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M. Roszkowski
K. Drabik
S. Barszcz
S. Jozwiak

Surgical treatment of intraventricular tumors associated with tuberous sclerosis

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M. Roszkowski (✉) · K. Drabik
S. Barszcz · S. Jozwiak
Pediatric Neurosurgical Department,
Children's Health Centre,
Al. Dzieci Polskich 20,
PL-04-736 Warsaw, Poland
Fax: 15 40 15

Abstract Six children with intraventricular tumors associated with tuberous sclerosis (TS) were treated at the Children's Health Center, Department of Pediatric Neurosurgery, in the period 1987–1992. The age of the patients ranged from 7 to 15 years. TS was diagnosed according to Gomez diagnostic criteria. Computer tomography (CT) and magnetic resonance imaging showed intraventricular tumors associated with ventricular enlargement and multiple subependymal nodules commonly observed in cases of TS. All tumors were removed totally through frontal transcortical approach, with uneventful postoperative recovery. One patient, with two parallel tumors in the two frontal horns, underwent one-stage surgery with successful total removal. Histopathological examination in all cases showed subependymal giant cell astrocytoma (SGCA). The growth pattern of SGCA associated with TS, documented by sequential CT scans over several years, is described. The diagnosis and surgical treatment of the tumor are discussed, and periodic CT scanning, at least every 2 years, is recommended for patients with TS.

Key words Tuberous sclerosis surgery · Subependymal giant cell astrocytoma · Children

Introduction

Tuberous sclerosis (TS) is of particular interest to the neurosurgeon because of its frequent association with para- and intraventricular tumors.These tumors are called subependymal giant cell astrocytomas (SGCA) and originate from the subependymal nodules which correspond to the germinal mantle of the developing brain [4, 11]. This entity has been interpreted as being intermediate between a neoplasm and heterotopia, histologically different from other astrocytomas. No instance of anaplasia has been reported [13]. Surgical treatment is not well standardized, because of the lack of agreement as to whether the basic nature of the lesion is neoplastic or not. However, SGCA can cause all the clinical problems that are associated with an intracranial tumor and are a source of considerable morbidity and mortality in patients with TS [15, 17]. Hence, improved surgical techniques and early intervention if a subependymal tumor develops should help reduce the associated mortality.

Patients and methods

In our department six children with intraventricular tumors associated with TS were treated surgically between 1987 and 1992. The age range at the time of surgery was 7–15 years, with a mean of 10.5 years. The clinical manifestations of TS were observed in five cases in the 1st year of life, and in one at the time of admission (patient admitted for surgery from an African country).

Gomez diagnostic criteria were used to establish the diagnosis of TS. Pathognomonic features included lesions of the central nervous system, visceral organs, and skin [5]. Table 1 shows the clinical presentation in all cases. All three features of Vogt's triad were found in four patients. In one case we found a family history of autosomal-dominant inherited disease. In the other cases no TS had ever been detected in the family.

Diagnostic studies included pre- and postcontrast computed tomography (CT) in four patients and magnetic resonance imaging

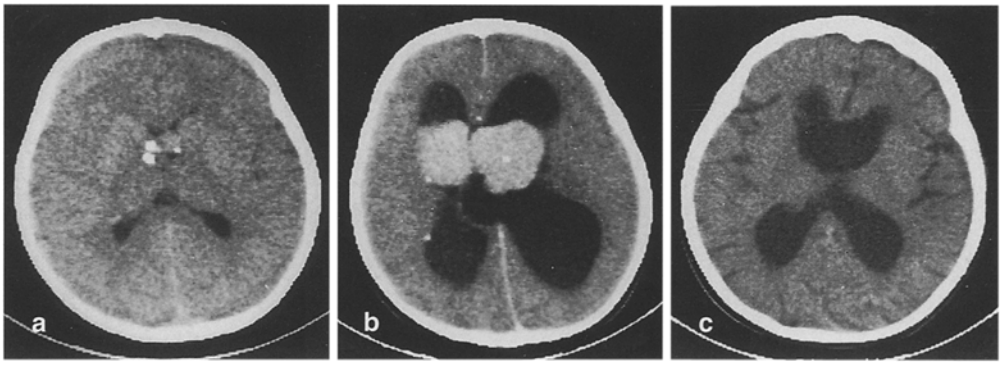

Fig. 1a–c A 7-year-old girl with tuberous sclerosis (TS). **a** Enhanced computed tomographic (CT) scan done in 1990, showing subependymal calcifications in the caudate nucleus area on the left side and a subependymal nodule on the opposite side. **b** Follow-up CT scan showing two parallel tumors that have developed over 2 years in the site of the previously seen abnormalities. Hydrocephalus is also seen. **c** Postoperative CT scan showing absence of residual tumor. Both lesions were removed in one session

Table 1 Clinical manifestations of tuberous sclerosis (TS) in six pediatric patients

Age at onset of brain tumor	7–15 years
Age at onset of TS	<1 year (5 patients)
Epilepsy	4 patients
Mental retardation	4 patients
Skin lesions	6 patients
Renal cyst	2 patients
Familial occurrence	1 patient

Table 2 Brain abnormalities found on computed tomography and/or magnetic resonance imaging in six patients

	No. of patients
Intraventricular tumors (mean diameter 3.5 × 4.5 cm)	6
Tumor site:	
Right frontal horn	4
Left frontal horn	1
Both frontal horn	1
Periventricular nodules	6
Cortical and white matter lesions	3
Documented transition from nodule to tumor	2
Chronic hydrocephalus (Evans ratio >0.5)	6

(MRI) in the most recent two cases. Seven presumed SGCA were diagnosed around the foramen of Monro in six patients; one patient having bilateral intraventricular tumors. Hydrocephalus was noted in all, but no precraniotomy shunt was placed.

All patients underwent surgical resection of the SGCA through a frontal transcortical approach. Radical total resection of the tumor, including both bilateral tumors, was attempted in all patients. Postoperatively, ventriculoperitoneal shunts were inserted in three cases to control progressive ventricular enlargement.

Histological studies revealed typical SGCA in all cases.

Follow-up ranged from 1 to 6 years.

Results

Clinical manifestation of intraventricular SGCA

Of 92 patients diagnosed with TS and treated at our institution during the last 6 years, 6 (6.5%) had intraventricular SGCA. All clinical signs developed slowly before the tumor was detected and were related rather to raised intracranial pressure and obstruction of the foramina of Monro than to the size and location of the lesion itself. All children were admitted with the symptoms of gradual worsening of their general condition: progressive drowsiness, headaches, nausea, vomiting, and visual disturbances. The duration of signs ranged from 2 weeks to 3 months. Seizures became more frequent and resistant to combination of anticonvulsant agents in four consecutive cases. Neurological examination in all patients at the time of tumor detection failed to show any progressive focal deficit related to the intraventricular lesion.

Radiological findings

The CT and MRI scans were analyzed with respect to localization and presence of intraventricular tumors, subependymal calcifications, and ventricular size (Table 2). CT scans at diagnosis showed solid tumors around the foramen of Monro with broad attachment to the inferolateral wall of the lateral ventricle in the region of the head of the caudate nuclei. These tumors extended into the frontal horn and obstructed the foramen of Monro bilaterally in all cases. The mean diameter of the lesion was 3.5 × 4.5 cm. These lesions enhanced much more than the rest of the subependymal nodules, and were much better visualized on postcontrast studies. Four tumors occupied the right frontal horn and one the left; in the sixth case, tumors were present in both frontal horns. Extension of the lesion into the III ventricle through the dilated foramen of Monro was noted in four cases. In two patients, who were followed for 9 and 2 years respectively by CT and/or MRI, we were able to demonstrate a subependymal nodule in childhood and its subsequent transformation into a SGCA (Figs. 1, 2).

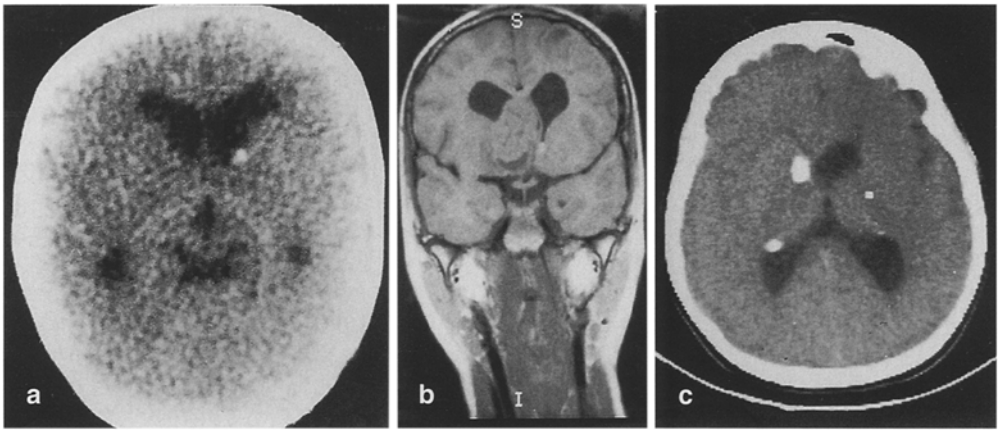

Fig. 2 **a** CT scan at the age of 6 months. Minute intraventricular calcification was observed in the left anterior horn with marked ventricular dilatation. **b** Magnetic resonance (T1-weighted) image of the same patient at the age of 9 years, showing a large left frontal tumor with hydrocephalus. **c** Postoperative CT scan showing resected tumor in the left frontal horn. Two minute calcifications were seen in the trigones of both lateral ventricles and a large one in the right frontal horn. The ventricles have decreased in size

CT visualized periventricular nodules, which were mostly calcified in all six patients. There were fewer than five nodules in all cases. We did not see any enhancement of nodules after contrast administration. However, in the case in which we observed the growth pattern of SGCA, the initial CT scan showed bilateral nodules around the foramen of Monro, which enhanced more than the other, similar lesions. The size of these nodules was less than 1 cm, and follow-up CT study after 2 years revealed parallel tumors in both frontal horns in exactly the same site. The size of each was 3×4 cm. On MRI (performed in two cases) the subependymal nodules were more difficult to identify.

All tumors were associated with chronic ventricular dilatation (Evans ratio >0.5). Hydrocephalus was due to tumor compression of both foramina of Monro or obstruction of the III ventricle by tumor mass protruding from the anterior horn.

Neurosurgical management

The surgical technique employed in our department to approach intraventricular lesions consists of frontal osteoplastic craniotomy followed by transcortical ventriculostomy according to the method described by Hirsch and Sainte-Rose [7]. Depending on where the major extension of the tumor was within the lateral ventricle, craniotomy was performed on the right side in five patients, including the one with bilateral tumors, and on the left side in one. To create a channel, a cortical incision was made with inflation of a balloon slipped over a blunt needle and inserted into the frontal horn. In this way, without suction of any gray or white matter of the frontal lobe, an access was formed between the cortical surface and the lateral ventricle. To determine the precise position of the lesion, the tip of the inflated balloon, and its distance from the surface, we used intraoperative ultrasonography. Once the tumor was reached, tissue samples were taken for intraoperative as well as for routine pathological studies. The entire tumor mass could then be debulked internally with the ultrasonic aspirator, care being taken to protect normal ependymal surface and choroid plexus. Intraoperatively, the tumors were generally well circumscribed, with the main portion located in the lateral ventricle; in four cases tumor protruded into the III ventricle and could easily be removed through the dilated foramen of Monro. All operated SGCAs were extensively vascularized with blood vessels presenting an angiomatous apperance and their resection required meticulous surgical technique. These tumors appeared to originate from the inferolateral wall of the frontal horn, the only site of attachment of the tumor to the ventricular wall. Large feeding vessels occur at this site after tumor resection, and special attention must be paid to control oozing with gelatin sponge rather than extensive coagulation.

The patient with bilateral tumors underwent resection of both lesions in a one-stage procedure. After the removal of the right frontal horn tumor, the septum was incised and the contralateral ventricle opened. This allowed complete removal of the opposite lesion inside the frontal horn without extension into the III ventricle.

Complete macroscopic removal of the tumor was achieved in all patients.

Three patients exhibited persistent or progressive hydrocephalus and required implantation of a ventriculoperitoneal shunt system. The shunts were placed 7 days and 1 and 2 months, respectively, after removal of the tumor. Postoperatively, all patients exhibited a similar physical and mental condition as in the preoperative period.

Follow-up examinations

Regular clinical examinations were performed every 6 months. The six patients were followed for postoperative periods of between 1 and 6 years. Good results were

achieved in all cases. Two children returned to normal school, three attended special schools for disabled children, and one severely retarded patient required home care. Follow-up neurological and psychological examinations showed no additional disability attributable to surgical intervention. Two of our patients who presented initially with intractable seizures suffered only rare seizures after tumor removal.

CT scans obtained during the 1st postoperative week revealed complete tumor removal in all cases. At different postoperative intervals, all patients have been examined by CT; so far there has been no evidence of any recurrence.

Histopathology

The histological features in all six cases were similar. The tumor contained three main kinds of cells: fibrillated spindle cells, swollen gemistocytic cells, and giant ganglion-like cells. No mitoses, endothelial proliferation, or necrosis were seen. All tumors showed the typical features of SGCA; no malignancy was found.

Discussion

Since the occurrence of TS with brain tumor is rather rare, it is important to collect data on the cases that do occur and analyze the clinical aspects and surgical prognosis of this peculiar type of tumor. The incidence of brain tumors associated with TS previously reported in the literature varied from 6% to 23% [10, 14, 16, 17]. This rate of brain tumor association may reflect the fact that neurosurgery is of importance in the treatment of brain tumor and its symptoms among various clinical aspects of this hereditary disease.

Diagnosis of TS in children is especially difficult. In the experience of Gomez, all three features of Vogt's triad were found only in 29% of patients with TS [5]. Most symptoms and lesions are absent at birth and develop with age. Multiple subependymal nodules, found in 98% of cases, are regarded by many authors to be pathognomonic of TS. These lesions can be detected early in life and their number may increase with age [1, 8, 11]. Another pathognomonic feature of TS, according to Gomez criteria, is the presence of intraventricular SGCA. This tumor rarely occurs in neonatal period, usually developing later; in our series the mean age at manifestation was 10.5 years, which is similar to reports in the literature [1, 2, 16]. Although various stigmata were examined, there was no definitive clinical presentation of TS that correlated with the occurrence of brain tumor. The presence of SGCA was not related to any other brain lesions seen on CT or MRI studies. However, it is well known that most patients (up to 80%) with cerebral tumors had associated cardiac rhabdomyomas diagnosed as neonates [6, 8,10].

In diagnosing intraventricular SGCA, CT and MRI are usually equally suitable. Administration of intravenous contrast improves the identification of tumors and improves the assessment of their size by enhancement; this enhancement is always greater than that of the subependymal nodules [1, 10, 17]. Menor et al. [10] considered that CT can be unreliable if the suspected tumor is under 1 cm in size. In these cases an astrocytoma can be recognized on MRI if there is marked enhancement of the lesion, either homogeneous or peripheral, or increasing with time following intravenous gadolinium-DTPA administration. Menor et al. [10] believe that the transition from nodule to active tumor with a potential for further growth can be suggested by a markedly enhanced lesion, size criteria being less important.

The surgical treatment of this tumor is still disputed. The controversy relates to the basic nature of the lesion – is it dysplastic or neoplastic? – the high operative mortality reported in the literature, and the timing of the surgical intervention. SGCA is believed to originate from the subependymal nodule, and is histologically different from other astrocytomas and from the tubers found in the cortex. Certain investigators believe that these tumors are of astrocytic lineage. It was on the basis of this opinion that Russell and Rubinstein [13] coined the term "subependymal giant cell astrocytoma". They interpreted it as an intermediate stage between the well-defined „neoplasm" and the smaller "heterotopia". In addition, others believe that a subependymal giant cell tumor consists of neurons or a mixture of cells with neuronal features and in addition cells with astrocytic features. All three major lesions of the central nervous system – the subependymal nodules, the SGCA and the retinal phakoma – show that the disease of TS is caused by problems not only with migration and alignment of cells, but also with control of proliferation of cells [17].

These tumors have not been reported as highly invasive in any published series. However, they may occasionally show more aggressive growth characteristics or even massive intratumoral hemorrhage [18]. Despite its benign features, SGCA can cause all the clinical problems that are associated with an intracranial tumor and is the source of considerable morbidity and mortality in patients with TS. Shepherd et al. [15] examined both life expectancy and causes of death among 355 patients with TS. Of 49 patients known to have died, 10 died as a result of brain tumor. These authors believe that the mortality attributable to brain tumors could probably be substantially reduced by monitoring patients with serial brain scans and intervening early with surgical treatment if an SGCA develops [15]. Another controversial factor relating to surgical indications is the high operative mortality reported in the previous series. In 1988, Conzen and Oppel [3] found 36 well-documented surgical cases with TS in the literature since 1948. Their review indicated that up to 1980 the more radical surgical approach with an attempt at complete tumor

excision carried a very high mortality (over 50%). The overall mortality in selected cases is now 41% [3]. Modern microsurgical techniques and careful neuroradiological examinations can minimize the operative risk. There was no surgical mortality in most recent series, and the reported 10-year survival rate for patients with SGCA is 90% [2, 9, 16]. These results, which accord with the present report, suggest that brain tumors associated with TS are biologically benign and thus can be successfully treated by surgical intervention.

Most authors considered the only indication for operation to be signs and symptoms caused by the mass, usually raised intracranial pressure or hydrocephalus, while a CT enhancing mass, if asymptomatic, may be followed using serial scans [9, 14]. The recent trend towards using regular, repeated scans of the head (preferably MRI, to avoid the cumulative effects of radiation from CT) at least every 2 years in young patients with cerebral TS facilitates early detection and treatment, which result in decreased mortality [4, 11, 14]. Other authors, however, advocate imaging surveillance every 12 months during the peak ages (8–18 years) of occurrence of SGCA [1]. In our opinion, early detection of neoplastic transformation by serial MRI justifies early surgical intervention. All tumors presented in this report were operated on at a stage of diffuse infiltration of the ventricles, so total removal was very difficult. The best time for surgical removal would seem to be when the tumor is less than 3 cm in diameter and is restricted to one ventricular compartment. However, this protocol is not suitable in neonates with TS and SGCA diagnosed soon after birth. In such exceptional cases, fatal ventricular arrhythmias developed during surgery due to multiple cardiac rhabdomyomas [12].

Total removal has so far been the treatment of choice for SGCAs, since these lesions do not appear to be very sensitive to radiation therapy, and partial removal results in tumor recurrence [3, 14, 16]. Palliative shunt procedures should probably be reserved only for tumors diagnosed in neonates. Patients with complete tumor resection are free from signs of intracranial mass for many years, and there is also an improvement in the seizure pattern, as in two of our cases. The life expectancy of patients with TS could be increased substantially by periodic monitoring of the brain with MRI and early intervention if tumor is discovered. This strategy should be applied to this progressive chronic disease in order to reduce the probability of premature death in patients with TS.

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