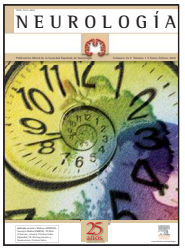
Neurología. 2010;**25(5)**:314-321

NEUROLOGÍA

www.elsevier.es/neurologia



ORIGINAL ARTICLE

Subependymal giant cell astrocytoma in tuberous sclerosis complex. A presentation of eight paediatric patients

I. Pascual-Castroviejo[a,*], S.I. Pascual-Pascual[a], R. Velázquez-Fragua[a], J. Viaño[b], F. Carceller[c], J.L. Hernández-Moneo[c], M. Gutiérrez-Molina[d] and C. Morales[d]

[a] *Servicio de Neurología Pediátrica, H.U. La Paz, Madrid, Spain*
[b] *Unidad de Imagen, Sanatorio Nuestra Señora del Rosario, Madrid, Spain*
[c] *Servicio de Neurocirugía, H.U. La Paz, Madrid, Spain*
[d] *Servicio de Neuropatología, H.I. La Paz, Madrid, Spain*

Received on 17th December 2009; accepted on 26th February 2010

KEYWORDS
Subependymal giant-cell astrocytoma;
Tuberous sclerosis complex;
Blindness;
Headache;
Hydrocephalus

Abstract
Objective: Presentation of 8 patients with subependymal giant-cell astrocytomas (SGCA) associated with tuberous sclerosis complex (TSC).
Material and methods: There are 8 patients, 6 males and 2 females with TSC, who presented with the tumour between the neonatal period and 24 years.
Results: All patients showed bilateral hypersignalised areas in zones close to the foramen of Monro. Three of the patients were admitted urgently due to blindness and increased intracranial pressure. Incomplete removal of the tumour has always been bad solution as it resulted in the death of the patient (in one case) or further surgery operation in the short term. Only one patient developed the tumour suddenly from pre-existing subependymal nodules from the childhood and they had to be removed at 24 years of age. By contrast, 32 patients with TSC and images of subependymal nodules whose CT or MR progress was followed up for between 10 and 30 years did not develop a tumour. One patient had to be operated four times over 20 years.
Conclusions: SGCA associated with TSC is a severe complication which as likely to develop and careful monitoring is required from neonatal age with periodic-clinical and imaging studies in order to avoid its irreversible complications. Hydrocephaly, blindness and even the death can be the main consequences. Reintervention of the recurrent tumour is often necessary.

* Corresponding author.
E-mail: i.pcastroviejo@neurologia.e.telefonica.net (I. Pascual-Castroviejo).

PALABRAS CLAVE
Astrocitoma subependimario de células gigantes;
Complejo de esclerosis tuberosa;
Ceguera;
Cefalea;
Hidrocefalia

Astrocitoma subependimario de células gigantes en el complejo de esclerosis tuberosa. Presentación de ocho pacientes infantiles

Resumen
Objetivo: Presentar 8 pacientes con astrocitomas subependimarios de células gigantes (ASGC) en relación con el complejo de esclerosis tuberosa (CET).
Material y métodos: Ocho pacientes, 6 varones y 2 mujeres, con CET, que desarrollaron el tumor entre la etapa neonatal y los 24 años.
Resultados: Todos mostraban áreas localizadas bilaterales de hiperseñal, en zonas próximas a los *foramina* de Monro. Tres ingresaron urgentemente con ceguera e hipertensión intracraneal. La extirpación parcial del tumor fue siempre una mala solución ya que acabó en reintervenciones a corto, medio o largo plazo o en la muerte de un paciente. Sólo en un caso vimos desarrollarse el tumor desde las zonas de hiperseñal subependimaria a partir de la preadolescencia para acabar en extirpación a los 24 años, mientras que 32 pacientes a los que se siguió la evolución de estas zonas de hiperseñal entre 10 y 30 años no desarrollaron tumor. Un paciente tuvo que ser operado cuatro veces a lo largo de 20 años por recidiva del tumor; se extirpó otro ASGC en el lado contralateral al mismo tiempo de la cuarta intervención en el lado del tumor primitivo. Otros 2 pacientes también mostraron recidiva y tuvieron que ser reintervenidos del tumor.
Conclusiones: El ASGC en relación con CET es una complicación grave cuya posibilidad de desarrollo hay que controlar cuidadosamente desde la época neonatal, con estudios periódicos clínicos y de imagen, para evitar sus complicaciones irreversibles. La hidrocefalia, la ceguera e incluso la muerte pueden ser sus consecuencias. La reintervención de tumores recidivados a menudo es necesaria.

Introduction

The term "Subependymal giant cell astrocytoma" (SGCA) was coined by Russell et al[1] to differentiate it from other types of intracranial neoplasms, as it had previously received numerous names, such as astrocytoma, ependymoma, spongioblastoma and possible ganglioglioma. It is a benign tumour that has thick fibres and large round or oval nuclei in its structure. Most patients who present this tumour show clinical and pathological symptoms between 8 and 19 years of age.[2,3] However, there are published cases that took place at later,[4] and especially at earlier[5] ages, many of them diagnosed in the prenatal[7] or neonatal[6] age and even as early as 19 weeks of gestation. It can take place with no relation to family history of tuberous sclerosis complex (TSC),[8] as these would be sporadic cases. It is considered that the criteria to be met by subependymal giant cell astrocytoma associated to TSC for preoperative diagnosis are: injury in the area of one or both foramina of Monro, size > 5 mm and incomplete calcification.[9-11] Once these criteria have been established, excision should take place as soon as possible.[11]

Although this is a histologically benign tumour, it may have behaviour and evolution that are not so benign, carrying severe problems and even death. In this study, we show the experience obtained with this tumour in a neurology-neurosurgery paediatric unit over 39 years (1965-2004).

Material and methods

We conducted a retrospective study in a series of 160 paediatric patients (aged under 16 years) who attended the Paediatric Neurology Service at La Paz Teaching Hospital in Madrid, between August 1965 and June 2004, and who underwent surgery when it was required. In addition to the clinical neurological and genetic history, especially seeking signs consistent with TSC diagnostic criteria, we performed a cranial radiological study: computed tomography (CT) and/or magnetic resonance imaging (MRI) with and without contrast on all patients. The study was repeated several times in all cases, with a frequency ranging from once every 6 months to once every 3 years, depending on the size of the hyperintense areas or intracranial hypersignal, especially those located in the heads of the caudate nuclei, close to the foramina of Monro. When growth was observed in these areas, the image was enhanced with intravenous contrast (gadolinium); when changes in size and density or signal were observed (thus making the tumour evident), usually MRI spectroscopy was performed to analyse if there were signs of histological malignancy. An imaging study was performed in all cases, specifically MRI in recent years. The ages of the patients were between newborn and 30 years (the latter had hyperintense areas of considerable size and confirmation that they had not changed since the previous year was necessary through annual controls).

Table 1 Clinical, imaging and pathological data from the series of 8 patients with SGCA related to TSC

Patient, no.	Gender	Epileptic crises (type, age)	Mental retardation	Age of SGCA diagnosis	Symptoms	Unilateral or bilateral tumour	Treatment	Evolution	Current condition
1	F	Focal and West syndrome (20 months)	Yes (discreet)	22 months	Mental retardation. Crises. External TSC signs	First, left unilateral, later bilateral	Surgery at 5 years	Recurrence of tumour many times. Last bilateral excision at age 25	39 years. Borderline IQ. Scarce partial crises and without complete loss of consciiousness. Assessed work.
2	F	Focal, West syndrome (3 months)	No (limit)	6 months	Sudden blindness at 9 years	Left unilateral	Surgery	Blindness. Limit IQ	25 years. Blindness. IQ at limit
3	M	Focal, West syndrome (3 months)	Yes (very severe)	24 years	Microphthalmic LE (always) and exophthalmos since patient was 9 and a half. Enucleation by astrocytoma of LE at 18	Left unilateral	Surgery	Focal crises. Severe mental retardation with autism. Blindness	39 years, severe mental retardation and autism. Blindness
4	M	Focal (newborn)	—	Neonatal	Achronic skin spots. Ocular hamartomas	Left unilateral	Surgery	Focal crises. Discreet PMR	Loss of monitoring at 2 years
5	M	Focal (2 years)	Yes	4 years	Microcephaly. Headaches. Vomiting. Right hemiparesis	Left unilateral	Surgery	PMR. Right hemiparesis	Loss of monitoring at 5 years
6	M	No	No	7 years	Headaches lasting 2 months. Vomiting. Diplopia	Left unilateral	Surgery	Towards normality	Was normal at 8 years. Monitoring was lost at 9 years
7	M	Focal (3 years)	No	12 years	Headaches from 1 month before. Vomiting	Right unilateral	Surgery	Towards normality	Loss of vision at 13 years
8	M	No (9 years)	No	9 years	Blindness. Headaches	Left unilateral	Surgery	Intraventricular haemorrhage during the operation. Death at 15 days	—

F: female; LE: left eye; M: male; PMR: psychomotor retardation; SGCA: subependymal giant cell astrocytoma; TSC: tuberous sclerosis complex.

In all cases, including those who had apparently achieved complete removal, periodic neurological inspections were performed, as well as vision, EEG and imaging studies (usually MRI). This was done to control epileptic crises, common in TSC, and to ensure that patients did not present recurrence of SGCA or new tumours.

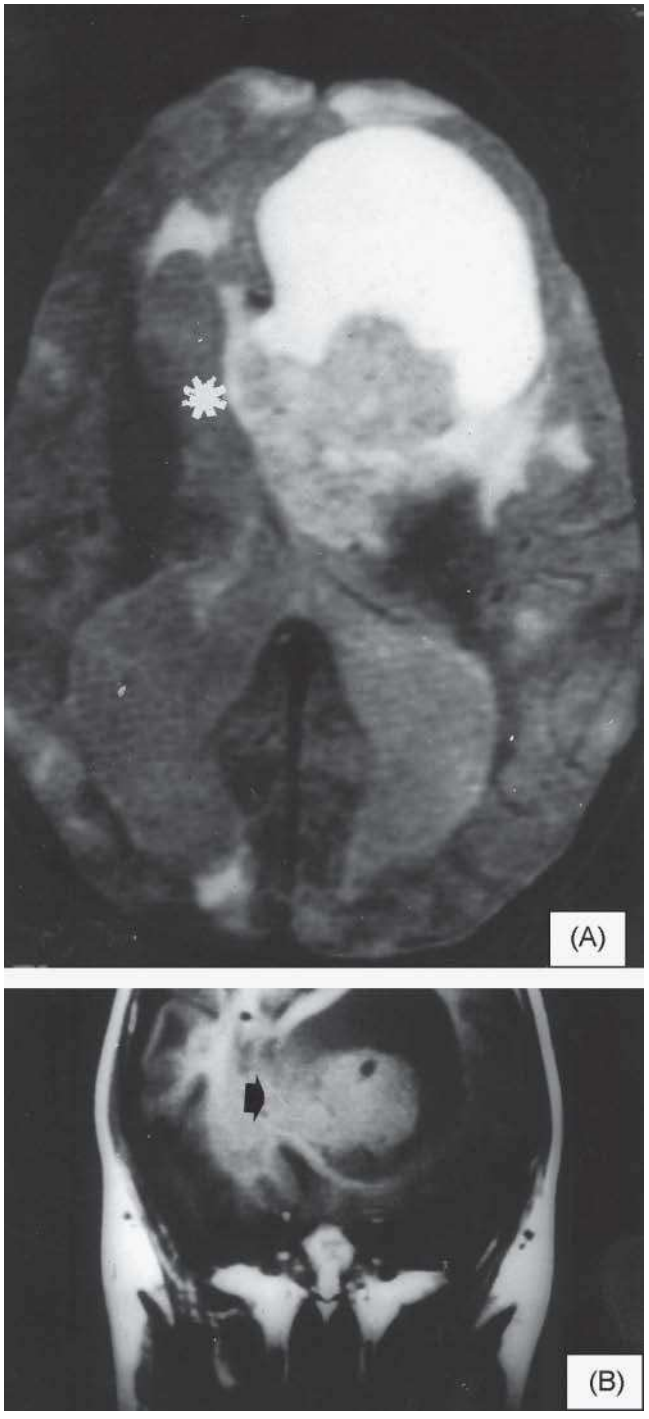


Figure 1 Case 2. Magnetic resonance imaging (MRI) at 9 years. A: axial section of MRI in T2 shows a bulky tumour in the left frontal area with a large external cystic component and an internal solid part (in the region of the foramina of Monro) with invasion of the medial area (asterisk). B: coronal section of the MRI in T1 showing the voluminous cystic (dark) and solid (inner area of the tumour) components with displacement of midline towards the right side (arrow).

Results

The clinical and laboratory findings for all patients are shown in table 1.

All patients showed bilateral hyperdensity or hypersignal areas, located in head of the caudate nuclei, in regions close to the foramina of Monro. Three patients had been admitted urgently with blindness and intracranial hypertension. These children were gradually losing vision without their families or schools becoming aware of this. The patients had not complained of a lack of vision either until the headache appeared suddenly and fundus examination showed papillary oedema. The MRI showed a severe degree of hydrocephalus with obstruction of the foramina of Monro by the solid component of the tumour. This was in turn accompanied by a large cystic component located in the anterior and external areas of the tumour, with contralateral displacement of the anterior parts of the ventricular system (fig. 1). One patient (case 4) already presented a tumour with large volume and dilatation and occupation of the ipsilateral ventricle at birth (fig. 2).

The tumours developed in childhood in all cases except for one with very slow development, from adolescence, which ended in removal at age 24 (fig. 3). During the development of the intracranial tumour, the patient required operations for an ocular astrocytoma with eye enucleation.[12] In 32 cases in which the evolution of hyperintense areas was monitored between 1 and 30 years, tumours failed to develop. Both the CT and MRI strongly highlighted the three fundamental facts that were expected from imaging methods: the existence of the tumour and whether or not it was accompanied by a cystic part; the size of the solid and cystic parts (if any) and the obstruction of one or both foramina of Monro with a blocking of the CSF exit towards the third ventricle; and the degree of

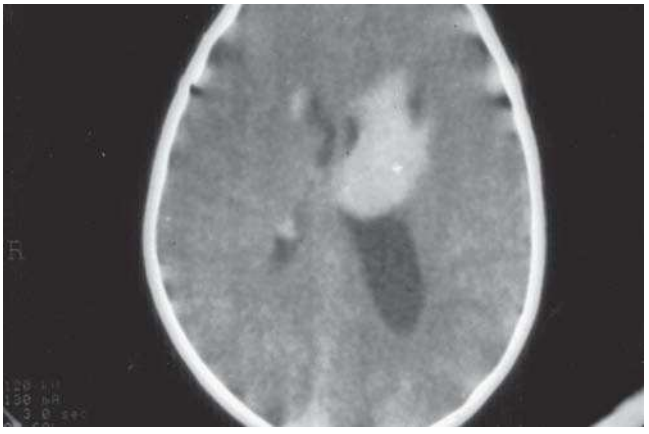


Figure 2 Case 4. Axial section of a neonate computed tomography (CT) scan, showing a tumour in the left lateral ventricle with dilatation and blocking.

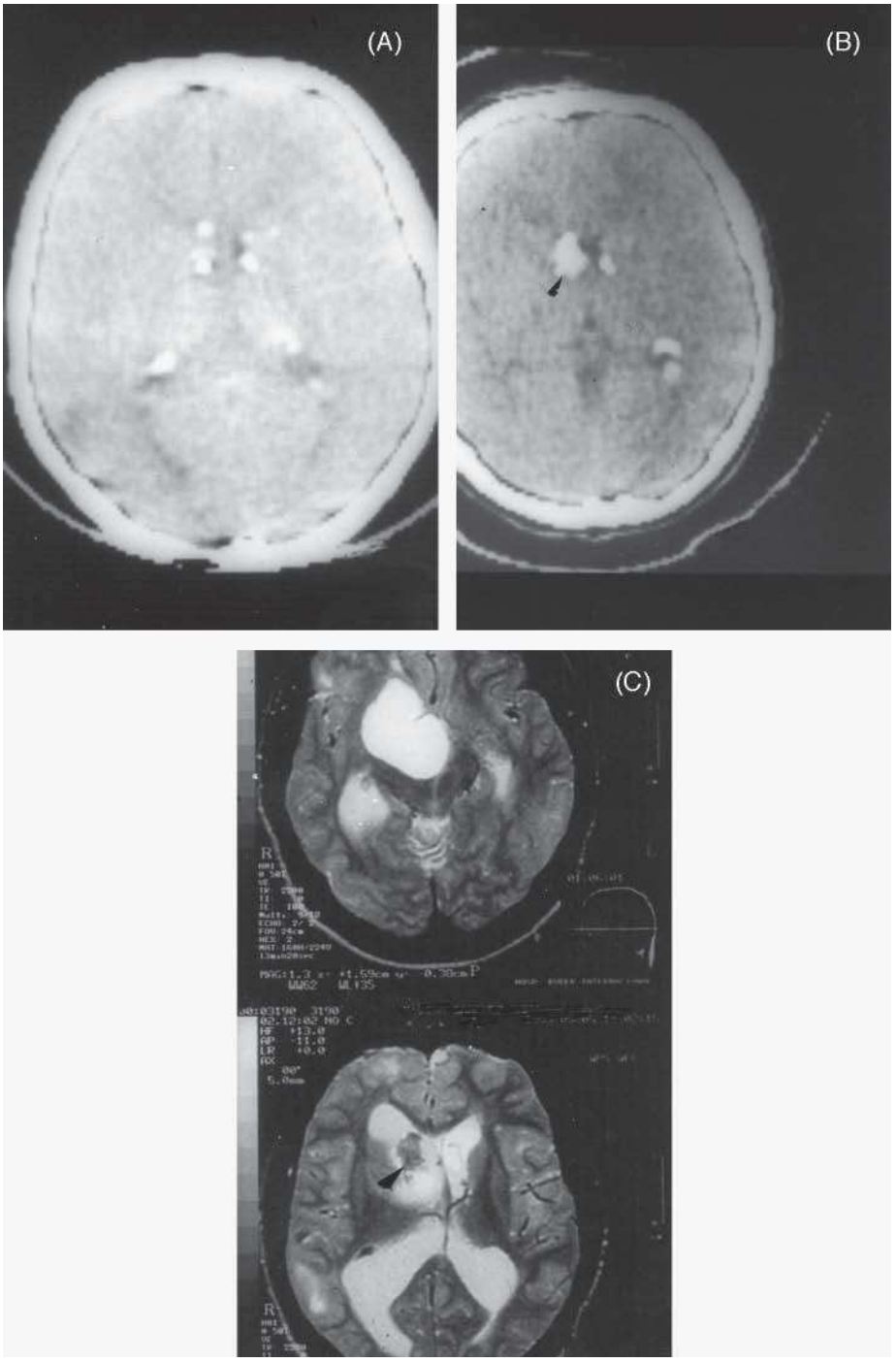


Figure 3 Case 3. A: computed tomography (CT) scan study at age 11. It shows small calcifications in areas of the anterior section in both lateral ventricles, perhaps somewhat larger and more numerous on the right. B: CT scan study at age 15. It shows a larger size of the hyperdensity on the right side (arrowhead) and also the beginning of a discrete left ventricular dilation. C: two axial sections of magnetic resonance imaging at age 24. Images of cystic tumour at two levels, with a small solid portion (arrowhead) and dilation of both lateral ventricles, the right side more so.

hydrocephalus, as well as the accompanying presence or not of interstitial cerebral oedema. One patient, who in the CT scan showed a tumour with multiple intracranial calcifications occupying the whole interior of the ventricle, remained asymptomatic —except for epileptic crises —up to 5 years of age (fig. 4). The partial removal of the tumour caused it to recur a few months later (fig. 4). Subsequently, three further resections were performed with as many relapses; in the fourth and final intervention, at age 26, the original tumour was removed along with a subtotal resection

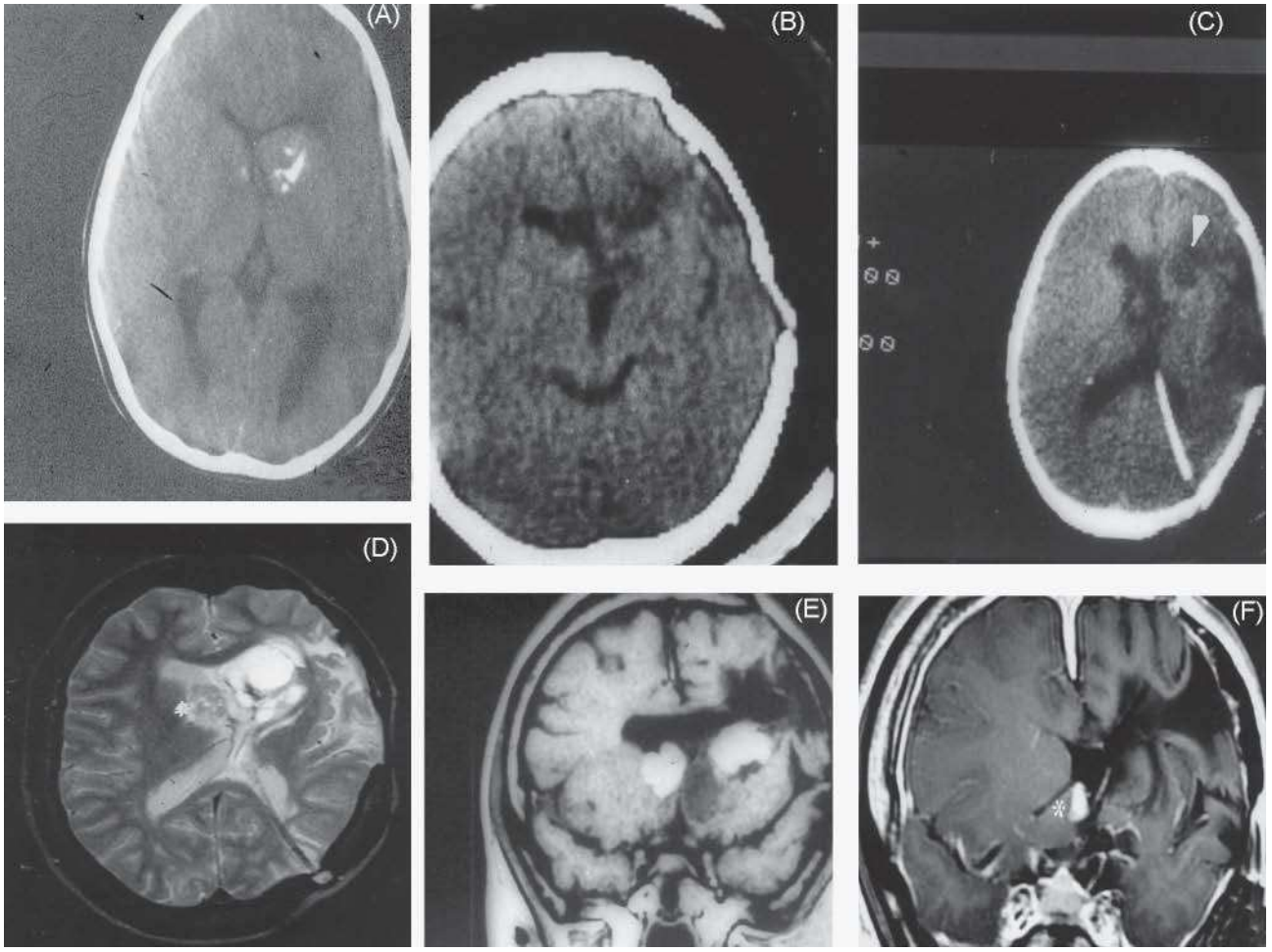


Figure 4 Case 1. A: computed tomography (CT) scan in axial projection at 5 years of age. Tumour with intratumoral calcification in the left lateral ventricle. B and C: CT scans of the same patient in axial projection 11 months later, showing the reproduction of the tumour that had been partially removed (arrowhead). D: Magnetic resonance imaging (MRI) in T2 and gadolinium-enhanced at 23 years of age. Tumour recurrence presenting tension and multi lobular appearance. Strong bulging of the tumour footprint in the head of the right caudate nucleus (asterisk). E: coronal section of gadolinium MRI at age 25 showing a third tumour recurrence that reaches the solid and cystic parts on the left side. Large size of the solid tumour area also on the right side. F: coronal section of gadolinium MRI at age 26, after the last tumour resection. There is no trace of the tumour in the left hemisphere, only a small remnant in the right side (asterisk). Large postoperative ventriculo-cortical sample in the left hemisphere.

of the contralateral side, which had also grown (fig. 4). The postoperative MRI study revealed the extent of tumour resection and the surgical track in the hemisphere on which the excisions had been made (fig. 4). The calcifications in areas of the caudate nuclei heads were inspected periodically by CT and/or MRI scans in all cases not lost during follow up, which exceeded 90%

Discussion

SGCA constitutes over 90% of intracranial tumours associated with TSC.[13] The 8 cases in this series presented all the clinical criteria described for this tumour and in other series.[2,3,13] About 10% originate in the subependymal nodules, usually bilateral, located near the foramina of Monro.[3] The tumour is most often located only on one side, but it may also appear on both sides at once, even several years apart. The prevalence of SGCA in TSC ranges between 5% as in the present series, 5.6%[14] and 20%[15] The nodules are detected in 80% of patients with TSC.[16] The identification of these nodules is currently possible using several imaging methods, such as ultrasound, CT or MRI, from the neonatal period or even during gestation.[5-8] The tumour, when not accompanied by a cystic area, tends to occupy a part —variable in each case —of the ipsilateral lateral ventricle or even the entire cavity, and to displace the supratentorial ventricular system contralaterally; this facilitates the occlusion of the contralateral foramen of Monro and precipitates clinical signs of intracranial hypertension. In those cases where, for some reason, tumour removal is not deemed convenient or is delayed, sequential brain studies by CT or MRI are required to observe its evolution.[17,18] In cases of tumours with large cystic components, the cystic cavity tends to grow

forwards and outwards in most cases. There are seldom diagnostic doubts about the identity of a subependymal giant cell astrocytoma when there are good MRI images available, the features of the TSC are known and the diagnostic criteria of this tumour are commonplace. However, some types of tumours showing similar location and MRI images can be observed, such as central neurocytoma,[19] thus making a differential diagnosis necessary.

The presence of subependymal giant cell astrocytoma in patients with TSC is often manifested early and is rarely associated with other types of intracranial tumours. However, one of our patients (case 3 in this series), who had been operated on at 18 years of age for a slowly progressive ocular astrocytoma (it had begun causing exophthalmos at 9 years) presented at age 24 a sudden case of intracranial hypertension by giant cell astrocytoma with extensive cystic area, for which he had to be urgently intervened.[12] The CT and MRI images showed a more or less extensive area of intratumoral calcification. There are cases where removal of the tumour is not easy and the attempt to do so may cause intraventricular haemorrhage, a severe complication that may jeopardize not only the vision (often lost irreversibly), but even the life of the patient.[20]

Postoperative imaging control, preferably by MRI although also possible by CT, is absolutely necessary: at first to check whether or not any tumour has remained and then periodically to be sure that there is no reproduction of the tumour from remains of the primitive astrocytoma. So far, early and complete macroscopic resection has been considered as the treatment of choice for tumours from a size of 5 mm that meet the diagnostic criteria for SGCA.[11] Results can be good when macroscopic removal is early and total[11] without having had time to reach vision loss; this may occur with a short evolution time in cases of voluminous intraventricular tumours or large cystic areas, as occurred in 3 patients in our series (cases 2, 3 and 8).

The preoperative implementation of CSF derivation systems is a very controversial approach. It is considered counterproductive by some experts because of its many local complications that can also have a general impact on the patient.[21] Not applying the derivation also carries many decompensated hydrocephalus risks. Although neuroradiological, ophthalmological and neurological controls are needed, there are cases of irreversible blindness described in the literature[22] and we have also seen some cases in this series. Some reasons for this are the low intellectual level of some of these patients — who have suffered infantile spasm-type epilepsy (West syndrome) during the first year of life, and have been treated late and with a poor response to therapy — their young age, not knowing how to draw attention to their vision loss, the slowness with which it occurs and insufficient attention to eye checks. In a series of 22 patients, 6 of them suffered visual deficit[23] in relation to tumour size and tumour proximity to the foramina of Monro (as we have also seen in our series), with no relation whatsoever with ependymal hamartomas away from that area.

In recent years, positive results are being described with rapamycin (sirolimus; Rapamune®) in the treatment of SGCA and even pilocytic astrocytomas, of both unilateral[24] and bilateral[25] cases. This is an immunosuppressive substance applied orally at standard doses (serum concentrations of 5-15 ng/ml) for a time ranging from 2.5 to 20 months. The effect of rapamycin could be its ability to shrink tumour cells or apoptosis.[24] Side effects seem to be considerably less than those of radiotherapy on this area highly sensitive to endocrine effects and chemotherapy; they consist basically of aphthous ulcers, acneiform eruptions, diarrhoea and arthralgia, as well as highly elevated serum cholesterol and lipoprotein levels.[24] The antitumor efficacy of rapamycin has also been described in brain tumours associated with type 1 neurofibromatosis (NF1) and in experiments with mice, in other types of tumours.[26]

It is indisputable that we are at the dawn of a new treatment for SGCA and perhaps for other types of other tumours associated with the TSC, possibly also with NF1. The only criterion that we possess is the comparative assessment of tumours by brain MRI images before and after treatment in the limited series published. Although there seems to be a difference in size, the tumours are generally small and their cystic component is scarce, with some exceptional examples. In any event, this is not comparable to the images seen in the patients in our series. Therefore, we should assess with care, but always with hope, the potential efficacy of rapamycin against intracranial tumours in relation to TSC.

Approximately 25% of patients with TSC who died were from brain tumours, a cause which was second only to kidney problems. Death occurred by the direct action of the tumour through a sharp decompensated hydrocephalus, or related to treatment,[3] mainly due to cerebral haemorrhage, as has been reported in the literature,[19] and as was the case in one of our patients.

Conflict of interests

The authors declare no conflict of interests.

References

1. Russell DS, Rubenstein LJ, Lumsden CE. Tuberose sclerose (Bourneville's disease), subependymal giant-cell astrocytomas: tuberose sclerosis, spongio neuroblastoma and tuberose sclerosis. In: Russell DS, Rubenstein LJ, editors. Pathology of tumours of the nervous system. London: Edward Arnold; 1959. p. 29-30. 105–6, 169.
2. Hollanda FJCS, Hollanda GMP. Tuberous sclerosis. Neurosurgical indications in intraventricular tumors. Neurosurg Rev. 1980;3: 139-50.
3. Shepherd CW, Gómez MR, Lie JT, Crowson CS. Causes of death in patients with tuberous sclerosis. Mayo Clinic Proc. 1991;66: 792-6.
4. Takata K, Gaspareto EL, Da Costa Leite C, Lucato LT, Reed UC, Matushita H, et al. Subependymal giant cell astrocytoma in patients with tuberous sclerosis: magnetic resonance imaging findings in ten cases. Arq Neuropsiquiatr. 2007;65:313-6.
5. Hahn JS, Bejar R, Gladson CL. Neonatal subependymal giant cell astrocytoma associated with tuberous sclerosis: MRI, CT and ultrasound correlation. Neurology. 1991;41:124-8.
6. Medhkour A, Traul D, Hussain N. Neonatal subependymal giant cell astrocytoma. Pediatr Neurosurg. 2002;36:271-4.

7. Hussain N, Curran A, Pilling D, Malluci CL, Ladusans EJ, Alfirevic Z, et al. Congenital subependymal giant cell astrocytoma diagnosed on fetal MRI. Arch Dis Child. 2006;91:520.
8. Raju GP, Urion DK, Sahin M. Neonatal subependymal giant cell astrocytoma: new case and review of literature. Pediatr Neurol. 2007;36:128-31.
9. Nabbout R, Santos M, Rolland Y, Delalande O, Dulac O, Chiron C. Early diagnosis of subependymal giant cell astrocytoma in children with tuberous sclerosis. J Neurol Neurosurg Psychiatry. 1999;66:370-5.
10. O'Callaghan FJ, Lux A, Osborne J. Early diagnosis of subependymal giant cell astrocytoma in children with tuberous sclerosis. J Neurol Neurosurg Psychiatry. 2000;68:118.
11. De Ribaupierre S, Dorfmüller G, Bulteau C, Fohlen M, Pinard JM, Chiron E, et al. Subependymal giant-cell astrocytomas in pediatric tuberous sclerosis disease: when should we operate? Neurosurgery. 2007;60:83-9.
12. Pascual-Castroviejo I, Patrón M, Gutierrez M, Carceller M, Pascual-Pascual SI. Tuberous sclerosis associated with histologically confirmed ocular and cerebral tumors. Pediatr Neurol. 1995;13:172-4.
13. Boesel CP, Paulson GW, Kosnick EJ, Earle KM. Brain hamartomas and tumors associated with tuberous sclerosis. Neurosurgery. 1979;4:4107.
14. O'Callaghan FJK, Martyn CN, Renowden S, Noakes M, Presdee D, Osborne JP. Subependymal nodules, giant cell astrocytomas and the tuberous sclerosis complex: a population based study. Arch Dis Child. 2008;93:7512-4.
15. Adriaensen ME, Schaefer-Prokop CM, Stignen T, Duyndam DA, Zonnenberg BA, Prokop M. Prevalence of subependymal giant cell tumors in patients with tuberous sclerosis and review of the litrature. Eur J Neurology. 2009;16:691-6.
16. Kingsley DPE, Kendall BE, Fitz CR. Tuberous sclerosis: a clinico-radiological evaluation of 110 cases with particular reference to atypical presentation. Neuroradiology. 1986;28:38-46.
17. Fujiwara S, Takaki T, Hikita T, Nishio S. Subependymal giant-cell astrocytomas associated with tuberous sclerosis. Do subependymal nodules grow? Childs Nerv Syst. 1989;5:43-4.
18. Morimoto K, Mogami H. Sequential CT study of subependymal giant-cell astrocytoma associated with tuberous sclerosis: Case report. J Neurosurg. 1986;65:874-7.
19. Beltrán-Marín M, Riaguas-Almanara A, Mazas-Artasona LV, Vela-Marín A, Marín-Cárdenas MA, Solanas-Alava S. Neurocitoma central: hallazgos en tomografía computarizada y resonancia magnética. Rev Neurol. 2009;49:383-4.
20. Waga S, Yamamoto Y, Kojima T, Sakakura N. Massive hemorrhage in tumor of tuberous sclerosis. Surg Neurol. 1977;8:99-101.
21. Cooper JR. Brain tumors in hereditary multiple system hamartomatosis (tuberous sclerosis). J Neurosurg. 1971;34:194-202.
22. Dotan SA, Trobe JD, Gebarski SS. Visual loss in tuberous sclerosis. Neurology. 1991;41:1915-7.
23. Bongiorni L, Arroyo HA, Lubienicki F. Complejo nódulo subependimario-astrocitoma subependimario gigantocelular en niños con esclerosis tuberosa. Medicina (Buenos Aires). 2009;69:8-14.
24. Franz DN, Leonard J, Tudor C, Chuck G, Care M, Sethuraman G, et al. Rapamycin causes regression of astrocytomas in tuberous sclerosis complex. Ann Neurol. 2006;59:490-8.
25. Koenig MK, Butler IJ, Northrup H. Regression of subependymal giant cell astrocytoma with rapamycin in tuberous sclerosis complex. J Child Neurol. 2008;23:1238-9.
26. Dasgupta B, Yi Y, Chen DY, Weber JD, Gutmann DH. Proteomic analysis reveals hyperactivation of the mammalian target of rapamycin pathway in neurofibromatosis 1 —associated human and mouse brain tumors. Cancer Res. 2005;65:2755-60.