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TOPIC REVIEW

Recommendations for the radiological diagnosis and follow-up of neuropathological abnormalities associated with tuberous sclerosis complex

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Abstract Tuberous sclerosis complex (TSC) is a genetic condition with multisystem involvement, characterized by the development of tumors and other abnormalities in organs such as the brain, retina, skin, heart, kidneys, and lungs. Most patients have neuropathological abnormalities such as cortical tubers, white matter radial migration lines, subependymal nodules, and subependymal giant cell astrocytomas (SEGAs). These lesions are associated with different neurological manifestations that are frequently associated with TSC. These manifestations consist of epilepsy, intellectual disability, and neurobehavioral and psychiatric problems, including autism spectrum disorder. Hydrocephalus may also develop in patients with SEGAs due to ventricular obstruction, when this usually slow-growing tumor reaches sufficient size. Surgery has been the classical approach to treat SEGAs, although this treatment is associated with substantial morbidity and does not completely prevent tumor recurrence. Recently, the mammalian target of rapamycin (mTOR) inhibitor, everolimus, has been approved by the Food and Drug Administration and the European Medicines Agency for the treatment of patients with SEGAs associated with TSC. However, the treatment of SEGAs with these agents requires the development of guidelines that establish a differential diagnosis between SENs and SEGAs, in which neuroradiological examinations play an essential role. With the aim of improving the neuroradiological diagnosis and follow-up of the neuropathological abnormalities associated with TSC, a group of experts in this field has reviewed different aspects related to these issues and put together, a series of statements and recommendations intended to provide guidance to specialists involved in the management of TSC.

Keywords Magnetic resonance imaging · Mammalian target of rapamycin inhibitors · Subependymal giant cell astrocytomas · Subependymal nodules · Tuberous sclerosis complex

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Introduction

Tuberous sclerosis complex (TSC) is a multisystem genetic disorder characterized by the development of tumors and hamartomas in various organs, such as the brain, retina, skin, heart, kidneys, and lungs. This genetic disease, which has a prevalence estimated of 1 in 6,000 live births, follows an autosomal dominant pattern of inheritance with complete penetrance and variable phenotype [1–5], in which the genes *TSC1* (*9q34*) and *TSC2* (*16p13*) have been implicated [6]. Spontaneous or inherited mutations in any of these tumor-suppressor genes, which are found in over 85 % of patients with TSC, result in activation of the mammalian target of rapamycin complex 1 (mTORC1) and, consequently, in the formation of hamartomas in different organs [5, 7–11].

Neurological manifestations of TSC are the most frequent (85 %) and are the major cause of morbidity and mortality in children [1, 3, 12]. These clinical manifestations are due to several neuropathological abnormalities, such as cortical tubers, white matter radial migration lines (RMLs), subependymal nodules (SENs), and subependymal giant cell astrocytomas (SEGAs) [1, 2, 12–17], and result in epilepsy, intellectual disability, and neurobehavioral and psychiatric problems, including autism spectrum disorder (ASD) [11, 16, 18–21].

SEGAs are benign and usually slow-growing tumors, more frequent in patients in the 5–19 years age group, although these tumors can develop at any age, with some presenting with hyperacute growth [6, 7, 9, 11–17]. Surgery has been the classical treatment of symptomatic SEGAs [22]. However, postoperative morbidity is substantial (20–50 %), and incomplete resection due to its typical deep location might leads to tumor recurrence requiring additional surgical procedures [23, 24]. The outcome of surgery is good to excellent in small and asymptomatic lesions, although early diagnosis of SEGAs is difficult as development is often insidious, particularly in children with intellectual disability [25]. As an alternative to surgery, patients who develop SEGAs may be treated with drugs targeting the pathogenesis of these tumors, i.e. mTORC1 inhibitors [26, 27]. However, the treatment of SEGAs with these agents requires the development of guidelines that establish a differential diagnosis between SENs and SEGAs, in which neuroradiological examinations play an essential role and determine the timing of initiation and duration of therapy with mTORC1 inhibitors [22, 28–31].

The present article is the result of work initiated by two coordinators (a neuroradiologist and a neuropediatrician) who, in collaboration with a group of six experts in the field of TSC, proposed a series of recommendations for optimizing the radiological diagnosis and follow-up of the neuropathological anomalies associated with this disorder. A questionnaire consisting of 10 questions, divided into four sections, was prepared by both coordinators and agreed with the invited experts. Each section was assigned to one neuroradiologist and one neuropediatrician, who collected the best evidence on that issue. Subsequently, in a meeting that took place in Barcelona in January 2013, the recommendations prepared by each team were discussed and a consensus reached on each topic. The contribution by neuroradiologists and neuropediatricians was equal at every step of the project. After the meeting, coordinators and experts wrote a draft document that included the main consensus statements and the bibliography supporting them.

The purpose of this article is to set out some statements and recommendations useful for clinical practice, based on the currently available scientific evidence and on experts' opinions.

Neuropathological abnormalities in patients with TSC

What are the neuropathological abnormalities in patients with TSC?

Neuropathological abnormalities in patients with TSC include brain and cerebellar tubers, white matter RMLs, SENs, SEGAs, and rarely vascular lesions including aneurysms. Not all these lesions are present in all patients.

Supratentorial tubers

Tubers are glioneuronal hamartomas, i.e. structures histologically composed of enlarged atypical and disorganized neuronal and glial elements with astrocytosis. They can be found in the cerebral and cerebellar cortex and in the subcortical white matter. Brain tubers are present in 90 % of patients and are multiple in 95 %. Tubers present a predominantly anterior location with 90 % localized in the frontal lobes (Fig. 1). These lesions can have a cortical or subcortical location and expand beneath the overlying gyri. They tend to be confined to a single gyrus, but sometimes span two or more gyri, which are commonly enlarged, and may even have a lobar or a hemispheric distribution (Fig. 2). Their size ranges from one to several centimeters and their gross appearance resembles potatoes; hence the disease is called tuberous sclerosis. Their signal intensity on magnetic resonance imaging (MRI) varies depending on the degree of myelination of the affected patient. In older infants with normal myelinated white matter, these lesions exhibit a hypointense signal on T1-weighted (T1W) sequences and a hyperintense signal on conventional or fluid-attenuated inversion recovery (FLAIR) T2-weighted (T2W), sequences. However, when tubers present with

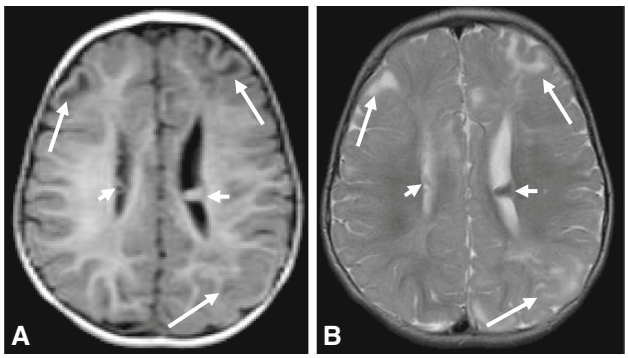

Fig. 1 Unenhanced T1- (**a**) and T2W (**b**) transverse images obtained in a 4-year-old boy with TSC. Multiple tubers can be identified on both frontal lobes and in the left parietal lobe (*long arrows*). The signal of these lesions show a typical adult pattern, hypointense on T1- and hyperintense on T2W images. Some SENs are also identified (*short arrows*)

calcification, significant signal loss and blooming artifact due to susceptibility effects, appear on T2*W sequences. The T1 and T2 signal pattern is inversed in neonates and young infants, due to the surrounding unmyelinated white matter (Fig. 3).

Less than 10 % of cortical tubers show contrast medium uptake [32]. Tubers may develop cyst-like changes, likely related to cellular degeneration, which are more common in children younger than 7 years of age. These cystic changes are shown as areas of low signal intensity surrounded by a high signal peripheral rim on T2W FLAIR sequences [33–35]. On computed tomography (CT), tubers show low attenuation, only 3–4 % exhibit contrast enhancement, whereas calcification can be identified in ~50 % of patients [33, 36]. Supratentorial tubers are usually stable lesions, although rarely they may increase in size and number [37].

SENs

SENs are scattered lesions appearing along the ependymal surface of the lateral ventricles, commonly located near the caudate nucleus behind the foramen of Monro, and adjacent to the ventricular atria. These lesions are commonly calcified in children >1 year [33]. On MRI, SENs exhibit a hyperintense signal on T1W sequences (particularly in neonates) and an iso/hypointense signal on T2W sequences because of calcification (Fig. 2). SENs commonly show variable contrast enhancement that has no prognostic value regarding the potential for transformation to SEGAs [36]. Unlike tubers and white matter abnormalities, no inverse signal intensity on T1W and T2W images is detected in SENs in neonates and young infants.

White matter RMLs

White matter RMLs represent heterotopic neuronal and glial elements that arrested during cortical migration. They are the most frequent neuroanatomical lesions in TSC patients, and are located in the subcortical white matter, extending from the ependymal ventricular surface towards the cortex, where these bands often terminate in a tuber. These lines are frequently missed on CT, whereas on MRI, particularly when using high resolution T2W images, they are clearly seen as curvilinear or band-shaped lesions traversing the deep white matter, [38] (Fig. 2). These lines

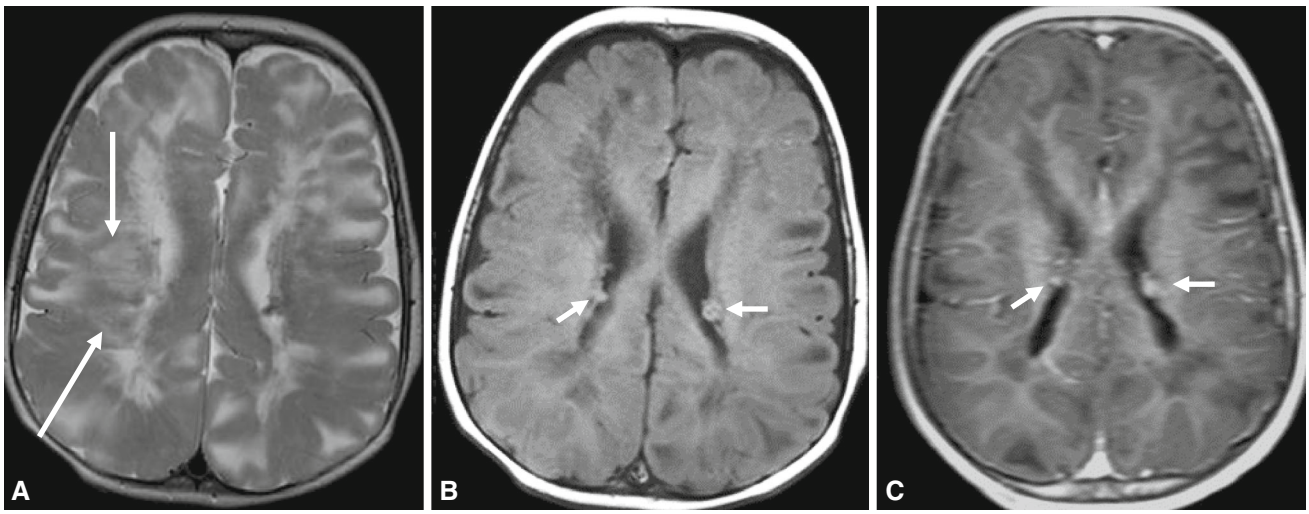

Fig. 2 Transverse T2- (**a**) and unenhanced (**b**) and contrast-enhanced (**c**) T1W images from a 5-year-old boy with TSC. Multiple tubers can be identified involving diffusely the grey matter of both frontoparietal regions, associated with RMLs involving the deep white matter of the right frontal lobe (*long arrows* in **a**) and multiple SENs of <10 mm in diameter that show contrast uptake (*short arrows* in **b**, **c**)

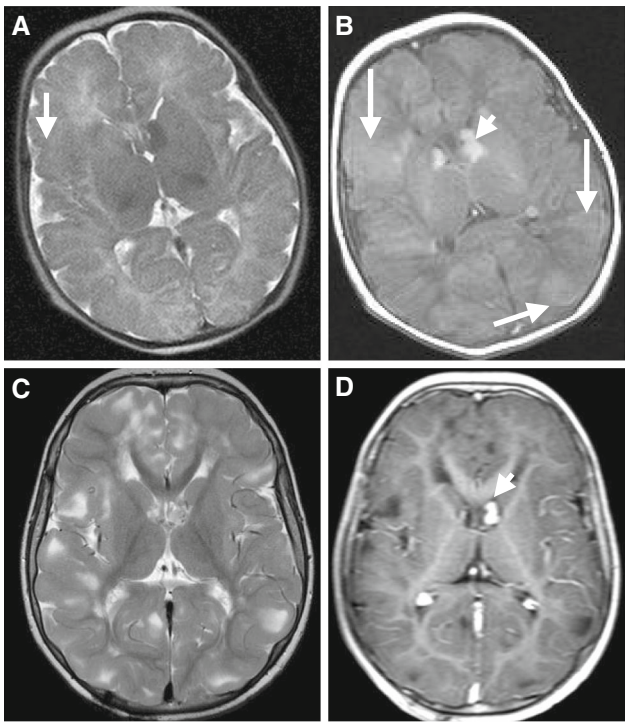

Fig. 3 Serial brain MRI in a patient with TSC and neonatal SEGA. The postnatal (5 days) T2- (**a**) and T1W (**b**) images show the typical neonatal signal pattern of cortical tubers, hyperintense on T1- and mildly hypointense or isointense on T2W images (*arrows*). A follow-up MRI scan performed when the patient was 5 years old, shows a typical adult pattern on both T2- (**c**) and T1W (**d**) images, with the lesions becoming hyperintense on T2 and hypointense on T1. In addition, the MRI scan shows a right subpendymal nodule and a left SEGA (*short arrows* in **b**, **d**)

rarely show contrast enhancement. The strong correlation between the presence of RMLs, tubers, and SENs supports that these lesions originate from a common biological dysfunction in the periventricular zone [38]. Other white matter lesions, detected in almost 50 % of patients with TSC, consist of small cysts presenting with low attenuation on CT and isointensity to the cerebrospinal fluid in all MRI sequences. These lesions do not show enhancement and resemble enlarged perivascular spaces [33] (Fig. 4).

SEGAs

SEGAs are the most common brain tumors in TSC, occurring in about one out of every 10 patients, with reported figures ranging from 6 to 18 % [1, 14, 16, 17]. These tumors are low-grade [World Health Organization (WHO) grade 1], mixed, glioneuronal, and highly vascularized neoplasms predominantly located near the foramen of Monro, and frequently with bilateral distribution. They represent a significant cause of morbidity and mortality because of the risk of sudden death from acute

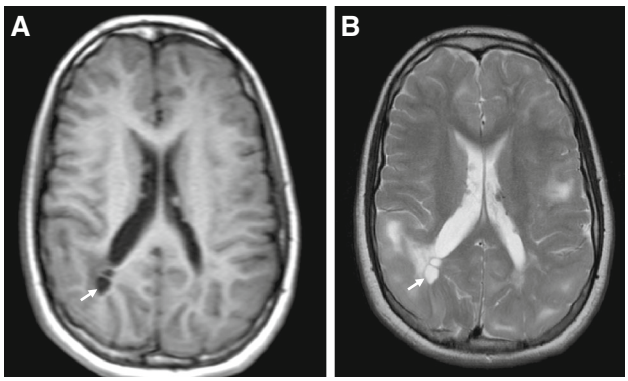

Fig. 4 Transverse T1- (**a**) and T2W (**b**) brain MR images in a 7 year old boy with TSC. Small cystic-like lesions, hypointense on T1 and hyperintense on T2, resembling an enlarged perivascular space is seen in the right posterior periventricular white matter (*arrows*). Multiple cortico-subcortical tubers and SENs are also identified

hydrocephalus [16], the risk of which is directly proportional to their volume [39]. SEGAs are commonly diagnosed when their size is >10 mm, when serial evaluations demonstrate enlargement and hence growth, or when their presence leads to cerebrospinal fluid obstruction and hydrocephalus, which is reported in 40 % of patients with TSC [33].

On CT, SEGAs appear as iso/hyperattenuating masses showing frequent calcification. On MRI, they have hypo/isointense signal on T1W sequences and hyperintense signal on T2W sequences, presenting intense, contrast enhancement [36] (Fig. 3). Sequential imaging demonstrates that SEGAs develop on previously present SENs [40], that do not regress spontaneously, and that the volume increases progressively once serial growth is demonstrated [39]. SEGAs may appear very early, in the neonatal or even in the prenatal stage of life [41], although the peak age of occurrence is 8–18 years [42]. Serial CT or MRI may identify SEGAs in patients with TSC before these lesions become symptomatic (Fig. 5). This preclinical diagnosis has an impact on the prognosis of the patient as the outcome of surgery is good to excellent in small and asymptomatic lesions by reducing morbidity and the risk of tumor recurrence [43]. Some of the main radiological indicators of SENs and SEGAs in the fetal and neonatal period, as well as in the infancy of the patient and beyond, are described in Table 1.

Infratentorial and miscellaneous neuropathological abnormalities

Patients with TSC may present infratentorial tubers in 9–44 % of cases [44], as well as other neuropathological abnormalities, such as aneurisms and hemimegalencephaly.

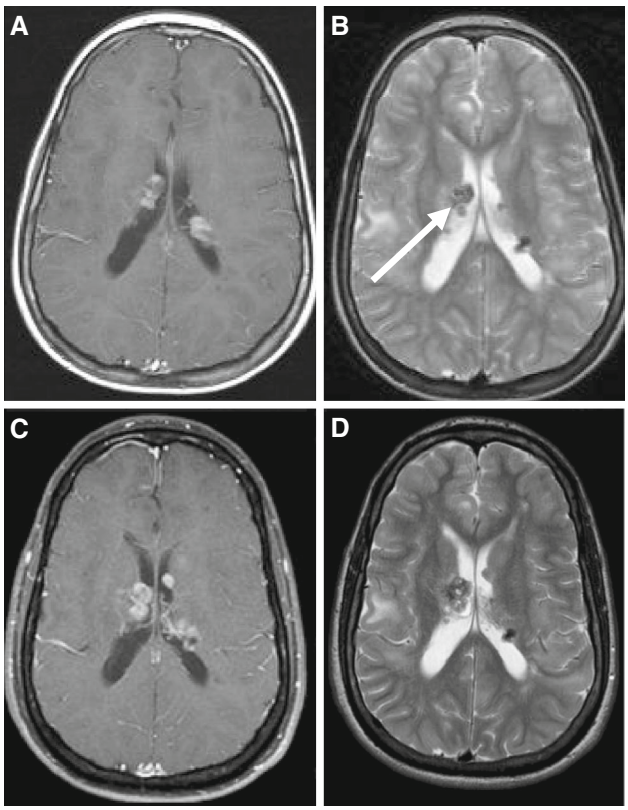

Fig. 5 Growing SEGAs in a patient with TSC. Initial brain scan performed when the patients was 11 years old shows multiple contrast enhancing subependymal nodes in both sides (**a**) with the typical hypointensity on T2W image (**b**). One of the nodules had a maximum diameter of 13 mm suggesting the diagnosis of SEGA (*arrow* in **b**). Contrast-enhanced T1- (**c**), and T2W follow-up MR scan performed 13 years later, clearly demonstrates growth of the nodules further supporting the diagnosis of SEGA

Table 1 Main topographical and imaging findings of SENs and SEGAs throughout life

Type of lesion	
SEN	SEGA
Fetal period	
Ultrasound:	Ultrasound:
Echogenic nodules in ventricular walls	Intraventricular/frontal mass close to Monro foramina
MRI:	MRI:
Hyperintense nodules on T1W images	Nodular lesion close to Monro foramina
Hypointense nodules on T2W images	Hyperintense on T1W images and hypointense on T2W images
	Size >10 mm
Neonatal period	
Ultrasound:	Ultrasound:
Echogenic nodules	Mass close to Monro foramina
	Echogenicity similar to surrounding brain
MRI:	MRI:
Hyperintense on T1W images	Hyperintense on T1W images
Hypointense on T2W images (more difficult to depict)	Hypointense on T2W images
Infants and beyond	
CT:	CT:
Rarely calcifies during first year	Mixed density
Progressive calcification	Partial calcification
	Enhancement
MRI:	MRI:
"Bumps" protrude from walls of lateral ventricle	Mixed signal intensity
Hypointense to white matter on T1W images	Strong enhancement
Enhancement	
If calcified: hypointense on GRE T2*W images or SWI	

CT computed tomography, *GRE* gradient echo, *MRI* magnetic resonance imaging, *SEN* subependymal nodule, *SEGA* subependymal giant cell astrocytoma, *T1W* T1-weighted, *T2W* T2-weighted, *SWI* susceptibility-weighted imaging

Cerebellar tubers are not reported to occur in the absence of cortical tubers. In a study by Vaughn et al. [44] cerebellar tubers were present in 24 % of 145 pediatric and young adult patients with TSC. Cerebellar tubers appeared as predominantly wedge-shaped lesions, with hyperintense signal on T2W sequences and hypo/isointense signal on T1W sequences (Fig. 6). These lesions are more likely to enhance than supratentorial tubers, (51 % versus <10 %) and often in a "zebra-like" pattern, which may reflect the underlying cerebellar anatomy of interposed cerebellar cerebrospinal fluid (CSF)-filled sulci between the neuronal elements [32]. Calcification in cerebellar tubers occurs in ~50 % of cases, with associated retraction deformity in 85 % of them [32]. More than half of cerebellar tubers demonstrate size changes in longitudinal studies [32]. Patients with TSC may also present cerebellar atrophy, detected in 4–13 % of TSC patients, and is frequently associated with cerebellar tubers. Infratentorial lesions also include linear and gyriform cerebellar folia calcifications, vermis and cerebellar hemispheric hypoplasia and agenesis, white-matter lesions, cerebellar hemisphere enlargements, as well as brainstem and fourth ventricle SENs and tubers. A cerebellar SEGA has also been reported in a newborn with TSC [45].

The association between TSC and CNS aneurysms is very rare. However, several cases have been reported, some of them describing vascular dysplasia, multiple aneurysms,

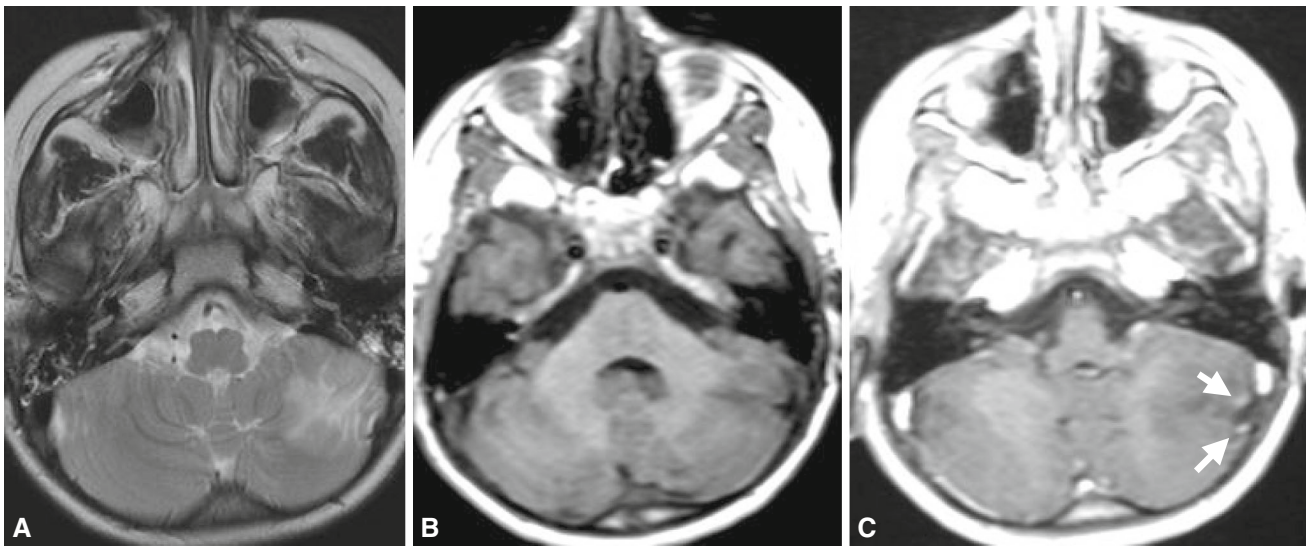

Fig. 6 T2W (**a**) and unenhanced (**b**) and contrast-enhanced (C) T1W transverse images obtained in an 11-year-old girl with TSC. A left cerebellar cortical tuber can be identified on the left side showing the "zebra" pattern of enhancement (*arrows* in **c**)

or severe ectasia and giant fusiform aneurysm formation [46].

The association between hemimegalencephaly and TSC was first reported in 1988 by Robain et al. [47] and subsequent reports have confirmed it. In fact, hemimegalencephaly was found in 12 % of patients in a cohort study carried out by Arca et al. [45]. Histologic evaluation of the lesion revealed characteristics of a giant cortical tuber that diffusely involved one brain hemisphere.

General statements and recommendations from the panel:

- The neurological manifestations of TSC are the most frequent, and in children, are the major cause of morbidity and mortality.
- Neuropathological abnormalities in patients with TSC include brain and cerebellar tubers, white matter RMLs, SENs, SEGAs, and rarely, vascular lesions including aneurysms.
- Supratentorial neuropathological abnormalities can be detected by CT or MRI in the vast majority of TSC patients.
- Cerebellar abnormalities, which are less frequent, are always associated with supratentorial lesions.
- Early diagnosis of SEGAs has an impact on the prognosis of the patients as the outcome of surgery is good to excellent in small and asymptomatic lesions.
- MRI has higher overall sensitivity in detecting the neuropathological abnormalities present in TSC, whereas CT better identifies calcification which is frequently present in cortical tubers, SENs, and SEGAs.

What are the chronological differences in terms of neuroimaging detection of the neuropathological abnormalities in TSC?

Prenatal period

Prenatal TSC has been classically diagnosed by the sonographic detection of cardiac rhabdomyomas (Fig. 7). Around 80 % of cardiac rhabdomyomas develop in infants with TSC, although only approximately half of the patients with TSC have cardiac rhabdomyomas, most of which are not present at the usual time of prenatal screening, i.e. at the 20th week of gestation [48]. In a fetus, the risk of presenting TSC when a cardiac rhabdomyoma is detected prenatally has been estimated to be 50 % [49]. Fetal MRI can reveal brain lesions not identified on sonographic examination after the 21st week of gestation. Among these lesions, cortical tubers are the most frequent with a reported incidence of 33–62 %. However, the number and size of brain lesions may increase during pregnancy [49, 50]; therefore, a negative early prenatal MRI does not exclude the diagnosis of TSC absolutely. Finally, it is important to highlight that the presence or absence of cerebral lesions in prenatal MRI is not predictive of the neurodevelopmental outcome in patients with TSC [51].

Neonatal period

According to Baron and Barkovich, 99 % of the lesions detected in neonates with TSC, such as RMLs, tubers, SENs, and SEGAs, exhibit hyperintense signal on T1W

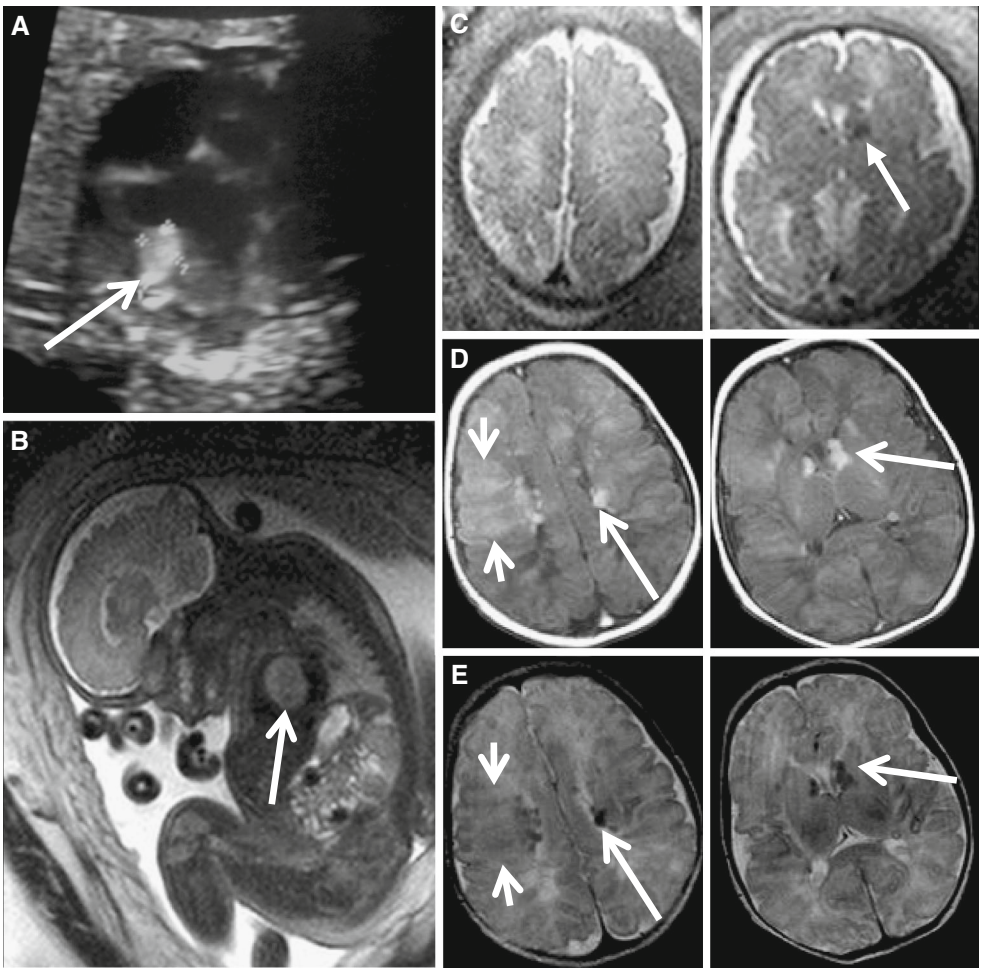

Fig. 7 Prenatal diagnosis of TSC. Intracardiac mass (*arrows*) was detected on routine ultrasound (**a**). The lesion had uniform echogenicity and was more echogenic than the surrounding myocardium, consistent with the typical appearance of cardiac rhabdomyomas. **a** Prenatal HASTE T2W image (35 weeks gestation) clearly identified the intracardiac mass (*arrows* in **b**), and SENs (*arrows* in **c**). Postnatal cerebral axial T1- (**d**) and T2W (**e**) MRI scan at age 5 days shows the SENs (*arrows* in **d**, **e**), and radiation migration lines extending from the right lateral ventricle to the ipsilateral frontal cortex (*short arrows* in **d**, **e**). These radiation migration lines show the typical neonatal signal pattern, hyperintense on T1- and hypointense on T2W images

sequences; whereas on T2W sequences, they are hypointense in 43 % of cases compared to the normally unmyelinated white matter [52] (Figs. 3, 7). This signal pattern is due to the high water concentration of the unmyelinated immature white matter, which is hyperintense compared to the normal gray matter, facilitating the identification of white matter anomalies, something that becomes more difficult as myelination progresses. Continued myelination produces a progressive reversal of this signal intensity in some of the lesions detected in neonates, leading to the classical adult intensity pattern in which lesions are hypointense on T1W and hyperintense on T2W images. As this signal intensity reversal starts at $\sim$6 months of age, and finishes at 12 months of age, this is the period when MRI has the lowest sensitivity for detecting brain abnormalities.

General statements and recommendations from the panel:

- The neuropathological findings of TSC are readily identifiable on brain MRI, with patterns that vary in accordance with the age of the patient.
- Cortical tubers and SENs can be seen prenatally; however, cardiac rhabdomyomas are the most common clue to diagnosis of TSC in the prenatal period.
- A normal prenatal brain MRI does not exclude the diagnosis of TSC.
- Early infancy assessment does not compromise, but facilitates, correct MRI diagnosis of TSC. Therefore, if TSC is clinically suspected within the first 3 months of life, imaging should not be delayed.

- White matter RMLs, SENs, and SEGAs are better detected using MRI in neonates than in children between 6 and 12 months of age.
- An adult pattern of TSC-related brain lesions can be appreciated from the age of 12 months onwards.

What are the correlations between cortical and white matter radiological abnormalities and the clinical outcome of patients with TSC?

As a general rule, brain lesion load correlates with neurological outcome in patients with TSC. However, to what extent size, type, number, or location of cortical and white matter abnormalities contribute to disease severity is still unknown. In addition, except for the role of cortical tubers, the clinical significance of neuropathological abnormalities remains unclear.

Epilepsy

About 60–90 % of patients with TSC develop epilepsy, which may originate in the tuberal and perituberal tissues [11, 16, 18–20]. In fact, epilepsy is the first symptom of the disease in 67 % of patients, and the debut occurs during the first 6 months of life in about 60 % of them. Data also show that in 65–85 % of patients, epilepsy presents a refractory course, which is associated with mental retardation and autism [19–21].

Surgical resection of the epileptogenic foci has the potential to achieve seizure control and improve long-term prognosis in these patients. Neuroradiological features play a key role in patients with TSC by identifying patients with a high risk of early-onset or severe epilepsy. A meta-analysis of MRI studies carried out by Goodman et al. [53] revealed that cortical tuber count could be a biomarker for mental impairment or seizure severity in patients with TSC. Patients presenting with moderate to severe epilepsy were five-times more likely to have more than seven MRI-detected cortical tubers than those presenting a mild course of the disease. Subsequent studies demonstrated that a higher cortical tuber count correlated with lower intelligence quotient scores, as well as with history of infantile spasms [54, 55]. Nonetheless, simple counts of cortical tubers seem to underestimate the effect of large lesions, which are frequently associated with refractory epilepsy and adverse cognitive outcome [56]. In addition, simple counts probably overestimate the effect of multiple small tubers on patient outcome [57]. Therefore, either estimation of the surface occupied by tubers, or estimation of the tuber/brain ratio may constitute a better predictor for cognitive impairment in patients with TSC [57, 58].

As previously mentioned, tuber burden tends to correlate with epilepsy incidence and severity. This is due not only to the tubers themselves, but also to the involvement of the surrounding tissue, as shown by invasive intracranial electroencephalogram monitoring with depth electrodes [59]. Using this technique, Major et al. [60] found that silent tubers present epileptiform activity in the perituberal tissue. Regarding tuber location, evidence points to a higher risk of severe cognitive and behavioral difficulties in patients presenting involvement of the temporal or occipital lobes, particularly the left temporal lobe. In fact, in a study carried out by Chou et al. [61], this location was associated with a more severe neurological score, which was based on the presence of seizures, developmental delay, and autism. In contrast, this study showed no correlation between seizure severity or mental ability and the incidence of white matter lesions or the number and location of SENs. In a recent study, van Eeghen et al. [38] showed that the frequency of white matter RMLs was strongly associated with the age of seizure and a history of seizure, suggesting that this abnormality could be a biomarker with prognostic relevance.

Cognitive and behavioral outcome

TSC is associated with a range of serious behavioral and cognitive anomalies [25]. In particular, there is strong evidence for high rates of ASD. The risk of ASD and mental retardation increases when tubers are located in the left hemisphere [21]. Other studies suggest that a high number of cortical tubers in the occipital lobe correlates with the same developmental disorders [54, 55]. This evidence is to be weighed against the results of a retrospective study in 103 patients with TSC [62], 40 % of whom developed ASD, which revealed no differences in the regional distribution of tuber burden on MRI between patients with or without ASD. Of note, patients with *TSC2* mutations and ASD demonstrated a higher prevalence of cyst-like tubers.

Cerebellar tubers, present in about 25 % of patients with TSC, have been associated with more severe clinical presentations [44, 63]. Patients suffer more severe communication and social disturbances when these tubers are located in the right cerebellar hemisphere [64]. Conversely, frequency of white matter RMLs is strongly associated with intelligence outcome and level of autistic features [38]. However, as visual quantification of RMLs is extremely time-consuming, prone to high inter- and intraobserver variability, and likely underestimates the extent of white matter microstructural damage, more sophisticated and sensitive methods for evaluating this type of abnormality, such as diffusion-tensor MRI (DTI) has been used in some studies [38, 65]. Different DTI-based measures,

such as fractional anisotropy (FA) and average mean, radial, and axial diffusivity DTI, could better detect these white matter abnormalities. Peters et al. [65] showed that significantly lower FA and higher average mean, radial, and axial diffusivity values were found in patients with TSC compared to controls, indicating abnormal integrity of white matter tracts, and that patients with TSC and ASD displayed significantly lower values of FA compared with those without ASD, whereas patients with TSC without ASD had similar FA values in comparison to healthy controls. These data indicate that quantification of white matter integrity by means of DTI could be used as a biomarker of neurological outcome in TSC.

Radiopathological characteristics of cortical tubers in patients with TSC

Brain MRI reliably identifies the main neuropathological lesions of TSC [61], namely cortical cerebral or cerebellar tubers, SENs, SEGAs, and white matter RMLs. Both white matter lesions and cortical tubers have the same hallmark histopathological feature, i.e. the presence of similar abnormal giant cells showing abnormal size and histological differentiation. These cells are indistinguishable from cortical dysplasia with balloon cells. Histopathologically, two types of tubers, namely type 1 presenting a smooth surface and type 2 presenting a cystic component, are classically recognized in patients with TSC [66]. Type 2 tubers are more frequently associated with epilepsy, infantile spasms, or refractory epilepsy. These tubers are detected more often in patients with *TSC2* mutations than in those with *TSC1* mutations or with no mutation identified.

MRI is valuable in distinguishing tuber subtypes. In a study by Gallagher et al. [57], three different types were reported, based on the visual inspection of the MRI signal intensity of the subcortical white matter tuber component: type A tubers appearing isointense on T1W sequences and subtly hyperintense on conventional or FLAIR T2W sequences; type B appearing hypointense on T1W sequences and homogeneously hyperintense on conventional or FLAIR T2W sequences; and type C tubers presenting a hypointense signal on T1W sequences, hyperintense signal on conventional T2W sequences, and a hypointense central region with a hyperintense rim on FLAIR T2W sequences (cystic-like appearance). According to these authors, type A tubers predominance is found in milder TSC phenotypes, type B in intermediate phenotypes, and type C in more severe phenotypes. Importantly, the mild signal anomaly of type A tubers can be easily missed, which can lead to false-negative MRI studies. In addition, some of the lesions associated with TSC escape the current resolution of diagnostic MRI, including several microstructural abnormalities such as focal dyslamination, heterotopic neurons, clusters of giant cells or "microtubers", and isolated or "sentinel" giant cells that are found in brains of patients with TSC [67]. These subtle anomalies, even if undetected by current imaging techniques, appear to contribute to the burden of disability in TSC patients.

General statements and recommendations from the panel:

- Early development and recurrence of seizures are the hallmark of the most severe end of the clinical spectrum of TSC, which often herald cognitive and behavioral impairments, including ASD.
- The number and size of cortical tubers, particularly when cystic, seem to correlate with neurological outcome.
- Cerebellar tubers are associated with more severe clinical presentations.
- Frequency of white matter RMLs is associated with onset and history of seizures and with intelligence outcome and ASD severity.
- Quantitative analysis of white matter integrity by means of DTI could be used as a biomarker of neurological outcome in TSC.
- MRI is valuable in distinguishing tuber subtypes, which correlate with disease severity.

Radiological techniques to assess neuropathological abnormalities

An accurate and early diagnosis of TSC cannot be based only on clinical features, as the cutaneous and intellectual deficits are not always clinically apparent in the first 2–3 years of life. As a consequence neuroradiological examinations have considerable clinical importance in the diagnosis and in defining the extension and type of central nervous system (CNS) involvement, not only in infants and young children, but also in the fetus. Prenatal and neonatal ultrasonography, CT and MRI are the three imaging techniques commonly used for the diagnosis of TSC, and their value in the identification of the different neuropathological abnormalities characterizing TSC will depend on the developmental stage of the patient.

Which is the optimal imaging technique for the detection of neuropathological abnormalities in patients with TSC?

Prenatal ultrasound

The main diagnostic contribution of fetal ultrasound is the detection of cardiac rhabdomyomas (Fig. 7), which are

usually found by mid third trimester of pregnancy [68–70]. This examination should be performed from 20 to 22 weeks in all pregnant women with a positive family history for TSC. However, the absence of cardiac neoplasm in a fetus at risk of TSC does not exclude this diagnosis [71]. Prenatal ultrasound is also able to identify cortical tubers and SENs, although the sensitivity is greater with prenatal MRI [72]. Therefore, fetal brain MRI is highly recommended when rhabdomyomas are found on fetal ultrasound.

Neonatal transfontanellar ultrasound

Transfontanellar ultrasound can detect cortical tubers and SENs in neonates [73], supporting the diagnosis of TSC in patients in whom rhabdomyomas have been diagnosed by prenatal ultrasound. However, this procedure cannot differentiate them from germinal matrix hemorrhage or heterotopias, and does not exclude the need to perform brain MRI.

CT

Before MRI was available, CT was the procedure of choice for the evaluation of TSC. CT can detect SENs and cortical tubers. However, this technique has serious drawbacks [33, 73, 74], such as radiation exposure and the failure to show uncalcified cortical tubers and other TSC abnormalities, particularly white matter RMLs. CT is still considered the reference standard for identifying parenchymal calcifications in TSC, as conventional MRI sequences are less sensitive in detecting calcifications and may not detect small calcified SENs. In fact MRI fails to detect SENs in up to a third of patients who show SENs at CT [75]. However, this increase in sensitivity is not known to have a prognostic value, and MRI remains the imaging technique of choice for screening patients with TSC.

Despite the overall lower sensitivity of CT compared to MRI for the identification of the different neuropathological abnormalities that characterize TSC, this examination should still be considered in the emergency setting or in the cases in which MRI is contraindicated or not available.

MRI

MRI is the method of choice for demonstrating brain involvement in patients with TSC [76], due to its high sensitivity for detecting the typical neuropathological abnormalities related to this condition, and to the null radiation exposure for the patient. However, one significant disadvantage of MRI is that anesthesia or sedation is often required, particularly in children under 5 years of age. In addition MRI is less sensitive than CT in detecting calcifications, although a recent study has shown that susceptibility-weighted imaging (SWI) has a similar sensitivity to CT in detecting calcifications in SEN [77].

General statements and recommendations from the panel:

- Neuroimaging plays an important role in both the diagnosis and the extension study of TSC in the CNS.
- The main contribution of fetal ultrasound is the detection of cardiac rhabdomyomas.
- In the absence of cardiac rhabdomyomas or family history, fetal brain ultrasound rarely shows abnormalities suggestive of TSC, due to the low sensitivity of this technique.
- When rhabdomyomas are found, fetal brain MRI should be undertaken to detect cerebral lesions.
- Due to its high sensitivity and safety profile, MRI is considered the method of choice for detecting brain abnormalities in TSC patients both in the pre- and postnatal periods.
- The higher sensitivity of CT compared to MRI for detecting SENs (due to its calcified content) has no known prognostic value.
- CT must only be used for the pediatric population in the emergency setting, or in the cases in which MRI is contraindicated or not available.

What are the main considerations for an optimal implementation of MRI in the diagnosis of TSC-related brain abnormalities?

Some key considerations for the optimal implementation of MRI are the use of adequate sequences depending on the age of the patient and the type of lesion. Other important aspects are the role of this technique in the early diagnosis of CNS abnormalities and follow-up.

Technical considerations regarding the age of the patient

Conventional MRI techniques obtained at a minimum field strength of 1.5 T, such as T1W (without and with contrast medium administration) and T2W (conventional and FLAIR) sequences, are commonly used for the detection of TSC-related neuropathological abnormalities. The MRI pattern of TSC lesions changes with the age of the patient and type of lesion. As a consequence, the selection of the most appropriate MRI sequence plays a key role in the accurate and early diagnosis of these abnormalities [36, 73, 78–80].

In neonates and infants <6 months of age, white matter RMLs and SENs are best appreciated on axial and sagittal T1W images (Fig. 7), probably because these planes allow maximal visualization of the longitudinal extent of most white matter anomalies and of SENs of the temporal horns

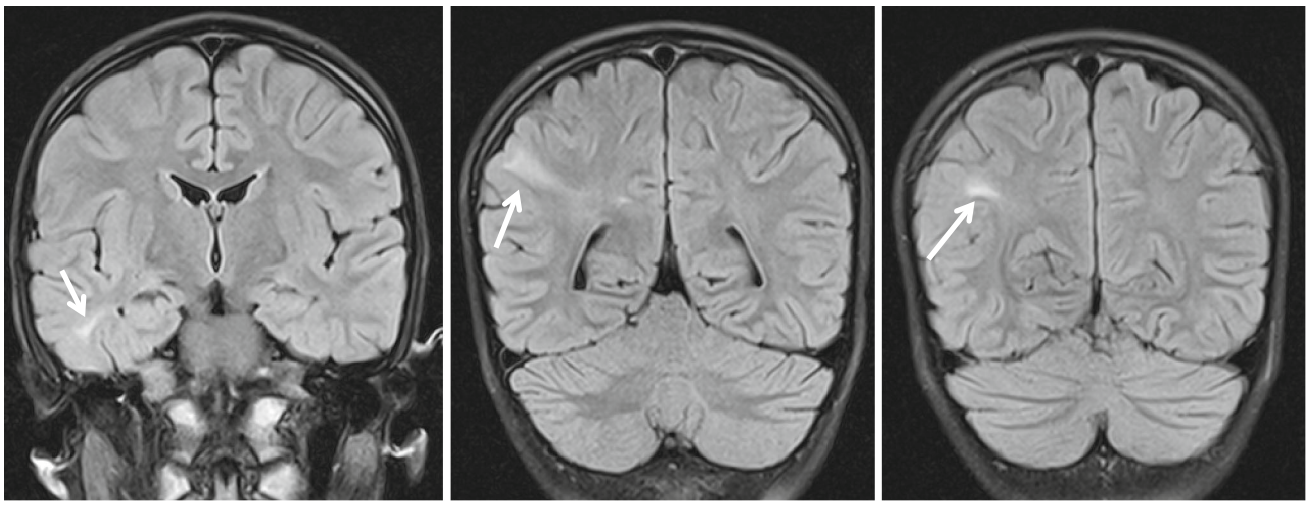

Fig. 8 Coronal T2W FLAIR sequence shows multiple cortical tubers with subcortical increased signal intensity in the right brain hemisphere (*arrows*)

[52]. Conventional/fast T2W sequences serve to exclude other causes of T1 shortening, such as hemorrhage, but are less important for assessing the number and extent of tuberous sclerosis lesions. Given the safety concerns of gadolinium administration in this age group, related to immature renal function, and the limited added value to unenhanced MRI sequences for assessing the number and extent of tuberous sclerosis lesions, contrast-enhanced T1W images are not recommended [52, 81].

In older children (>12 months old) and adults, T2-FLAIR sequences are more sensitive for detecting cortical tubers and white matter RMLs compared to conventional/fast T2W sequences (Fig. 8). In patients between 6 and 12 months old, the reliability of MRI is particularly low [82]. Gradient echo T2* or susceptibility-weighted (SWI) sequences are sensitive for the detection of calcifications in cortical tubers and SENs (Fig. 9), and this sensitivity also increases with the age of the patient. Contrast-enhanced T1W sequences are required for the study of possible SEGAs, and should be obtained in patients older than 2 years. Non-conventional MRI techniques are increasingly being used, in addition to the conventional MRI sequences, to improve the diagnosis and monitoring of TSC [36, 73, 80]. T1W sequences with magnetization transfer (T1 MT) seem to increase the sensitivity for the detection of cortical tubers and, in particular, white matter RMLs, whereas SWI increases the sensitivity of MRI for detecting calcifications.

The role of fetal MRI in the early diagnosis of neuropathological abnormalities

Fetal MRI is sensitive for detecting cardiac rhabdomyomas, which are usually the first radiological manifestation

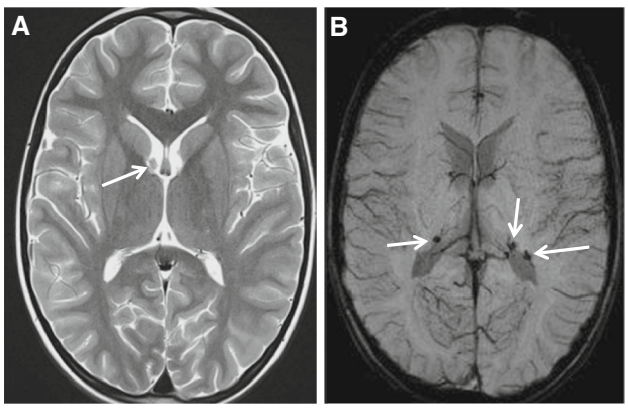

Fig. 9 Brain MRI scan in a 15-year-old female patients with TSC. T2W image (**a**) only shows a small SEN near to the right foramen of Monro (*arrow*), while the susceptibility-weighted image (**b**) clearly identifies additional small-calcified subpendymal nodules (*arrows*)

of TSC [51, 83], and is also a sensitive procedure for the detection of cerebral lesions in these patients [42], although they only rarely represent the first sign of this disease [70]. Fetal brain MRI allows visualization of SENs and cortical tubers without maternal or fetal sedation from the 21st week of gestation, although the sensitivity increases as pregnancy progresses [48] (Fig. 7). The TSC Consensus Conference (TSCCC) criteria for the diagnosis of TSC can be implemented for fetal MRI; however, a negative MRI does not exclude the diagnosis [51]. Half-Fourier acquisition single-shot turbo spin-echo (HASTE) T2W MRI is the technique of choice in the fetal brain, as each image can be acquired in <1 s in the three maternal planes, i.e. axial, sagittal, and coronal [48, 51, 84]. In addition, gradient-echo T1W sequences must be acquired, whenever possible, due to the high lesion/tissue contrast obtained. Nevertheless,

these sequences are of limited value in fetuses <27th gestational weeks [51].

General statements and recommendations from the panel:

(a) The type of MRI sequences, obtained at a minimum field strength of 1.5 T, will depend on the developmental stage of the patients:

1. Prenatal period:
   - T2W HASTE sequences in different planes
   - Gradient echo T1W sequences
2. Neonatal period:
   - Gradient echo/spin echo T1W sequences
   - Conventional T2W sequences
   - Gradient echo T2* or SWI sequences
3. Patients >2 years:
   - Volumetric T1W sequences (with and without contrast medium administration)
   - Conventional and FLAIR T2W sequences
   - Gradient echo T2* or SWI sequences

(b) Fetal MRI is a sensitive procedure for the detection of cerebral lesions in patients with TSC, although a negative MRI does not exclude the diagnosis of TSC.

(c) In neonates and young infants contrast-enhanced T1W sequences are not recommended during baseline MRI screening of patients with TSC.

Diagnosis and follow-up of SENs and SEGAs

The appearance of SENs and SEGAs can vary slightly depending on the MRI technique used and the stage of life of the patient with TSC.

What are the main radiological features that distinguish SENs from SEGAs?

The criteria by which subependymal lesions in TSC should be diagnosed as SEGAs rather than SENs is still a matter of debate, and in fact, the prevalence of SEGAs varies based on the criteria used. According to a meta-analysis published by Adriaensen et al. [85] which included five studies that used radiological evidence to diagnose SEGA, the estimated prevalence was 0.16 (95 % CI 0.12, 0.21). The criteria used in these studies were different and included the following: (a) markedly enhancing lesion on CT/MRI around the foramen of Monro; (b) large partly calcified masses around the foramen of Monro that frequently enhance markedly; and (c) an intraventricular tumor with slightly higher radiodensity than brain on CT, and enhancement after contrast medium administration. The same study estimated the prevalence of SEGAs from seven studies using histopathological evidence to diagnose SEGA (biopsy sampling, surgical resection, or autopsy), resulting in 0.09 (95 % CI 0.07, 0.12), which is significantly lower than in the group of patients diagnosed by radiological criteria. However, these studies did not mention the histopathological criteria used to differentiate SENs from SEGAs, and a selection bias probably exists as these studies selected the more severe cases. This distinction between SENs and SEGAS is largely semantic as both types of lesions are histologically indistinguishable [16, 86]. However, SEGAs, based on serial imaging, appear to arise from SENs and are associated with the potential to grow and become symptomatic, as opposed to SENs, which remain stable (Fig. 5). Common radiological criteria used to diagnose SEGAs include a location close to the foramen of Monro, size $\geq$1 cm, and intense enhancement after contrast medium administration [52, 87]. However, as most SENs also exhibit contrast enhancement, this last feature is not able to differentiate both types of lesions (Fig. 2). In addition, the value of size criterion is limited as it does not consider normalization with brain and ventricular size, which differ according to age and among individuals. Moreover, several authors have indicated that not all lesions fulfilling these criteria will progress to cause symptoms [76, 88, 89], indicating that these radiological criteria do overdiagnose SEGAs. In fact, the key characteristics to suggest that a lesion may be a SEGA are the documented enlargement in serial image examinations (Fig. 5) and hydrocephalus caused by a subependymal lesion in a patient with TSC, regardless of its size or pattern of contrast uptake [16, 33]. One key aspect is the identification of radiological characteristics of the SENs that predict conversion into SEGAs. Nabbout et al. [40] examined these characteristics in a pediatric population with TSC before the age of 10 years at an early preclinical stage with the purpose of defining potential risk factors for further growth of SENs, and found that nodules with >5 mm diameter size, incomplete calcification or no calcification, and gadolinium enhancement, had a higher risk of growing, particularly in children with a familial history of TSC [40, 90].

General statements and recommendations from the panel:

- Radiological criteria used for SEGAs diagnosis based on size and pattern of contrast enhancement likely overdiagnose this type of lesion.
- The key characteristic to consider a subependymal lesion in TSC as a SEGA is the documented growth at serial image examinations.

- A subependymal lesion that causes hydrocephalus in a patient with TSC, regardless of its size or pattern of contrast uptake, is considered by definition a SEGA.
- A diameter >5 mm, location close to the Monro, incomplete calcification and marked contrast enhancement are risk factor for further growth of SENs

What is the optimal frequency of neuroimaging assessments in patients with SENs and SEGAs?

In spite of the fact that SEGAs are histologically benign tumors, they represent potentially dangerous lesions and are one of the two most frequent causes of death in patients with TSC [86, 91, 92]. Without intervention, SEGAs typically continue to grow slowly over weeks to months, with only sparse evidence of regression or growth stabilization [93]. When patients present with clinical features of increased intracranial pressure, emergency surgery is frequently performed. However, the mortality rate and the postoperative outcomes of emergency procedures are poor in comparison with an attempt to complete the resection of the tumor in a non-acute phase. In addition, these tumors are responsible for 25 % of the excess mortality attributable to TSC [94]. Therefore, the early identification and treatment of SEGAs, before the onset of intracranial pressure and irreversible neurologic deficit, has the potential to dramatically improve the duration and quality of life of this population. In line with this, the postoperative outcomes of a clinic-based population with SEGAs and TSC were poor in patients who were not screened with MRI at regular intervals, while surgical outcomes were excellent, with no postoperative or long-term complications, in the majority of patients who were screened regularly with MRI [16, 43].

Children and adolescents seem more likely to develop SEGAs than adults. Therefore, a reasonable approach may be to scan asymptomatic adults less frequently. However, monitoring limits in respect of the age of the patient is a topic under discussion. In most studies, the reported mean age of patients with TSC and SEGAs was under 18 years old. However, a population-based study reported a mean age of 24 years for patients with TSC and SEGAs [95]. In addition, according to a retrospective study that investigated the prevalence of SEGAs in patients with TSC, the mean age of patients was 31 years old, and the age of patients with TSC and complicating hydrocephalus ranged between 21 and 43 years [85].

At present, most authors agree on recommending serial neuroimaging examinations every 1–3 years for pediatric patients (older than 2 years old) with TSC, even in the absence of symptoms [25]. In those patients with SENs having features indicating a higher risk of conversion to growing SEGAs, (the examinations should probably be obtained at shorter intervals. In patients with SENs demonstrating growth over the interval of routine imaging evaluation, or with subependymal lesions >1 cm, follow-up neuroimaging assessments every 3–6 months are probably appropriate [16, 93, 96]. In any patient developing symptoms that suggest progression [93], such as positional (supine) headache, sudden worsening of epilepsy seizures, nausea or vomiting, diplopia or lethargy, an emergency imaging test should be performed. Finally, from the third decade onwards, no monitoring is needed for stable SEGA, while follow-up is recommended to detect recurrence if surgical removal is incomplete or in the rare cases in which the tumor has histopathological features of malignancy [25, 39, 97].

General statements and recommendations from the panel:

- Serial brain MRI every 1–3 years are recommended for pediatric patients older than 2 years old with TSC and until their mid-20 s, even in the absence of symptoms.
- In those patients with SENs having features indicating a higher risk of conversion to growing SEGAs, the examinations should probably be undertaken on a yearly basis.
- In patients with subependymal lesions >1 cm, or diagnosed with SEGAs based on demonstration of lesion growth over the interval of routine imaging evaluation, shorter follow-up imaging assessments (every 3–6 months) are appropriate.
- From the third decade onwards, no monitoring is needed for stable SEGA.
- In TSC patients presenting symptoms of progression, an emergency imaging evaluation should be performed.

What are the main factors governing the treatment of SEGAs?

Three therapeutic options are available for the management of SEGAs namely, surgical resection, gamma knife stereotactic surgery (GK-SRS), and pharmacotherapy with mTORC1 inhibitors [93, 98]. However, to date, limited data regarding GK-SRS safety and effectiveness are available. Therefore, surgery and mTOR inhibitors remain the only realistic treatment options. Early gross surgical resection is the standard of care for patients with SEGAs demonstrating growth on neuroradiological evaluations, particularly when progressive ventriculomegaly or symptomatic hydrocephalus is observed [98, 99]. Nonetheless, the specific timing for surgical procedures remains controversial. On one hand, classical indicators for surgery, such as acute hydrocephalus, worsened seizure burden, or significant interval growth on serial neuroimaging

evaluations, are associated with increased surgical morbidity and mortality [16, 39]. On the other hand, recent data suggest that early surgery for small asymptomatic lesions, identified by neuroimaging surveillance, reduces surgical morbidity and recurrence rates [16, 98, 99]. Additionally, new neurosurgical techniques, such as neuroendoscopy or imaged-guided endoscope-assisted microsurgery, offer effective and minimally invasive options able to decrease surgical morbidity [98].

Pharmacotherapy with mTOR inhibitors [93, 98], i.e. sirolimus, temsirolimus, and everolimus, represents an effective treatment option for SEGAs. Everolimus has been approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of patients with SEGAs associated with TSC. These agents can lead to a significant reduction in the volume of SEGAs [26, 27], often with an improvement of ventriculomegaly and the symptoms of obstructive hydrocephalus. However, there is no consensus on their specific indications or on the optimal dose and duration of therapy, although some recommendations have been recently proposed [25]. In addition, suspension of therapy with an mTOR inhibitor may result in tumor regrowth [100]. Because mTOR inhibitors may be used as a chronic and possibly life-long therapy in the future, safety and efficacy issues arise.

General statements and recommendations from the panel:

(1) Surgical resection is the standard therapy for SEGA with documented growth or if producing obstructive hydrocephalus or clinical symptoms.
(2) mTOR inhibitors are a reasonable treatment option for patients ≥3 years of age:
    - with asymptomatic SEGAs, who have not presented with tumor growth on neuroimaging surveillance in the absence of obstructive hydrocephalus or papilledema or for patients presenting with asymptomatic growing SEGAs who are not eligible for surgery
    - in symptomatic patients when surgery is contraindicated or when total resection is unlikely
    - in patients with recurrent lesions, in which distorted anatomy and postoperative scarring markedly increase surgical morbidity and mortality

Quantitative analysis of SEN and SEGA growth with MRI

Most authors agree on recommending serial neuroimaging for pediatric patients with TSC until their mid-20 s, even in the absence of symptoms, with the purpose of early diagnosis of SEGAs that may benefit of surgical or pharmacological intervention. This diagnosis is mainly based on an accurate neuroimaging identification of growing SENs, which by definition correspond to a SEGA (Fig. 5).

How may a reliable growth rate for SENs and SEGAs be established?

A growth rate of >20 % based on serial neuroimaging studies seems to be a reliable method to identify SEGAs. This rate should be ideally quantified by volumetric measurements, instead of a single linear measurement, i.e. the maximal diameter of the lesion in one dimension, as linear measurements are not sensitive enough to detect changes in a slow-growing lesion such as a SEGA [90].

Recommendations and general agreements of the panel:

- Linear measures on neuroimaging studies are not sensitive enough to detect size changes in SEN or SEGA.
- Volumetric measurements on neuroimaging studies are recommended for accurate detection of size changes in SEN or SEGA.

What are the most appropriate methods to assess SENs and SEGAs growth?

Despite few data being available regarding SEGAs growth, Michelozzi et al. [90] showed that over a median period of 2.5 years, the median SEGA diameter significantly increased from 14 to 15 mm ($p = 0.017$), whereas tumor volume significantly increased from 0.589 to 0.791 mm^3 ($p = 0.006$). In this study, single linear measurements (maximal diameter) demonstrated an increase >20 % in only 7 % of the lesions, whereas volumetric measurements demonstrated this increase in >50 % of the lesions. However, volumetric measurements are time-consuming and difficult to implement in clinical practice. Some linear methods are comparable to volumetric methods, but simpler to implement for routine clinical practice. In fact, a feasible alternative to volumetric methods is to measure the maximal diameter in the three dimensions of the lesion (D1, D2, and D3) and to estimate the lesion volume using the ellipsoid formula [90]:

$$V = 4/3\,\Pi D1 \times D2 \times D3/8$$

This approximation provides a simple and effective way to estimate growth rate in SEGAs [101]. Clinicians should consider treating a SEGA if an increase in volume >20 % is demonstrated in two consecutive neuroimaging evaluations, compared with the nadir evaluation or with the

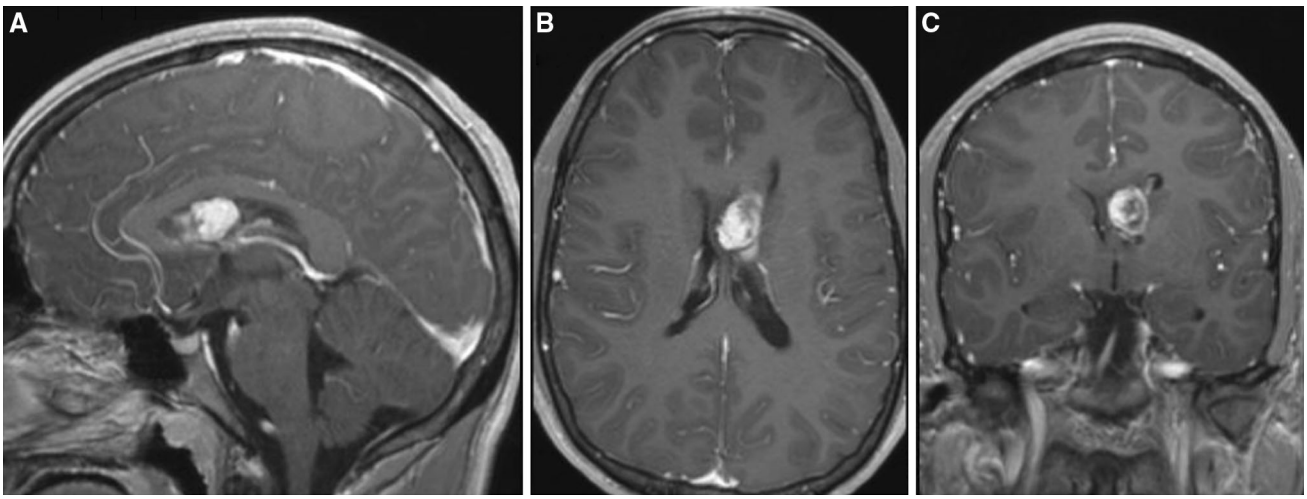

Fig. 10 Multiplanar reconstructed images obtained from a single isotropic three-dimensional contrast-enhanced T1W sequence in 25-year-old patients with TSC and left side SEGA. According to the ellipsoid formula, we can calculate the lesion volume based on the maximal lesion diameter in the sagittal (19 mm), transverse (21 mm) and coronal (13 mm) planes. Lesion volume was 2.715 mm^3

lowest result in terms of lesion volume. For time-saving purposes, only enhancing nodules >5 mm and located near the Monro region require this volumetric estimation, as these are the lesions with a higher risk of converting into SEGAs. As SEGAs are lesions with diffuse and intense contrast-uptake, the three-diameter measurement of these lesions should be assessed on three-dimensional isotropic contrast-enhanced T1W sequences, which can obtain reformatted images in all the three orthogonal axes with one single MRI acquisition (Fig. 10).

Recommendations and general agreements from the panel:

- Contrast-enhanced MRI is the imaging method of choice for monitoring SEGA growth.
- The definition of SEGA growth is an increase >20 % in terms of volume, demonstrated in two consecutive MRI evaluations, compared with nadir or with the MRI assessment with the lowest value.
- A feasible method to assess tumor growth is the measurement of its maximal diameter in the three dimensions, i.e. D1, D2, and D3, and the estimation of the lesion volume using the ellipsoid formula. This method should be only implemented for those lesions with a moderate to high risk of becoming SEGAs, i.e. enhancing lesions with a minimal diameter >5 mm located at the peri-Monro region, or which demonstrate a significant growth on consecutive MRI evaluations.
- To assess the maximal diameter of SEGAs in three dimensions, the implementation of volumetric isotropic contrast-enhanced T1W sequences, with reconstruction in all three orthogonal planes, is required.

Conclusions

Neurological manifestations of TSC are due to several neuropathological abnormalities, such as cortical tubers, white matter RMLs, SENs [1, 2, 15] and SEGAs. An accurate and early diagnosis of TSC cannot be based only on clinical features and as a consequence neuroradiological examinations have considerable relevance in the diagnosis and in defining the extension and type of CNS involvement. Imaging features vary in accordance with the age of the patient, a fact that also influences the selection of the most appropriate imaging technique. SENs and SEGAs are the abnormalities more frequently associated with morbidity. However, the natural history of SEGAs has not been completely elucidated. Transformation of a SEN into a SEGA is usually a gradual process, with the highest rate of transformation during the first two decades of life. The management of SEGAs includes monitoring by periodic MRI, which is age and tumor-size dependent. Typically, serial MRI, with volumetric contrast-enhanced T1W sequences, should be performed every 1–3 years in pediatric patients (older than 2 years) until their mid-20 s, even in the absence of SEGA-related symptoms. Nonetheless, in patients with an identified SEGA, i.e. nodule size >1 cm, MRI examinations every 6 months are appropriate to determine lesion growth. From the third decade of life onwards, no monitoring is required for stable SEGAs, but continued monitoring is recommended for growing SEGAs. Resection is the standard of care for patients presenting with growing tumors and/or tumors causing intracranial hypertension or obstructive hydrocephalus. However, surgical complications are frequent and SEGA

regrowth can occur despite apparently complete lesion resection. mTOR inhibitors have been demonstrated to induce SEGA regression and may provide the first pharmacotherapy alternative to surgery.

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Conflict of interest The authors declare that they do not have any conflict of interest that may inappropriately influence this work.

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