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Tuberous Sclerosis Complex: new criteria for diagnostic work-up and management

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Summary Tuberous sclerosis complex (TSC) is a rare genetic multisystem disorder, characterized by predominantly benign tumors in potentially all organ systems. System involvement, severity of clinical symptoms and the response to treatment are age-dependent and heterogeneous. Consequently, the disorder is still not recognized in a considerable number of patients. The diagnostic criteria and the guidelines for surveillance and management of patients with TSC were revised, and the establishment of specialized TSC-centers was strongly recommended during an International Consensus Conference in 2012. TOSCA (TuberOus SClerosis registry to increase disease Awareness), an international patient registry, was started to allow new insights into the causes of different courses. Finally, there are—since the approval of the mTOR inhibitor Everolimus—promising new therapeutic approaches.

This review focuses on the various TSC related symptoms occurring at different ages, the novel recommendations for diagnosis and treatment as well as the need for multidisciplinary follow-up.

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Keywords Tuberous sclerosis complex · Everolimus · TOSCA · EPISTOP · mTOR-Inhibitor

Neue Kriterien für Diagnostik und Management der Tuberösen Sklerose

Zusammenfassung Die Tuberöse Sklerose (TS) ist eine seltene, genetisch bedingte Multisystemerkrankung, die zu (vorwiegend) benignen Tumoren in nahezu allen Organsystemen führen kann. Sowohl Ausprägung und Schweregrad der klinischen Symptome als auch das Ansprechen auf therapeutische Interventionen sind altersabhängig und zudem individuell äußerst heterogen. Es wird daher angenommen, dass viele Betroffene spät oder gar nicht erkannt werden.

2012 wurden im Rahmen einer internationalen Konsensus Konferenz die diagnostischen Kriterien, sowie die Richtlinien für Therapie und Überwachung überarbeitet und die Etablierung spezialisierter multidisziplinärer TS-Zentren dringend empfohlen. Mit TOSCA (TuberOus SClerosis registry to increase disease Awareness) wurde zudem ein internationales Patienten-Register geschaffen, das neue Erkenntnisse über die Ursachen unterschiedlicher Ausprägung und Verläufe der Erkrankung ermöglichen soll. Seit der Zulassung des mTOR-Inhibitors Everolimus 2011 ist nun erstmals eine spezifische Multisystem-Therapie verfügbar. Der folgende Review Artikel gibt einen umfassenden Überblick über die verschiedenen Symptome und präsentiert die rezenten Neuerungen bezüglich Diagnostik, Therapie und Verlaufsbeobachtung.

Schlüsselwörter Tuberöse Sklerose · Everolimus · TOSCA · EPISTOP · mTOR- Inhibitor

Introduction

Tuberous sclerosis, also known as tuberous sclerosis complex (TSC), is a complex genetic neuro-cutaneous disorder with an autosomal dominant pattern of inheritance, variable expressivity, and incomplete penetrance.

Pathogenic mutations in two genes have been found so far: TSC1 located on chromosome 9q34 and encoding for the protein hamartin (discovered in 1997) and TSC2 located on chromosome 16p13 and encoding for the protein tuberin (discovered in 1993) [1, 2].

In 75–80 % of all individuals with TSC these mutations can be detected, in about 15 % genetic testing does not locate the mutation. In 60 % the mutations are spontaneous. In familial cases, TSC is an autosomal dominant disorder. Rarely, individuals acquire TSC through gonadal mosaicism.

Mutations in TSC2 are more frequent, found in 80–90 % of patients [3, 4] and usually associated with a more severe disease course. In addition, TSC2 is contiguous with PKD1, a gene involved in one form of polycystic kidney disease (PKD). Gross deletions affecting both genes may account for 2 % of individuals with TSC who also develop PKD.

Hamartin and Tuberin form a heterodimer which suppresses the mechanistic target of Rapamycin—formerly:

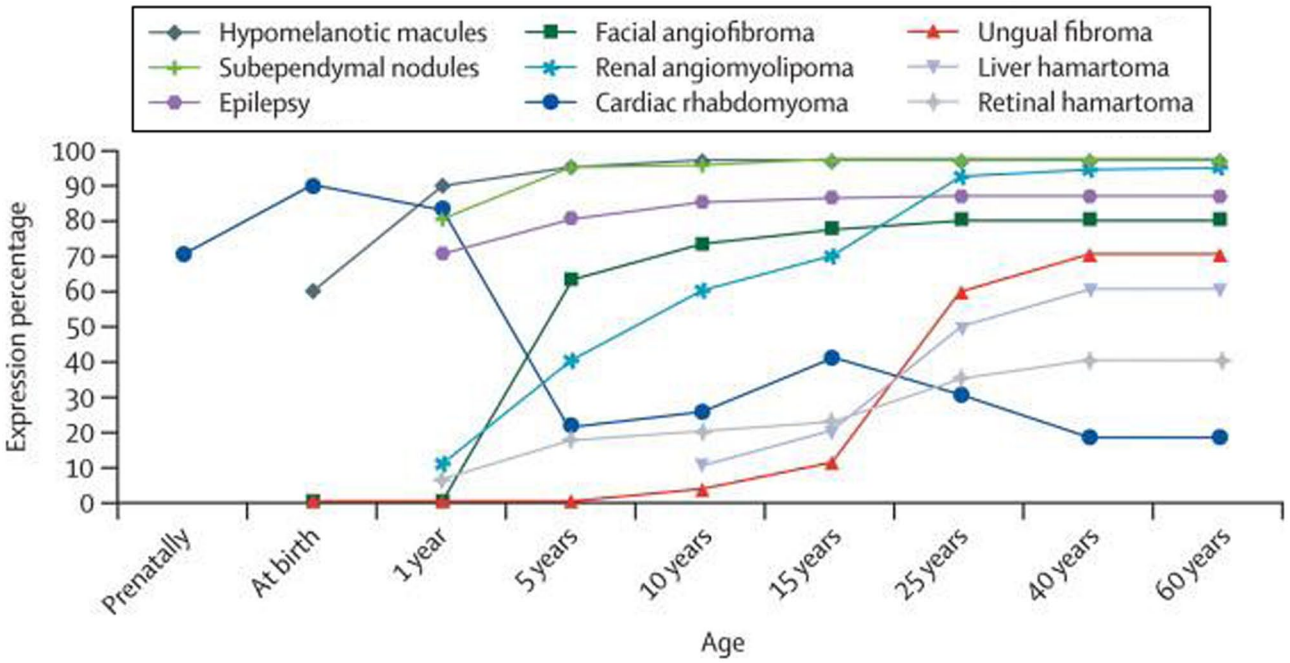

Fig. 1 Age-dependent expression of clinical manifestations in TSC. Reprinted from The Lancet, Vol. 372, Paolo Curatolo, Roberta Bombardieri, Sergiusz Jozwiak, Tuberous sclerosis, pp 657–668, 2008, with permission from Elsevier

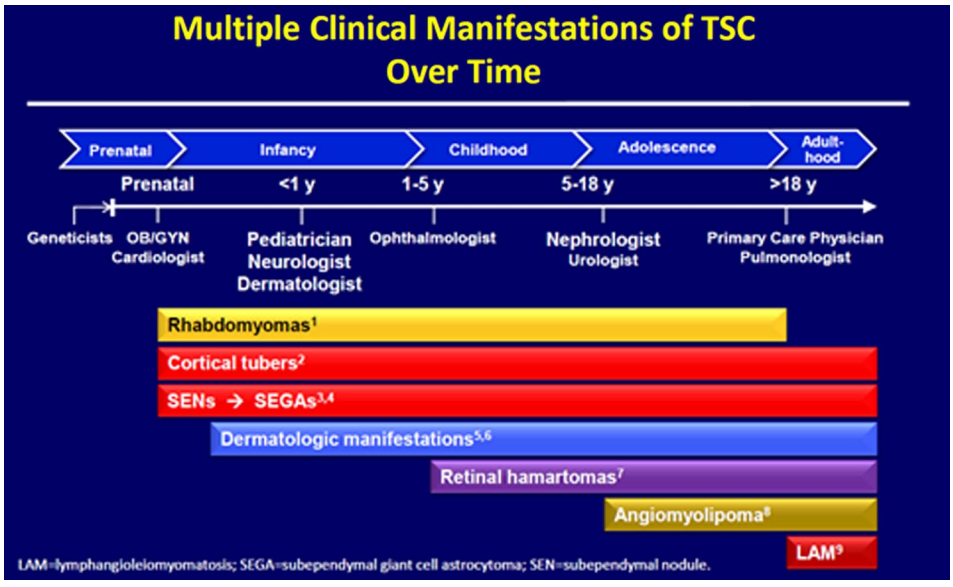

Fig. 2 Age-dependent expression of clinical manifestations in TSC. References cited: [1]Jozwiak S et al., Pediatrics. 2006; [2]Richardson EP, Jr Ann NY Acad Sci. 1991; [3]Park SH et al., Acta Neuropathol. 1997; [4]Wiestler OD et al, Brain Pathol. 1996; [5]Jozwiak S et al, J child Neurol. 2000; [6]Sweeney SM, Adv Dermatol. 2004; [7]Franz DN, J Child Neurol. 2004; [8]RoachES et al, J Child Neurol. 2004; [9]Sparagana SP et al, Curr Opin Neurol. 2000. This image was kindly provided by Novartis

mammalian target of Rapamycin—(mTOR). mTOR is involved in cell proliferation and growth [5, 6]. Inactivating mutations on TSC loci cause loss of control of cell growth and cell division, and a predisposition to forming tumors. The resulting tumors are normally benign although they can cause severe complications due to growth and displacement.

TSC is a rare disease with a live-birth prevalence of about 1:5800 and a total population prevalence of 1:12.500 [7].

According to the results of recent epidemiological studies, TSC is underestimated, as a significant percentage of cases remain undetected, despite the invention of new diagnostic tools (i.e. ultrasound, modern neuroimaging, genetic testing). TSC occurs in all races and ethnic groups, and in both genders.

TSC can affect many different organ systems, causing a variety of signs and symptoms—even within the same family. Most manifestations of the disorder are age dependent with symptoms becoming evident at different time points (Figs. 1 and 2) [8].

Affected organ systems and their treatment (ordered according to the predominant age of onset)

Prenatal period to infancy

Heart

Cardiac rhabdomyomas are often the first indication of the disease (Fig. 3), as TSC is diagnosed in 96% of all fetuses and newborns with cardiac rhabdomyomas [9]. These tumors usually have a diameter of 3-25 mm and are frequently located in the ventricles. Two thirds do not produce clinical consequences and most of them spontaneously regress during childhood [10]. However, because of the possibility of hemodynamic effects, rhabdomyomas need regular and close clinical observation and appropriate and early therapeutic intervention if required. Clinical complications include tachycardia, arrhythmia, outflow obstruction, Wolff-Parkinson-White syndrome, prenatal hydrops fetalis or intrauterine fetal death [9].

Central nervous system (CNS)

Approximately 85% of the patients with TSC suffer from CNS symptoms, and structural lesions in the brain can be found even in up to 95% [8].

According to Magnetic Resonance Imaging (MRI) and histopathology white matter radial migration lines (RML), cortical and subcortical tubers, subependymal nodules (SEN) and subependymal giant cell astrocytomas (SEGA) are distinguished. Rare manifestations are vascular lesions (including aneurysms) and hemimegalencephaly. Not all types of lesions are found in each patient [11].

RML are the most frequent neuroanatomical alterations [11, 12]. RML are neuronal and glial elements, whose cortical migration stagnated during brain development. They are located in the subcortical white matter and often terminate in a tuber. On Cranial Computed Tomography (CCT) these lines are frequently missed, but on MRI—depending on the selected program and grade of myelination—they can be seen as band-shaped lesions traversing the deep white matter [11, 12]. Brain tubers are glioneural hamartomas and are present in 90% of patients—in 95% they are multiple. 90% are localized (cortically or subcortically) in the frontal lobes, infraten-

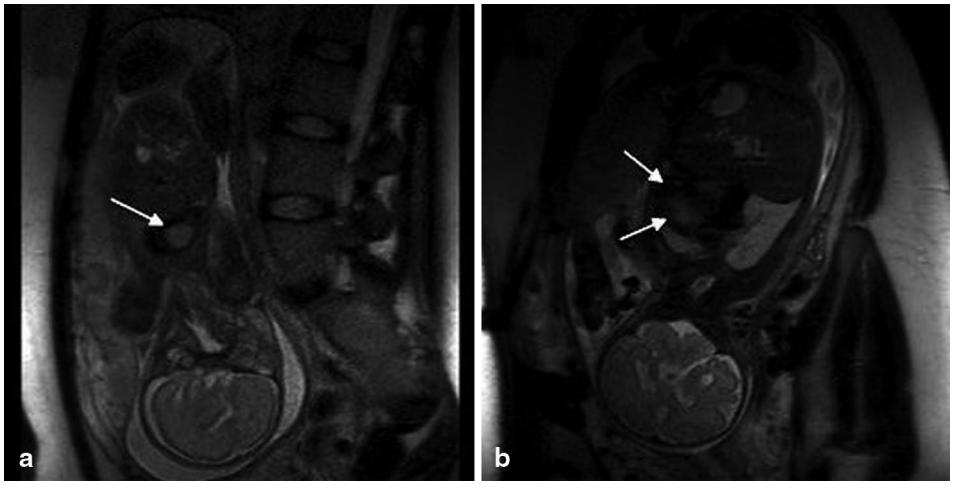

Fig. 3 Fetal MRI, Department of Biomedical Imaging and Image-guided Therapy, General Hospital of the Medical University of Vienna. **a** Cardiac rhabdomyoma on fetal MRI, 25+1 weeks of gestation. The diameter is 1cm. **b** Check-up of the fetal MRI, 35+1 weeks of gestation. It shows a marked cardiomegaly with a transverse diameter of ¾ of the thorax diameter and several – held-to 2.2 cm in diameter –rhabdomyomas. In pregnancy week 36 + 3, the planned cesarean section was performed with subsequent therapy with Everolimus for 1.5 years – the tumors regressed under the therapy. This image was kindly provided by the Department of Biomedical Imaging and Image-guided Therapy

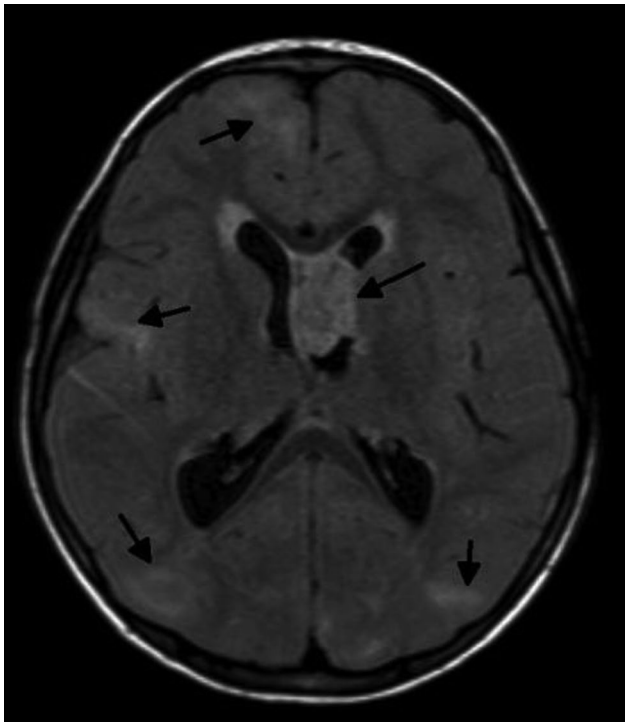

Fig. 4 cMRI, Department of Biomedical Imaging and Image-guided Therapy, General Hospital of the Medical University of Vienna. SEGA 3 × 1,5 × 3,5 cm in the left lateral ventricel of a 6 year old TSC patient. In addition appear multiple cortical tubers. The SEGA was partially resected, on the basis of acute intracranial pressure symptoms after closure of the foramen of Monro. This image was kindly provided by the Department of Biomedical Imaging and Imageguided Therapy

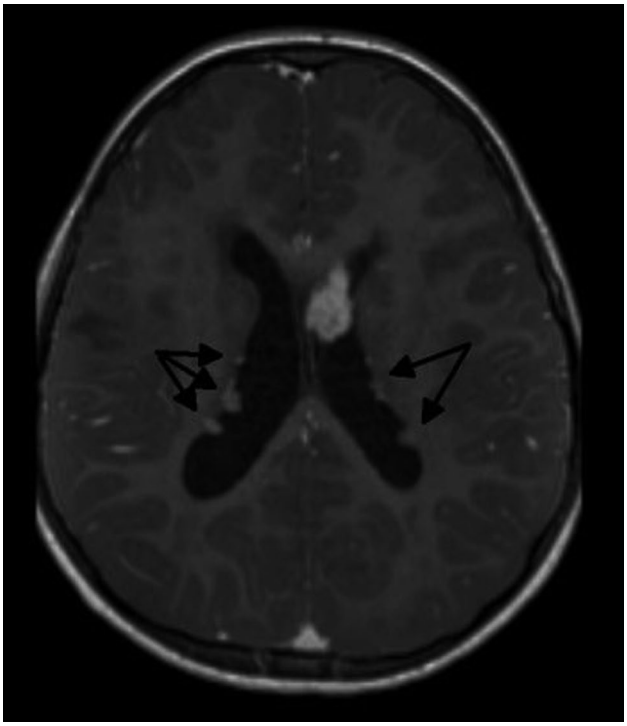

Fig. 5 cMRI, Department of Biomedical Imaging and Image-guided Therapy, General Hospital of the Medical University of Vienna. Multiple SEN located along the walls of the lateral ventricles of a 6-year-old TSC patient. The SEGA in the left lateral ventricle is clearly visible on this picture. This image was kindly provided by the Department of Biomedical Imaging and Image-guided Therapy

torial localizations are rare. SEN are usually located near the foramen of Monro, adjacent to the caudate nuclei. In children > 1 year they are often calcified and then easily detected by computerized tomography (CT).

SEGA develop from SEN in 5–15 %. SEGA are low grade (WHO grade I) mixed glioneural und highly vascularized tumors, that usually grow slowly and develop within the first 2 decades of life. However, due to their anatomical proximity to the foramen of Monro they can lead to obstructive hydrocephalus and thus to life—threatening complications (Figs. 4 and 5). Although SEGA can occur already prenatally or in the neonatal period, the main age of onset is between 8 and 18 years (Fig. 6).

The most common neurological symptoms in TSC patients are epileptic seizures, occurring in 80–90 % [13–15]. Onset of TSC-associated epilepsy is usually within the first year of life. Although seizures of all types may occur, the most frequently observed are focal seizures. These can proceed into infantile spasms or coexist with them. Two thirds of the TSC patients with epilepsy are pharmaco-resistant [13, 16, 17]. About 30 % of TSC patients develop cognitive impairment and about 50 % do have average intelligence (IQ > 70), but may have deficits in memory, attention, or executive skills [8].

Various psychiatric comorbidities occur also in the context of TSC, e.g. autism spectrum disorder (ASD; repoted in 25–50 %), attention deficit hyperactivity disorder (ADHD; reported in 20–55 %), conduct disorder (CD), obsessive compulsive disorder, anxiety disorder, depression and psychosis They are subsumed under the concept of "TSC-associated neuropsychiatric disorders (TAND)" [18].

Annual follow up including MRI, as well as neurological, neuropsychological and psychiatric investigations is therefore strongly recommended. Treatment recommendations for CNS related complications in TSC patients include medical and surgical interventions:

In 2012 the current guidelines and recommendations for the management of SEGA were defined as follows [19]; Small asymptomatic SEGA should be regularly monitored by MRI. Neurosurgical resection should occur in a timely manner, because an early operation is associated with a good outcome regarding morbidity and tumor recurrence [11]. Large or growing SEGA must be closely monitored by imaging to be able to recognize and treat cerebrospinal fluid (CSF) flow obstruction on time. Obstructive hydrocephalus is a neurosurgical emergency needing immediate surgery. Total or sub-total resection of the causative SEGA and—if necessary—additional shunting is the treatment of choice. Asymptomatic slowly growing SEGA with risk of CSF flow obstruction can be treated conservatively using mTOR inhibitors. Since November 2013 Everolimus

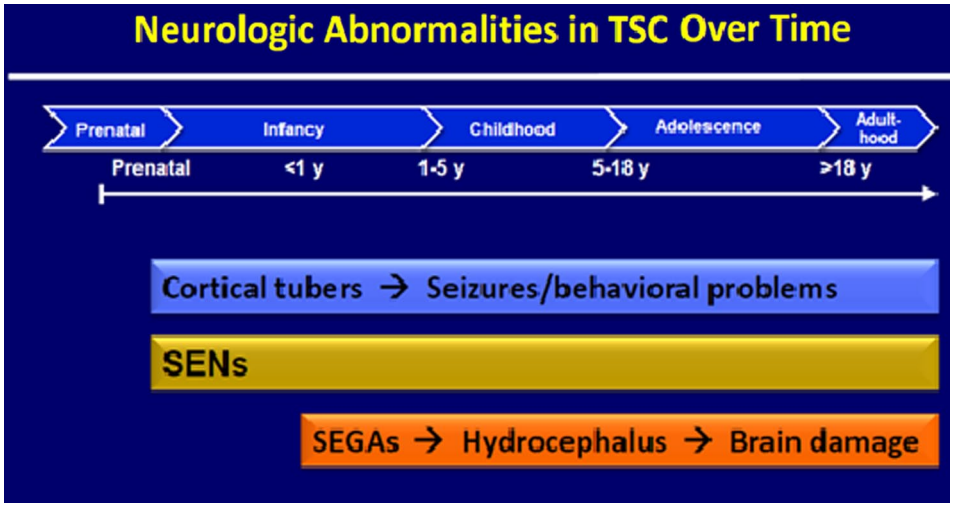

Fig. 6 Age-dependent expression of neurological manifestations in TSC. References: Richardson EP, Jr Ann NY Acad Sci. 1991; Park SH et al., Acta Neuropathol. 1997; Wiestler OD et al, Brain Pathol. 1996. This image was kindly provided by Novartis

(Votubia®) is approved in the EU for adults and children for the treatment of SEGA—if neurosurgery is not appropriate because of location and/or size [20].

Early and effective treatment of epilepsy with anticonvulsant drugs (AED) is essential to prevent developmental deterioration. Vigabatrin is the AED of choice for infantile spasms. In case of Vigabatrin failure ACTH can be used [21, 22]. Treatment of other types of seizures depends on the current treatment recommendations of the International League Against Epilepsy (ILAE). In case of drug resistance, candidacy for epilepsy surgery should be evaluated at specialized centers, as both seizure freedom and favorable developmental outcomes can be achieved in well-selected patients [23, 24]. According to recent studies, AED treatment already started at the onset of epileptiform discharges in the EEG and prior to the occurrence of clinically overt seizures seems to be more efficient in preventing developmental deficits [25].

Screening for TAND should be performed at least once per year by child and adolescent psychiatrists using standardized tools. At key developmental time points recommended age-appropriate neuropsychological tests should be carried out (Table 2). Treatment should be evidence-based and follow the actual guidelines/practice parameters for individual disorders [18].

Eyes

Retinal hamartomas are observed in 40–50 % of TSC patients and multiple lesions are not unusual. They can have different manifestations: The most common are subtle, relatively flat, smooth-surfaced, salmon-colored, circular or oval-shaped lesions, located near or at the posterior pole [26, 27]. Usually they cause no visual problems and they can be an important clue to the disease in the absence of other TSC-specific characteristics. Retinal achromic patches occur in 39 % of TSC patients [27, 28].

For patients with previously identified ophthalmologic lesions or visual symptoms annual ophthalmological control visits are recommended. Development of any new visual symptoms must be investigated by specialist doctors. In rare cases, retinal hamartomas can lead to complications such as bleeding in the vitreous body or retinal detachment. In this case the treatment of choice is laser or photodynamic therapy [29].

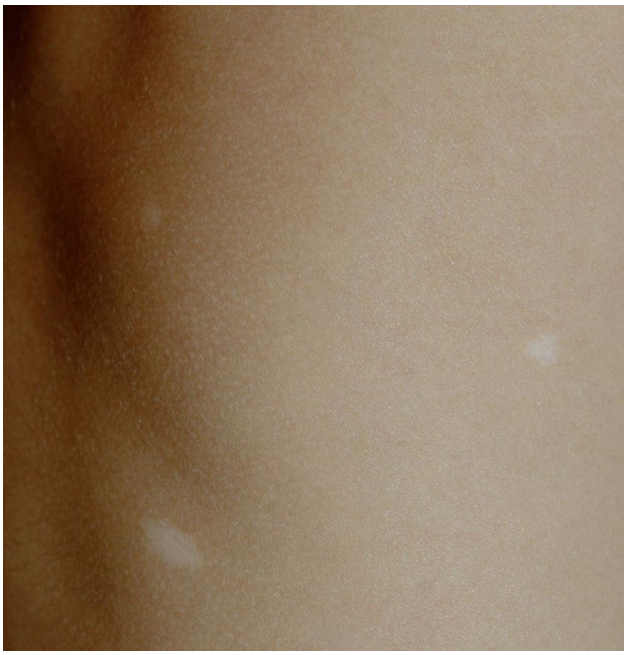

Fig. 7 Picture, Department of Dermatology, General Hospital of the Medical University of Vienna. Hypomelanotic macules or „ash – leaf – spots“ on the torso of a TSC patient. This image was kindly provided by the Department of Dermatology. Informed consent was given

School age to adolescence

Skin

Pigment disorders like hypomelanotic macules “ash—leaf—spots” or “confetti lesions” are often the only skin alterations detected during childhood (Fig. 7). They

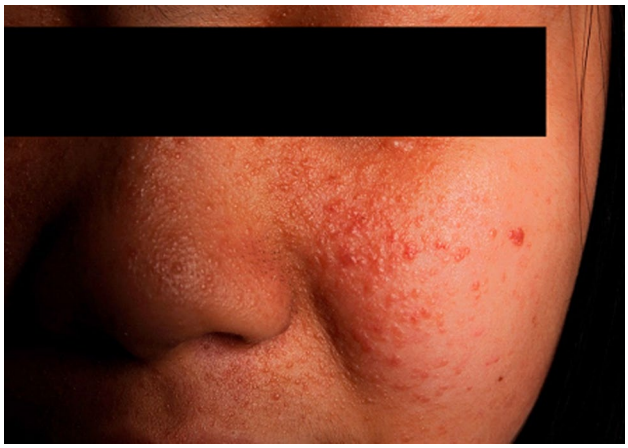

Fig. 8 Picture, Department of Dermatology, General Hospital of the Medical University of Vienna. Facial angiofibromas of an adolescent TSC patient. This image was kindly provided by the Department of Dermatology. Informed consent was given

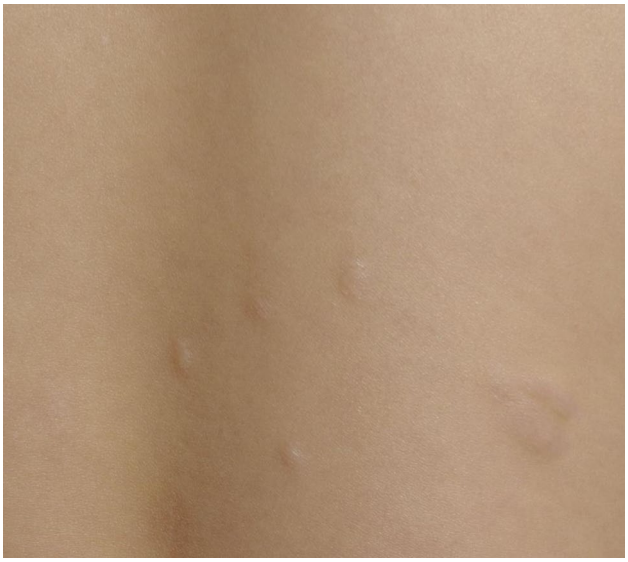

Fig. 9 Picture, Department of Dermatology, General Hospital of the Medical University of Vienna. Lumbosacral Chagrin-patches in a TSC patient. This image was kindly provided by the Department of Dermatology. Informed consent was given

occur in approximately 90 % of patients and may already be evident in the neonatal period [3, 30–34]. They can be visualized by "Wood light".

Facial angiofibromas usually occur during late childhood in about 75 % of the patients (Fig. 8). Forehead plaques and Chagrin-patches (large plaques on the lower back that have a bumpy or orange-peel surface) are found in 50 % of children older than 5 years (Fig. 9). Ungual fibromas—also known as "Koenen's tumors"—are small, reddish-brown, fibromatous nodules, that emanate from the nail fold. They typically become manifest in adolescence or young adulthood (Fig. 10) [35].

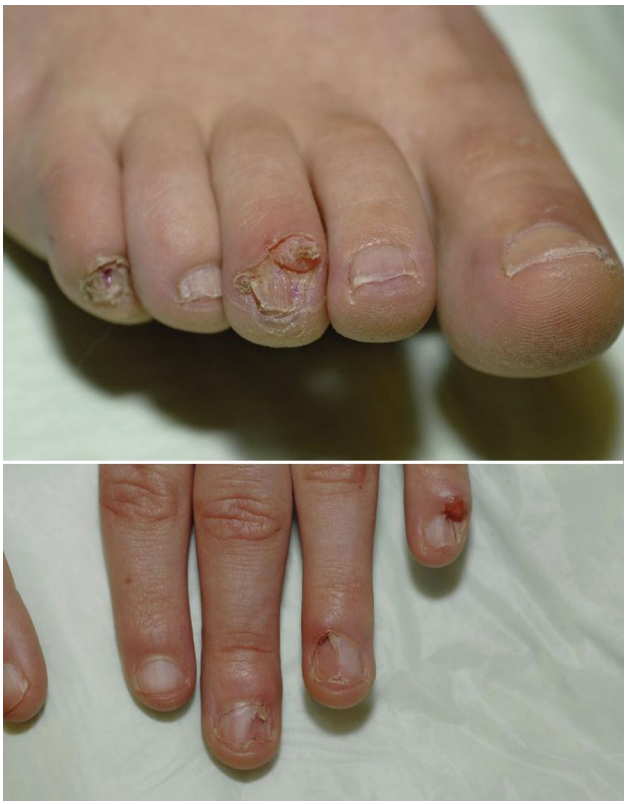

Fig. 10 Picture, Department of Dermatology, General Hospital of the Medical University of Vienna. Ungual fibromas „Koenen's tumors" on the toes and fingers of an adolescent TSC patient. This image was kindly provided by the Department of Dermatology. Informed consent was given

Hypomelanotic macules (≥ 3), Angiofibromas (≥ 3) or forehead plaques, Chagrin-patch and ungual fibromes (≥ 2) are among the major diagnostic criteria for TSC [36].

UV radiation induces, in addition to the existing TSC1/TSC2 mutation, a further DNA damage ("second hit"). This leads to increased development of angiofibromas on sun exposed areas. Prevention of sun exposure and use of effective sun protection can have a positive effect on their number and severity [37].

Annual dermatological control examinations performed by dermatologists, familiar with the disorder, are recommended. Therapeutically especially laser therapy, surgical resection and local drug agents come to use. As a new treatment option in the future, mTOR inhibitors can also be applied locally as an ointment preparation [38, 39].

Mucosa and teeth

"Dental enamel pits" are rounded dental enamel defects and occur in 90 % of the patients with TSC. About 20–50 % develop intraoral fibromas on gingiva, buccal mucosa or tongue [8, 36]. TSC patients should receive semiannual dental checks and a panoramic radiograph should be performed in case of bony jaw lesions, like asymptomatic swelling, abnormal tooth eruption or asymmetry [36].

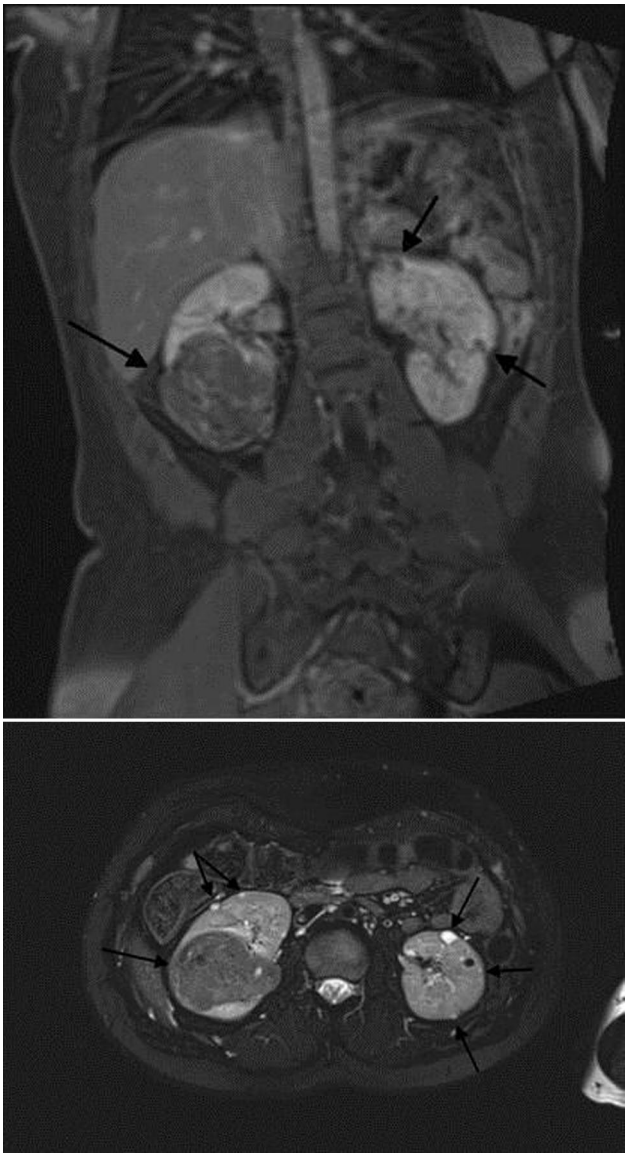

Fig. 11 MRI kidney, Department of Biomedical Imaging and Image-guided Therapy, General Hospital of the Medical University of Vienna. 21 year old TSC patient with multiple renal AML. The largest lesion in the right kidney measures 6.7 × 5 × 6.2 cm. This image was kindly provided by the Department of Biomedical Imaging and Imageguided Therapy

Adolescence to Adulthood

Kidneys

TSC specific renal lesions include angiomyolipoma (AML), renal cysts and—rarely—renal cell carcinomas. Although AML and renal cysts can be present already during childhood and adolescence, related complications occur primarily in adult patients [8].

Renal complications are the most common cause of TSC-associated death [40]. 70–90 % of adult TSC patients (women > men), but only 16 % of 2-year-old children, have—most often multiple and bilateral—renal angiomyolipomas (AML) (Fig. 4) [41, 42]. These tumors usually grow slowly and consist of smooth muscle cells, fat cells and blood vessels; Microaneurysms may reduce vessel stability. Spontaneous intra-renal or intraperitoneal bleedings are the most common complications associated with tumors of > 4 cm diameter [43]. Singular or multiple renal cysts occur in 20 % of patients and are usually asymptomatic. A polycystic kidney disease type I, with the potential complication of end stage renal failure, occurs in the case of an additional PKD1 mutation [44]. Renal cell carcinomas develop in 2–3 % of patients [45–47].

Worldwide about 1 million TSC patients suffer from chronic renal failure, which can be caused by both AML and renal cysts. 1 % of all TSC patients with normal intellect develop end-stage renal failure [48].

Renal hypertension is a serious complication in the majority of TSC patients with renal manifestations. The response to angiotensin-converting-enzyme inhibitors (ACE inhibitors) and angiotensin receptor blockers is very good. However, concomitant use of ACE inhibitors and mTOR inhibitors has been reported to minimize the effect of the mTOR inhibitor and increase the risk of angioedema [49–51].

Nephrological control examinations should be performed every 1–3 years and include MRI and laboratory examinations to test renal function. For asymptomatic and growing AML with a diameter of > 3 cm, the treatment with an mTOR inhibitor is the recommended first line therapy in patients > 18 years [52]. In the second line selective embolization, kidney-sparing resection, or ablative therapy for exophytic lesions are recommended. In case of acute hemorrhage embolization followed by corticosteroids is the treatment of choice. Nephrectomy should be avoided, because it increases the risk of end-stage renal failure.

Regular assessment of blood pressure is required. Patients with renal hypertension should be treated with a renin-aldosterone-angiotensin inhibitor (CAVE: no concomitant use of ACE inhibitors and mTOR inhibitors).

Lung and liver

1–3 % of TSC patients develop pulmonary lymphangioleiomatosis (LAM). LAM is characterized by alveolar smooth muscle cell proliferation and cystic remodeling and destruction of the lung parenchyma [53]. LAM primarily affects premenopausal women, is difficult to treat and has an overall poor prognosis.

Patients usually reach grade 2 on the Medical Research Council (MRC) dyspnea scale after an average of 5.7 years and grade 3 after 9.3 years (walking distance < 100 m). The 10 year survival rate is 90 % [54]. Dyspnoea is the most common symptom and occurs in about 70 %. Pneumothorax may be the first manifestation of LAM in some cases. It affects 50 % of patients and recurs frequently. The increased awareness for LAM is leading to earlier diagnosis—when the condition is completely asymptomatic or only characterized by cough and mild dyspnea—before such severe complications occur [55].

Estrogens appear to play a major role in the development and progression of LAM. LAM cells express a high number of α-estrogen receptors, an important mediator of estrogen-induced cell proliferation in uterine and breast cancer. The clinical manifestation in the premenopausal age, the exacerbation in pregnancy and the exacerbation caused by oral estrogen preparations suggest a strong influence of estrogens on LAM [56].

Evaluation of TSC patients at risk for LAM should be performed at regular intervals: Imaging studies, using HR CT, are recommended every 5–10 years in asymptomatic patients and every 3 years in patients with known lesions. Patients with known lung cysts need lung function tests on an annual basis (Table 2).

Currently, the only proven treatment for LAM is lung transplantation, but circulating LAM cells can lead to a relapse [57, 58]. The results of recent studies suggest, that mTOR inhibitors could improve the prognosis, by slowing the evolution of LAM [59, 60].

In 16–24% of TSC patients (primarily adults) AML occur in the liver. They grow slower than renal AML and do not lead to significant complications [61].

Rare organ manifestations

Bone cysts and hamartomas in adrenals, pancreas, gonads and intestine (hamartomatous rectal polyps) are described only in individual cases and are not considered as specific for TSC. Treatment is symptomatic [62].

Central and peripheral aneurysms and large and medium size arterial stenotic-occlusive disease have been reported [63].

Diagnostic criteria

In 2012, the diagnostic criteria were revised at an International TSC Consensus Conference [36]. Based on clearly defined major and minor criteria and molecular genetics, definitive or possible TSC diagnosis can be made.

For the definitive diagnosis of TSC two major criteria *or* one major criterion and ≥2 minor criteria have to be present. For a possible diagnosis, 1 major criterion or ≥2 minor criteria should be found.

A pathogenic mutation in the TSC1 or TSC2 gene is by itself sufficient for a definite diagnosis, even in the absence of major and minor clinical criteria at diagnosis (Table 1).

Table 1 Diagnostic criteria for tuberous sclerosis complex. (From: Northrup H, Krueger DA, on behalf of the International Tuberous Sclerosis Complex Consensus Group. Tuberous Sclerosis Complex Diagnostic Criteria Update: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. Pediatr Neurol 2013; 49: 243–254. © The authors)

Definite diagnosis	2 major criteria *or* 1 major criterion and ≥2 minor criteria
Possible diagnosis	1 major criterion *or* ≥2 minor criteria
Major criteria	
Angiofibromas (≥3) or forehead plaque	
Hypomelanotic macules (≥3)	
Ungual fibromas (≥2)	
Chagrin patch	
Multiple retinal hamartomas	
Cortical dysplasias (≥3, include tubers and cerebral white matter radial migration lines RML)	
Subependymal nodules (SEN)	
Subependymal giant cell astrocytoma (SEGA)	
Cardiac rhabdomyoma	
Lymphagioleiomatosis (LAM)[a]	
Renal angiomyolipomas (AML), (≥2)[a]	
Minor criteria	
Dental enamel pits (≥3)	
Intraoral fibromas (≥2)	
Non-renal hamartomas	
Retinal achromatic patch	
Confetti skin lesions	
Multiple renal cysts	
Genetic diagnostic criteria	
A pathogenic mutation in the TSC1 or TSC2 gene is by itself sufficient for a definite diagnosis.	
Pathogenic mutation (out-of-frame indel, nonsense mutation, frameshift mutation, large genomic deletion):	
Clearly prevents protein synthesis	
Inactivates the function of the TSC1 or TSC2 protein	
Other TSC1 or TSC2 variants whose effect on function is less certain are not sufficient to make a definite diagnosis of TSC	
CAVE: About 15% of TSC patients have no mutation identified by conventional genetic testing. A normal result does not exclude TSC!	
[a]Combination of LAM and AML without other features does not meet criteria for a definite diagnosis	

Monitoring and management of TSC patients

TSC is a life-long disease that currently cannot be cured. Therefore, prophylaxis of possibly life-threatening complications is of highest priority. Moreover, the nature and extent of organ manifestations and thus potential complications change continuously with age. Therefore, the management of patients with TSC requires regular follow-up by a multidisciplinary team of specialists. The recommendations of the International TSC Consensus Conference in 2012 for monitoring and management of TSC patients and their complications are summarized in Table 2. Guidelines for the management of newly diagnosed TSC patients or patients with suspicious TSC were also published (Table 3).

Recent advances in the treatment of TSC

So far, the treatment of TSC was limited to the symptomatic treatment of secondary complications. In autumn 2011 the first drug for the causal treatment of various organ manifestations has been approved in Europe.

Table 2 Recommendations for monitoring and management of TSC patients. (From: Krueger DA, Northrup H, on behalf of the International Tuberous Sclerosis Complex Consensus Group. Tuberous Sclerosis Complex Surveillance and Management: ecommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. Pediatr Neurol 2013; 49: 255–265. © The authors)

Genetics	Offer genetic testing for family counseling or when TSC diagnosis is in question but cannot be clinically confirmed
Brain	MRI of the brain every 1–3 years in asymptomatic TSC patients < 25 years to monitor for new occurrence of SEGA
	Large or growing SEGA, or SEGA causing ventricular enlargement—but still asymptomatic—should undergo MRI scans more frequently and the patients and their families should be educated regarding the potential of new symptoms
	Patients with asymptomatic SEGA in childhood should continue to be imaged periodically as adults to ensure there is no growth.
	Surgical resection should be performed for acutely symptomatic SEGA. Cerebral spinal fluid diversion (shunt) may also be necessary.
	For growing but asymptomatic SEGA: surgical resection or medical treatment with mammalian target of rapamycin complex (mTOR) inhibitors may be used.
	Screening for TAND
	Detailed history at annual inspections
	Age appropriate neuropsychological tests at developmental time points
	0–3y
	3–6y
	6–9y
	12–16y
	18–25y
	Treatment and management should be evidence-based and follow the actual guidelines/practice parameters for individual disorders
	Sudden change in behavior should prompt medical/clinical evaluation to look at potential medical causes (e.g., SEGA, seizures, renal disease)
	Routine EEG in patients with known epilepsy; 24h video-EEG when seizure occurrence is unclear or when unexplained sleep, behavioral changes, or other alteration in cognitive or neurological function is present
	Vigabatrin is the recommended first-line therapy for infantile spasms. Adrenocorticotropin hormone (ACTH) can be used if treatment with Vigabatrin is unsuccessful
	Anticonvulsant therapy of other seizure types in TSC should generally follow that of other epilepsies
	Epilepsy surgery should be considered for medically refractory TSC patients, but special consideration should be given to children at younger ages experiencing neurological regression and is best if performed at epilepsy centers with experience and expertise in TSC
Kidney	MRI every 1–3 years, to assess for the progression of AML and renal cystic disease
	Assess renal function (including determination of glomerular filtration rate [GFR]) and blood pressure at least annually
	Embolization followed by corticosteroids is first-line therapy for AML presenting with acute hemorrhage
	For asymptomatic, growing AML > 3 cm in diameter, treatment with an mTOR inhibitor is the recommended first-line therapy
	Selective embolization or kidney-sparing resection are acceptable second-line therapy for asymptomatic AML
	Nephrectomy is to be avoided!
Lung	Clinical screening for LAM symptoms, including dyspnea and shortness of breath, at each clinic visit
	Counseling regarding smoking risk and estrogen use should be reviewed at each clinic visit for individuals at risk of LAM
	HRCT every 5–10 years in asymptomatic individuals at risk of LAM, if there is no evidence of lung cysts on their baseline HRCT
	Individuals with lung cysts detected on HRCT should have annual pulmonary function testing (including 6-min walk) and HRCT interval reduced to every 2–3 years
	mTOR inhibitors may be used to treat LAM patients with moderate to severe lung disease or rapid progression
	TSC patients with LAM are candidates for lung transplantation but TSC comorbidities may impact transplant suitability
Skin	Detailed clinical dermatologic inspection/exam annually
	Rapidly changing, disfiguring, or symptomatic TSC-associated skin lesions should be treated as appropriate for the lesion and clinical context (surgical excision, laser, topical mTOR inhibitor)
Teeth	Detailed clinical dental inspection/exam at minimum every 6 months
	Panoramic radiographs by age 7 years (if not performed previously)
	Symptomatic or deforming dental lesions, oral fibromas, and bony jaw lesions should be symptomatically treated
Heart	Echocardiogram every 1–3 years in asymptomatic pediatric patients until regression of cardiac rhabdomyomas is documented
	More frequent or advanced diagnostic assessment may be required for symptomatic patients
	Electrocardiogram every 3–5 years in asymptomatic patients of all ages to monitor for conduction defects
	More frequent or advanced diagnostic assessment may be required for symptomatic patients
Eye	Annual ophthalmologic evaluation in patients with previously identified ophthalmologic lesions or vision symptoms
	Reevaluation is necessary if new visual symptoms develop
	More frequent assessment, including those treated with Vigabatrin, is of limited benefit and not recommended unless new clinical concerns arise.

Table 3 Recommendations for management of newly diagnosed or suspected TSC patients. (From: Krueger DA, Northrup H, on behalf of the International Tuberous Sclerosis Complex Consensus Group. Tuberous Sclerosis Complex Surveillance and Management: Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. Pediatr Neurol 2013; 49: 255–265. © The authors)

Genetics	Family tree over three generations to detect other family members with disease risk
	Genetic testing; also for family members
Brain	cMRI
	TAND evaluation
	Training of parents to recognize infantile spasm
	Asymptomatic, but growing SEGA, with risk of CSF—flow obstruction can be treated conservatively using mTOR inhibitors or resected early
	Routine EEG and 24h video-EEG Monitoring with changes in routine EEG or TAND symptoms to detect subclinical seizures
Kidney	MRI of abdomen
	Screening for renal hypertension –> measurement of blood pressure laboratory examinations to test renal function (including GFR)
Lung	pulmonary function testing, including 6-min walk
	Evaluation of other risk factors: smoking and estrogen therapy
	HRCT—in asymptomatic high-risk patients (women > 18 years) and men with pulmonary symptoms
Skin	Detailed clinical examination
Teeth	Detailed examination
Heart	Fetal echocardiogram if there is suspicion of a cardiac rhabdomyoma after prenatal ultrasound
	ECG in all patients
Eye	Ophthalmologic examination, including funduscopy

Based on molecular genetic findings and the understanding of the pathophysiology of TSC, mTOR inhibitors, were developed that showed the ability to reduce—as a potential systemic treatment—the size of tumors, improve kidney and lung function and reduce skin symptoms.

Rapamycin is an antibiotic macrolide and mTOR inhibitor with immunosuppressive and antiproliferative effect, which is used in oncology for tumor therapy and for the prevention of organ rejection after organ transplantation since many years. Rapamycin regulates the uninhibited, activated mTOR mechanism, and multiple studies suggest that Rapamycin and its analogs may be effective in the treatment of the different TSC related manifestations [64].

Two studies (EXIST-1 and EXIST-2) demonstrated the efficacy of Everolimus, a Rapamycin-analog, in SEGA, renal angiomyolipoma, pulmonary lymphangioleiomatosis and dermatological manifestations of TSC [20, 52]. Everolimus is now approved in Europe since 2011 as an orphan drug for the treatment adults and children from birth (upgrade of indication in 2013) presenting with SEGA not suitable for surgery and patients > 18 years presenting with renal angiomyolipoma [65, 66]. A "side effect" of the tretatment with Everolimus recognized in EXIST-1 and -2 studies was a reduction in seizure frequency in some of the TSC patients with epilepsy. This effect is currently investigated systematically (EXIST-3 study). First results of this study are expected in 2015/2016".

However, a number of side effects, ranging from mild symptoms to serious complications, have been reported to be associated with Everolimus treatment. The side effects noticed most frequently are ulcerations of oral and nasal mucosa and stomatitis, rhinopharyngitis, cephalea, diarrhea, dyslipidemia, disorders of menstrual cycle and ovarian cysts [67]. Treatment with mTOR inhibitors should therefore only be performed at specialized centers.

TuberOus SClerosis registry to increAse disease awareness (TOSCA)

In 2011, an international, multicenter registry "TuberOus SClerosis registry to increAse disease awareness (TOSCA)" was launched. The study aims of TOSCA include a better understanding of the various disease manifestations and their prognosis, the identification of rare symptoms and comorbidities as well as patients at risk for serious complications. The registry is supervised by an international scientific expert committee. In the substudy PASS (Post Authorization Safety Study), the long-term efficacy, safety and tolerability of Everolimus (Votubia®) is also investigated.

EPIleptogenesiS in a genetic model of epilepsy—Tuberous sclerOsis comPlex (EPISTOP)

In November 2013, the international, multicenter project EPISTOP (EPIleptogenesiS in a genetic model of epilepsy - Tuberous sclerOsis comPlex) started. The aim of this project, which is supported by the European Union (EU), is to improve the understanding of epileptogenesis in order to develop both preventive and new therapeutic strategies and to identify clinical and biological bio-

markers. Furthermore, the question should be answered whether early AED treatment—already after appearance of epileptiform discharges in the EEG and prior to the onset of overt clinical seizures—can improve psychomotor development in infants with TSC. In this study TSC patients, under the age of 4 months and without clinical seizures, can be included. Further information can be obtained through the EPISTOP website: www.epistop.eu.

Pediatric Tuberous Sclerosis Centre—Vienna

At the TSC center, at the Department of Pediatrics and Adolescent Medicine of the General Hospital Vienna, more than 50 affected children <18 years and their families are cared for by a multidisciplinary team. Close cooperation with specialists from other departments (dermatology, neuroophthalmology, nephrology, radiology, and neurosurgery)—and regular interdisciplinary meetings ensure comprehensive evidence based patient care.

A transition clinic, which was initiated in close cooperation with the department of neurology, guarantees the well-orchestrated transition from pediatric to adult health care.

The pediatric tuberous sclerosis centre Vienna is actively involved in ongoing research projects—TOSCA, EPISTOP—and in contact with other TSC centers and international specialists.

Conflict of interest

Dr. Samueli has received travel support from Novartis. Dr. Feucht has received travel support and honoraria for schientific advisory boards from Novartis.

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