Extraventricular subependymal giant cell tumor in a child with tuberous sclerosis complex

Case report

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Subependymal giant cell tumors (SGCTs) are observed in 5–20% of patients with tuberous sclerosis complex (TSC) but account for ~25% of neurological morbidity. The authors report the case of a 7-year-old girl with TSC and multiple cortical tubers who presented with worsening seizures in the context of the rapid growth of a cystic, calcified, extraventricular SGCT in the right frontal lobe, initially thought to represent a cortical tuber. The tumor and surrounding tubers were excised, and clinical seizures resolved. This is the first report of an extraventricular SGCT in a child with TSC outside the neonatal period. (DOI: 10.3171/2009.3.PEDS08225)

KEY WORDS • epilepsy • tuberous sclerosis • subependymal giant cell tumor

TUBEROUS sclerosis complex is a multisystem disorder affecting ~9 in 100,000 individuals;23 it results from the improper differentiation, proliferation, or migration of neuroglial progenitor cells during fetal development.14,16,20 The variable clinical expression of this disease is the result of mutations in 1 of 2 genes, TSC1 and TSC2, which encode for the proteins hamartin and tuberin, respectively.3,33,34

Clinically, TSC is characterized by developmental delay, autism, and seizures.2 Patients with TSC harbor characteristic intracranial lesions including cortical tubers, subependymal nodules, and SGCTs.4,5,26 Cortical tubers are seen in 80% of patients with TSC, may be calcified or undergo cystic degeneration, and in 3–4%, MR imaging demonstrates enhancement after the administration of Gd.1,5,15 In contrast, according to published series, SGCTs occur in only 5–20% of patients in whom TSC is diagnosed.6,8,9,12,18,32 These tumors most often present as a space-occupying intraventricular mass.6,8,32 Their growth may lead to obstructive hydrocephalus, and SGCTs with documented growth or associated hydrocephalus are commonly treated by resection.3,12,28

We report the case of a 7-year-old girl with TSC and multiple, bilateral cortical tubers who presented with worsening seizures and rapid growth of a cystic, calcified, extraventricular SGCT in the right frontal lobe, initially thought to represent a cortical tuber. The patient underwent tumor resection in the context of iatral focus resection with invasive video EEG monitoring.35 Although atypical histological features of cortical tubers associated with refractory seizures have been reported,30 this is, to our knowledge, the first report of an extraventricular SGCT in a child with TSC.21,24,25 Institutional review board exemption was obtained prior to data collection.

Case Report

History. This 7-year-old girl was initially diagnosed with sporadic TSC at 9 months of age after presenting with myoclonic seizures. At that time, typical major and minor clinical features of TSC were noted,27 including a shagreen patch, facial angiomatosis, hypopigmented macules, multiple

Abbreviations used in this paper: EEG = electroencephalography; TSC = tuberous sclerosis complex; SGCT = subependymal giant cell tumor.

renal angiomyolipomas, and a retinal hamartoma of the right eye. Subsequent genetic testing confirmed mutation in the TSC2 gene. Routine seizure evaluation included video EEG monitoring demonstrating seizure onset in the right frontal lobe, and structural MR imaging that revealed multiple bilateral cortical tubers as well as intraventricular subependymal nodules. In addition, a 3-mm calcified, cystic, nonenhancing intraxial mass was identified in the right frontal lobe, separate from the frontal horn, thought to be an atypical cortical tuber (Fig. 1). There was no evidence of hydrocephalus. Magnetoencephalography revealed bilateral independent multifocal spikes and bilateral frontal slowing. Seizures were initially treated with a combination of phenobarbital and topiramate.

At 18 months of age, follow-up MR imaging demonstrated slight growth of the right frontal mass and new Gd enhancement. In addition, T2 hyperintensity was noted in the white matter surrounding the mass.

Examination. At 3.5 years of age, the patient was referred to our institution for treatment of refractory partial epilepsy, with a pattern of multiple daily seizure clusters. Clinically, seizures consisted of staring, dystonic axial posture, extension of the left leg, and automatisms of the left foot. Magnetic resonance imaging demonstrated continued growth of the calcified, enhancing right frontal lesion, which appeared separate from the lateral ventricle (Fig. 1). The patient’s antiepileptic regimen was changed to vigabatrin and oxcarbazepine, which led to the remission of seizure activity.

At the age of 5 years, MR imaging demonstrated dramatic interval growth of the right frontal lesion, now 2.5 cm in maximal diameter, with cystic degeneration (Fig. 1). In addition, multiple bilateral tubers were identified (Fig. 2). Noninvasive video EEG monitoring again localized the ictal onset zone to the right frontal lobe. Follow-up MR imaging 9 months later showed further growth of the right frontal lesion, now overlapping the right frontal horn (Fig. 1). At this time, the nature of this lesion was questioned, as its growth and enhancement were more consistent with a tumor than with a neuroglial hamartoma (tuber).

Operation. The patient underwent right frontal craniotomy and transcortical resection of the right frontal lesion together with an overlying tuber (Fig. 2). Intraoperatively, the calcified mass was purplish brown and was distinct from the surrounding white matter, with only a small connection to the frontal horn of the lateral ventricle (Fig. 1 upper). Because the patient had refractory seizures with right frontal onset, 3 subdural strips were placed over the right frontal lobe around the resection cavity (Figs. 3A and 4).

Postoperative Course. Magnetic resonance imaging confirmed proper electrode position and demonstrated gross-total resection of the enhancing mass lesion (Fig. 3). No ictal events were recorded, but frequent interictal spikes were seen over the inferior right frontal pole, corresponding to the location of an additional cortical tuber (Fig. 4).

Reoperation. On postoperative day 6 the patient underwent reoperation that consisted of electrode removal, resection of the remaining right frontal tuber and surrounding ictal focus, and placement of new subdural strip.

![Fig. 1. Serial preoperative MR images. Axial T1-weighted images obtained after the administration of Gd (upper) and axial FLAIR (lower). The patient’s age at the time of each study is noted at the bottom of the figure. Note the progressive increase in the size and complexity of the right frontal SGCT (black arrows) as well as the development and progressive increase in T2 hyperintensity of the surrounding white matter (white arrows). Also note the lesion appears separate from the right frontal horn (double white arrows) until its rapid growth between 52 and 65 months of age.](image-url)
Extraventricular SGCT in tuberous sclerosis complex

![Fig. 2. Preoperative axial FLAIR (upper) and axial T2-weighted MR images (lower) demonstrating increased T2 signal consistent with multiple, bilateral cortical tubers. Note prominent right frontal tuber (white arrows). This was resected with the cortex overlying the SGCT at the first operative stage.](image)

electrodes around the resection cavity. The patient then underwent a second invasive video EEG monitoring period. After 7 days, no additional ictal events or interictal discharges were recorded, and the patient underwent electrode removal 14 days after the initial surgery.

**Pathological Finding.** Histological examination of the right frontal lobe cystic lesion was consistent with an SGCT (Fig. 5). The tumor cells were immunopositive for vimentin, GFAP, and neurofilament protein, focally positive for synaptophysin, and negative for Neu-N. The MIB-1 labeling index was 1–2%. Taken together, the histological appearance and immunostaining pattern were typical for an SGCT. The second specimen exhibited pathological features consistent with a neuroglial hamartoma (tuber). Microscopic evaluation of the tuber resected during the second operation demonstrated reactive and degenerative changes including scattered TS cells (large, dysmorphic neurons typical of neuroglial hamartomas [tubers] found in patients with TSC), marked microglial activation, and brisk proliferation, with a moderate MIB-1 labeling index. Both Neu-N and neurofilament protein stained few cells, and GFAP and synaptophysin immunostaining were negative.

**Second Postoperative Course.** The immediate postoperative course was uneventful, and the patient remains seizure free while receiving a single antiepileptic medication (lamotrigine) and exhibiting no evidence of tumor recurrence at 1-year follow-up (Fig. 3).

**Discussion**

We describe the case of a 7-year-old-girl with TSC and medically refractory seizures who harbored a right frontal extraventricular SGCT associated with progressive growth and worsening seizures. Intraoperatively, the medial aspect of the tumor margin extended into the right frontal horn, with the greater part of the lesion invading the deep white matter of the right frontal lobe (Fig. 1). While it is certainly possible that this tumor arose from the ventricle and invaded the surrounding deep white matter, serial MR imaging performed between 21 and 52 months of age showed contrast enhancement and T2 hyperintensity initially in the white matter of the frontal lobe, separated from the ventricle by the genu of the corpus callosum, with subsequent growth into the right frontal horn (Fig. 1). In either case, the radiographic appearance and growth pattern are highly atypical for SGCT. Histologically, the tumor had a cellular appearance and staining pattern typical of an SGCT (Fig. 5). Although we combined tumor resection with the placement of intracranial electrodes and invasive video EEG monitoring, the surgical management of this patient’s epilepsy reflects our institutional experience. Alternative surgical strategies include tumor resection combined with intraoperative electrocorticography.

While the origin of SGCTs and their relationship to subependymal hamartomas remain unclear, they typically exhibit indolent intraventricular growth. A minor-
ity of SGCTs occur primarily within the third ventricle (8.6% in one series).\textsuperscript{30,33} Whereas SGCTs are observed in only 5–20% of patients and most remain stable in size, they are responsible for as much as 25% of the morbidity observed in patients with TSC.\textsuperscript{5,6,12,18,22} Although the vast majority of these tumors follow a benign course, intraventricular growth may lead to the obstruction of CSF circulation and hydrocephalus. This is the most frequent indication for neurosurgical intervention.\textsuperscript{8,12}

Both TSC1 and TSC2 encode the tumor suppressor proteins hamartin and tuberin, respectively.\textsuperscript{5,11,33,24} Hamartin and tuberin directly interact to form a heterodimer regulating cellular growth and differentiation via the mTOR pathway. Tuberin contains guanosine triphosphatase activity when complexed with hamartin, leading to the deactivation of Rheb, a guanosine triphosphatase that activates mTOR. Disease-causing mutations in TSC1 or TSC2 prevent the hamartin/tuberin heterodimer from deactivating Rheb, leading to constitutive activation of mTOR, which controls cell size and entry into the cell cycle.\textsuperscript{5,11,19,33} Our patient underwent genetic testing documenting mutation in TSC2.

To our knowledge, this is the first reported case of an extraventricular SGCT in a child with TSC, with the exception of neonates in whom it has only been reported rarely.\textsuperscript{30,12,21,24,25} Published clinical series of children with TSC and symptomatic SGCTs include only intraventricular tumors.\textsuperscript{12,33} Oikawa and colleagues\textsuperscript{24} have reported the case of a full-term, 6-day-old infant with sporadic TSC in whom they diagnosed an enormous SGCT filling the posterior right lateral ventricle and exhibiting significant

\begin{figure}
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\caption{Axial T1-weighted MR images with (A and E) and without (B and F) Gd and axial FLAIR (C and G) and T2-weighted MR (D and H) images. A–D: Studies obtained after resection of a right frontal lesion, demonstrating the resection cavity (single black arrow) and implantation of subdural electrodes around remaining anterior right frontal tuber (double black arrows). E–H: Images acquired 3 months following staged resection, demonstrating mature right frontal resection cavity (white arrows).}
\end{figure}
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Fig. 5. Subependymal giant cell tumor. Sheets of large cells with abundant eosinophilic cytoplasm and marginally placed nuclei. H & E x 40.

extraventricular growth into the right hemisphere; clinical seizures were absent. This tumor was completely resected when the patient was 16 days of age, and the patient did well until developing myoclonic seizures 6 months later.24 Other authors have described large, aggressive intraventricular SGCTs in neonates with TSC.26 Medlhkour and colleagues21 have described a 7-week-old boy with cutaneous stigmata of TSC, worsening seizures, and progressive somnolence in the context of a large, cystic, intraventricular mass in the left frontal horn with extraventricular growth into the left frontal lobe. The mass was resected, but 2 weeks after surgery deterioration occurred, and imaging revealed an increase in the size of a right central lesion, which was also found to be an extraventricular SGCT at resection. The patient's condition subsequently deteriorated 2 weeks later due to the recurrence and rapid growth of the left SGCT.21 Telfian and colleagues20 have reported the case of a 17-year-old patient with TSC who presented with acute hydrocephalus in the context of an enlarging right lateral ventricle SGCT obstructing the foramen of Monro; there was also evidence of intracranial and spinal leptomeningeal tumor dissemination. Despite resection of a histologically benign intraventricular SGCT, resolution of the hydrocephalus, and adjuvant therapy with temozolomide, the patient developed communicating hydrocephalus 10 weeks after surgery, and the family chose to withdraw care.20

Painter and colleagues have reported 2 cases of neonates presenting with refractory seizures, hydrocephalus, and a large, calcified, cystic mass occupying an intraventricular and extraventricular location.25 Chen and Dai32 have detailed the cystic, calcified appearance of a left parietal extraventricular SGCT in a 52-year-old woman. One common theme that emerges from these reports is an unpredictable rate of growth,5,32 as well as the possibility for the lesion's aggressive clinical behavior, especially in young children. A highly variable growth rate and poor outcome in patients without close radiographic surveillance have been reported.6,12

Of interest, most reports highlighting aggressive clinical behavior of SGCTs do not demonstrate aggressive features such as a high mitotic rate or necrosis.21,24,28 In our patient, histopathological analysis revealed a typical, benign SGCT, despite the rapid extraventricular growth (Fig. 5). The MIB-1 labeling index was 1–2%. Rapid tumor recurrence has also been reported in the context of a low mitotic index.13 Others have reported unusual or aggressive histopathological features in the context of benign clinical disease, suggesting that the presence of necrosis or a high mitotic rate is not associated with a poor prognosis.30 Recent evidence suggests that treatment with rapamycin effectively promotes regression of SGCT,21 and this emerging therapy will likely play a central role in the treatment of aggressive tumors in the near future.

In conclusion, between 5 and 20% of patients diagnosed with TSC develop an SGCT according to published series.5,8,32 Although an SGCT most often appears as an enhancing intraventricular mass near the foramen of Monro, and usually presents with obstructive hydrocephalus,6,8,11,18,25,32 several reports including ours have documented rapid growth despite benign histological features.21,24,32 Patients with TSC and harboring a SGCT should be followed closely with serial MR imaging to ensure early neurosurgical management. In addition, an SGCT should be considered in the differential diagnosis when evaluating patients with TSC and those with an intraaxial mass demonstrating calcification or enhancement, even in the context of refractory seizures referable to the lesion and a long period without growth.

Disclaimer
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References


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