The management of subependymal giant cell tumors in tuberous sclerosis: a clinician's perspective

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Abstract
Background Tuberous sclerosis (TSC) is a genetic multisystem disorder associated with hamartomas in several organs including subependymal giant cell tumors (SGCT). SGCT have the potential to grow and therefore to become symptomatic and are one of the main causes of death in TSC individuals. Surgical resection is the procedure of choice for SGCT. However, the discovery of mTOR pathway upregulation in TSC-associated tumors and recent evidence that mTOR inhibitors may induce regression of SGCT open up new treatment strategies. Based on a review of the currently available literature and on personal experience, current options for the management of TSC patients and appropriate indications, taking into account benefits and risks of surgery and pharmacotherapy, are discussed.

Discussion An earlier diagnosis of SGCT in neurologically asymptomatic children may allow a precocious surgical removal of the tumor, thus minimizing surgery-related morbidity and mortality. Biologically targeted pharmacotherapy with mTOR inhibitors such as sirolimus and everolimus provides a safe and efficacious treatment option for patients with SGCT and has the potential to change the clinical management of these tumors. However, whether pharmacotherapy is sufficient to control growth or if it only delays the need for surgical removal of symptomatic SGCT remains unclear. Further studies are needed to determine the optimal levels of mTOR inhibitors that preserve maximal anti-tumor efficacy while minimizing side effects.

Keywords Tuberous sclerosis · Subependymal giant cell tumors · Neurosurgery · mTOR inhibitors

Introduction
Tuberous sclerosis (TSC) is a genetic, multisystem disorder that can cause circumscribed, benign, non-invasive lesions in several organs. TSC is caused by a mutation in the tumor suppressor gene TSC1, located at the chromosome 9q34, and TSC2, located at the chromosome 16p13; loss of gene function is linked to enhanced mammalian target of rapamycin (mTOR) signaling and results in a spectrum of neurological symptoms including epilepsy, cognitive impairment, challenging behavioral problems, and autism [1]. Pathologic brain lesions include cortical tubers, subependymal nodules (SENs), subependymal giant cell tumors (SGCTs), and white matter abnormalities [2, 3]. Cortical tubers are characterized by proliferation of glial and neuronal cells and loss of the six-layered structure of the cortex. SENs develop during fetal life in the subependymal wall of the lateral ventricles, are present in most patients with TSC, and are usually asymptomatic. SGCTs are slow-growing tumors of mixed cellular lineage, occurring in about 5–20% of TSC patients, and represent a significant cause of morbidity and mortality because of the risk of sudden death from acute hydrocephalus [4–6]. Neurosurgical resection is the treatment of choice for SGCTs, since the complete removal of the tumor may provide a definite cure and since the tumor will not recur after total removal [7, 8].

Recent reports suggested that mTOR inhibitors have efficacy in reducing the volume of SGCTs [9–11]. The use of everolimus has been recently approved by the FDA as the first pharmacotherapy alternative to surgery for the TSC-associated SGCTs in patients who require therapy.
intervention but are not candidates for curative surgical resection. Therefore, in treatment decisions, the clinician is confronted by the challenge of balancing risks and benefits of alternative options.

The aim of this paper is to present an overview of the current options for the management of SGCTs.

**Tumorigenesis of SGCTs**

The development of hamartomas in TSC fits a two-hit mutational mechanism that results in biallelic TSC gene inactivation. The first hit corresponds to a first mutation of either TSC1 or TSC2, and the second hit is a loss of heterozygosity (LOH) of this gene. This model applies perfectly to most of the hamartomas in TSC, but it is particularly rare in SGCTs [12]. However, this issue is controversial, as some studies indicate that SGCTs in TSC could likely arise from a LOH mechanism, leading to activation of the mTOR kinase [13–15]. SGCTs might share a common feature mimicking LOH, due to an inactivation of TSC by a phosphorylation process or to a direct activation of mTOR through protein kinase B (AKT) and extra-cellular signal-regulated kinase (ERK). ERK activation has been regularly detected in SGCTs and might be a molecular trigger for their development [16]. Immunohistochemical evidence shows that mTOR activation appears to be a central event in the pathogenesis of SGCTs; increased levels of different proteins that have been shown to indicate mTOR activation have been found in cultured TSC1 and TSC2 null cells [13]. Figure 1 summarizes the role of the mTOR complex and the subsequent downstream cascade that leads to the development of TSC-associated lesions.

The observation of immunoreactivity for both glial- and neuron-associated epitopes within tumor cells of the same morphology suggests that SGCTs represent proliferations of cell lineages with the capacity to undergo divergent glioneuronal as well as neuroendocrine differentiation to a greater extent than do other mixed glial-neuronal neoplasms [17].

**Clinical presentation and natural course**

SGCTs are typically reported between 4 and 10 years of age, but rare antenatal and neonatal cases have been
occasionally described [18–22]. Although SGCTs are more frequently observed in subjects with a TSC2 mutation rather than in patients presenting a TSC1 mutation, this difference is not statistically significant [23].

These tumors are histologically benign and do not undergo malignant transformation. Many patients with TSC have small lesions that remain stable over time and do not require intervention but do warrant following a clinical and imaging surveillance [24]. Growth of these lesions over 10 mm in diameter at the foramen of Monro can block circulation of the cerebrospinal fluid, leading to progressive lateral ventricular dilatation and increased intracranial pressure [4]. SGCTs almost exclusively occur near the foramen of Monro; they may also be present more rarely at other sites, such as the atrium of the lateral ventricles, the temporal horns, the fourth ventricle, and the third ventricle [25]. Serial neuroimaging studies have shown that SGCTs usually correspond to growing SENs; cytologically, there are no differences between SENs and SGCTs [26, 27]. Transformation of a SEN into a SGCT is usually a gradual process, of which the highest rate is in the first two decades of life [4]. The growth of SEN peaks at puberty and stops by the end of the third decade of life [28]. The minimum interval between detection and significant growth ranges from 1 to 3 years [29]. A SEN presenting a diameter above 5 mm, incomplete calcification, location at the perimonro region, and enhancement after gadolinium administration, is more likely to transform itself into a SGCT [29, 30]. SGCTs show a preferentially intermediate signal on T1 and high signal on T2-weighted images, with intense enhancement after contrast administration. The presence of an associated ventricular enlargement and documentation of increase in size on serial examinations are other neuroradiological criteria suggestive of SGCTs [30] (Fig. 2). Tumors are circular or oval, and in most cases, they do not infiltrate the cerebral parenchyma. Double SGCTs are present in about one third of patients (Fig. 3). Cyst formation in SGCTs is a rare event that may cause compression of midline structures, producing the sudden onset of new neurological signs [31, 32].

It is still difficult to distinguish a tumor from SENs, especially at an earlier stage when the lesion is very small, taking into account the fact that some SENs might have slight enhancement on radiological images [4, 31].

The clinical diagnosis of a SGCT can be extremely difficult. They often present insidiously with subtle changes in behavior, cognitive function, or seizure frequency long before clear-cut symptoms of increased intracranial pressure, including headache and vomiting, are evident [24, 33] (Fig. 4). Hydrocephalus with clinical signs of intracranial hypertension or progressive hydrocephalus without obvious signs of increased intracranial pressure, new neurological deficits, such as blindness or worsening of a pre-existing deficit, are considered indications in favor of prompt surgical resection [8, 32]. In patients in whom the occurrence of hydrocephalus was associated with a worsening of seizures, the tumor removal and the correction of increased intracranial pressure were followed by a significant reduction in seizure frequency [34].

SGCTs are responsible for 25% of the excess mortality attributable to TSC [29, 35]. The potential for poor outcome from these lesions has led to recommendations to use cranial imaging to help identify SGCTs at a pre-symptomatic stage [33]. According to guidelines of the NIH Consensus conference, children with a diagnosis of TSC should have a brain MRI performed every 1 to 3 years, generally up to the age of 21 years [36, 37]. Once a probable SGCT was detected, brain MRI should be

**Fig. 2** Progressive growth of a lesion at the foramen of Monro in an asymptomatic 4-year-old boy. Coronal T1-weighted image with gadolinium shows a small enhancing lesion (a). A marked growth is visible (b), at a 24 months follow-up.
performed more frequently [4]. This recommendation was based on evidence that neuroradiological surveillance, early detection, and early surgical intervention for SGCTs in TSC were associated with better neurological, cognitive, and behavioral outcomes than in children with TSC who did not have surveillance for SGCTs [4].

Management of SGCTs

Surgical treatment

As SGCTs are benign lesions, the surgical goal in the management of SGCTs is a complete and safe removal whenever possible, which means an almost complete cure [7, 30]. Therefore, previous attitudes toward operating on only symptomatic patients have evolved toward a more aggressive approach to avoid the sequelae of raised intracranial pressure and hydrocephalus [30].

The surgical approach depends upon tumor extension and the presence of an associated hydrocephalus. Transcortical, transventricular, and transcallosal interhemispheric routes remain the most used approaches to the foramen of Monro [7]. However, surgical strategies have evolved with time, and new tools such as endoscopic procedures allow a less aggressive approach and are associated with lower morbidity [30].

In the majority of children operated on early, the surgical outcome fluctuates between good and excellent. A better outcome has been reported for younger patients; in one study, complications occurred in all the patients who were older than 11 years at the time of surgery, whereas the outcome was excellent in all children younger than 11 years [4]. Other studies confirmed the benefits of an early surgical removal of SGCTs, especially when the tumor's diameter is less than 3 cm [31, 38].

The complications after surgical removal of SGCTs rejoin those of any tumor surgery within the cerebral ventricles and around the foramen of Monro. Transient or permanent motor deficits, hemorrhage, or compressive subdural collection have been reported in about 10–20% of the patients who underwent surgery [4, 30, 31, 39]. An acute postoperative fatal hydrocephalus, generally secondary to infection or hemorrhage, may also occur [30, 39]. In recent reports, the perioperative mortality rate is very low (0 out of 15, two out of 19) [30, 31]. Since major complications tend to occur more frequently in patients who are symptomatic for raised intracranial pressure or major hydrocephalus before surgery [4, 40], a SGCT should be removed as soon as clear evidence of growth on two subsequent images has been determined [30]. Early resection of the tumor before the onset of irreversible neurological deficit is critical to improve the quality of life of this population, and it is associated with a low recurrence rate and low morbidity [30, 38]. Sometimes, the intraventricular mass can reach considerable size before causing symptoms, and this can make surgery difficult. Total resection of a large SGCT is nearly impossible; incomplete removal is generally the peculiarity of bulky SGCTs that lead to the deformation of the local anatomy and a bad dissection plane. If the complete resection is not feasible because of excessive tumoral bleeding or the absence of a dissection plane, a close clinical and radiological follow-up is necessary. Partially resected SGCTs could remain stable over years, but they almost invariably present recurrence that is sometimes fatal [40–42].

Fig. 3 A 9-year-old-girl with “double tumors” characterized by the presence of SGCTs with different evolution in the two lateral ventricles that show moderate dilatation

Fig. 4 This MRI shows the presence of a large-sized SGCT extending into the lateral ventricle in a 15-year-old boy with symptoms of increased intracranial pressure and who underwent surgical resection. A compression of the midline structures is also evident.
Medical treatment

In animal models, mTOR inhibitors showed that mTORC1 blockade alone and PI3K-mTOR blockade lead to suppression of tumor development and a longer survival of the treated animals [43, 44]. Rapamycin, the first mTOR inhibitor used in individuals with TSC-associated lesions, was able to determine regression of SGCTs [9]. Its efficacy has been subsequently confirmed in later studies and even in lesions other than SGCTs, such as angiomyolipomas [10, 45–47]. Actions of mTOR inhibitors within the mTOR pathway result in decreased protein synthesis and cell-cycle arrest, as well as decreased angiogenesis. More recently, a new mTOR inhibitor, RAD001 (everolimus), has been used in the treatment of 28 patients with TSC-associated brain lesions but with no symptoms of increased intracranial pressure [11].

In particular, this study reports a reduction of at least 30% in tumor size in 75% of patients and at least 50% in 32% of treated individuals. Different degrees of reduction of SGCT size have been observed in all the 38 patients treated with mTOR inhibitors (sirolimus or everolimus) up to now (Table 1). Most SGCT reductions happen in the first 3 months of mTOR inhibitor treatment, and then, the rate slows. In recent case reports, a similar anti-tumor efficacy was achieved even with lower serum levels of everolimus [47]. None of the patients treated with mTOR inhibitors required surgery or developed new SGCTs while receiving treatment [9, 11]. CSF obstruction was relieved with the reduction of the SGCT size [11]. The treatment was also associated with a clinically relevant reduction in the overall frequency of seizures and an improvement in quality of life.

Common, typically self-limited, side effects are mostly linked to the immunosuppressive action of mTOR inhibitors and included aphthous ulcers, acneiform rash, diarrhea, arthralgias, thrombocytopenia, and non-infectious pneumonitis and may require temporary dose reduction or cessation.

Table 1 Efficacy and side effects of pharmacotherapy in 37 TSC patients with SGCTs who underwent treatment with mTOR inhibitors (sirolimus or everolimus)

<table>
<thead>
<tr>
<th>No. of pts</th>
<th>Treatment duration (months)</th>
<th>Serum levels (ng/ml)</th>
<th>Mean SGCT size reduction</th>
<th>Serious adverse events</th>
<th>Re-growth after drug discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Franz et al., 2006 [9]</td>
<td>4</td>
<td>2.5–20 (rapamycin)</td>
<td>5–15</td>
<td>53%</td>
<td>No</td>
</tr>
<tr>
<td>Koenig et al., 2008 [10]</td>
<td>1</td>
<td>5 (rapamycin)</td>
<td>11–13</td>
<td>35%</td>
<td>No</td>
</tr>
<tr>
<td>Lam et al., 2009 [46]</td>
<td>3</td>
<td>At least 3 (rapamycin)</td>
<td>10–15</td>
<td>55%</td>
<td>No</td>
</tr>
<tr>
<td>Birca et al., 2010 [47]</td>
<td>1</td>
<td>At least 5 (rapamycin)</td>
<td>3.3–4.5</td>
<td>65%</td>
<td>No</td>
</tr>
<tr>
<td>Yalon et al., 2010 [49]</td>
<td>1</td>
<td>11 (RAD001)</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Hypertension, elevated CPK</td>
</tr>
<tr>
<td>Krueger et al., 2010 [11]</td>
<td>28</td>
<td>4.7–34.4 (RAD001)</td>
<td>2–11</td>
<td>45%</td>
<td>Infections</td>
</tr>
</tbody>
</table>

Different degrees of reduction in SGCT volume have been observed in all the patients reported.
Severe adverse events may include upper respiratory tract infections and a potentially dramatic elevation of serum cholesterol and lipoproteins, sometimes requiring dietary adjustment or even an adjunctive pharmacological treatment [9, 11, 48].

Unfortunately, SGCTs tended to re-grow a few months after drug discontinuation in all but one of the reported patients [49]. mTOR inhibition may need to be continuous for the benefit to persist, and the benefit and hazard of long-term treatment with low dosage of mTOR inhibitors should be evaluated.

Lessons learned and future perspectives

Diagnosis of TSC is now possible in the prenatal or early postnatal period, allowing a close monitoring in order to detect, as soon as possible, TSC-related lesions, including SGCTs. An earlier diagnosis of SGCT in neurologically asymptomatic children with TSC may allow a precocious surgical removal of the tumor before the appearance of increased intracranial pressure signs, an attitude that is being progressively adopted to lessen the morbidity/mortality rate. Surgical treatment is obviously mandatory in case of life-threatening symptoms. However, the dramatic response of TSC-associated SGCTs to mTOR inhibitors suggests that these drugs could be a potential alternative to surgery.

Taking into account the risks and benefits of the current therapeutic options, an algorithm for the management of SGCTs is suggested in Fig. 5. mTOR inhibitors could be recommended when an asymptomatic SGCT is growing in two subsequent MRI evaluations. mTOR inhibitors could also be used as initial treatment to facilitate subsequent surgery in individuals with bilateral lesions. Medical therapy may also have a role when SGCTs present in an atypical location or exhibit aggressive growth. Furthermore, in case of re-growth after a first resection, due to the higher risk of a second surgery, pharmacotherapy could help to keep lesion size under control. Little is known about long-term efficacy and safety of low-dosage use of mTOR inhibitors and if re-growth could be prevented by a more prolonged treatment course. In animal models, rapamycin dosing comparison studies indicated that the duration of rapamycin treatment is more important than dose intensity in terms of efficacy; prolonged treatment with low doses of mTOR inhibitors resulted in more complete and durable tumor responses [50, 51]. Our knowledge of continuous mTOR inactivation in individuals with TSC is still poor. mTOR inhibitors may also activate pathways that we do not want to be activated, and this issue will need to be taken into account when a long-term treatment is proposed.

Whether and when it is possible to discontinue the pharmacotherapy is still unclear, and further studies are required to explore the optimal duration of treatment. Since it is known that SGCTs' growth tends to slow in early adulthood, mTOR inhibitor treatment should therapeutically be undertaken until the patient reaches around 20 years of age. Strategies for future clinical trials with mTOR inhibitors may include the investigation of longer treatment duration with minimum dosage.

When choosing between surgical and/or medical intervention, clinicians should take into account the risks and benefits of each option. There are several issues to be considered, and every decision should be discussed thoroughly with the parents and tailored to the individual case. Depending on the age of the patient, one option would be more valid than the other. For example, pharmacotherapy could be preferred when a growing SGCT is discovered in adolescents, as the duration of the therapy could last only a few years. On the other hand, in childhood, a one-off surgical removal could be preferred to many years of pharmacotherapy. The positive effect that mTOR inhibitors have on several of the TSC manifestations is an important issue in favor of pharmacotherapy and should be considered in patients presenting also with renal angiomylipomas, pulmonary lymphangioleiomyomatosis, and/or intractable epilepsy. Since the activation of the mTOR pathway has been implicated in epileptogenesis, mTOR inhibition can have antiepileptic effects in patients with TSC [11, 52].

The inhibition of the mTOR pathway might provide a biologically targeted therapy and has the potential to change the clinical practice and the management of SGCTs. Currently, it is still unclear whether pharmacotherapy is able to avoid or to delay the need for surgical resection of SGCTs. During the coming years, medical treatment will certainly take more place in the management of children with TSC in proportion as the pathogenesis at the molecular level will be better understood.

References


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42. Pollizzii K, Malinowska-Kolodziej I, Stumm M, Lane H, Kwiatkowski D (2009) Equivalent benefit of mTORC1 blockade and combined PI3K-mTORC1 blockade in a mouse model of tuberous sclerosis. Mol Cancer 8:38

effects on mTORC1 and Akt signaling lead to improved survival and function. J Neurosci 28:5422–5432