Management of subependymal giant cell tumors in tuberous sclerosis complex: the neurosurgeon's perspective

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Background: **Tuberous sclerosis complex (TSC), an autosomal dominant genetic disorder, can lead to the development of hamartomas in various organs, including the heart, lungs, kidneys, skin and brain. The management of subependymal giant cell tumors (SGCTs) is still controversial, and peri- and/or intraventricular neoplasms may lead to life-threatening hydrocephalus. In the last years, many progresses have been made in research into the tumorigenesis and behaviors of SGCTs. This review aims to clarify the specific role of neurosurgeons in the multidisciplinary management of SGCTs in children with TSC.**

Data sources: **Based on the recent scientific literature and personal experience, we reviewed the up-to-date data and discussed the trends in the management of SGCTs in children with TSC. The data were collected after a bibliography made using PubMed/Medline with these terms: subependymal, subependymal giant cell astrocytoma, subependymal giant cell tumor, and tuberous sclerosis complex.**

Results: **SGCTs are shown to be generated from a glioneuronal lineage, but their filiation with subependymal nodules (SENs) is still under debate. While SENs may develop anywhere in the ventricular walls, SGCTs arise almost exclusively around the Monro foramina. In children with TSC, precise clinical and/or imaging criteria are mandatory to differentiate SENs that are always asymptomatic and riskless from SGCTs that have the potential to grow and therefore to obstruct cerebrospinal fluid pathways leading to hydrocephalus.**

Conclusions: **An earlier diagnosis of SGCT in neurologically asymptomatic children with TSC may allow a precocious surgical removal of the tumor before the installation of increased intracranial pressure signs, an attitude that is being progressively adopted to lessen the morbimortality rate.**

World J Pediatr 2010;6(2):103-110

Key words: **cerebral ventricle;**
hydrocephalus;
intraventricular tumor;
microsurgery;
subependymal giant cell astrocytoma;
tuberous sclerosis

Introduction

Tuberous sclerosis complex (TSC) is an autosomal dominant genetic disorder, with a low and variable penetrance, characterized by the formation of multiple tumors in different organs. The disease is caused by mutations in either the *TSC1* gene (Chromosome 9) or the *TSC2* gene (Chromosome 16) which encodes hamartin and tuberin respectively. These proteins form an intracellular complex involved in the regulation of the cellular growth and energetic pathways, through the inhibition of the mammalian target of rapamycin (mTOR) within the akt-mTOR-S6 kinase cell growth trail. TSC, also known historically as Bourneville's disease (1880), has been initially described by von Recklinghausen in 1862, while Vogt (1908) reported the typical and characteristic clinical triad of the disease associating facial angiofibromatosis, epilepsy and mental retardation.[1,2]

TSC is one of the more common single gene disorders, with an incidence of one in 5800 to 6000 live births, a prevalence of one in 30 000 and a frequency of one per 150 000 live births.[3,4] There is neither ethnic linking nor differences according to gender.[5] In spite of all the progresses carried out in the comprehension of the pathogenesis of the disease, TSC remains a disabling situation for the affected child and his entourage in terms of social and educational integration. The disease usually leads to epilepsy, learning difficulties and behavioral anomalies. It is broadly admitted that about 50% of children with TSC have an intelligence quotient within a

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doi:10.1007/s12519-010-0025-2

normal range while the other half will usually suffer from severe cognitive impairment.[4] Among the different sites of tumor development, the brain remains undoubtedly the most problematic regarding to therapeutic management and screening, as this location is directly related to life expectancy. This location leads to more than 50% of deaths among children with TSC.[6] Since many years, several interrogations are pending especially concerning subependymal giant cell tumors (SGCTs) in children with TSC: cytological origin and pathological classification, probable filiation with subependymal nodules (SENs), diagnosis criteria and screening, and neurosurgical indications.[7-11] Indeed, while symptomatic SGCTs in children with TSC do not require any debate concerning their surgical management, asymptomatic ones remain more problematic to handle even if a recent more "interventionist" tendency is emanating from the neurosurgical literature.[1,3,9,12,13] Thus, after a brief reminder of the main clinical features of TSC and a compilation of the current data concerning the pathogenesis of TSC and the management of SGCTs, the author tries to clarify the modest role of the neurosurgeon in the multidisciplinary management of SGCTs in children with TSC.

Clinical background

An accurate diagnosis of TSC is based on precise criteria resulting from consensus conferences.[14,15] Roughly, the diagnosis is retained when at least two hamartomas are found in two different organs in an individual. Because of the variable penetrance of the disease, children with TSC may display a wide range of intelligence levels. Generally it is admitted that 50% of TSC children have a normal intelligence quotient while the other half suffers from severe learning difficulties, leading to social and educational marginalization.[16] Besides, three main types of lesions might be encountered during the evolution of the disease: cortical tubers, SENs and SGCTs. Firstly, tubers are developmental cortical abnormalities of the brain, present in more than 88% of children with TSC.[3] Tubers lead to the loss of the classical six-layered cyto-architecture of the cerebral cortex. These lesions are better detected on MRI. Classically, they appear as hypointense lesions in T1 sequence and hyperintense in T2 sequence.[3,17,18] These frequent lesions are thought to be responsible for more than 75% of epileptic disorders in patients with TSC.[3,14] During the first year of life, infantile spasms are common and respond habitually to GABA inhibitors especially vigabatrin.[19] Later in life, protean seizures including atonic, focal or atypical fits are generally refractory to medical treatments. These can benefit nowadays from epilepsy surgery since it is technically possible to identify clearly epileptogenic tubers with the use of functional imaging and cortical mapping techniques.[20,21] The second more frequent lesions in children with TSC are SENs. These are small hamartomas developed on the walls of the lateral ventricles. There is no evidence that SENs can cause any neurological symptoms. Only SENs located in the region of the Monro foramina may have the potentiality to grow and to transform into SGCTs. The last but not least encephalic lesion is SGCT, also known improperly as subependymal giant cell astrocytoma, affecting an average of 10% of children with TSC. The filiation between SENs and SGCTs is still a great matter of debate. The main enigma remains to understand why SGCTs develop almost exclusively near the Monro foramina. In addition to these neurological manifestations, TSC children may display other potentially lethal systemic locations (heart, lungs, kidneys).[22-25]

Genetic acquirements

Despite TSC is an autosomal dominant genetic disease, about 70% of cases result from new mutations (unaffected parents). Otherwise, the gonadal mosaicism phenomenon applies to TSC, i.e., an apparently unaffected parent has a population of affected cells confined to his gonads, so that unaffected parents may have more than one affected child.[26] More than 15 years ago, linkage studies have individualized the 2 genes responsible for TSC, namely *TSC1* (chromosome 9) and *TSC2* (chromosome 16).[27-29] A mutation in either of the 2 genes might induce all the manifestations of the disease. Meanwhile, two facts have been noted. First, *TSC2* phenotype related disease seems to be more severe.[30] Second, the frequency of mutations appears to be higher in the *TSC2* gene.[31] In spite of the improvements made in the genetic field, only 80% of TSC cases are being detected during the prenatal screening because of the occurrence of somatic mosaicism. Hence, an affected child has 2 populations of cells, i.e., one population expresses a genetic mutation (*TSC1* or *TSC2*) while the other pool of cells does not.[32] At a molecular level, *TSC1* product is hamartin, a 140 kDa protein expressed in several adult tissues and playing a key role in the regulation of cell adhesion. Tuberin (*TSC2* product) is a 200 kDa protein involved in the GTPase activating protein activity.[33] Hamartin and tuberin act together in the akt-mTOR-S6 kinase cell growth pathway, interfering directly in the regulation of cell growth, differentiation and proliferation.[34] Recent insights in the comprehension of the disease set the course to new trails in the therapeutic possibilities. Consequently, the use of drugs that may counterbalance the deficit of hamartin or tuberin seems tempting. It is the case with

rapamycin, a well-known immunosuppressor that is also thought to be an inhibitor of the mTOR and therefore would theoretically inhibit the S6kinase activity in children with TSC. Rapamycin has been successfully used to shrink SGCTs in patients with TSC but the lack of sufficient data concerning the requisite duration of treatment and the existence of side effects (aphtous ulcerations, interstitial pneumonitis) restrict its common use in children with TSC at the present time.[35,36] Further studies to determine the duration of treatment and the risk of tumor recurrence after discontinuation of rapamycin are certainly needed.

Tumorigenesis and behavior of SGCTs

For many decades, SGCT has been improperly classified among astrocytomas even in the last WHO classification of central nervous system tumors. This terminology definitively merits revision. Recent pathological studies including molecular biology, electron microscopy and immunochemistry categorically rectified this erroneous nomenclature, confirming the glioneuronal lineage of SGCTs.[12] This explains why the term SGCT is actually being preferred to the widely used "subependymal giant cell astrocytoma". Cytological features are highly characteristic and of an important interest in differentiating SGCTs from other intraventricular neoplasms mainly ependymomas and gemistocytic astrocytomas: cell clustering, hypercellularity and fibrillarity.[12] Immunochemistry contributes also to grounding the diagnosis as SGCTs are glial fibrillary acidic protein, neuron specific enolase, synaptophysin, and neurofilament positive. In the meantime, histological and immunohistochemical data do not provide any useful information on the behavior of SGCTs. There is a complete lack of correlation between the tumoral course and the pathological features.[12,37-39] Thus, an increased mitotic index, pleiomorphism, endothelial proliferation and necrosis seem to have no prognostic value in SGCTs.[3,12]

It has been noted that MIB-1 labeling indices are low in these neoplasms even in recurrences.[12,40] It has also been established that there is no correlation between kinetic index (Ki-67) and SGCTs growth.[3,12] As the tumorigenesis is concerned, the development of hamartomas in TSC fits the two-hit model presented by Knudson:[41] the first hit corresponds to a congenital lesion 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 neoplasms in TSC, but only 30%-60% of SGCTs and cardiac rhabdomyomas show effectively LOH. This latter is particularly rare in SGCTs.[42,43] Therefore, it has been hypothesized that SGCTs might share a common feature mimicking LOH, corresponding probably to an inactivation of TSC by a phosphorylation process or to a direct activation of mTOR through two mighty protein kinases: protein kinase B (AKT) and extra-cellular signal-regulated kinase (ERK). While the first one is not regularly detected, the second seems to be hyperactive in all SGCTs.[7] Jozwiak et al[7] postulated recently that ERK activation might be a molecular trigger for the development of SGCTs. Despite all the recent data based on molecular biology concerning the tumorigenesis in children with TSC, we still do not understand why the different hamartomas associated with TSC do not appear at the same age of the evolution of the disease and have flagrant discrepancies in growth profile. For example, renal angiomyolipomas grow rapidly and usually appear in adolescents and young adults. Cardiac rhabdomyomas emerge during fetal life and generally regress at birth, while SGCTs slowly but rarely become symptomatic in adults.[22,44]

Filiations SEN-SGCT

SGCTs are estimated to occur in about 6.1% to 18.5% of children with TSC.[3,6,8,38] The fact that these tumors arise from pre-existing SENs is still a great matter of debate. This hypothesis lies not only on growth evidence of SENs shown by serial imaging studies, but also on the pathological similarity between the two lesions.[9,17,45] The LOH and/or a protein phosphorylation process has been put forth as trigger factors in the transformation phase of SENs into SGCTs.[46-48] For this filiation SEN-SGCT, we consider why SGCTs arise almost exclusively around the foramen of Monro when SENs may appear anywhere in the lateral ventricle walls? Up to now, no valid explanation has been proposed, while 88% to 95% of patients with TSC present SENs,[9,45] and about one child with TSC out of ten will develop SGCT(s). Exceptionally, SGCTs have been described in other ventricular compartments than the foramen of Monro, such as the lateral ventricle wall[2] or the temporal horn.[49] Elsewhere, extremely rare cases of neonatal SGCTs have contributed to our incomprehension of tumorigenesis and call in question again the supposed filiation SEN-SGCT.[50] Distinguishing SENs from SGCTs is essential, since it is mostly admitted that SENs do not grow and never induce clinical signs, while SGCTs have the potential to enlarge and become symptomatic. Therefore, the therapeutist needs to identify which SEN should be diagnosed as a tumor in order to take effect early. Clinical and radiological criteria to differentiate these two entities are still in debate.[1,3,10,51] SENs are totally asymptomatic lesions, whereas the existence of raised intracranial pressure (ICP) signs, visual disturbances, focal neurological signs, or a worsening of epilepsy

suggest the presence of SGCT(s) in children with TSC.

It is also admitted that SGCTs are exceptionally revealed in adults.[6,12] Thus no new SGCTs are diagnosed after the age of 21 even if a known SGCT may continue to grow in adulthood.[10] Nowadays, with the multiplication of MRI centers, a majority of children with TSC are diagnosed earlier before the apparition of the above-mentioned neurological signs and symptoms. In such cases, radiological criteria are important in distinguishing SENs from SGCTs. Thus, a subependymal expansive lesion measuring more than 5 mm of diameter, developed immediately around the foramen of Monro, containing fine calcifications and displaying frank contrast enhancement associated with hydrocephalus, is more likely to be a SGCT.[1] The author emphasizes the growth evidence on serial MRI as important distinctive criteria rather than a fixed and arbitrary diameter of the lesion (Table).

Neurosurgical management of SGCTs

Timing of surgery

In the past only symptomatic children with TSC were operated on (tumor removal and/or ventriculoperitoneal shunt), and there is actually a general belief that a more precocious surgical intervention provides a lesser morbidity or mortality than when increased ICP or hydrocephalus is already installed, i.e., surgery in asymptomatic children.[1,10,12,52] SGCTs represent about 1.4% of all pediatric brain tumors.[3,37] Clinical series showed a mild male predominance, with a mean age at surgery of 11 years.[3,10,13,17] Habitually, these neoplasms evolve on several weeks or months. They are revealed by increased ICP symptoms, epilepsy recrudescence and behavioral modifications. Exceptionally, a severe onset may disclose the tumor through an acute hydrocephalus, an intraventricular hemorrhage or even a sudden death.[53,54] Actually, a rationale trend advocates an earlier tumoral removal in asymptomatic TSC children, an attitude from which we easily understand the importance of the distinctive criteria between SENs and SGCTs. This surgical procedure proposed to neurologically asymptomatic TSC children amounts to discuss the hazards of the so-called preventive surgery. This situation reminds the similar dilemma of an incidental colloid cyst of the third ventricle discovered by an imaging done for head injury. Nevertheless, several established facts strengthen this proceeding:

First, serial imaging studies have already proven that SGCTs have the potential to grow and therefore to become symptomatic. Because of their preferential proximity with the foramen of Monro, SGCTs may obstruct cerebrospinal fluid (CSF) pathways or cause intraventricular hemorrhage, and in both cases they can lead to death. In contrast, SENs do not possess this growth potentiality. In Cuccia's series, all SENs (about 70 nodules), except those near the foramen of Monro, remained unchanged or even decreased in size.[3]

Second, it has been stated that the growth of SGCTs may worsen epileptic seizures in terms of frequency and intensity, probably through the associated hydrocephalus and/or the direct irritation of the interventricular septum.[1]

Third, large SGCTs induce a deformation of the foramen of Monro, leading to difficulties in operative hemostasis and problems of tumoral dissection from surrounding structures such as the fornix, the head of caudate nucleus, the ependyma and its veins, and the interventricular septum. For this reason, it is obvious that operating on smaller lesions might avoid these surgical drawbacks.

Fourth, it is proven that major complications occur in operated symptomatic children with TSC when increased ICP is already installed.[1,10,12]

For all these reasons, it seems rational to recommend early tumoral resection as soon as a subependymal expansive lesion shows the distinctive criteria of SGCTs in asymptomatic screened children with TSC, primarily when there is evidence of growth on successive MRI.

Management of associated hydrocephalus

Hydrocephalus is present in the majority of children at

Table. Clinical and radiological distinctive criteria between subependymal nodules (SENs) and subependymal giant cell tumors (SGCTs)

Criteria	SENs	SGCTs
Clinical signs and symptoms	Asymptomatic	- Raised intracranial pressure - Epilepsy worsening (intensity and frequency of seizures) - Neurological focal signs - Visual disturbances - Accentuation of cognitive impairment and behavioral changes
Disclosure age	Asymptomatic	Exceptionally revealed after 21 years[10]
CT-scan	Hyperdense Frequent pat calcifications	- Isodense or slightly hyperdense - Rare thin calcifications
MRI	Variable signal depending on relaxation time Slight contrast enhancement	- Hypointense in T1 - Hypointense in T2 - Marked contrast enhancement
Growth on serial imaging	Absent	3 to 4 mm per year[3]
Diameter	Inferior to 5 mm	Superior to 5 mm[1]
Cerebral ventricles	Normal	Frequent hydrocephalus
Predilection site	Anywhere on the lateral ventricle walls	Foramen of Monro

the moment of the diagnosis of SGCT. Twelve of the 15 patients of Cuccia's series and 7 of the 11 patients of Goh's one displayed hydrocephalus.[3,10] This is the main factor contributing to the increase of ICP rather than the tumoral volume itself. Nevertheless, increased ICP may be present even in the absence of ventriculomegaly in children with TSC, because of the abnormal architecture of the subependymal region, thus modifying the cerebral compliance.[10] The treatment of hydrocephalus lies on the surgical resection of the tumor that blocks the foramen of Monro. There is no place actually for the placement of a ventriculoperitoneal shunt before the tumor's removal, except in the rare cases of acute life-threatening hydrocephalus. Elsewhere, it appears that an abnormal high level of CSF proteins in non-removed SGCTs leads to the frequent obstruction of CSF diversion devices in shunted children. This CSF proteins level may normalize after resection of the tumor.[10,13] This last fact corroborates the uselessness of ventriculoperitoneal shunt in hydrocephalic children with TSC before the resection of SGCTs. Finally, it is important to keep in mind that even after a complete removal of SGCTs, hydrocephalus can evolve on itself and even lead to postoperative deaths in 10% to 20% of removed SGCTs.[1,37] Following surgical resection of SGCTs, a rigorous postoperative clinical and radiological surveillance is mandatory to detect an eventual hydrocephalus in time (Fig. 1).

Surgical technique and outcome

As SGCTs are benign lesions, complete removal remains the treatment of choice. This removal is synonymous with a nearly cure. These lesions develop almost always in the surroundings of the foramen of Monro, generally bulging within the lateral ventricle, sometimes in the third ventricle, nay in both (Fig. 2).[10,49,55] Surgical approach depends upon tumor extension and the presence of an associated hydrocephalus, but above all the surgeon's experience. Transcortical transventricular and transcallosal interhemispheric

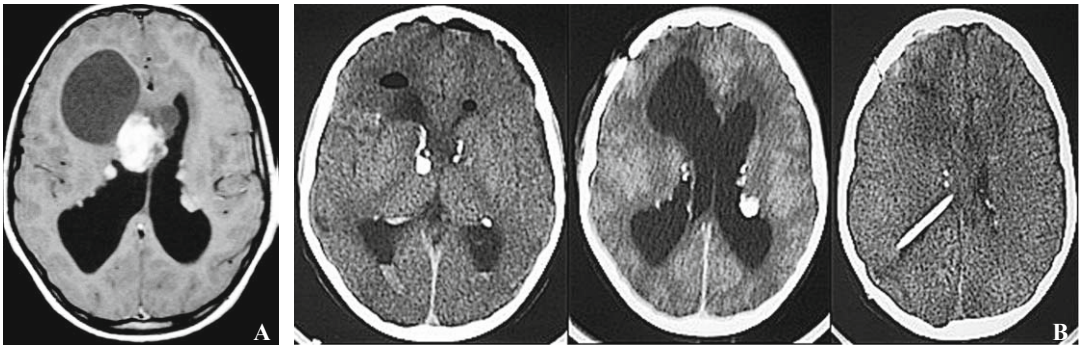

Fig. 1. A: Axial T1-weighted image with gadolinium showing a bulky SGCT around the right Monro foramina, extending into the homolateral frontal horn with a cystic extension and a markedly contrast enhanced solid part. The tumor leads to hydrocephalus. Note also the presence of many calcified SENs on the walls of both lateral ventricles; **B**: Serial postoperative CT-scans of the same child (**A**) without contrast. Left: Immediate postoperative scan demonstrating a complete removal of the tumor performed through a right-sided transfrontal transventricular route, with some blood clots within the occipital horns. Middle and right: First postoperative day after a rapid neurological deterioration (Glasgow coma score 7/15), concomitant with a critical acute hydrocephalus requiring an urgent ventriculoperitoneal shunt, resulting in an immediate resolution of the ventriculomegaly and a complete neurological recovery.

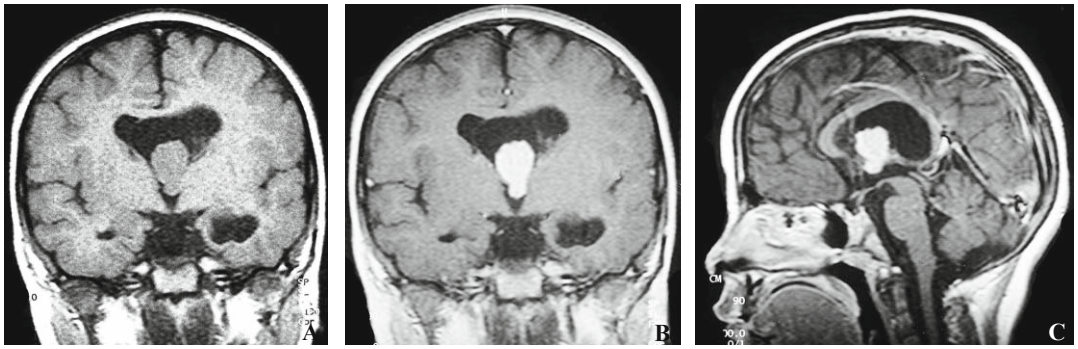

Fig. 2. A: Coronal T1-weighted image without gadolinium: Isointense intraventricular mass developed in the right Monro foramina and extending in the right lateral ventricle as well as in the third ventricle, with a subsequent asymmetric hydrocephalus; **B**: Coronal T1-weighted image with contrast showing an intense and homogeneous contrast enhancement of the SGCT; **C**: Sagittal T1-weighted image with gadolinium: typical aspect of SGCT developed on horseback between the lateral ventricle and the third ventricle through a blocked right Monro foramina.

routes remain the most used approaches to the foramen of Monro, while endoscopic procedures are taking an increasing place among the surgical armamentarium of ventricular surgery, even in cases of small ventricles (stereoendoscopy).[1] Incomplete removal is generally the peculiarity of bulky SGCTs (Fig. 3) that lead to the deformation of local anatomy and a bad dissection plane (Fig. 4). The surgical outcome fluctuates between good and excellent in the majority of children operated on early. In Goh's series of 11 patients with a mean age of 11 years at surgery, an excellent surgical outcome was reported in 5 of the 8 preoperatively screened patients, while a poor outcome was noted for the 3 non-screened patients.[10] On the long term, complications occurred in all the patients who were older than 11 years at the time of surgery whereas this outcome was excellent in all children younger than 11 years. Goh's study suggests that young patients operated on have a better long-term outcome than older ones.[10] Other studies confirmed the benefits of an early surgical resection of SGCTs, i.e., when surgery is undertaken in young patients especially when tumor's diameter is less than 3 cm.[3,56] The complications after surgical removal of SGCTs rejoin those of any tumor surgery within the cerebral ventricles and around the foramen of Monro and its adjacent anatomical structures, namely the head of the caudate nucleus, the fornix and the ependymal veins (Fig. 5): transient hemiparesis (10%-12%),[3,49] permanent motor deficit (6%-12.5%),[3,10,37] reintervention for hemorrhage or compressive subdural collection (13%-20%).[1,3,57] An acute postoperative fatal hydrocephalus is not a rare event as it may occur in 10% to 20% of cases, generally secondary to infection or hemorrhage.[1,37,57] A postoperative cognitive impairment may also be observed, but problematical to assess as it occurs in

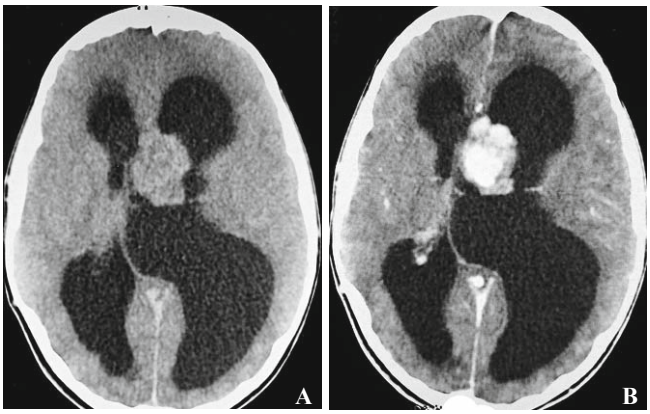

Fig. 3. A: Axial CT-scan without contrast demonstrating a left expansive intraventricular isodense and homogeneous mass obstructing the left Monro foramina associated with an important asymmetric hydrocephalus; **B**: Axial CT-scan with contrast showing an important but heterogeneous enhancement of the SGCT.

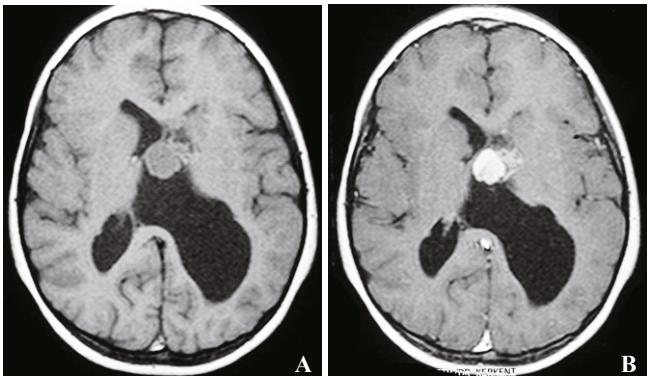

Fig. 4. A: Axial-T1 weighted image without gadolinium: SGCT blocking the left Monro foramina and leading to a unilateral ventriculomegaly; **B**: Axial-T1 weighted image with contrast: homogeneous enhancement of the mass with a heterogeneous bad-defined extension toward the head of the left caudate nucleus, predicting potential difficulties of surgical dissection.

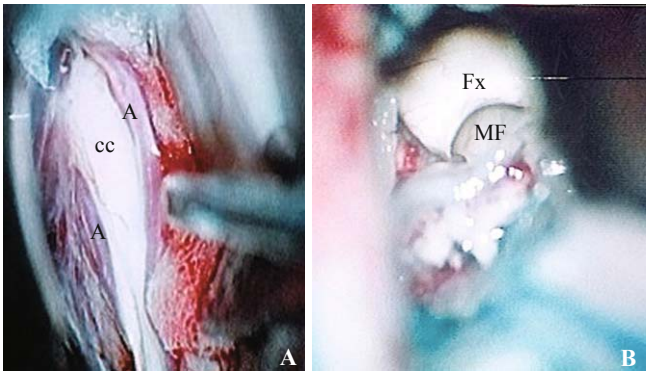

Fig. 5. A: Operative photograph of a transcallosal interhemispheric approach showing clearly the corpus callosum (cc) before its section between the 2 pericallosal arteries (A); **B**: After a longitudinal callosotomy, the pursuit of the homolateral choroid plexus allows the surgeon to reach the right Monro foramina (MF), anteriorly edged by the fornix (Fx), laterally by the head of the caudate nucleus and medially by the interventricular septum.

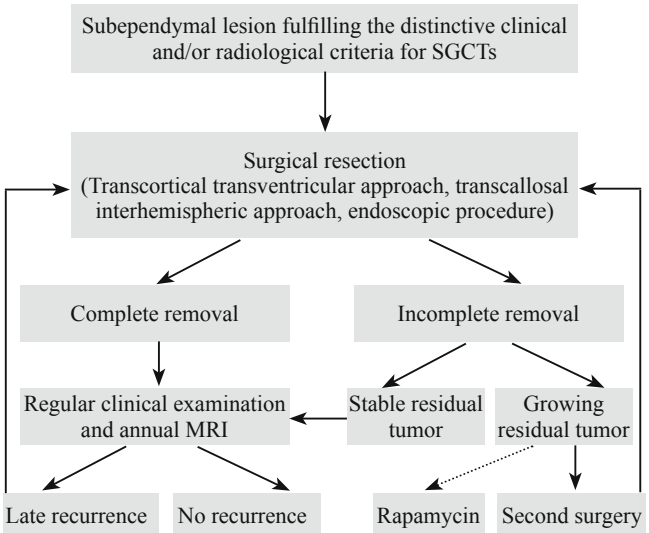

Fig. 6. Suggested algorithm for the management of subependymal giant cell tumors (SGCTs).

young children with already preoperative cognitive anomalies and is not always imputable to a surgical damage to the fornix.[1] As previously stated, the surgical goal in the management of SGCTs is the complete and safe removal whenever possible, which means almost cure as no recurrences were noted at the end of 6.2 years of follow-up.[1] 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 with the following two situations (Fig. 6). Firstly, the residual tumor remains stable over years[12] but will require all the same a prolonged and close follow-up since late recurrences, sometimes fatal, have been reported.[3,58] Nevertheless, there is a general belief that SGCTs stop growing in adulthood even if it is not the rule.[55,58] Secondly, the residual tumor progresses on serial follow-up imaging. In this eventuality, a second surgery through the same approach or a different one may be proposed.[1,3,12,37,56] Another possibility relies on the use of the medical treatment (rapamycin) as this latter showed preliminary hopeful ascertainments resulting in tumoral shrinkage, but its side-effects and the duration of necessary treatment need to be evaluated in further studies.[35,36] 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.[59,60]

Acknowledgement

The author thanks Prof. Hafedh Jemel for his constant scientific support.

Funding: None.
Ethical approval: Not needed.
Competing interest: None.
Contributors: Berhouma M is the single author of this paper.

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Received May 12, 2009
Accepted after revision February 9, 2010