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Treatment Strategies for Huge Central Neurocytomas*

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Summary: Central neurocytomas (CNs), initially asymptomatic, sometimes become huge before detection. We described and analyzed the clinical, radiological, operational and outcome data of 13 cases of huge intraventricular CNs, and discussed the treatment strategies in this study. All huge CNs (*n*=13) in our study were located in bilateral lateral ventricle with diameter ≥5.0 cm and had a broad-based attachment to at least one side of the ventricle wall. All patients received craniotomy to remove the tumor through transcallosal or transcortical approach and CNs were of typical histologic and immunohistochemical features. Adjuvant therapies including conventional radiation therapy (RT) or gamma knife radiosurgery (GKRS) were also performed postoperatively. Transcallosal and transcortical approaches were used in 8 and 5 patients, respectively. Two patients died within one month after operation and 3 patients with gross total resection (GTR) were additionally given a decompressive craniectomy (DC) and/or ventriculoperitoneal shunt (VPS) as the salvage therapy. Six patients received GTR(+RT) and 7 patients received subtotal resection (STR)(+GKRS). Eight patients suffered serious complications such as hydrocephalus, paralysis and seizure after operation, and patients who underwent GTR showed worse functional outcome [less Karnofsky performance scale (KPS) scores] than those having STR(+GKRS) during the follow-up period. The clinical outcome of huge CNs seemed not to be favorable as that described in previous reports. Surgical resection for huge CNs should be meticulously considered to guarantee the maximum safety. Better results were achieved in STR(+GKRS) compared with GTR(+RT) for huge CNs, suggesting that STR(+GKRS) may be a better treatment choice. The recurrent or residual tumor can be treated with GKRS effectively.

Key words: huge central neurocytomas; treatment; tumor

Central neurocytomas (CNs) are rare intraventricular brain tumors and thought to be benign neoplasms with neuronal differentiation[1]. They account for only 0.1%–0.5% of all primary brain tumors and mainly affect young adults[2, 3]. Having an indolent clinical course, they sometimes grow huge at presentation with intracranial hypertension due to obstructive hydrocephalus. Given benign biological behavior of CNs, gross total resection (GTR) of the tumor is the treatment of choice and leads to cure and long-term survival[4]. More and more reports have demonstrated the clear superiority of GTR over subtotal resection (STR) in CNs[4, 5]. However, GTR of CNs is a surgical challenge for neurosurgeons and it is difficult to perform especially when the tumors become huge and hypervascular, and the incidence of GTR was less than 50% in previous reports[2, 6]. Furthermore, CNs have a deep-seated intraventricular location and are close to critical structures, such as the fornix and thalamus, and GTR of CNs may pose a serious risk to the patients[7]. Additionally, surgical mortality cannot be negligible, and most are related to complications after treatment and thus possibly avoidable. All the risk factors of treatment are particularly important and noteworthy in huge CNs. Meanwhile, conventional radiation therapy (RT) and gamma knife radiosurgery (GKRS) have been effectively and frequently applied to the management of residual or recurrent CN and have also been used as a primary or secondary treatment option for CNs[8, 9]. However, to our knowledge, there have been no reports focusing on the treatment strategies for huge CNs. In the present study, we retrospectively analyzed the clinical, radiological, operational and outcome data of 13 huge CNs diagnosed and treated in our institution in recent seven years, and discussed the treatment strategies for the huge CNs.

1 MATERIALS AND METHODS

Between Feb. 2006 and June 2013, 13 patients with intraventricular tumors which were ≥5.0 cm in diameter and had a broad-based attachment to at least one side of the ventricle wall, were diagnosed as having CNs and treated at the Department of Neurosurgery of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, China. All medical, radiological, operational, histopathologic, and clinical outcome data were retrospectively reviewed.

The preoperative radiological data of computed to-

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mography (CT) and magnetic resonance imaging (MRI) in the 13 patients were reviewed to determine the tumor characteristics (size, location, ventriculomegaly, calcification, cystic degeneration and enhancement). The tumor volume was estimated by taking measurements of the 3 major axes (a, b, and c). Diagnosis was made by specialists in neuropathology and histopathologically confirmed with the light microscopic findings and immunohistochemical characteristics [synaptophysin (Syn), neuron special enolase (NSE), neuron specific nuclear protein (NeuN), glial fibrillary acidic protein (GFAP), and MIB-1 antibody (MIB-1 labeling index)]. All the operation charts and postoperative imaging data were reviewed to determine the surgical approach (transcortical or transcallosal), and the salvage therapies including preoperative extra ventricular drainage (EVD), intraoperative decompressive craniotomy (DC) and postoperative ventriculoperitoneal shunt (VPS) were recorded. Postoperative images were compared with preoperative ones to determine the extent of resection (GTR or STR). The clinical outcomes of the patients, including functional outcomes [defined as Karnofsky performance scale (KPS) scores], adverse events of recurrence and progression and complications, were evaluated during the follow-up period. The median follow-up period was 48 months (range, 16–101 months).

2 RESULTS

2.1 Patients and Neuroradiological Characteristics

All 13 patients, with median age of 23 years at surgery (range, 14–46 years) and a male-to-female ratio of 9:4, had a median preoperative KPS score of 90. Most patients presented with the symptoms of raised intracranial pressure (ICP), including headache, nausea and vomiting. General seizure, motor weakness and visual disturbance were also found (table 1). The duration of symptoms varied from 1 month to 2 years (average 10.1 months). On neurological examination, the most common signs were papilledema (table 1). CT scans generally revealed that the tumors were isodense or slightly hyperdense and had a broad-based attachment to at least one side of the ventricle wall. All tumors were confined to the bilateral lateral ventricle with ventriculomegaly, and extended into the third ventricle in eight cases and extended into the pineal region in one case (table 2). Seven CNs had cystic changes, six had vascular flow-void signal (FVS), and calcifications were found in nine cases. All the tumors showed hypo-intensity to iso-intensity on T1-weighted images and iso-intensity to hyper-intensity on T2-weighted MR images, and most revealed moderate and mixed enhancement (table 1, fig. 1).

Table 1 Summary of demographics and tumor characteristics of 13 patients with huge CNs

Demographics and tumor characteristics (*n*=13)	
Age (year, median)	23 (14–46)
Sex (male/female)	9/4
Median preoperative KPS score	90 (70–100)
Mean duration of symptoms (months)	10.1 (1–24)
Mean clinical follow-up duration (months)	48 (16–101)
Main symptoms and signs at initial presentation [*n* (%)]	
Headache	8 (61.5 %)
Nausea and vomiting	5 (38.5 %)
Visual disturbance	6 (46.2 %)
Seizure	2 (15.4 %)
Decreased balance	1 (7.7 %)
Motor weakness	2 (15.4 %)
Papilledema	8 (61.5 %)
Memory disturbance	3 (23.1 %)
Neuroradiological features [*n* (%)]	
Calcification	9 (69.2 %)
Cystic degeneration	7 (53.8 %)
Vascular FVS	6 (46.2 %)
Moderate-marked enhancement	10 (76.9 %)
Heterogeneous enhancement	7 (53.8 %)
Ventriculomegaly	13 (100 %)
Histopathological and immunohistochemical features [*n* (%)]	
Syn	13 (100 %)
NSE	7 (7/7)
NeuN	13 (100 %)
GFAP	3 (23.1 %)
Mean MIB-1 labeling index	2.1% (1 %–3 %)
Microvascular proliferation (MPV)	2 (15.4 %)

Table 2 The location, size, treatment and outcome of huge CNs in 13 patients

No.	Site	Size (cm)	Surgical approach	Adjuvant therapy	Salvage therapy	Complications	Clinical outcome	KPS
1	BLV	5.8×5.1×6.6	Transcortical	GTR	None	Paralysis	No recurrence	60
2	BLV, 3V	5.2×6.5×5.1	Transcallosal	STR	EVD	Secondary bleeding	Death	0
3	BLV	6.4×5.0×5.2	Transcallosal	STR+GKRS	None	None	Recurrence	90
4	BLV	5.1×5.4×5.2	Transcortical	GTR	None	None	No recurrence	80
5	BLV, pineal region	8.6×5.4×5.6	Transcortical	GTR	DC	Seizure, visual field defect	No recurrence	60
6	BLV, 3V	7.3×5.2×6.7	Transcallosal	GTR	DC+ VPS	Hydrocephalus paralysis, seizure	No recurrence	60
7	BLV, 3V	5.7×6.0×5.5	Transcallosal	GTR	None	Secondary bleeding	Death	0
8	BLV, 3V	6.9×7.8×6.1	Transcallosal	GTR+RT	VPS	Hydrocephalus	No recurrence	70
9	BLV, 3V	5.5×5.0×5.0	Transcortical	STR	None	Memory loss	Progression	80
10	BLV, 3V	6.1×5.7×6.0	Transcallosal	STR+GKRS	None	None	No recurrence	80
11	BLV	5.2×5.5×5.3	Transcortical	STR+GKRS	EVD	Hemiparesis	No recurrence	70
12	BLV, 3V	6.4×5.3×5.2	Transcallosal	STR+GKRS	None	None	No recurrence	90
13	BLV, 3V	5.6×5.4×5.0	Transcallosal	STR+GKRS	None	None	No recurrence	90

BLV: bilateral ventricle; 3V: the third ventricle; GTR: gross total resection; STR: subtotal resection; EVD: extra ventricular drainage; RT: conventional radiation therapy; GKRS: gamma knife radiosurgery; DC: decompressive craniotomy; VPS: ventriculoperitoneal shunt

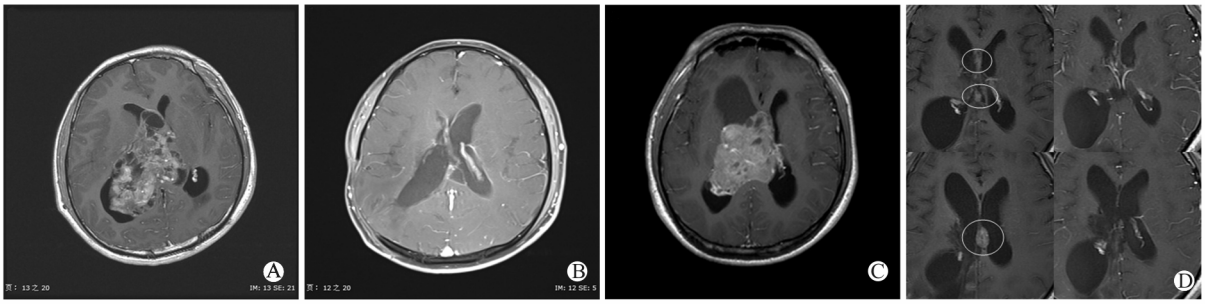

Fig. 1 Contrast-enhanced MR images of huge CNs
A and B: the MR images of a huge CN in a patient (No. 5) who was given GTR via a transcortical approach; C and D: the MR images of a huge CN in one patient (No. 11) who received the STR through a transcortical approach , and GKRS effectively as the adjuvant therapy for the residual tumor (circle) 3 months after operation

2.2 Surgical Treatment, Adjuvant Therapy and Clinical Outcome

Two patients underwent EVD due to acute intracranial hypertension before operation. All patients underwent microsurgical resection, and external ventricular drains were placed for 48–84 h after resection of the tumors and were removed as soon as the blood in the cerebrospinal fluid (CSF) was cleared. The surgical approach and resection results are shown in table 2. The transcallosal approach was used in 8 patients and GTR was achieved in 3 of them. The transcortical approach was used in 5 patients and GTR was successfully performed in 3 of them. Two patients died within one month postoperatively because of secondary bleeding and untreatable brain swelling. Three patients who underwent GTR were given a decompressive craniectomy (DC) and/or ventriculoperitoneal shunt (VPS) as the salvage therapy due to intraoperative cerebral edema and high intracranial pressure or postoperative complication of hydrocephalus. Five patients with STR received GKRS for the residual tumor (fig. 1) and one patient with GTR received RT postoperatively. No patients were administrated with adjuvant chemotherapy. The clinical outcomes of the patients, including scores on the KPS, adverse events of recurrence and progression and complications, are summarized in table 2. Complications reflecting dysfunction included hemiparesis, paralysis, seizure, visual field defect, memory loss and hydrocephalus are shown in table 2. During the follow-up, one patient was treated with STR+GKRS and recurred in 43rd month and another patient was treated with STR alone and the residual tumor progressed at 37th month postoperatively. These two patients were treated with the (repeated) GKRS and no recurrence was found during the follow-up.

2.3 Histopathological Features

On the light microscopy, all tumor tissues consisted of small uniform cells with remarkably round nuclei in a fine neuropil and the cells were strongly immunoreactive for Syn (fig. 2). The cytoplasms were not well defined and the nuclei were round to slightly lobulated. Tumor cells with rounded nuclei and scant cytoplasm resembled

perinuclear halos ("fried egg" appearance). Microcalcifications were observed in most tumors and mitotic figures were absent or infrequent (fig. 2). Atypical histological features of microvascular proliferation (MPV) were shown in two patients. The immunohistochemistry results are summarized in table 1, including the expression of Syn (13 of 13 patients), NSE (7 of 7), NeuN (13 of 13), GFAP (3 of 13), MIB-1 labeling index (1%–3%) (fig. 2).

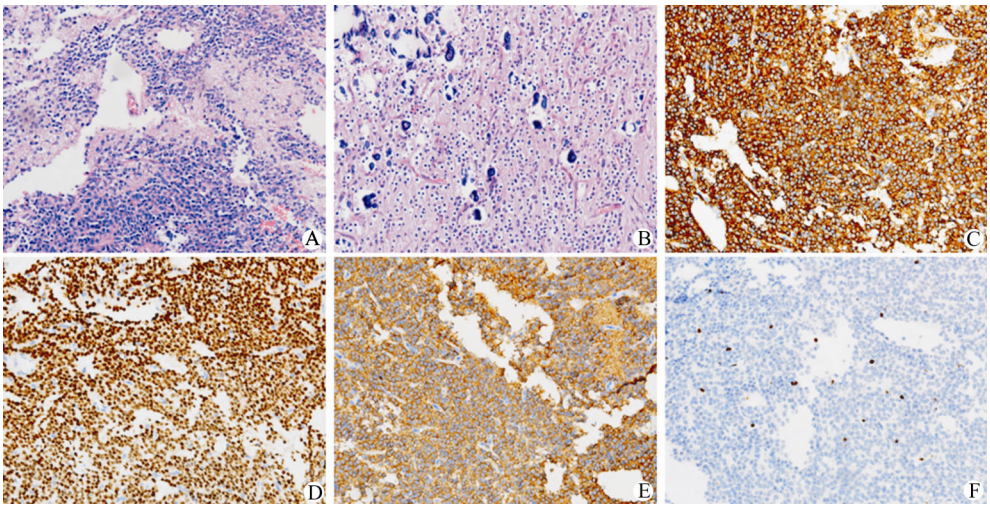

Fig. 2 Histopathological images of huge CNs (hematoxylin and eosin staining, ×200)
A and B: homogenous, small, round tumor cells under the light microscope with nucleus-free neuropil islands (A) and calcifications (B). C, D, E and F: Immunohistochemically, all tumors were positively immunoreactive for Syn (C), NSE (D) and NeuN (E), with MIB-1 labeling index <3% (F).

3 DISCUSSION

CNs are initially asymptomatic, and have a propensity to grow to a significant size before they present with the symptoms of intracranial hypertension due to obstructive hydrocephalus. Patients with huge CNs in our study usually presented with long-term headache and visual disturbance, and the mean duration of clinical symptoms and signs was much longer than the duration (less than 6 months) previously reported[10, 11]. Huge CNs in our study, with diameter ≥5.0 cm and a broad-based attachment to the superior and lateral wall of the ventricle, were characterized by greater frequency among young adults, intraventricular location, and specific neuroradiological and histopathological features[11–13]. These 13 huge CNs occurred most commonly in young adults in the third decade of life and showed a slight male predominance. Radiologically, CT scans typically demonstrated an isointense or slightly hyperintense mass with intratumoral calcifications and cystic areas within bilateral lateral ventricles. MRI findings of huge CNs characteristically included third ventricle extension, attachment to the wall of the lateral ventricle, and heterogeneous hypointensity to isointensity on T1-weighted image and hyperintensity on T2-weighted image, with moderate contrast enhancement and regular vascular FVS. These neuroradiological features were clearly present in our series, strongly supporting the diagnosis of CNs[11, 13–16].

In the current study, all huge CNs were of typical histopathological features, which are also described in previous studies[5, 10, 12, 17, 18]. They were composed of homogenous, small, round cells with neuronal differentiation in the neuropil and were strongly immunoreactive for Syn. The examined tumor tissues were positive immunoreactively for Syn, NSE, and NeuN, supporting the neuronal nature of the neoplasm. Scant mitotic activity and low MIB-1 index demonstrated the benign nature and low proliferation of CNs. Accordingly, the diagnosis of huge CNs was established on above features of clinical presentations, neuroradiological expression and histopathological manifestations in this series.

The benign biological behavior and large size of huge CNs make them unsuitable for any treatment other than surgical resection. However, huge CNs pose a surgical challenge as they are very large, deeply situated, in close proximity to vital intraventricular structures and often hypervascular. Aggressive and excessive resection necessarily poses a serious risk of neurological deterioration. Surgical resection for huge CNs should be meticulously considered, and excising them from their intraventricular location requires a good knowledge of the cortical anatomy and important structures in the vicinity. Most huge CNs are supplied by the anterior and posterior choroidal, pericollosal, and lenticulostriate arteries, and venous drainage is directly into Galen's vein or the internal cerebral vein or the basal vein[19]. Complications such as paralysis and secondary bleeding in our study mostly resulted from the injury to the periventricular parenchyma (fornix and thalamus) and deeper ventricular ependymal vasculature (especially the thalamostriate, caudate, and internal cerebral veins). It is important to avoid injuring the subependymal layer during the resection, and the ependymal veins and the choroid plexus are important guides for the depth of resection. Moreover, huge CNs tend to displace the choroidal vessels medially, leading to difficulty in controlling bleeding from the vessels supplying the CNs during surgery, and the vascular supply is often encountered until a major portion of the tumor is debulked.

Given that huge CNs are located in bilateral ventricle and frequently extend into the third ventricle, the

transcallosal approach was primarily performed in our series as this approach offers short access to the third ventricle and the greatest flexibility for operating on both the right and the left sides of the ventricle. Transcortical approach was also used with easy access to the lateral ventricle and a reduced risk of damage to the fornix and parasagittal vein[6, 19, 20]. In the present study, transcallosal approach was used in eight patients and GTR performed in three of them. Three patients underwent GTR via the transcortical approach. Previous studies reported that there was no significant difference in the extent of resection between the surgical approachs used[6, 19]. For huge CNs involving multiple ventricular regions, we believe that the operative approach is supposed to facilitate the exposure of the entire tumor.

In our series, two (15.4%) patients died within one month postoperatively due to secondary bleeding and untreatable brain swelling after surgical resection. Three (23.1%) patients with GTR were given a DC and/or VPS as the salvage therapy and suffered from permanent dysfunction of paralysis, memory loss and seizure, and the KPS of them was below 70 on the follow-up. Patients with huge CNs seemed to have an unfavorable clinical outcome in our study compared with those described in previous reports[6], and these serious outcomes occurred in four patients undergoing GTR and in one patient undergoing STR. In previous reports, it remains controversial that GTR in CNs correlates significantly with overall survival[2, 5, 8, 21, 22], and that GTR for CNs was not associated with an increased rate of postoperative complications compared with STR[6, 19]. All these conclusions need to be further confirmed especially for huge CNs. Adjacent structures and calcifications significantly reduced the rate of GTR[19], and we should fully consider risks of aggressive resection and balance the pros and cons of the surgery.

Owing to the radiosensitive nature of CNs and anatomical factors (well-demarcated borders and an intraventricular location)[6, 8], excellent local control in residual or recurrent CNs after the administration of adjuvant therapies, such as RT and GKRS, has been reported in many studies[22, 23]. GKRS as a primary or secondary treatment option for CNs was also demonstrated in several researches[6, 9, 24, 25]. In our series, CNs in two patients with STR(+GKRS) recurred or progressed postoperatively and were treated with (repeated) GKRS, and no recurrence was found during the follow-up period. Higher KPS scores were found in patients with huge CNs treated by STR(+GKRS) than those treated by GTR(+RT) in our study, and no radiation-induced complications were found in patients receiving adjuvant therapy. STR with adjuvant GKRS may be the treatment of choice for huge CNs in our series. Given the rarity and relatively recent recognition of huge CNs, the optimal management strategies for huge CNs need to be further examined.

In conclusion, the clinical outcome of huge CNs seemed not to be favorable as those previously reported in the current study. Surgical resection for huge CNs should be meticulously considered to guarantee the maximum safety. STR(+GKRS) may be a better treatment choice than GTR(+RT) for huge CNs. The recurrent or residual tumor can be treated with GKRS effectively.

Conflict of Interest Statement

None of the authors have any personal, financial, or professional conflicts of interest to report.

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