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Hydrocephalus after resection and adjuvant radiochemotherapy in patients with glioblastoma

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ABSTRACT

Objective: Glioblastomas are the most common primary malignant brain tumors in adults with a poor prognosis. The current study sought to identify risk factors in glioblastoma patients that are closely associated with communicating hydrocephalus.
Methods: We retrospectively analyzed data from 151 patients who were diagnosed with a glioblastoma between 2007 and 2011 and underwent complete surgical resection closely followed by adjuvant radiochemotherapy.
Results: We observed a significant tendency toward communicating hydrocephalus in cases of ventricular opening during surgical tumor resection (Fisher's exact test $p < 0.001$) and a noticeable, although not statistically significant, correlation between the onset of communicating hydrocephalus and evidence of leptomeningeal tumor dissemination (Fisher's exact test $p = 0.067$). Additionally, there was a trend toward frontal tumor location and a larger tumor volume in patients with communicating hydrocephalus. The majority of patients suffering from communicating hydrocephalus received a cerebrospinal fluid (CSF) shunt implantation after radiation therapy (63.6%, Fisher's exact test $p = 0.000$).
Conclusion: We identified the following risk factors associated with the onset of communicating hydrocephalus in glioblastoma patients: ventricular opening during tumor resection and leptomeningeal tumor dissemination. Shunt implantation seems to be safe and effective in these patients.

1. Introduction

Glioblastoma is the most common primary malignant brain tumor in adults, with an incidence of 3.5 per 100,000 inhabitants [1,2]. With the development of combined treatment approaches, the overall survival rate for glioblastoma patients has improved from 3.3 months up to 14.2 months in the past 25 years, although the median survival period remains less than one year [3]. Moreover, there are several complications that can occur during the course of the disease, often leading to a decline in neurological function and Karnofsky performance scale status [4]. In rare cases, communicating hydrocephalus is diagnosed as the source of neurological deterioration. Inamasu et al. [5] described in 2003 that only five of 50 patients with supratentorial malignant glioma treated within the last 10 years of their report developed a hydrocephalus. Patients affected with a hydrocephalus often show general motor deterioration, gait disturbances, and progressive mental impairment [6]. Montano et al. [4] previously identified various predisposing factors for the onset of a hydrocephalus in patients with glioblastoma. Our current study sought to identify risk factors in patients suffering from glioblastomas that are closely associated with the onset of communicating hydrocephalus requiring ventriculoperitoneal (VP) shunt implantation.

2. Patients and methods

We collected data retrospectively from 151 patients who were diagnosed with glioblastoma multiforme (WHO grade IV) between 2007 and 2011. Additional inclusion criteria consisted of complete resection, MRI within 72 h after surgery for resection control and radiochemotherapy administered shortly after surgical treatment. We considered a resection "complete" in cases in which no residual tumor tissue (defined as gadolinium contrast enhancement) was

Abbreviations: CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; VP shunt, ventriculoperitoneal shunt.

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diagnosed in a MRI scan performed within 72 h after surgery. We achieved complete surgical resection in 63.4 percent of the glioblastoma patients. All patients received an average total radiation dose of 47 Gy (range 22–60 Gy) and were treated with temozolomide (EORTC guidelines [7]). In some cases, patients received several temozolomide treatments. In other cases, different chemotherapeutic drugs were used in addition to temozolomide, such as avastin or lomustine. Intraoperative chemotherapeutics were not administered to any patient.

Three patients with subperiostal cerebrospinal fluid (CSF) collection in the region of the craniotomy were excluded from the study.

The median follow-up period was 15 months after the initial MRI, which was performed within the first 72 h after surgery. All included patients were screened for the following factors: Karnofsky score before surgery, tumor location, size of the tumor (measured in cm^3), number of preceding surgical treatments, ventricular opening during tumor resection, the presence of leptomeningeal tumor spreading during the course of the disease (examined using MRI scans), CSF analyses, evidence of hydrocephalus, and the need for VP shunt placement.

Communicating hydrocephalus was suspected in patients with ventricular enlargement compared to previous imaging and corresponding clinical symptoms (headaches, cognitive decline, ataxia, urinary incontinence and clinical deterioration not due to tumor progression). A lumbar tap test (30–50 ml CSF) was routinely performed to evaluate whether symptoms would improve with VP shunt implantation. Ventricular enlargement, especially focal ventriculomegaly, in the absence of clinical symptoms was regarded as *ex vacuo* enlargement after parenchymatous mass resection. If medically indicated, a Codman HAKIM® valve or a Sophysa® valve was implanted.

We divided our patient sample into two groups. The first group consisted of patients with clinical and radiological evidence indicating a communicating hydrocephalus, and the second group of patients did not demonstrate this complication. Descriptive statistics were performed for these two groups. The Mann–Whitney test was performed to compare the above-mentioned variables between the groups. Factors influencing the onset of hydrocephalus were tested for significance by Fisher's exact test. $p < 0.05$ was considered to indicate a statistically significant difference, and $p < 0.1$ was considered a statistical trend (statistically not significant). All statistical calculations were performed using the statistical software package SPSS (PASW Statistics 19). This study was approved by the university's ethics committee (KEK-ZH-Nr: 2012-0257).

2.1. Illustrative clinical case

A 49-year-old patient presented with progressive headaches refractory to analgesics. MR imaging (Fig. 1A and B) showed a space-occupying, ring-enhancing lesion in the left frontal lobe with perifocal edema. A craniotomy with tumor resection was performed. The ventricular system was opened during surgery. Histopathological examination verified the diagnosis of a glioblastoma. The postoperative MR imaging for resection control on the second day after surgery showed no residual tumor (Fig. 1C and D). The patient received adjuvant radiochemotherapy (total dosage of 60 Gy and temozolomide) [7]. Three months following the initial surgery, the patient was hospitalized due to symptoms of hydrocephalus (strong headaches, nausea, and ataxia) and ventriculomegaly, as observed by CT scan (Fig. 1E and F). VP shunt implantation was performed and the patient showed clinical improvement, particularly with regards to his ataxia.

3. Results

The patient sample included 151 patients (94 men and 57 women), with a mean patient age of 58 years (range 23–83 years). Eleven patients developed a communicating hydrocephalus after surgical resection of the tumor (Table 1); the other 140 patients (88 men and 52 women) were used as the control group in our study (Table 2). The 11 patients with communicating hydrocephalus (6 men, 5 women, mean age 53 years, range 37–74 years) required VP shunt implantation (7.28%) after a positive lumbar tap test. Among these patients, 4 received VP shunt implantation prior to radiation therapy, and the remaining 7 patients received implantation after radiation therapy (63.6%) (Table 2). The median time for VP shunt implantation after initial surgery (tumor resection) was 110 days (range 6–728 days).

The tumor location in our control group was frontal in 53 patients (37.9%), temporal in 47 patients (33.6%), parietal in 20 patients (14.3%), occipital/suboccipital in 7 patients (5.0%), and in the insular region together with the basal ganglia in 13 patients (9.3%). Of the 11 patients with communicating hydrocephalus, the tumor location was frontal in 7 cases (63.6%), temporal in 3 cases (27.3%) and occipital/suboccipital in one case (5.3%). We observed a tendency toward frontal tumor locations in patients with communicating hydrocephalus (Fisher exact test $p = 0.115\%$). Tumor volume was on average 58.6 cm^3 in patients with a communicating hydrocephalus compared to 35.1 cm^3 in the control group.

In 99 cases from the control group (70.7%), one craniotomy was performed for tumor resection, whereas in the remaining 41 cases (29.3%), two craniotomies were performed. The patients who showed signs of communicating hydrocephalus underwent one (5 patients, 45.5%), two (5 patients, 45.5%), or three (1 patient, 9.1%) surgical procedure(s) to achieve the greatest possible tumor resection. Ventricular opening during surgical tumor resection occurred in 24 cases (17.1%) from the control group (140 patients without communicating hydrocephalus) and 8 of the 11 patients with communicating hydrocephalus (72.7%). In this regard, we identified a significant deviation between the two groups (Fisher's exact test $p < 0.001$), and this result indicated a significant tendency toward communicating hydrocephalus in cases of ventricular opening during surgical tumor resection.

We further compared these two groups concerning leptomeningeal tumor dissemination, which was revealed on postoperative MRI scans. This condition was identified in 11 (7.9%) cases among the 140 patients in our control group and in 27.3% (3 of 11) of the patients with communicating hydrocephalus. Similar to the presence of ventricular opening, there was a noticeable difference (although not significant) between the two groups concerning leptomeningeal tumor dissemination (Fisher's exact test $p = 0.067$). Hence, we identified a correlation between the onset of communicating hydrocephalus and evidence of leptomeningeal tumor dissemination.

In 7 of 11 cases with communicating hydrocephalus, CSF analysis was performed prior to shunt placement, but these data were not available for the other 4 cases.

In all 7 analyzed cases, the CSF cytology was negative for tumor cells. In addition, only two out of these 7 cases demonstrated increased CSF protein content. Overall, the CSF protein content was not significantly higher compared to 13 analyzed patients in our control group who did not show radiological or clinical signs of communicating hydrocephalus.

4. Discussion

Data regarding the onset of communicating hydrocephalus in the postoperative course of glioblastoma are rarely discussed