Original Article

Subependymal Giant Cell Astrocytoma: Diagnosis, Screening, and Treatment. Recommendations From the International Tuberous Sclerosis Complex Consensus Conference 2012

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ABSTRACT

BACKGROUND: Tuberous sclerosis complex is an autosomal dominant disorder predisposing to the development of benign lesions in different body organs, mainly in the brain, kidney, liver, skin, heart, and lung. Subependymal giant cell astrocytomas are characteristic brain tumors that occur in 10% to 20% of tuberous sclerosis complex patients and are almost exclusively related to tuberous sclerosis complex. Subependymal giant cell astrocytomas usually grow slowly, but their progression ultimately leads to the occlusion of the foramen of Monro, with subsequent increased intracranial pressure and hydrocephalus, thus necessitating intervention. During recent years, secondary to improved understanding in the biological and genetic basis of tuberous sclerosis complex, mammalian target of rapamycin inhibitors have been shown to be effective in the treatment of subependymal giant cell astrocytomas, becoming an alternative therapeutic option to surgery. **METHODS:** In June 2012, an International Tuberous Sclerosis Complex Consensus Conference was convened, during which an expert panel revised the diagnostic criteria and considered treatment options for subependymal giant cell astrocytomas. This article summarizes the subpanel's recommendations regarding subependymal giant cell astrocytomas. **CONCLUSIONS:** Mammalian target of rapamycin inhibitors have been shown to be an effective treatment of various aspects of tuberous sclerosis complex, including subependymal giant cell astrocytomas. Both mammalian target of rapamycin inhibitors and surgery have a role in the treatment of subependymal giant cell astrocytomas. Various subependymal giant cell astrocytoma—related conditions favor a certain treatment.

Keywords: subependymal giant cell astrocytoma, tuberous sclerosis complex, surgery, mTOR inhibitor

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Introduction

Tuberous sclerosis complex (TSC) is an autosomal dominant disorder with high penetrance and variability and characterized by the formation of benign lesions in multiple organ systems, mainly in the brain, kidney, liver, skin, heart, and lung.[1-3] Incidence of TSC is estimated to be 1:6000.[4]

The clinical manifestations result from mutations in either of two tumor suppressor genes: *TSC1* (located on

9q34) or *TSC2* (located on 16p13).[5] Protein products of the *TSC1* and *TSC2* genes, hamartin and tuberin, respectively, form a heterodimer that suppresses the mammalian target of rapamycin (mTOR), a major cell growth and proliferation controller. In TSC, increased mTOR activation leads to disorganized cellular overgrowth, abnormal differentiation, increased protein translation, and the formation of tumors.

Characteristic TSC brain lesions include cortical tubers, subependymal nodules (SENs), and subependymal giant cell astrocytomas (SEGAs). The latter occur in 10% to 20% of TSC patients and are a major cause of TSC-related morbidity and mortality during the pediatric age.[6]

In June 2012, an International Tuberous Sclerosis Complex Consensus Conference convened to revise the diagnostic criteria for TSC along with the guidelines for its management.[7,8] This paper summarizes the work of a subgroup of conference participants who reviewed the diagnosis and management of SEGAs.

Definitions and terms

Tubers are pathognomonic for TSC and present in 80% to 100% of patients. They arise supratentorially and, in about 25% to 33%, also infratentorially.[9,10] Tubers are a collection of abnormal neurons and glia usually located in the cortex, stable throughout life, and thought to be possibly associated with seizure and autistic spectrum disorder.

SENs are usually small asymptomatic, intraventricular calcified protrusions, appearing in more than 90% of patients. They are located in the lateral ventricles and, as recently shown in a large cohort of patients, can be located adjacent to the caudate nucleus (in the lateral ventricle, atrium, and temporal horns).[11] SEGAs are benign tumors (World Health Organization I) of glioneuronal origin, distinct from astrocytomas. Several authors have suggested using the term "subependymal giant cell tumor"; however, most authors still use the term SEGA.

SEGAs typically arise at the caudothalamic groove adjacent to the foramen of Monro. In the past, many of these tumors were diagnosed late, with patients presenting with symptoms of elevated intracranial pressure from obstructive hydrocephalus. In the current era of magnetic resonance imaging neuroimaging, many of these tumors are now diagnosed at an early stage as part of the screening process of TSC patients. These slow-growing tumors rarely arise de novo (i.e., a new lesion that was not present on prior scans) after the age of 20-25; however, a known SEGA may grow at an older age.

Exceptions to the typical intraventricular location of SEGAs may occur, and extraventricular lesions have been described.[12] SEGAs may arise bilaterally or at several different locations; invasive lesions invading the fornix, hypothalamus, basal ganglia, and genu of the internal capsule have been reported.

The literature is conflicting regarding the potential of SENs to transform into SEGAs and does not clearly delineate the radiological differences between these two lesions. Some authors believe that SEGAs arise from SENs[3]; however, this is controversial.[11] SENs and SEGAs have similar histopathological features,[13] although SENs are rarely examined because they are virtually never resected. The main differences between SENs and SEGAs are size (with

cutoff size ranging between 5 and 10 mm) and location: SEGAs are typically at the caudothalamic groove as opposed to SENs that are located in the ependymal lining of the lateral ventricles along the caudate nucleus.[11] Usually SENs are calcified and nonenhancing lesions, whereas SEGAs show avid enhancement after contrast; however, the radiologic appearance of both pathologies may overlap. Regardless, the most important difference between these two TSC brain lesions is evidence of serial growth: SEGAs will grow, whereas SENs remain stable in size.

Diagnostic criteria

Before the 2012 consensus conference, the diagnostic criteria developed for TSC during the 1998 consensus meeting were still in use.[14]

At the 2012 Washington Consensus Conference, it was decided by the invited expert panel to document the diagnostic criteria related to TSC brain lesions in the following manner:[7]

1. The presence of tubers (and other types of cortical dysplasia, such as cortical migration lines), SENs, or SEGAs will each individually be defined as major criteria (two major criteria will suffice for the diagnosis of TSC as previously defined in 1998).
2. For diagnostic purposes, the definition of SEGAs will include a lesion at the caudothalamic groove with either a size of more than 1 cm in any direction or a subependymal lesion at any location that has shown serial growth on consecutive imaging regardless of size. Most SEGAs will show avid enhancement after contrast administration; however, a growing subependymal lesion even in the absence of enhancement should be considered a SEGA.

Screening protocols

Current evidence suggests, even though literature regarding the natural history of SEGAs is sparse, that new SEGAs very rarely arise after 20-25 years of age.[6]

Hence brain imaging, preferably magnetic resonance imaging with and without contrast, should be performed every 1 to 3 years until the age of 25 years. Because of a lack of knowledge of SEGA growth behavior beyond 25 years of age, follow-up magnetic resonance imaging may not be needed every 3 years but intervals may be prolonged in the presence of a stable lesion and a stable patient.

Screening and follow-up scans frequency should be tailored according to various clinical factors. New onset of symptoms such as headaches, visual complaints, nausea or vomiting, or increase in seizure activity should trigger an earlier scan. Similarly, a growing SEGA should prompt a more frequent clinical and radiological follow-up. Parents and patients should be educated regarding relevant symptoms that should prompt referral to medical evaluation.

Treatment of SEGA

Treatment of SEGAs has been solely surgical because of a lack of responsiveness to other strategies such as
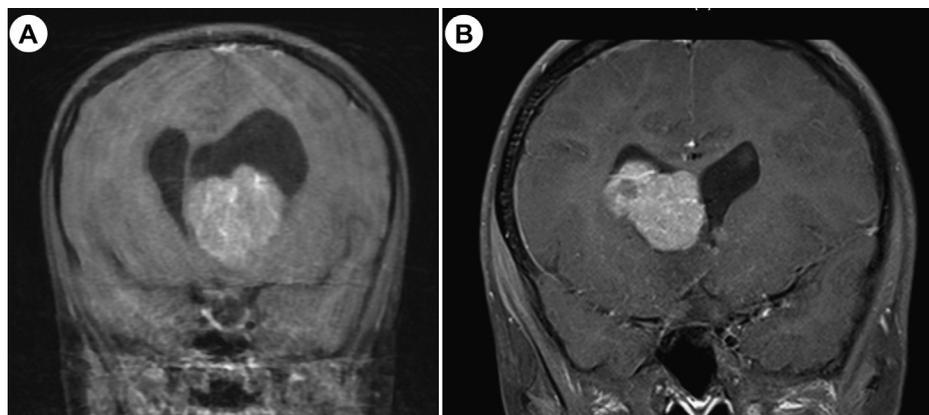
FIGURE 1.
Two girls ([A], 9 and [B], 12 years old) with acute headaches and vomiting. On examination, both had papilledema. Brain magnetic resonance imaging shows ventricular subependymal giant cell astrocytomas with secondary hydrocephalus. Surgical resection is recommended in this situation.

chemotherapy or radiation. These modalities may also be associated with an increased risk of secondary malignancies.[15] Many retrospective series have focused on surgical outcome, some of which include a heterogeneous group of patients with very different tumor anatomy and size as well as major differences in the number of patients treated; hence, there are different conclusions regarding risk of mortality, morbidities, and outcomes.[16-22]

Generally, it is agreed that small tumors are usually less invasive, and that resecting noninvasive small tumors, diagnosed while still asymptomatic, is associated with excellent clinical outcomes, with low morbidity and mortality. However, when diagnosed at a later stage, the tumor more often affects and invades neighboring structures such as the fornix, hypothalamus, basal ganglia, and genu of internal capsule, and resection is associated with higher surgical morbidity and mortality.[20]

Recent prospective trials documented successful SEGA shrinkage with mTOR inhibitors (mTORi).[23-26] In two large prospective studies, the mTOR inhibitor everolimus significantly decreased the volume ($>$50%) of SEGAs in 35% to 42% at 6 months of treatment.[23,25] Long-term efficacy and safety has been demonstrated for up to 3.5 years in prospective studies with everolimus. Patients from the initial report of rapamycin for SEGAs have been receiving this agent for in excess of 10 years with acceptable adverse events. It may be possible to reduce the dose of mTORi after an initial response with preservation of tumor volume reduction.[24] Despite these encouraging results, for unknown reasons, the response to mTORi is variable. SEGA growth during mTORi therapy is extremely uncommon, and most of the individuals who exhibit such growth have remained asymptomatic.[25,27] Also, although usually insignificant, mTORi use is associated with side effects, most common of which are stomatitis and upper respiratory tract infections. Additionally, it has been shown that cessation of treatment may result in tumor regrowth.[28]

Several recent review articles have presented the relative advantages and disadvantages of surgical versus pharmacological treatment.[29-31] Current practice still is dependent on the experience of the individual physician. Despite the growing evidence on mTORi-induced SEGA shrinkage, many centers still strictly advocate surgical treatment, whereas others prefer

medical therapy. Institutional expertise is certainly essential in respect to treatment choices. The risk of surgical morbidity must be weighed against a potential lifelong medical therapy with potential long-term risks yet to be determined. Incompletely resected SEGA will grow again; therefore, the following aspects may aid in the decision making.

Based on extensive discussions by the expert panel, we recommend that treatment decisions should be balanced and should be based on multiple factors that are unique to the individual TSC patient, including his or her clinical condition, anatomic considerations specific to the SEGA, surgeon experience, experience of the center with using mTORi, prior history of SEGA resection, other TSC related comorbidities, and patient/parental preference.

Clinical condition

SEGAs presenting in an acute manner, such as with symptomatic hydrocephalus, or with an acute intratumoral hemorrhage may pose a life-threatening condition and should be addressed surgically (Fig 1). Despite the acute presentation, which often is associated with large tumors, total gross resection can many times be safely achieved, but care should be taken to minimize injury to neighboring brain structures.

In sharp contrast to this scenario are those patients who harbor asymptomatic tumors. These tumors may be diagnosed during screening magnetic resonance imaging scanning and often are not associated with hydrocephalus or other mass effect. These tumors can be often followed with close clinical and imaging follow-up. It is important to educate the patient and family regarding potential presenting symptoms. Most SEGAs, even in the presence of ventricular dilatation, do not present acutely because of the insidious growth of the lesion and gradual development of hydrocephalus.

The indication for treatment includes new onset of symptoms or radiological evidence of tumor growth. These patients may be treated surgically or medically in accordance with other factors, as stated previously (Fig 2). Other important factors that must be considered in decision-making include both the age and the cognitive status of the patient. Many TSC patients are significantly
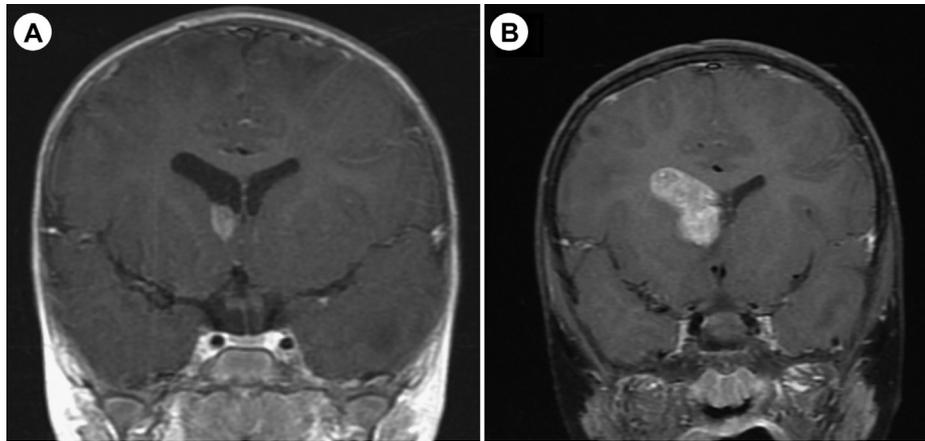
FIGURE 2.
This 6-year-old girl had a growing but asymptomatic tumor. (A) Her screening magnetic resonance imaging at age 2 revealed a, subependymal giant cell astrocytoma with mild enlargement of the right lateral ventricle. (B) By age 6 years, the lesion had enlarged markedly. This is an example for which there is no clear advantage for either treatment but advantages for each treatment (surgical or medical).

developmentally delayed and thus may not be able to convey early or subtle symptoms.

Anatomical consideration

SEGAs invasive to neighboring structures such as fornix (especially the dominant one), hypothalamus, basal ganglia, or genu of internal capsule, have a higher associated surgical morbidity.[32] Similarly, large-sized tumors are associated with higher morbidity because of the need for more aggressive tissue retraction and higher bleeding risks. Recurrent tumors may suggest a more invasive nature of the tumor.[27] These conditions favor mTORi (Fig 3). Medical treatment is favored as well in the case of multiple tumors, which are often bilateral, and lesion(s) for which gross total resection is unlikely, as residual tumor invariably will regrow (Figs 3,4).

Surgical experience

Not all neurosurgeons have extensive experience with intraventricular tumors in general or SEGAs in particular.

mTORi as a single treatment, or as neoadjuvant (before resection) treatment, may shrink the tumor and increase surgical safety or obviate the need for surgery at all.

TSC-related comorbidities

Contraindication to surgery posed by cardiac, renal, or pulmonary function would balance for mTORi, too.[33] Despite their benign nature, cardiac rhabdomyomas may cause arrhythmias and cardiac dysfunction, especially during infancy. Renal and pulmonary dysfunctions are rare but may pose a high surgical-anesthesiological risk, especially in adults. In addition, mTORi may offer benefits that can never be expected from a neurosurgical procedure in this population, such as reduction in angiomyolipoma volume, improvement in facial angiofibromas, and improvement in pulmonary function when intercurrent lymphangioleiomyomatosis is present.[34-36] Recent studies have suggested a beneficial effect on epilepsy as well.[26,37-39] Additionally, early treatment with mTORi may alter the natural disease course and prevent the development of TSC-
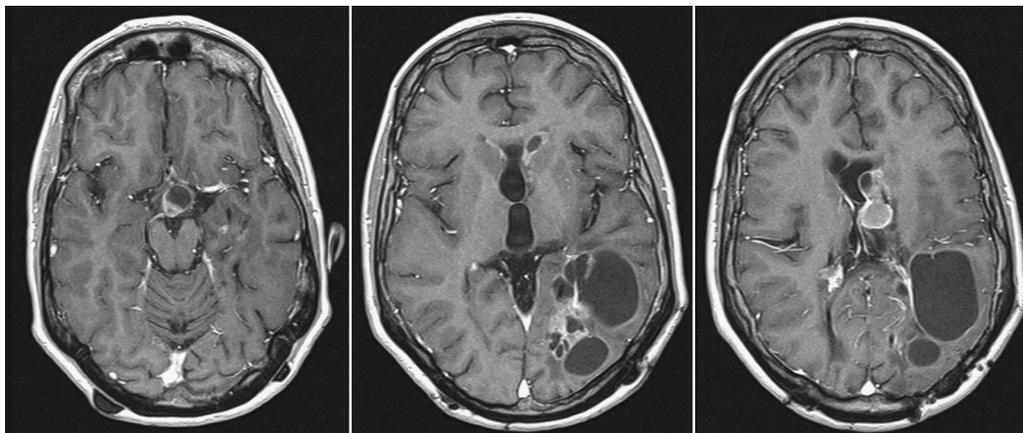

FIGURE 3.
A 26-year-old man with multiple intracranial subependymal giant cell astrocytomas following bilateral shunts and partial resection of the left posterior tumor. The multiple and anatomically unfavorable lesions justify mTOR inhibitor treatment.
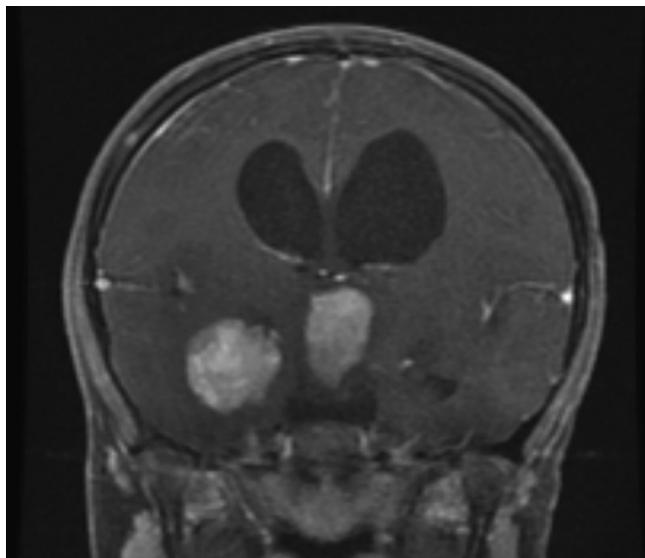
FIGURE 4.
This 9-year-old girl underwent subtotal resection of a right ventricular subependymal giant cell astrocytoma 4 years earlier. She was lost to follow-up until she presented with visual decline but no headaches. On examination, she had optic atrophy and was nearly blind. Brain magnetic resonance imaging showed a third ventricular tumor and a right temporal horn tumor. This is an example of a patient for whom a shunt can be placed followed by mTOR inhibitors.

related lesions.[40] Thus, when contemplating treatment options in patients with other TSC-related comorbidities that may benefit from mTORi, this should be favored over surgery.

Patient/parental preference

Nowadays many growing SEGAs are identified pre-symptomatically and may be treated either surgically or medically. It is important to present both treatment options to the family in a balanced way, taking into account not only the SEGA, but the specific individual with the variance of TSC associated comorbidities. Currently there is no evidence for the superiority of one treatment over the other, unless there are specific factors that favor one treatment over another as discussed previously. SEGA patients should be discussed in a multidisciplinary team including neurologists/oncologists and neurosurgeons to thoroughly weigh pros and cons of the respective treatment modality before finalizing an individualized treatment recommendation.

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