TUBEROUS SCLEROSIS COMPLEX: CLINICAL CHARACTERISTICS, DIAGNOSIS AND MANAGEMENT

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Abstract

Tuberous Sclerosis Complex (TSC) is a rare genetic disorder caused by germline mutations in TSC1 and TSC2 genes. Loss of function genetic alterations in TSC1 and TSC2 lead to hyperactivation of the downstream mammalian target of rapamycin pathway (mTOR), which represents an important cellular circuit in the regulation of cell proliferation and survival. From a phenotypic standpoint, TSC is characterized by the development of benign hamartomatous tumors in different parts of the body, and thus a diverse clinical picture for each affected individual. The most frequently involved organ systems include the brain, the skin, the kidneys, the heart, the eyes, and the lungs. Central nervous system involvement manifests with a combination of symptoms such as seizures, impaired intellectual development, autism and behavioral problems. Accurate diagnosis is essential in implementing appropriate surveillance and treatment in patients with this disorder. The treatment is supportive and symptomatic, and requires the expertise of multiple disciplines. New treatment approaches and novel drugs, such as mTOR inhibitors, have been introduced in order to manage specific manifestations and have resulted in better outcomes and improvement of the patients' quality of life. In this review, we summarize the current data on the clinical characteristics, diagnosis and management of TSC from a neurologic perspective.

Key words: tuberous sclerosis, TSC, antiepileptic drugs, mToR inhibitors

1. INTRODUCTION

Tuberous sclerosis complex (TSC) is a genetic disease with autosomal dominant inheritance, marked by the presence of benign tumors, called "hamartomas", in various organs [1]. It is manifested simultaneously in many organs, with a special preference for the heart, the skin, the nervous, renal and pulmonary systems [2]. It affects 1 out of 6.000 to 10.000 individuals, without discrimination for gender or ethnicity [3, 4]. It represents the second most common neurocutaneous syndrome, after neurofibromatosis [5].

2. ETIOPATHOGENESIS

Molecular genetic studies [6-10] have demonstrated the involvement of two highly penetrating genes, the TSC1 gene in 9q34 chromosome and the TSC2 gene in 16p13 chromosome, coding the proteins hamartin and tuberin respectively. These proteins create a complex, responsible for cellular proliferation and proteinosynthesis, which suppresses the mammalian target of rapamycin (mTOR) pathway. More specifically, hamartin and tuberin in connection with TBC1D7, create the TSC protein complex, which uses RhebGTPase to control the function of the mTORC1. Tumor cells in tuberous sclerosis demonstrate hyperactivation of the mTORC1 signaling network. Therefore, mutations in the TSC1 and TSC2 genes result in the production of defective proteins, leading to uncontrolled cellular growth and tumor formation [11]. It should be noted that, over half of the cases are sporadic and there is no family history. This mainly concerns the TSC2 gene, the impairment of which usually leads to more serious clinical manifestations [12].

3. CLINICAL CHARACTERISTICS

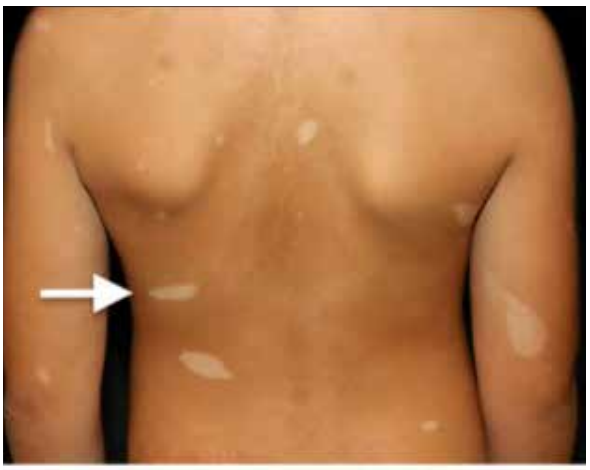
TSC is highly heterogeneous with a wide phenotypic spectrum, ranging from presentations with severe mental retardation and seizures, to affected individuals with normal intelligence and absence of epilepsy, even within the same family [12]. The most affected parts of the body are the brain and the skin with patients presenting with epileptic seizures and skin manifestations that lead patients to seek medical assistance. The most dangerous complications originate in the nervous and the renal systems and can cause death if not treated promptly [1].

3.1. Dermatologic manifestations

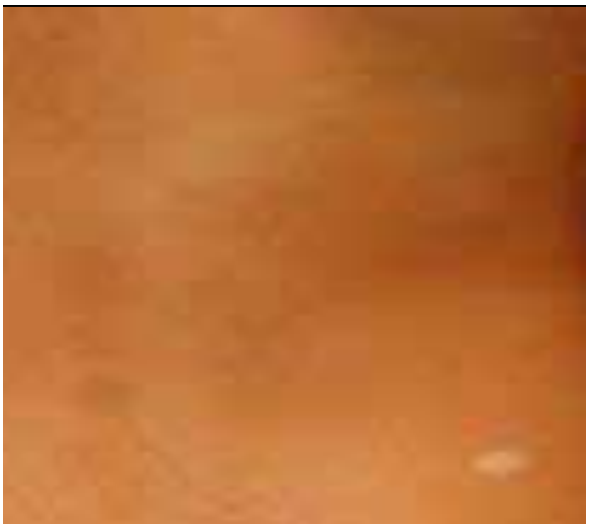
Hypomelanotic macules are found in about 90% of TSC patients [1]. Their presence consists a diagnostic criterion, if more than 3 lesions exceeding 5 mm in

Dermatologic manifestations in patients with TSC

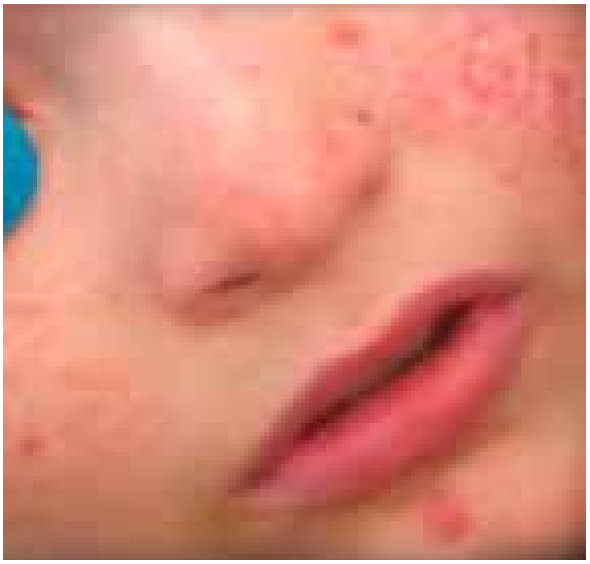
Picture 1. Hypomelanotic macules



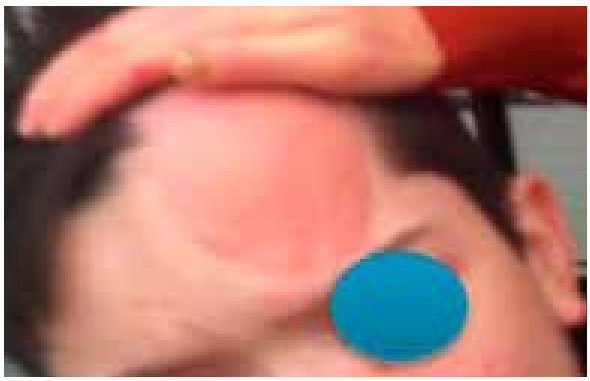
Picture 2. Hypomelanotic macules



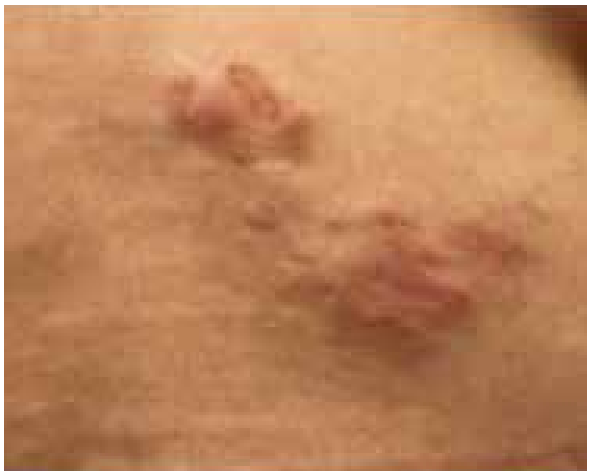
Picture 3. Facial angiofibromas



Picture 4. Fibrous cephalic plaque



Picture 5. Shagreen patch

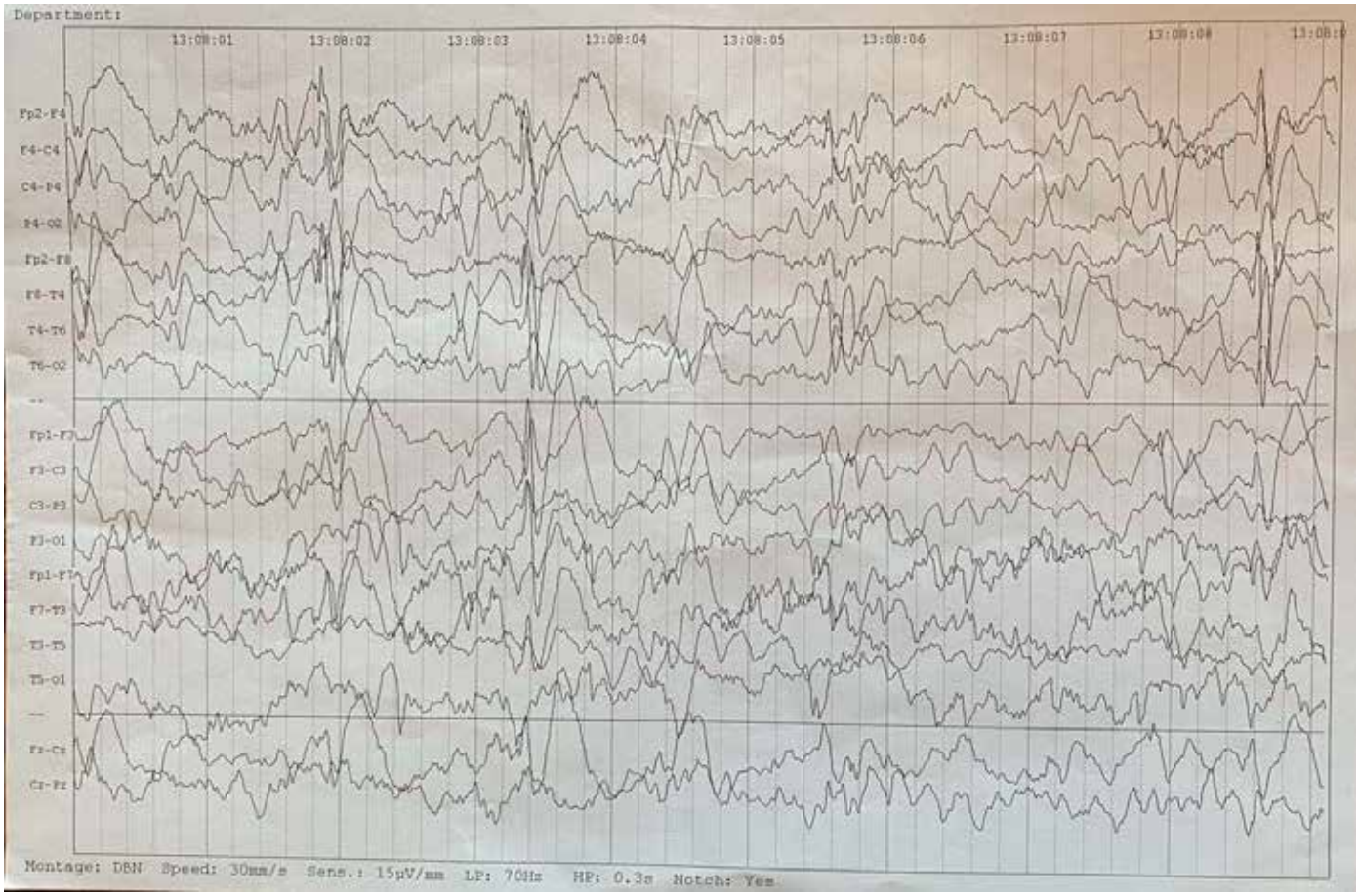


diameter are present [4]. Their shape resembles a leaf, so they are also called "ash-leaf macules". These hypomelanotic macules appear early in life, sometimes since birth, facilitating the diagnosis (Pictures 1 and 2). Over time, they usually recede and smaller lesions, "confetti-like", take their place [1]. Hypopigmented lesions, also include hypomelanotic patches of hair (poliosis) [12].

Facial angiofibromas (Picture 3) are common among young patients, around 4 years of age, in 83 to 90% of cases [1]. They look like swollen fibrous lesions, localized above blood vessels, which gives them an almost violet color. Angiofibromas are usually based on the nose and nasolabial folds, common areas of acne, from which they should be distinguished [1, 12].

An uncommon, but very specific for TSC, skin finding is the fibrous cephalic plaque (Picture 4), observed in the forehead of approximately 25% of individuals [1, 12]. In addition, clinical examination in about half of the patients with TSC reveals shagreen patches in the lumbar area (Picture 5), which are specific skin lesions with an orange peel surface [1, 12].

Picture 6. Stage 2, non-REM Sleep EEG of a 27 month-old child with TSC, post-recovery from infantile spasms. Bilateral synchronous epileptiform discharges with right hemisphere predominance



Ungual fibromas are lesions of the nails that appear later, in adulthood, at a rate of 80% [12]. They are mainly observed in women and in the toes [1].

Lesions of the oral cavity, include dental enamel pits and intraoral fibromas. Dental enamel pits can also observed in the general population, therefore they are not specific to the disease. Intraoral fibromas may be detected at the anterior gingival, oral and lips mucosa at 20 to 50% of adults with TSC [1, 12].

3.2. Neurological manifestations

The involvement of the central nervous system (CNS) is a key feature of TSC, with the typical triad of epilepsy, intellectual disability and autism spectrum disorders (ASD) [12]. More specifically, epilepsy is present in 70 to 90% of TSC cases, usually in children under the age of three [1].In about 50% of cases, it appears in infants as infantile spasms [2], described as tonic or clonic flexion or extension movements of neck, torso and limbs, with the characteristic hypsarrhythimic pattern in electroencephalographic investigation (EEG) [13]. However, every type of seizure can be part of TSC and as mentioned above with a variety of epileptiform abnormalities on EEG (Picture 6). In addition, there are cases with no neurological involvement [12]. Epilepsy indicates TSC in 10-25% of children [2].

De Vries and colleagues introduced the term "TSC-associated neuropsychiatric disorders (TAND)" in order to describe the diverse neuropsychiatric manifestations of TSC individuals [14, 15]. They also created the TAND Checklist (Table 1) in order to help the clinician detect the respective symptoms [14]. TAND involves ASD and other behavioral impairments such as aggressiveness, anxiety disorders, sleep difficulties and attention deficit hyperactivity disorder in about 40 to 50% of individuals [1]. Most TSC patients with ASD also face cognitive and learning difficulties in about 75% of cases [1]. Mental retardation is present in almost half of TSC individuals, in varying degrees of severity [12].

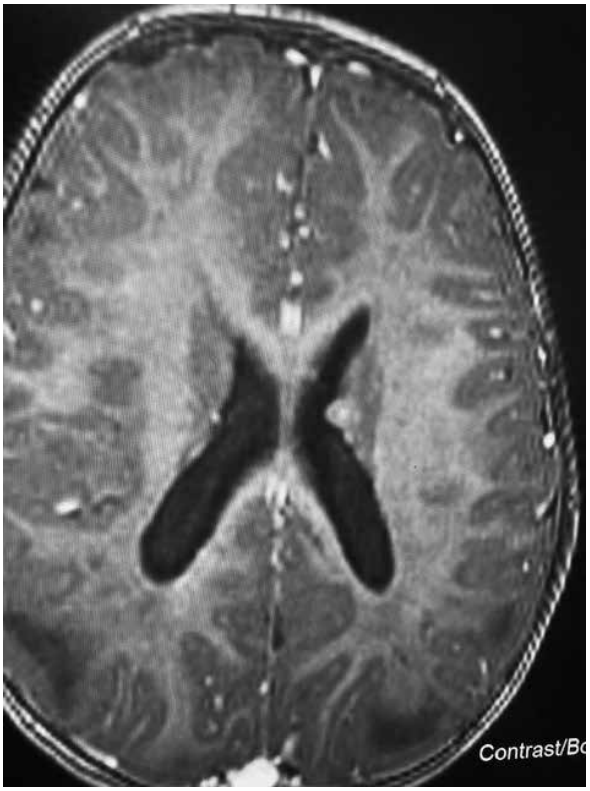
In addition, imaging methods have revealed structural abnormalities of the brain of TSC patients, including subependymal nodules (Picture 7), cortical tubers (Picture 7, 8, 9, 10) and subependymal giant cell astrocytomas (SEGAs) [1, 2, 12]. Cortical tubers are the typical imaging finding of TSC, easily de-

Table 1. TAND Checklist plan

Section	Field of study
1	Age of developmental landmarks
2	Present level of daily functionality
3	Worrying way of behaving
4	Ascertained mental health problems
5	Mental capability
6	School performance
7	Executive functions
8	Interpersonal relationships and level of self-complacence
9	Parent, carer or patient's assessment of the effect of TAND
10	Precedencies
11	Further worries
12	Doctor's/interviewer's assessment of the effect of TAND

Adapted from de Vries et al., 2015

Picture 7. 18 months of age: Subependymal nodules and cortical tubers on gadolinium-enhanced T1-weighted MR

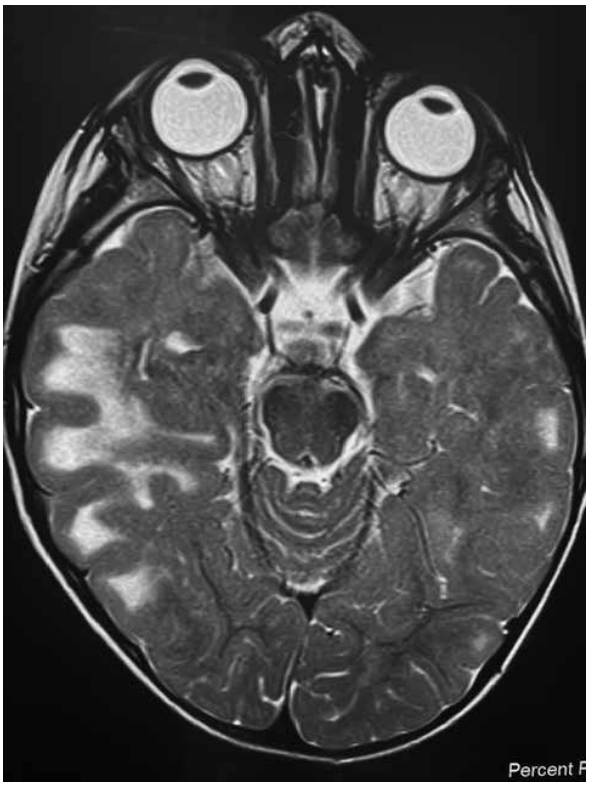


tected on magnetic resonance imaging (MRI) [12]. Approximately 80% of TSC individuals have cortical tubers in brain MRI, which do not increase in size over the years [2]. Cortical tubers are associated with the onset and severity of epilepsy [2, 12]. Subependymal nodules, calcified or not, are apparent in 80 to 90% of patients' brain MRIs, located in the wall of the lateral ventricles [1, 2, 12]. When there are more than one intraventricular subependymal nodules next to each other, the impression of a melting candle is given, known as the ''candle guttering sign'' [16]. They are often asymptomatic, but at a rate of 5 to 15% they evolve into benign SEGAs, which increase in size over time and may occlude the drainage system of the ventricles, leading to obstructive hydrocephalus [1, 12]. As a result, patients present with acute symptoms such as headache, focal neurologic signs, behavioral and mental changes and uncontrolled seizures [2, 12]. The characteristics and number of brain lesions are related to the severity of epilepsy and to the presence and severity of neuropsychiatric symptoms, and eventually determine the patient's neurologic condition [12, 15].

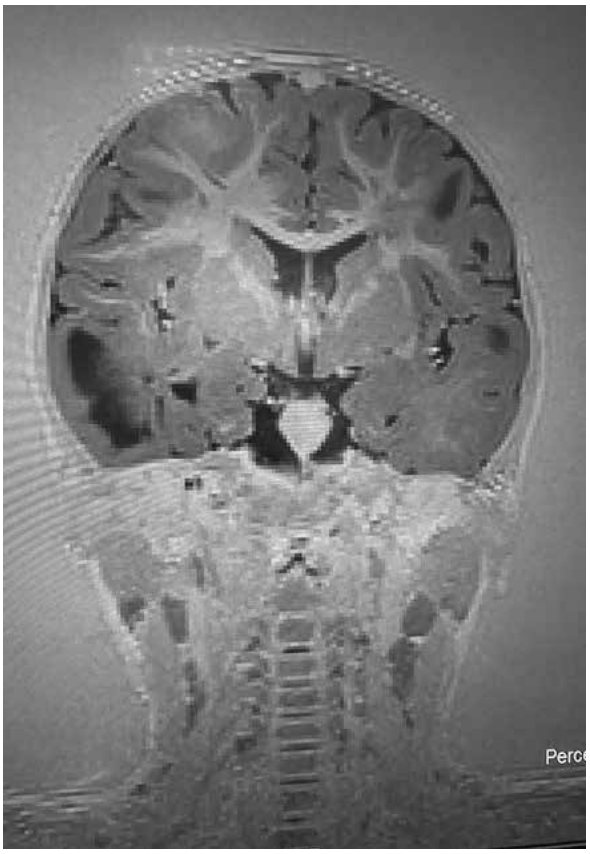
3.3. Renal manifestations

Renal involvement is mainly manifested as renal angiomyolipomas (AMLs) in 80% of TSC patients [1, 2]. In childhood and puberty, these benign tumors gradually increase in size, though they are usually asymptomatic [1]. Typically there are multiple AMLs affecting both kidneys [12]. In adults, AMLs can cause symptoms when they exceed 4 cm in diameter and can lead to death [12]. Hematuria, tumor hemorrhage, arterial hypertension and kidney failure are some of the most serious complications they can cause [1, 2, 12].

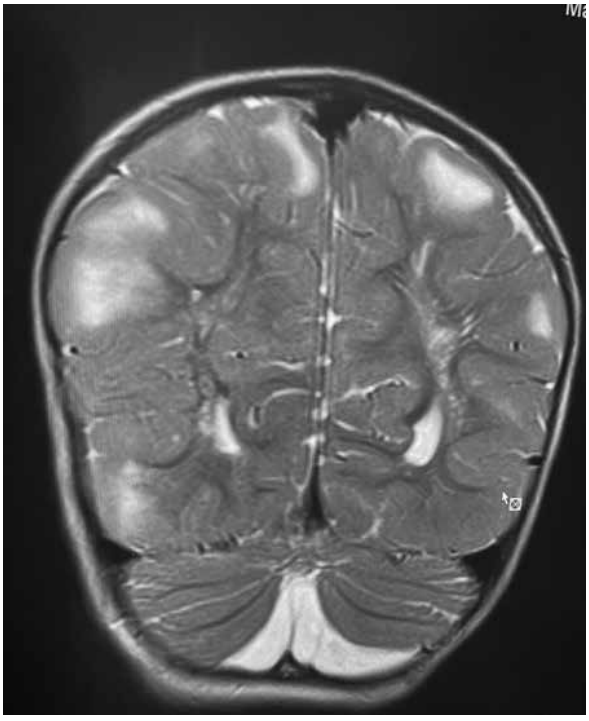
Picture 8. 18 months of age: Cortical tubers on T2-weighted MR sequence



Picture 9. 18 months of age: Cortical tubers on T2-weighted Inversion Recovery MR sequence



Picture 10. 18 months of age: Cortical tubers and white matter lesions on MR T2-weighted MR sequence



Frequently enough, AMLs are combined with renal cysts in about 45% of patients [2]. In a small portion of TSC individuals, approximately 1-2% of cases, TSC and adult polycystic kidney disease coexist, probably owing to the vicinity of the TSC2 gene and the responsible for polycystic disease gene (PKD1 gene) [12, 17].

Rarely, renal malignancy is observed in 1-2 % of TSC cases [1]. When it is not clear whether it is a benign or malignant tumor, a biopsy is necessary in order to confirm the behavior of the tumor [1].

3.4. Cardiac manifestations

Cardiac rhabdomyomas are present during ultrasound examination of the fetus in half of the cases [2, 12]. These benign tumors can be detected from the 20th week of pregnancy and there may be more than one, usually three, located in the cardiac ventricle wall [1]. Ordinarily, rhabdomyomas regress by the age of three or earlier, and they are asymptomatic [1, 2]. Depending on their dimensions, multitude and position, these tumors can cause symptoms such as heart failure, cardiac enlargement, murmurs, arrhythmias (most commonly Wolff-Parkinson-White syndrome), and even death [1, 12]. In children, enlargement of rhabdomyomas and heart block has been reported

after corticotropin and carbamazepine treatment for seizures [18, 19].

3.5. Pulmonary manifestations

Lymphangioleiomyomatosis (LAM) is the substitution of alveoli by cysts and multiplication of smooth muscle cells [1]. LAM appears almost exclusively in adult women, in approximately 40% of patients with TSC [1, 2] and remains asymptomatic before the age of 40 [2, 12]. The most frequent pulmonary symptoms involve cough, dyspnea, hemoptysis and pneumothorax [1, 2, 12]. Another pulmonary manifestation is the multifocal micronodular pneumonocyte hyperplasia (MMPH) in 60% of TSC individuals [2]. This typically affects premenopausal women and is asymptomatic when it does not coexist with LAM. It is detected on chest CT as ground-glass nodules with a maximum diameter of 10 mm [20].

3.6. Ophthalmologic manifestations

Ophthalmologic manifestations in TSC manifest as retinal astrocytic hamartomas (30-50%) [1] and retinal hypomelanotic macules (12%) [12]. Hamartomas of the retina are present during the first years of life and they rarely harm the patient's vision [1]. More than one retinal lesion can be detected in both eyes [12] and involvement of the retina usually implies impairment in the TSC2 gene [21].

3.7. Other manifestations

AMLs can be identified by MRI in different organs of the gastrointestinal and endocrine systems in about 25% of TSC individuals [2]. It is the liver of female patients which is usually affected [1].

4. DIAGNOSIS

The diagnosis of TSC is clinical and relies on a thorough examination of the patient, looking for the characteristic findings of the disease. Northrup and colleagues presented the updated 2012 international Tuberous Sclerosis Complex Diagnostic criteria (Table 2) [4]. Clinical criteria are separated into major and minor. Definite diagnosis is the result of the presence of two major criteria or one major and at least two minor criteria. Probable TSC diagnosis results from the presence of one major or at least two minor criteria [4]. Of note, although LAM and AML are included in the major criteria, they cannot confirm the diagnosis of TSC on their own, because TSC2 gene mutations, unrelated to TSC disease have been reported, which lead to LAM and AML co-existence [12]. A genetic test seeking the deactivating mutations in TSC1 and TSC2 genes can confirm the definite diagnosis. However, in 10-25% of cases, genetic tests are unable to detect the responsible mutations in patients who present with clinical manifestations of TSC. This does not exclude the TSC diagnosis when clinical suspicion is strong, because of the possibility of somatic mosaicism [4, 12]. Notably, patients with TSC1 or TSC2 mosaicism often have mild clinical features [12].

Clinical suspicion of TSC should be raised in any case of infantile spasms or other type of seizures and ASD. It should be supplemented by a thorough physical examination of all body systems (Table 3) [22]. The careful clinical evaluation helps to find the typical skin, dental and retinal lesions. Skin examination under the black light of Wood's lamp helps to detect the hypopigmented macules, scattered all over the body [2]. Fundoscopy can reveal retinal alterations connected with TSC [1, 22]. Moreover, imaging tests can identify the characteristic brain, kidney and heart lesions. Cerebral MRI has a high sensitivity in detecting the brain lesions related to TSC [12]. Subependymal nodules, especially the non-calcified ones, are obvious on T2-MRI, as high-signal areas. Calcified nodules can be detected either on CT as high-density areas or MRI. Cortical abnormalities are low-density regions on CT and can be better illustrated with MRI. SEGAs are the evolution of subependymal nodules, explaining why they are intraventricular and often calcified, better visualized on contrast- enhancement CT or MRI [12]. EEG is necessary to detect subclinical epilepsy and describe the type of seizures [1, 22]. TAND checklist detects the presence of neuropsychiatric symptoms as well [22]. Concerning heart involvement, rhabdomyomas can be detected with echocardiogram (ECHO) and the arrhythmias and conduction impairments that may ensue, with electrocardiogram (EKG). ECHO should be carried out in all patients under three years old and in the fetus, if there is suspicion of rhabdomyoma prenatally [22]. Imaging of the abdomen by ultrasound, CT or preferably MRI constitutes a diagnostic key for renal AML and renal cysts [1, 22]. Renal function can be estimated by measurement of blood pressure (BP) and glomerular filtration rate (GFR) [2, 22]. Pulmonary function should be checked in all adult women and only in symptomatic adult men via suitable pulmonary function tests and high-resolution chest computed tomography (HRCT) for the search of LAM [22]. Three-generation family history can investigate other possible TSC cases in the same family and is necessary for genetic counseling and confirmation of possible but no clinically proven cases [22].

5. MANAGEMENT

The management of patients with TSC requires a multidisciplinary approach due to the diverse nature

Table 2. Genetic and clinical diagnostic criteria of TSC

GENETIC DIAGNOSTIC CRITERIA
The detection of a pathogenic mutation in responsible TSC genes, either TSC1 or TSC2 gene is capable of making a definite diagnosis of TSC. Defined as a pathogenic mutation is a mutation that clearly impairs the function of the TSC1 or TSC2 proteins (e.g., out-of-frame indel or nonsense mutation), prevents protein synthesis (e.g., large genomic deletion), or is a missense mutation whose effect on protein function has been established. Other TSC1 or TSC2 variants with uncertain result on protein function are incapable of making a definite diagnosis of TSC. In 10-25% of TSC patients no mutation can be identified by genetic tests, so a normal result does not exclude TSC or recant the clinical diagnostic criteria to diagnose TSC.
CLINICAL DIAGNOSTIC CRITERIA
Major criteria
1. Hypomelanotic macules (≥3, ≥5mm in diameter)
2. Angiofibromas (≥3) or fibrous cephalic plaque
3. Ungual fibromas (≥2)
4. Shagreen patch
5. Multiple retinal hamartomas
6. Cortical dysplasia
7. Subependimal nobules
8. Subependymal giant cell astrocytoma
9. Cardiac rhabdomyoma
10. Lymphangioleiomyomatosis (LAM)
11. Angiomyolipomas (AML) (≥2)
Minor criteria
1."Confetti" skin lesions
2. Dental enamel pits (>3)
3. Intraoral fibroma (≥2)
4. Retinal achromic patch
5. Multiple renal cysts
6. Nonrenal hamartomas

Adapted from Nurthrup & Krueger, 2013.

of the phenotypic and clinical manifestations. Thus, the management addresses the intracranial and the extracranial manifestations of TSC.

5.1. Intracranial manifestations of TSC

The management of intracranial manifestations of TSC includes epilepsy treatment and the management of secondary CNS tumor development. Treatment can be symptomatic or it may address the inhibition of mTOR pathway. Herein, we will summarize the current data on the treatment options.

5.1.1. *TSC-associated epilepsy*

Effective management of epileptic seizures associated with tuberous sclerosis is the most important aspect in the multifaceted treatment approach of these patients. The management of epileptic seizures of TSC includes a plethora of pharmacologic and not-pharmacologic treatment modalities. Effective and timely epilepsy treatment in TSC patients is of paramount importance for the optimization of cognitive development and the improvement of quality of life of young patients [23, 24].

Vigabatrin (VGB) is the drug of choice as first line treatment for infantile spasms and/or focal epilepsy

Table 3. Assessment of possible TSC

ORGAN SYSTEM	ASSESSMENT INSTRUCTIONS
Genetics	Three-generation family history, genetic counseling
Skin, teeth, eyes	Profound clinical examination, Wood's lamp examination, fundoscopy
Brain	CT, MRI, EEG, TAND checklist
Heart	ECHO, EKG, prenatal ultrasound
Kidneys	MRI, CT, ultrasound, measurement of BP &GFR
Ists	Pulmonary function tests, HRCT

Adapted from Krueger & Northrup, 2013..

for children with TSC in their first year of age [23, 24]. VGB administration has been demonstrated to effectively control seizures in the infantile population [25-28]. Moreover, preventive treatment with VGB in infants was associated with a lower risk of clinical seizures and infantile spasms in comparison to conventional treatment [29]. The EPISTOP trial demonstrated that the administration of VGB in infants with TSC without history of seizures reduced the risk of clinical seizures, infantile spasms and drug resistant epilepsy [30]. Thus, the preventive administration of VGB may potentially alter the natural course of epileptic seizures in patients with TSC. However, in the EPISTOP trial, the preventive administration of VGB did not significantly affect the developmental delay or autism in children aged two years [30]. The PREVeNT trial [ClinicalTrials.gov identifier: NCT02849457] is a double-blind, placebo-controlled study that is currently under way and is designed to evaluate the effect of preventive VGB in infants less than 6 months of age. The results of the PREVeNT trial will provide valuable information on the potential role of preventive VGB administration in the cognitive development of patients with TSC [31].

The initial recommended dose of VGB for infantile spasms (infants and children 1 month - 2 years) is 50mg/kg/day in two daily doses. Depending on the patient's response the daily dose can be increased by 25mg/kg/day to 50mg/kg day every 3 days. The maximum dose is 150mg/kg/day [32-34]. VGB administration is generally safe. The most important side effect of VGB is retinopathy that can lead to permanent bilateral concentric visual field constriction, but the benefit-risk ratio is strongly in favor of this treatment option [23, 27, 28, 34-36]. Each patient should be examined by an ophthalmologist, with visual field testing before initiation of treatment and then this should be repeated every 3-6 months. However, in most cases (infants and children under the age of 9-10 years) the perimetry is difficult to perform, therefore there are other tests that are recommended, such as Visual Evoked Potentials (VEP), Electroretinogram (ERG) or Electro-Oculogram (EOG) [37].

If the epileptic seizures are refractory to vigabatrin, treatment with other pharmacologic and non-pharmacologic interventions should be carried out.

Pharamacologic interventions include **ACTH** (natural or synthetic) or **corticosteroids** administration as second-line therapy in children with infantile spams of TSC [22, 24]. The daily dosage of ACTH is 150 units/m^2 and the recommended dose of corticosteroids, specifically prednisolone, is 4-8 mg/kg/day or 40-60 mg/day for 14 days, followed by gradual tapering [38-41].

AEDS that enhance GABAergic transmission, such as **topiramate** and **carbamazepine**, are also used for the treatment of TSC-related seizures [24]. If the first AED is not effective, a different AED or two or more AEDS could be prescribed. There is not enough evidence to address the effectiveness of other conventional antiepileptic drugs in the treatment of seizures in patients with TSC [24].

Everolimus is a small molecular inhibitor of the mammalian target of Rapamycin (mTOR) involved in the cellural pathway that is constantly activated due to *TSC1* or *TSC2* loss of function genetic alterations [42-47]. Everolimus efficacy for refractory epilepsy due to TSC was investigated in a phase III, randomized, placebo-controlled trial (EXIST-3) [48]. In this, everolimus was demonstrated to significantly reduce seizures in patients with TSC and treatment resistant epilepsy [49]. Thus, it has received regulatory approval in the USA and in the EU for children older than two years of the age suffering from treatment resistant partial epileptic seizures [50-55]. Common side effects of its usage include mucositis, respiratory tract infections, pyrexia and pneumonitis among others. Everolimus is metabolized in the liver primarily by CYP3A4 and since antiseizure medications typically used for individuals with TSC also interact with the aforementioned enzymes the dose of everolimus

should be modified for patients with severe hepatic impairment and for patients taking concomitant medication that interacts with CYP3A4 inhibitors. Subsequently, the efficacy of everolimus for the treatment of seizures in TSC patients has also been reported in a few single-arm trials and real-world retrospective studies [50-56].

Everolimus dosage for seizure control begins at 5mg/m^2 once daily with subsequent titration in order to achieve plasma concentrations in the range of 5 ng/ml to 15ng/ml [49].

Cannabidiol is a substance derived from the *Cannabis sativa* plant. It is thought to be effective by reducing the activity of mTOR. The European Commission (EC) has approved cannabidiol as an adjunctive treatment of seizures associated with TSC in patients aged 2 years and older since April 2021 [57, 58].

Non-pharmacologic interventions for the management of treatment resistant epileptic seizures for patients with TSC consist of ketogenic diet, vagus nerve stimulation and surgery.

Ketogenic diet (KD) has been reported in experimental models to be associated with downregulation of the mTOR pathway [57-62]. By applying ketogenic diet the liver produces ketones as an alternative energy source. KD should be considered in patients (in early infancy and early childhood) with refractory seizures, who are not candidates for surgery [20, 61, 62].

Vagus nerve stimulation (VNS) –a method of application of electrical stimuli to the vagus nerve– is recommended by the consensus TSC guidelines to be considered in combination with the KD or in cases where the KD is not acceptable [23, 24]. Improvement in seizure frequency has been noted with VNS however, although the relevant data is limited, seizure freedom is quite rare [63-66].

European guidelines recommend that if the first two appropriately chosen anti-epileptic drugs fail to control seizures, a **pre-surgical evaluation** should be promptly started, to assess the possibility of **surgical resection** of the epileptic focus that is mainly responsible for the seizure symptomatology [23]. While studies have reported the benefits of epilepsy surgery, this has been underutilized. However, novel techniques are being developed, with the potential to expand the number of eligible patients, while reducing the risk of complications [67-71].

5.1.2. *Management of CNS tumors development*

The presence of a germline mutation in *TSC1* or *TSC2* genes is associated with the development of secondary CNS tumors, most commonly cortical glioneuronal hamartomas and subependymal giant cell tumors (SGCTs), also known as subependymal giant cell astrocytomas (SEGAs) [72]. Thus, individuals with known TSC must be followed up with brain MRIs every 1-3 years until the age of 25 years [22].

SEGAs can be treated with surgery or with mTOR inhibitors [22]. Treatment decision between surgery or medical treatment with everolimus must be individualized for each patient. However, in the case of a solitary and unilateral SEGA that is amenable to complete surgical resection, surgical treatment should be the treatment of choice. Importantly, due to the unique inherent genetic background of patients with TSC the risk of malignant transformation is high in the setting of radiation therapy administration. It has been reported that radiation treatment can transform SEGAs to malignant glioblastomas [73, 74]. Thus, radiation treatment should be avoided in these patients.

5.2. Extracranial manifestations of TSC

There is a wide spectrum of phenotypic manifestations ranging from skin disorders to pulmonary lymphangiomatosis [22]. Due to the diversity of these lesions a multidisciplinary management is recommended for these individuals and a regular follow-up system has to be established by nephrologists, pulmonologists, etc, in order to address the problems that arise with time. The management of organ specific alterations in the context of TSC is beyond the scope of this review.

6. CONCLUSION

TSC is a genetic disorder, affecting multiple organ systems, most predominantly the skin and the CNS, and is characterized by wide phenotypic heterogeneity even within members of the same family. High clinical suspicion followed by detailed clinical examination and genetic confirmation result in making the correct diagnosis of TSC in most of the suspected cases. Despite significant improvements in understanding the mechanisms involved in the molecular pathogenesis and subsequent pathophysiology in TSC, the management of the individuals that bear a germline mutation in *TSC1* and *TSC2* genes remains challenging and requires a multidisciplinary approach. Importantly, prompt identification and management of the CNS complications of the syndrome can be associated with significant improvements in quality of life and cognitive development for these individuals. Furthermore, the introduction of mTOR inhibitors in clinical practice has offered a new option that can alter the natural disease course and can additionally act as a significant treatment option for secondary tumor development. Finally, it is a paradigm for the development of novel treatments that are not merely symptomatic but mainly address the etiopathogenesis of the disorder.

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