed all consecutive operations performed during the study period to identify all awake craniotomy cases. The selected patients had presented with newly diagnosed supratentorial tumors located within or in proximity to eloquent brain areas as determined by preoperative MRI scans. Eloquent brain regions were defined as those involving primary and secondary motor, sensory, or language functions, as well as major functional tracts, such as the corticospinal tract and the arcuate fasciculus. Recurrent tumors were excluded from analysis. A total of 137 patients were identified and included in the present analysis.

Clinical Characteristics

Patients were divided into 4 groups according to their tumor location: the SMA, frontal non-SMA, temporal, and parietal regions (tumors located in occipital regions were usually surgically treated under general anesthesia). The SMA region was defined according to a previously described method in which a plane vertical to the anterior commissure line was used. Pathological diagnosis was determined by a neuropathologist and based on the WHO criteria. The patients' clinical, operative, and hospitalization data were recorded. The Karnofsky Performance Scale (KPS) was used to assess preoperative functional status. Postoperative MRI was performed within 48 hours of surgery to assess extent of tumor resection, and this was categorized as follows: gross-total resection if no residual tumor enhancement was detected for enhancing tumors or complete resection of the preoperative FLAIR signal abnormality for LGGs. Subtotal resection (> 90%) if slight residual tumor enhancement was detected in HGGs or a residual nodular FLAIR signal abnormality was detected in the resection cavity in LGGs or biopsy.

Perioperative mortality was recorded within 30 days after surgery. Postoperative neurological outcome was assessed within 7 days from surgery. Length of hospital stay (LOS) was captured from the hospital records.

Preoperative Evaluation

The preoperative evaluation of patients considered for awake craniotomy and the intraoperative management included multiple procedures as previously reported by our group.

Determining the Mutational Status of IDH1

The IDH1 analysis was performed in 102 patients. Only patients harboring glioma tumors (113 patients) were included in this analysis. Data in 11 patients with glioma were excluded due to either poor quality or an insufficient amount of preserved tumor tissue for IDH1 analysis. Methods for detecting the IDH1 R132H mutation by immunohistochemistry with mouse monoclonal antibody H09 (catalog no. DIA H09, Dianova) on an automated immunostainer (BenchMark, Ventana Medical System) have been previously described in detail.

Statistical Analysis

Descriptive statistics are presented as means and SD for continuous variables and as frequency distribution for categorical variables. The chi-square or Fisher exact tests were used to examine the differences in categorical variables between groups. Mann-Whitney and Kruskal-Wallis tests were used to compare the groups for continuous variables. For multivariate analysis a logistic regression was applied. Statistical analyses were performed using SPSS 17.0 for Windows and SAS for Windows version 9.2. A p value < 0.05 was considered statistically significant.

Results

Patient Population

During the study period 137 patients (80 males) underwent awake craniotomy for tumor resection. Fifteen patients with tumors located in the SMA region were compared with 70 patients with tumors located in the non-SMA frontal regions, 33 with tumors in the temporal lobe, and 19 with tumors in parietal regions. The mean age did not differ between groups (p = 0.314), with a slight male predominance in all groups. Most (88%) of the patients were right-handed, and there was no difference in handedness between the study groups. At presentation the mean KPS was 88.9 ± 12.3, and there was no difference between the groups (p = 0.148). Most of the patients in the SMA group (73.3%) harbored a low-grade glioma (LGG), whereas the majority of patients in the non-SMA frontal, temporal, and parietal groups suffered from a high-grade glioma (HGG) (53.6%, 66.7%, and 78.9%, respectively, p = 0.004). There was no significant difference in antiepileptic drug (AED) treatment between the study groups. Phenytoin was the most commonly used AED among all study patients, followed by valproic acid and carbamazepine. In all patients, preoperative blood levels of the AED...
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were within the therapeutic range. Four patients (3%) underwent a biopsy only. The clinical and demographic characteristics of the patients in each group are presented in Table 1.

**Incidence of Seizures**

A total of 28 patients (20.4%) had experienced an intraoperative seizure during awake craniotomy. Seizure incidence according to tumor location was 73.3% (11 of 15) in the SMA group, 20% (14 of 70) in the non-SMA frontal region, 10.5% (2 of 19) in the parietal region, and 3% (1 of 33) in the temporal group ($\chi^2 = 30.321$ [3 df, n = 137], $p < 0.001$) (Fig. 1). Most of the patients who experienced intraoperative seizures had partial motor or language seizures (79.3% [23 patients]) compared with 20.7% (6 patients) who had experienced a generalized seizure during surgery. In contrast, most of the patients with a history of seizures had experienced generalized seizures prior to surgery (63.5% [40 patients]), compared with 36.5% (23 patients) who had experienced partial seizures.

Assessment of the patients’ history of seizures revealed that 9 (60%) in the SMA group experienced preoperative seizures compared with 30 (42.9%) in the non-SMA frontal group, 17 (51.5%) in the temporal group, and 7 (36.8%) in the parietal group. This difference did not reach statistical significance, however ($\chi^2 = 2.508$ [3 df, n = 137], $p = 0.444$) (Fig. 2).

**Seizures and Cortical Stimulations**

There was no significant difference in current intensities applied during cortical stimulations between patients who experienced intraoperative seizure and those who did not (applied intensity [mean ± SD]: 3.52 ± 1.46 mA for low-intensity and 6.36 ± 2.94 mA for high-intensity cortical stimulation; $\chi^2 = 2.224$ [5 df, n = 137], $p = 0.817$). There was also no difference in maximal current intensities used during cortical mapping in the different groups (maximal applied intensity [mean ± SD]: 6.92 ± 3.12 mA for the SMA group, 6.10 ± 3.12 mA for the non-SMA frontal group, and 3.51 ± 3.07 mA for the nonfrontal group; $\chi^2 = 11.687$ [15 df, n = 137], $p = 0.703$). As expected, in all groups the majority of seizures (62%) occurred during cortical stimulation. In the majority of the patients who had experienced seizures during cortical stimulation (24 patients [83%]), positive mapping for motor or language functions was achieved. Two patients had experienced seizures before cortical mapping, and thus no cortical stimulations were performed. Three patients had negative mapping.

**Postoperative Outcome**

There was no perioperative mortality. Four patients in the SMA group (26.7%) had experienced a new postoperative motor deficit, compared with 9 patients in the non-SMA frontal group (12.9%), 2 in the temporal group (13.3%), and 1 in the parietal group (5.3%).

**TABLE 1: Characteristics of 137 patients who underwent awake craniotomy, stratified by tumor location**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SMA</th>
<th>Frontal Non-SMA</th>
<th>Temporal</th>
<th>Parietal</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>total no.</td>
<td>15 (10.9)</td>
<td>70 (51.1)</td>
<td>33 (24.1)</td>
<td>19 (13.9)</td>
<td></td>
</tr>
<tr>
<td>age in yrs</td>
<td>41.2 ± 17.7</td>
<td>49.54 ± 18.1</td>
<td>50 ± 16.38</td>
<td>50.42 ± 16.45</td>
<td>0.314</td>
</tr>
<tr>
<td>male sex</td>
<td>11 (73.3)</td>
<td>35 (50.0)</td>
<td>21 (63.6)</td>
<td>13 (68.4)</td>
<td>0.206</td>
</tr>
<tr>
<td>rt hand dominant</td>
<td>12 (80)</td>
<td>62 (88.6)</td>
<td>27 (81.8)</td>
<td>19 (100)</td>
<td>0.207</td>
</tr>
<tr>
<td>tumor on lt side</td>
<td>12 (80)</td>
<td>51 (72.9)</td>
<td>32 (97)</td>
<td>17 (89.5)</td>
<td>0.22</td>
</tr>
<tr>
<td>KPS score</td>
<td>93.33 ± 8.2</td>
<td>90.14 ± 13.1</td>
<td>86.36 ± 16.36</td>
<td>85.79 ± 11.69</td>
<td>0.148</td>
</tr>
<tr>
<td>pathological diagnosis</td>
<td>HGG</td>
<td>LGG</td>
<td>metastases</td>
<td>other</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 (20)</td>
<td>11 (73.3)</td>
<td>1 (6.7)</td>
<td>0 (0)</td>
<td>0.004</td>
</tr>
<tr>
<td>anticonvulsant‡</td>
<td>phenytoin</td>
<td>valproic acid</td>
<td>carbamazepine</td>
<td>&gt;1 drug</td>
<td>0.940</td>
</tr>
<tr>
<td></td>
<td>7 (46.7)</td>
<td>3 (20)</td>
<td>1 (6.6)</td>
<td>4 (26.7)</td>
<td></td>
</tr>
<tr>
<td>extent of resection§</td>
<td>gross total</td>
<td>subtotal</td>
<td>biopsy</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>13 (86.7)</td>
<td>2 (13.3)</td>
<td>0 (0)</td>
<td>10 (52.6)</td>
<td>0.631</td>
</tr>
<tr>
<td></td>
<td>42 (60.9)</td>
<td>25 (36.2)</td>
<td>2 (2.9)</td>
<td>13 (88.4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>21 (63.6)</td>
<td>11 (33.3)</td>
<td>1 (3.0)</td>
<td>5 (26.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>13 (88.4)</td>
<td>5 (26.3)</td>
<td>1 (5.3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Values for age and KPS score are expressed as the mean ± SD.
† Chi-square test, 3 df for all comparisons (SMA vs non-SMA frontal lobe and nonfrontal regions).
‡ Data for 1 patient from the “temporal” group are missing.
§ Data for 1 patient from the “frontal non-SMA” group are missing.
SMA vs frontal; p = 0.05 for frontal vs other).

SMA vs frontal non-SMA, temporal, and parietal groups; p < 0.0001 for during awake craniotomy classified by tumor location (p < 0.001 for

Sixty percent (31 of 52) with a preoperative history of seizures had an IDH1 mutation (p = 0.02), and 68.2% (15 of 22 patients) who experienced intraoperative seizures had an IDH1 mutation (p = 0.03).

Multivariate Analysis: Tumor Location, Tumor Pathology, and IDH1 Mutation

To identify independent variables associated with intraoperative seizures, logistic regression was applied using tumor location, tumor pathology, and IDH1 mutation as possible predictors. Results showed that tumor located at the SMA region was a significant independent predictor of intraoperative seizures (OR 11.36, 95% CI 1.904–67.79; p = 0.002). The predictive value of IDH1 mutation was close to significance and can be related as a statistical trend (OR 2.859, 95% CI 0.940–8.701; p = 0.06). Finally, the independent contribution of tumor pathology to intraoperative seizure occurrence was not significant (p = 0.15).

Discussion

Our data demonstrate a significant association between tumor location and the occurrence of intraoperative seizures during awake craniotomy. A statistical trend was found with IDH1 mutation as an independent factor, and it may posit additional risk for intraoperative seizures. Patients with tumors located in the SMA region had a significantly higher incidence of intraoperative seizures compared with patients with non-SMA frontal, temporal, and parietal tumors. Assessment of patients’ seizure history revealed that in the frontal non-SMA, temporal, and parietal groups, although a history of seizures was common, less than half of those with a seizure history experienced an intraoperative seizure. In contrast, all but 1 patient in the SMA group who had a history of preoperative seizures had experienced an intraoperative seizure. Three patients in the SMA group who did not have a history of seizures did experience intraoperative seizures. Thus, it seems that within the SMA group, a history of seizures may predict the occurrence of intraoperative seizures, whereas in the other groups no such prediction can be made.

The IDH1 enzyme, which is NADP+ dependent, is located in the cytosol and mitochondria. Mutant IDH reduces α-ketoglutarate to 2-hydroxyglutarate (2-HG), resulting in a 100-fold raised 2-HG level in gliomas with IDH1 mutations. Köller et al. have reported that 2-HG has structural similarities to glutamate that may activate N-methyl-d-aspartate receptors,11 and thus may have epileptogenic potential. The IDH1 mutations are more frequently found in LGGs and secondary glioblastoma multiforme. Parsons et al.16 were the first to report a survival benefit in patients with glioblastoma multiforme whose tumor contained IDH1/2 mutations (45.6 vs 13.2 months in IDH1 mutations vs IDH1 wild type, respectively). We have found a higher rate of IDH1 mutation in tumors located in the SMA region, which were more susceptible to development of pre- and intraoperative seizures. One potential explanation for the susceptibility to the development of seizures is regional metabolic changes that occur in the tumor environment and may increase regional epileptogenic activity. Stockhammer et al.23 have recently described an association between IDH1 or IDH2 mutations and seizures as a presenting symptom in patients with LGG, most probably due to increased glutathione synthesis and the cystine/glutamate antiporter subunit (xCT) expression in LGG.22

The IDH1 or IDH2 mutations are known to be found mostly in patients with tumors located in the frontal lobe or insula.12 The majority of LGGs tend to occur in these same brain regions and have mutations in the genes encoding IDH1/2 that are associated with potentially epileptogenic metabolic changes.21 This correlation may partially explain our current findings because most tumors in the SMA region in our patients were LGGs. However,
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TABLE 2: Postoperative outcome of 137 patients who underwent awake craniotomy, stratified by tumor location

<table>
<thead>
<tr>
<th>Outcome</th>
<th>SMA</th>
<th>Frontal Non-SMA</th>
<th>Temporal</th>
<th>Parietal</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>postop mortality</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>new motor deficit</td>
<td>4 (26.7)</td>
<td>9 (12.9)</td>
<td>2 (6.1)</td>
<td>2 (10.5)</td>
<td>0.408</td>
</tr>
<tr>
<td>new language deficit</td>
<td>1 (6.7)</td>
<td>6 (8.6)</td>
<td>2 (6.1)</td>
<td>3 (15.8)</td>
<td>0.570</td>
</tr>
<tr>
<td>LOS in days, mean ± SD</td>
<td>4.36 ± 4.25†</td>
<td>5.06 ± 5.73‡</td>
<td>4.16 ± 3.35§</td>
<td>6.26 ± 5.44</td>
<td>0.281</td>
</tr>
</tbody>
</table>

* Chi-square test, 3 df for all comparisons (SMA vs frontal non-SMA, temporal, and parietal regions).
† Data for 4 patients from the “SMA” group are missing.
‡ Data for 6 patients from the “frontal” group are missing.
§ Data for 2 patients from the “temporal” group are missing.

the full mechanism of this phenomenon is still not clear. Notably, none of these studies9,16,17 differentiated between the SMA and the rest of the frontal lobe. When reviewing the distribution of lesions in the current study population, it appears that LGGs were much more prevalent in the SMA region, whereas HGGs are more prevalent in the non-SMA frontal lobe, suggesting differential tumor environments. Given the strong association between lesion, location, IDH mutation status, and seizures as a symptom (both pre- and intraoperatively), future research of the metabolic effect of IDH mutations within the SMA region may enhance our ability to understand the dynamics behind the higher seizure rate in these patients.

Intraoperative seizures during awake craniotomy may negatively affect the quality of intraoperative monitoring, and in extreme cases may lead to conversion to general anesthesia. This may result in a reduced rate of tumor resection or an increased risk for postoperative functional deficit.4,7 Despite adequate AED levels prior to operation, patients did experience seizures during the mapping procedure. Cordella et al. recently reported a rate of 36% intraoperative cortical stimulation–evoked seizures, with 8% new, permanent neurological deficits.5 These results emphasize the need to be prepared during awake craniotomy for seizure control, especially in patients with tumors located in the SMA region and regardless of an adequate preoperative AED level.

In our patient cohort, intraoperative seizures had no long-term implications on the patients’ clinical course and outcome except for a short-term postoperative new motor deficit. The rate of new motor deficits 7 days postoperatively was more than twice as much in the SMA group as in the other 3 groups (Table 2). However, this difference was not statistically significant, perhaps due to the small number of patients in each group. Due to the high occurrence of postoperative new motor deficits within the SMA group, motor function was reassessed at 30 days after surgery and showed complete resolution of the motor deficit in all patients. This recovery may be related to what has been previously described as the SMA syndrome, characterized by temporary motor and language deficits that appear after resection of the SMA region and that resolve within days to weeks after surgery.10 The LOS was not prolonged in the SMA group, possibly the result of prompt intraoperative seizure control and appropriate patient management.

Limitations of the Study

There are several limitations to this study. This is a retrospective study with the inherent limitations and potential bias such as selection bias, loss to follow-up, and observation bias found in such a study. Furthermore, previous studies have shown that seizures are more common in patients with right hemisphere tumors than in patients with tumors in the left hemisphere.11 In our study there was a significant predominance of left hemisphere tumors (82% of the patients) because awake craniotomy is mostly performed for tumors in the left (dominant) hemisphere. In addition, although we have found a correlation between SMA tumor location and intraoperative seizures, we are unable to provide an explanation for this observation. One possible explanation is associated with IDH status. It is already known that most LGGs tend to occur in certain brain regions such as SMA or insula, and also tend to have mutations in the genes encoding IDH1/2.21

Furthermore, we report the data on pre- and intraoperative seizures in our patient population but were unable to obtain the postoperative seizure status in many patients who were followed by their home neurologists and oncologists. Finally, there was a considerable difference in the size of our 4 study groups. Whereas the temporal and frontal non-SMA group consisted of 33 and 70 patients, 19 were included in the parietal group and only 15 in the SMA group. Nevertheless, the highly significant difference observed does suggest that our observations are valid.

Conclusions

This study describes a previously unreported association between tumor location in the SMA region and the occurrence of intraoperative seizures during awake craniotomy. Patients with tumors located in the SMA region have an increased risk of developing intraoperative seizures compared with patients in whom tumors are located in other brain regions. This information can be incorporated into the preoperative preparation and intraoperative management of patients in whom awake craniotomy is planned.

Disclosure

The authors report no conflict of interest concerning the mate-
Author contributions to the study and manuscript preparation include the following. Conception and design: Ram, Gonen, Grossman. Acquisition of data: Ram, Gonen, Grossman, Nossek, Yanaki. Analysis and interpretation of data: Ram, Gonen, Grossman, Sitt, Cagnano. Drafting the article: Ram, Gonen, Grossman. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Ram. Statistical analysis: Gonen. Administrative/technical/material support: Gonen, Grossman, Sitt, Nossek, Yanaki, Cagnano, Hayat, Korn. Study supervision: Ram. Surgical team member: Hayat. Intraoperative electrophysiological monitoring: Korn.

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Manuscript submitted December 2, 2013. Accepted July 17, 2014

Please include this information when citing this paper: published online August 29, 2014; DOI: 10.3171/2014.7.JNS132657.

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