International Journal of Contemporary Pediatrics
Bonilla NC et al. Int J Contemp Pediatr. 2024 May;11(5):616-624
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20241048

Review Article

The tuberous sclerosis complex: a review of the literature

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Received: 03 April 2024
Revised: 17 April 2024
Accepted: 18 April 2024

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ABSTRACT

Tuberous sclerosis complex (TSC) is a neurocutaneous autosomal dominant genetic disorder characterized by mutations in the TSC1 and TSC2 genes, this leads to dysregulation of the mechanistic target of rapamycin (mTOR) pathway resulting in cellular hyperplasia and the formation of benign tumors in various organs, including the brain and skin. Clinical manifestations encompass a wide range of mainly neurological and dermatological symptoms, often presenting during early childhood and posing diagnostic challenges due to phenotypic variability. Recent advancements in diagnostic criteria, genetic testing, and imaging techniques have facilitated earlier diagnosis and increased disease incidence awareness. Neurologically, TSC commonly presents with cortical tubers, subependymal nodules (SENs), and epilepsy, with seizure control being paramount in preventing long-term neurodevelopmental sequelae. Dermatologically, hypomelanotic macules, facial angiofibromas, and ungual fibromas are hallmark features, often causing significant psychological distress due to disfigurement. Management of TSC requires a multidisciplinary approach, with emerging therapies such as mTOR inhibitors showing promise in addressing both neurological and dermatological manifestations. Early intervention, including epilepsy surgery and targeted treatments for skin lesions, is essential for optimizing outcomes and improving the quality of life for patients with TSC. Continued research into novel therapeutic modalities holds potential for further enhancing the management and prognosis of this complex disorder.

Keywords: Tuberous sclerosis, TSC1, TSC2, MTOR pathway, Treatment, Genetic

INTRODUCTION

Tuberous sclerosis complex (TSC) is a neurocutaneous autosomal dominant genetic disorder caused by excessive activation of genes TSC1 (Chromosome 9q34) and TSC2 (Chromosome 16p13) which are primarily involved in the downregulation of the mechanistic target of rapamycin (mTOR) pathway and code for the proteins tuberin and hamartin respectively.[1,2] This leads to a dysfunction in cell differentiation, proliferation and migration which leads to cellular hyperplasia in areas such as the brain, skin, heart, kidneys, eyes, and lungs.[2] This disease was first described by Virchow and Von Recklinghausen in necropsies of pediatrics with intellectual disability and seizures, though it wasn't until the early 20th century that Bourneville established the correlation between cutaneous manifestations and other clinical symptoms and called them ‘a tuberous sclerosis of the cerebral circumvolutions’

which would ultimately end up contributing in the naming of this disease as 'tuberous sclerosis". Years later Campbell and Vogt identified the triad that defines TSC: mental deficiencies, epilepsy, and the characteristic Pringle-type sebaceous adenoma (angiofibroma).[3-6] Finally, diagnostic criteria were established in 1998, later reviewed in 2012 and ultimately in 2021 to include genetic testing, refine clinical criteria and to establish new concepts such as TSC-Associated Neuropsychiatric Disorders (TAND).[6-8] Clinical manifestations of this complex usually appear during early childhood and can often pose a diagnostic challenge when genetic testing is not available due to its large phenotypic variability.[1]

EPIDEMIOLOGY

The refinement of diagnostic criteria, development of molecular and genetic testing techniques, and use of imaging technologies, have led to a rise in the diagnosis and incidence of this disease in recent years. The incidence of this disease is currently reported with the frequency of roughly 1/6000 to 1/10,000 in live births through multiple studies across Europe.[8-10] It is possible to diagnose this disease during pregnancy and the early postnatal through advanced neuroradiologic techniques, genetic testing, and Electroencephalography (EEG) which can influence outcomes of the disease.[11,12]

There has not been reported that a difference in incidence according to sex or ethnicity exists.[10]

Though the disease follows an autosomal dominant pattern, it has been reported that 70% of cases could be caused by sporadic somatic mutations. It is also worth mentioning that cases of familial transmission have been associated with mild to moderate disease and present changes in TSC1 gene more frequently.[13]

PATHOPHYSIOLOGY

TSC1 and TSC2 are the main responsible genes involved in TSC. There have been efforts to find another loci causative of the disease, though these efforts have yet not been successful.[2]

TSC1 consists of 23 exons and encodes a hamartin protein weighing 130 kDa, comprising 1164 amino acids.TSC2 consists of 42 exons and encodes tuberin which has a molecular mass of 198 kDa, spanning 1807 amino acids. The Hamartin-Tuberin complex, formed by the combination of proteins TSC1 and TSC2 along with TBC1D7, inhibits the GTPase activity of Rheb, which is key in the downregulation of mTORC. Mutations in TSC1 and/or TSC2 result in the phosphorylation of translation regulator proteins S6K and 4E-BP1 by mTORC1, leading to aberrant protein synthesis, unregulated cellular growth, and the initiation of tumorigenesis. Other affected cellular processes include the ones of glycolysis, angiogenesis, lipid synthesis, suppression of autophagy, mitochondrial biogenesis, and inflammation/immune regulation.[9,11,14]

mTORC1 is a serine-threonine kinase, composed of mTOR, RAPTOR, MLST8, PRAS40, and DEPTOR. It plays a key role in regulation of metabolism, nutrient and growth signaling and also is involved in the coordination of lysosomal binding. Inhibition of the mTOR complex drives the cell into a state resembling nutrient scarcity, which consequently ends in the stopping of the G1 cell cycle phase. Additionally, it can also trigger other cellular starvation responses such as autophagy.[15]

mTORC1 integrates signaling cascades from growth factors, amino acids, and energetic substrates to orchestrate cellular processes encompassing growth, division, and pro-survival mechanisms. In brain tissue , cell proliferation, growth, dendritic formation, axon elongation, apoptosis, migration, and autophagy are mainly affected. During brain development, dysregulation leads to abnormal development of the cerebral cortex, characterized by changes in cortical lamination, cell size, and the growth of axons and dendrites.

The mTORC1 pathway plays a crucial role in the differentiation of oligodendrocytes, responsible for producing myelin, as well as maintaining mitochondrial homeostasis. The malfunctioning of the mTORC1 pathway leads to the development of hamartomas, benign tumors that can arise virtually in any organ. They are typically made up of cell types native to the host organ or tissue, hamartomas often present symptoms related to the disruption or invasion of the specific structure of that organ or tissue.[1,2,14,15]

GENETIC BASIS

Clinical and genetic features are related and thus influence the course of the disease. Patients with TSC2 mutations appear to experience an earlier onset of symptoms, with an average age of onset approximately 7 years earlier than those with TSC1 mutations. Individuals with TSC2 mutations have displayed a heightened prevalence of self-injury, Autism Spectrum Disorder (ASD), academic challenges, and neuropsychological deficits.

Notably, individuals with TSC1 mutations demonstrated elevated rates of impulsivity, anxiety, depressed mood, hallucinations, psychosis, ADHD, as well as anxiety and depressive disorders. Individuals with TSC2 mutations also appear to have markedly higher rates of Intellectual Disability (ID). When comparing genders, males have exhibited significantly higher rates of impulsivity, overactivity, ASD, and ADHD in contrast to females.[16]

Genetic analysis of both tumorous and non-tumoral tissues uncovered mutations in 97% of the patients, with 84.9% attributed to TSC2 and 12.1% to TSC1, respectively. The remaining <3% of cases without these identified mutations could be attributed to factors like intronic mutations influencing splicing, tumoral mosaicism, or the presence of TSC1/TSC2 mutations yet to be identified.[2]

CLINICAL FEATURES

TSC has a variable age of onset and has the potential to impact any organ system. The clinical manifestations and severity of the disease are directly tied to the specific system(s) affected by the cellular overgrowth and the extent of such lesions.

TSC appears during early childhood and can be considered prenatally upon detection of cardiac rhabdomyomas via ultrasound during the second to third trimester of pregnancy, though most often patients seek medical attention due to the presence of skin lesions or epilepsy. Morbidity and mortality are most commonly associated with renal and neurological complications.[8,11,13]

NEUROLOGICAL MANIFESTATIONS

Cortical tubers (CTs) are one of the most common manifestations of TSC, appearing in >80% of patients, their main characteristics are disruption of cortical gray matter to subcortical white matter, they can often contain dysmorphic neurons, reactive astrocytes and giant cells. These can be located within all lobes, though they are most often found in frontal and parietal lobes. Posterior fossa CTs are less common and are usually associated with worse prognosis.

In the early stages of the disease, these can often pass unnoticed due to their structural similarities in magnetic resonance imaging (MRI) with the unmyelinated brain. During infancy, these can be localized as hyperintense in T1 and hypointense in T2 with the appearance of cortical thickening within a broadened gyrus. Later in life, T2 and FLAIR sequences show a more marked differentiation within gray-white matter and CTs. They can also present calcifications or cystic degeneration.[17]

Subependymal nodules (SEN) are slow growing benign lesions composed mainly of astrocytes, these can grow and give rise to subependymal giant cell astrocytomas (SEGAs). SEN are often located in areas close to the lateral and third ventricles, while SEGAs are more often found near the foramen of Monro, which can lead to ventriculomegaly and obstructive hydrocephalus. SEN can be identified in MRI T2 sequences since they often contain calcified components. They can be T1 hyperintense and T2 hyper-isointense. About half of the patients present with 10 or more SEN at the time of diagnosis and are always accompanied by the presence of CTs. SEGAs are more common in TSC2 mutations and present in around 20% of the patients with a peak incidence around the age of 20, patients who have not presented SEGAs at the age of 25, most likely never will.[1,9,11,17]

Epilepsy occurs in 70 to 90% of the individuals with TSC, it is the sign which most often leads to the diagnosis. This occurs most commonly during the first 3 years of life and is most often presented as infantile spasms or focal seizures.

Around 40% of patients are diagnosed with epileptic spasms before the age of 1, focal seizures with or without epileptic spasms are diagnosed at 2-3 years of age in 65% of patients. Early onset of seizures and epileptic spasms in these patients are linked to a higher risk of developing neuropsychiatric disorders and intellectual disability later in life. It can often progress to Lennox-Gastault syndrome or refractory epilepsy.[1]

Seizure type can vary depending on the location of the lesions, cortical tubers, SEN and SEGAs are the main lesions found in TSC. There is typically a dominant epileptogenic trigger which arises from a tuber, and is crucial in therapeutic planning, nuclear medicine can be used to differentiate epileptogenic from non-epileptogenic tubers. Since radiation is an important issue especially in pediatrics, some MRI techniques such as ADC quantification have been proposed.

Epileptiform discharges can be detected before the onset of clinical seizures through the use of serial electroencephalography, this may provide an opportunity for preventive treatment before epileptogenesis in early stages of the disease. Since early epileptogenesis and neurodevelopmental comorbidities have been found closely related, this may prove an opportunity to improve early outcomes.[12,17]

NEUROPSYCHIATRIC MANIFESTATIONS

Neuropsychiatric manifestations were encompassed since 2012 under the term TAND. These manifestations include behavioral, psychiatric, intellectual, academic, neuropsychological, and psychosocial difficulties and disorders. Despite being a significant aspect of TSC, TAND issues are often overlooked and not adequately managed with existing treatments.[8]

There are six different levels of TAND which include: behavioral, psychiatric, intellectual, academic, neuropsychological, and psychosocial levels. These are used to categorize these distinct aspects, ensuring each is examined within the TAND checklist. These are summarized in Table 1.

Clusters group naturally co-occurring TAND manifestations, considering the overlap and co-occurrence of items beyond levels. These are scholastic, neuropsychological, dysregulated behavior, overactive/impulsive, eat/sleep, mood/anxiety, and autism spectrum disorder-like. This approach aims for a more personalized identification and treatment by referencing an individual's unique TAND profile or 'signature'.[18] It is highly advised to conduct a TAND screening annually. A thorough TAND assessment should be carried out at critical age milestones, specifically at ages 0-3, 3-6, 6-9, 12-16, and 28-35 years. Additional evaluations may be

performed as deemed necessary by the healthcare professionals in charge. Early intervention is highly advised, families of patients are encouraged to respond promptly to any concerns regarding behavioral changes.[19,20]

Table 1: TSC associated neuropsychiatric disorders (TAND).[16]

TSC	
Behavioral level	Agression
	Temper tantrums
	Anxiety
	Depressed mood Self-injury
	Inattention
	Hyperactivity
	Impulsivity
	Language delay
	Poor eye contact
	Repetitive behaviors
	Sleep problems
Psychiatric level	Autism spectrum disorder
	ADHD
	Anxiety disorder
	Depressive disorder
Intellectual level	Intellectual disability
	Uneven intellectual profiles
Academic level	Reading
	Writing
	Spelling
	Mathematics
Neuropsychological level	Sustained attention
	Dual-tasking
	Attentional switching
	Memory recall
	Spatial working memory
	Cognitive flexibility
Psychosocial level	Self-esteem
	Self-efficacy
	Parental stress
	Relationship difficulties

The TOSCA study aimed at identifying clinical profiles within the TSC population, observed distinct symptom patterns based on patient age. They found that children exhibited predominantly behavioral symptoms, including Attention deficit and hyperactivity disorder (ADHD), impulsivity, and overactivity. In contrast, adults (<18 years old) displayed more internal mood-related symptoms, such as anxiety, depression, sleep disturbances, and mood swings.[21]

OPHTHALMOLOGIC MANIFESTATIONS

Current diagnostic criteria for tuberous sclerosis include ophthalmic manifestations as major and minor criteria. These are multiple retinal hamartomas and retinal achromic patches respectively.[8]

In about 50% of the individuals with TSC, retinal hamartomas can be observed. These are also seen in cases of neurofibromatosis and retinitis pigmentosa or otherwise healthy patients. Upon dilated fundus examination, these present as flat/translucent, multinodular lesions on the retina.[11,22]

Retinal achromic patches, which manifest as small, flat regions of chorioretinal hypopigmentation in the mid-peripheral retina, have been documented in roughly 5% of patients. Additional neuro-ophthalmological observations include cranial nerve palsies (most commonly III and VI), visual field alterations, optic nerve hamartomas, iris hamartomas (Lisch nodules), cortical visual impairment (visual deficits without ocular disease), and increased intracranial pressure. It's also noteworthy that vigabatrin, a therapeutic agent utilized for infantile spasms, has the potential to induce ocular toxicity.

Case reports have documented hypopigmented lesions in the iris and ciliary body, as well as colobomas affecting the iris and choroid. Additionally, hamartomas have been observed in the iris and ciliary epithelium. Some cases have also reported angiofibromas on the eyelids.[22-24]

RENAL MANIFESTATIONS

The primary renal manifestations include angiomyolipomas (AML) and cysts, with other tumors such as renal cell carcinoma (RCC) or renal oncocytoma being less common, especially in children. Females with TSC tend to exhibit a higher burden of renal disease compared to males. The majority of TSC patients develop multiple multifocal AML and epithelial renal cysts. Although less common, RCC can occur at an early age and is a leading cause of morbidity and mortality in TSC patients.

Chronic kidney disease (CKD) resulting from surgical interventions for TSC-associated tumors or acute hemorrhage from AML and RCCs is a significant contributor to mortality. Renal cysts and AML are prevalent in children with TSC, with RCC affecting up to 80% of patients by the age of 10. AML, often detected in early childhood, are prone to spontaneous hemorrhage and can lead to compromised renal function. About 35-50% of TSC patients develop multiple renal cysts, which are typically mild and asymptomatic.

RCC occurs in about 2-4% of TSC patients, with a median age of onset in their forties. Multiple bilateral RCCs can develop in the same patient, each presenting distinct pathological features and different second-hit mutations. Early detection and management of renal manifestations are crucial for optimizing patient outcomes in TSC, which is why it is recommended to do annual surveillance of renal disease for most patients with TSC. Magnetic

resonance imaging (MRI) is the preferred imaging modality, kidney ultrasound is acceptable if initial MRI findings indicate typical AML appearance.[25-27]

PULMONARY MANIFESTATIONS

Lymphangioleiomyomatosis (LAM), the most common pulmonary manifestation of TSC(TSC), ranks as the third leading cause of TSC-related mortality. Characterized by diffuse infiltration of the lungs with atypical smooth muscle cells and cystic replacement of pulmonary parenchyma, TSC-associated LAM (TSC-LAM) occurs almost exclusively in females with TSC, typically diagnosed in women of childbearing age. Symptoms include dyspnea on exertion and recurrent pneumothorax, occasionally with lymphadenopathy and abdominal lymphangiomyomas.

Sporadic LAM (S-LAM), occurs in women without TSC and presents later in life, around the second or third decade, with symptoms similar to TSC-LAM but without central nervous system or dermatological involvement.It has been proposed that LAM behaves as a metastatic neoplasm, with documented lymphatic and hematogenous spread, recurrence in transplanted lungs, and a shared mutational profile across different sites. Histopathologically, LAM is characterized by diffuse smooth muscle-like cell proliferation expressing melanocyte lineage markers.

TSC2 mutations correlate with more severe clinical presentations, including in LAM. Sporadic LAM patients lack germline TSC gene mutations and carry no risk of genetic transmission of TSC or LAM. Discovery of LAM typically occurs through symptoms like dyspnea on exertion or spontaneous pneumothorax, with dyspnea being the most common symptom. Exogenous estrogen use and pregnancy can exacerbate the disease. Left untreated, LAM leads to progressive decline in lung function, ultimately causing severe respiratory insufficiency and death. The rate of decline in lung function varies among patients, with TSC-LAM patients possibly showing a more favorable decline rate compared to sporadic LAM, though this may be influenced by earlier screening in TSC patients.[28-31]

DERMATOLOGICAL MANIFESTATIONS

Dermatological manifestations are frequently the first signs of disease, and are present in nearly 100% of individuals with Tuberous sclerosis Complex, since they start to appear in the first year of life and they tend to evolve with time, some becoming less evident in adulthood and others occurring during adolescence or even adulthood.

The principal tegumentary manifestations observed in patients with TSC include hypomelanotic macules (ash-leaf spots), facial angiofibromas, shagreen patches, and ungual fibromas. While these lesions typically do not lead to significant medical problems, when they are prominent, facial angiofibromas can result in disfigurement and often trigger severe psychological distress.[32,33] Hypomelanotic macules are present in approximately 90% of patients, they tend to appear in the first 12 months of life and they turn less visible in older ages. These macules and patches exhibit various morphologies, including medium/large ‘ash-leaf’ types, polygonal ‘thumbprint-like’ patterns, and small ‘confetti-like’ types (multiple lesions from 1- to 3-mm diameter). Identifying these types of lesions in otherwise healthy adults is not as significant due to the similarity they have with chronic sun exposure depigmentation.[32-34]

Angiofibromas tend to be found in 75% of patients with tuberous sclerosis, appearing around the ages of 2-5 and during adolescence they can become an aesthetic problem due to their disfiguring evolution. In young childrens it can look similar to acne and be misdiagnose. They usually are bilateral, hamartomatous nodules made of vascular and connective tissue, and can have a butterfly pattern of distribution.

Fibrous cephalic plaques can develop on the forehead or other craniofacial regions. Histologically, they exhibit similarities to angiofibromas and are present in 25% of patients with TSC. Ungual fibromas or Koenen tumors exhibit the latest onset among all dermatological manifestations. They occur during adolescence and even during adulthood. When situated at the base of the nail, they can create a groove. While ungual fibromas are present in approximately 20% of patients with TSC, they can also be triggered by direct trauma to the nail.

Shagreen patch of large size is a distinctive feature associated with TSC. Typically found on the trunk, these lesions manifest as sizable plaques with an uneven surface. They frequently emerge during the first decade of life and are observed in approximately 50% of TSC patients.[32,33]

DIAGNOSIS

The International TSC Clinical Consensus Group underscores the importance of both independent genetic and clinical diagnostic criteria for TSC. A pathogenic variant in TSC1 or TSC2 found through genetic analysis is sufficient for diagnosing TSC, regardless of clinical presentation, emphasizing early genetic diagnosis to enable timely surveillance for optimal outcomes. While some pathogenic variants are well-documented, novel ones continue to emerge.

TSC diagnosis is determined based on specific criteria. These can be found in Table 2. Definite TSC is identified by either two major features or one major feature accompanied by two minor features. Possible TSC is indicated by either one major feature or two minor features. Genetic diagnosis confirms TSC when a pathogenic variant is detected in TSC1 or TSC2 genes. Notably, a combination of two major clinical features,

such as LAM and AML, without additional features does not fulfill the criteria for a definite diagnosis.

A three-generation family history should be obtained to assess familial risk. Diagnostic imaging, including MRI of the brain, is recommended to detect cortical or subcortical tubers, among other abnormalities. Focal seizures and epileptic spasms are common in infants with TSC, emphasizing the importance of educating caregivers to recognize these symptoms. Referral to specialists, such as pediatric neurologists or adult neurologists with expertise in epilepsy, is important for proper evaluation and management.

Table 2: TSC diagnostic criteria.

Major features	Minor features
Hypomelanotic macules (≥3, at least 5 mm diameter)	'Confetti' skin lesions
Angiofibromas (≥3) or fibrous cephalic plaque	Dental enamel pits (>3)
Ungueal fibromas (≥2)	Intraoral fibromas (≥2)
Shagreen patch	Retinal achromic patch
Multiple retinal hamartomas	Multiple renal cysts
Cortical dysplasias*	Non-renal hamartomas
Subependymal nodules	
Subependymal giant cell astrocytoma	
Cardiac rhabdomyoma	
Lymphangioleiomyomatosis (LAM)	
Angiomyolipomas (≥2)	

Note: *Definite diagnosis: two major features or one major feature with ≥2 minor features; possible diagnosis: either one major feature or ≥2 minor features.

At diagnosis, comprehensive assessment for TAND manifestations is necessary to identify areas requiring intervention. Abdominal imaging, preferably MRI, is advised for all patients to evaluate angiomyolipomas. Females and symptomatic males aged 18 years or older should undergo clinical assessment for lymphangioleiomyomatosis (LAM) and chest CT. Dermatological evaluation, cardiac assessment, and ophthalmologic examination are also recommended at the time of diagnosis to detect potential manifestations. Molecular testing aids in TSC diagnosis, with positive results observed in a significant majority of patients. However, a normal result does not definitively rule out TSC, emphasizing the importance of clinical assessment alongside genetic testing.

Diagnostic suspicion arises from various findings, including detection of cardiac rhabdomyomas (usually prenatally), post-natal identification of hypopigmented macules, childhood seizures, and cognitive impairment during autism assessment. A multidisciplinary approach involving genetic testing, imaging, and clinical evaluation is crucial for accurate diagnosis and management of TSC.[8,9,13]

TREATMENT AND EMERGING RESEARCH OF THERAPEUTIC ADVANCES

TSC management requires a comprehensive treatment approach, primarily focusing on symptom management and preventive measures to limit organ dysfunction. Due to its systemic nature, a multidisciplinary care team comprising genetics, neurology, ophthalmology, pulmonology, nephrology, and odontology is essential for effective management.

Neurological

Infantile spasms and seizures

Early treatment with anti seizure medications like vigabatrin can improve long-term outcomes. Vigabatrin is recommended as first-line therapy for infantile spasms and can halt TSC-related spasms in the majority of cases.[1,13,35]

Epilepsy

Combination therapy with multiple antiseizure medications may be necessary for adequate seizure control. Surgical options and dietary therapies, including ketogenic diet, are considered for refractory cases.

Vagal nerve stimulation is an alternative for patients ineligible for surgery.[36,37]

TAND

Although no TSC-specific interventions exist, personalized treatment strategies based on individual TAND profiles are essential. Disorder-specific guidelines should be followed for optimal management.[18-21]

SEGAs and SENs

Surgical resection is indicated for acute symptoms related to obstructive hydrocephalus or tumor hemorrhage. mTOR inhibitors or surgical resection are options for non-urgent cases, especially for those who are poor candidates for surgery.

Epilepsy surgery

Surgery is recommended for patients with medication-refractory seizures, especially after a trial of two antiseizure medications. It may also be considered for individuals with seizure-related impairments affecting quality of life.[1,38,39]

Renal

Angiomyolipomas

mTOR inhibitors (mTORi) are recommended as first-line treatment for asymptomatic growing renal angiomyolipomas. For acute hemorrhage, embolization followed by corticosteroids is considered.[26]

Hypertension

Renin-aldosterone-angiotensin system inhibitors are preferred for managing hypertension associated with renal manifestations.[28] Novel therapies in mice include guanylate nucleotide biosynthesis inhibitors such as Mizoribine as potential metabolic agents for therapy.[25.26]

Cardiac

Cardiac rhabdomyomas

In infants, most cardiac rhabdomyomas regress without treatment. Pharmacotherapy may be considered for hemodynamic compromise or arrhythmias. mTORi or surgical resection is indicated for refractory cases.[40]

Pulmonary

LAM

Sirolimus is recommended as first-line therapy for patients with abnormal lung function or problematic effusions. Lung transplantation may be considered for end-stage LAM. It is also recommended to vaccinate these patients against pneumococcus and influenza.[28-30]

Dermatological

Management with mTOR inhibitors (mTORis) are increasingly being used as new nonsurgical treatments.

Facial angiofibromas

Topical sirolimus is effective for treating facial angiofibromas, potentially improving other TSC-related skin lesions. Surgical excision, dermabrasion, excision, and skin grafting, and laser therapy may be considered for symptomatic or disfiguring lesions,that are prone to bleeding or cause pain.[8,9,33]

Ophthalmologic

Retinal astrocytic hamartomas

Intervention may be necessary for aggressive hamartomas or those causing vision loss. Treatment options include laser therapy, intravitreal injections, surgery, and mTOR inhibitors.[22-24] Early treatment of TSC-related manifestations, including seizures and neuropsychiatric symptoms, is crucial for improving long-term outcomes and quality of life. Prompt initiation of therapy can prevent disease progression and reduce the risk of complications.[1,9,13]

CONCLUSION

In conclusion, the multifaceted nature of TSC, encompassing both neurological and dermatological aspects, underscores the importance of a comprehensive approach to patient care. The elucidation of TSC pathophysiology, particularly its association with dysregulation in the mTOR pathway, has not only deepened our understanding of the disease but also propelled the development of targeted therapeutic interventions. Advances in early detection through genetic testing and diagnostic imaging have facilitated timely interventions, leading to personalized management strategies tailored to individual patient needs. The collaborative efforts of multidisciplinary care teams have been instrumental in optimizing patient outcomes. Looking ahead, ongoing research endeavors promise continued innovation in therapeutic modalities, offering hope for further improvements in the prognosis and quality of life of individuals affected by TSC.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Curatolo P, Specchio N, Aronica E. Advances in the genetics and neuropathology of tuberous sclerosis complex: edging closer to targeted therapy. Lancet Neurol. 2022;21(9):843-56.
2. Martin KR, Zhou W, Bowman MJ, Shih J, Au KS, Dittenhafer-Reed KE, et al. The genomic landscape of tuberous sclerosis complex. Nat Commun. 2017;8:15816.
3. Recklinghausen F. Ein Herz von einen Neugeborene welches mehrere thels nach aussen, theils nach den Hohlein prominirende Tumoren (myomata) trug. Monatschr Gebrutsheklkd. 1862;20:1-2.
4. Bourneville DM. Sclerose tubereuse des circonvultions cerebrales: idotie et epilepsie hemiplegique. Arch Neurol. 1880;1:81-91.
5. Vogt, Doz. On the pathology and pathological anatomy of the various forms of idiocy. Eur Neurol 1908;24:106-17.
6. Roach ES, Gomez MR, Northrup H. Tuberous sclerosis complex consensus conference: revised clinical diagnostic criteria. J Child Neurol. 1998;13(12):624-8.
7. Northrup H, Krueger DA, International Tuberous Sclerosis Complex Consensus Group. Tuberous sclerosis complex diagnostic criteria update: recommendations of the 2012 Iinternational Tuberous Sclerosis Complex Consensus Conference. Pediatr Neurol. 2013;49(4):243-54.

8. Northrup H, Aronow ME, Bebin EM, Bissler J, Darling TN, de Vries PJ, et al. Updated International Tuberous Sclerosis Complex Diagnostic Criteria and Surveillance and Management Recommendations. Pediatr Neurol. 2021;123:50-66.
9. Wataya-Kaneda M. Tuberous Sclerosis Complex. Keio J Med. 2023.
10. Pfirmann P, Combe C, Rigothier C. Tuberous sclerosis complex: A review. Rev Med Interne. 2021;42(10):714-21.
11. Dragoumi P, O'Callaghan F, Zafeiriou DI. Diagnosis of tuberous sclerosis complex in the fetus. Eur J Paediatr Neurol. 2018;22(6):1027-34.
12. Ridder J, Verhelle B, Vervisch J, Lemmens K, Kotulska K, Moavero R, et al. Early epileptiform EEG activity in infants with tuberous sclerosis complex predicts epilepsy and neurodevelopmental outcomes. Epilepsia. 2021;62(5):1208-19.
13. Portocarrero LKL, Quental KN, Samorano LP, Oliveira ZNP, Rivitti-Machado MCDM. Tuberous sclerosis complex: review based on new diagnostic criteria. An Bras Dermatol. 2018;93(3):323-33.
14. Yin K, Lin N, Lu Q, Jin L, Huang Y, Zhou X, et al. Genetic analysis of 18 families with tuberous sclerosis complex. Neurogenetics. 2022;23(3):223-30.
15. Szwed A, Kim E, Jacinto E. Regulation and metabolic functions of mTORC1 and mTORC2. Physiol Rev. 2021;101(3):1371-426.
16. Vries PJ, Belousova E, Benedik MP, Carter T, Cottin V, Curatolo P, et al. Tuberous Sclerosis Complex-Associated Neuropsychiatric Disorders (TAND): New Findings on Age, Sex, and Genotype in Relation to Intellectual Phenotype. Front Neurol. 2020;11:603.
17. Russo C, Nastro A, Cicala D, De Liso M, Covelli EM, Cinalli G. Neuroimaging in tuberous sclerosis complex. Childs Nerv Syst. 2020;36(10):2497-509.
18. Vanclooster S, Bissell S, van Eeghen AM, Chambers N, De Waele L, Byars AW, et al. The research landscape of tuberous sclerosis complex-associated neuropsychiatric disorders (TAND)-a comprehensive scoping review. J Neurodev Disord. 2022;14(1):13.
19. Vries PJ, Heunis TM, Vanclooster S, Chambers N, Bissell S, Byars AW, et al. International consensus recommendations for the identification and treatment of tuberous sclerosis complex-associated neuropsychiatric disorders (TAND). J Neurodev Disord. 2023;15(1):32.
20. de Vries PJ, Heunis TM, Vanclooster S, Chambers N, Bissell S. International consensus recommendations for the identification and treatment of tuberous sclerosis complex-associated neuropsychiatric disorders (TAND). J Neurodev Disord. 2023;15(1):32.
21. Alperin S, Krueger DA, Franz DN, Agricola KD, Stires G, Horn PS, et al. Symptom rates and profile clustering in tuberous sclerosis complex-associated neuropsychiatric disorders (TAND). J Neurodev Disord. 2021;13(1):60.
22. Wan MJ, Chan KL, Jastrzembski BG, Ali A. Neuro-ophthalmological manifestations of tuberous sclerosis: current perspectives. Eye Brain. 2019;11:13-23.
23. Hodgson N, Kinori M, Goldbaum MH, Robbins SL. Ophthalmic manifestations of tuberous sclerosis: a review. Clin Exp Ophthalmol. 2017;45(1):81-6.
24. Maio T, Lemos J, Moreira J, Sampaio F. Tuberous sclerosis complex: a clinical case with multiple ophthalmological manifestations. BMJ Case Rep. 2018;2018:bcr2018226662.
25. Lam HC, Siroky BJ, Henske EP. Renal disease in tuberous sclerosis complex: pathogenesis and therapy. Nat Rev Nephrol. 2018;14(11):704-16.
26. Trnka P, Kennedy SE. Renal tumors in tuberous sclerosis complex. Pediatr Nephrol. 2021;36(6):1427-38.
27. Kumar P, Zadjali F, Yao Y, Bissler JJ. Renal cystic disease in tuberous sclerosis complex. Exp Biol Med (Maywood). 2021;246(19):2111-7.
28. Franz DN, Bissler JJ, McCormack FX. Tuberous sclerosis complex: neurological, renal and pulmonary manifestations. Neuropediatrics. 2010;41(5):199-208.
29. Gupta N, Henske EP. Pulmonary manifestations in tuberous sclerosis complex. Am J Med Genet C Semin Med Genet. 2018;178(3):326-37.
30. Rebaine Y, Nasser M, Girerd B, Leroux C, Cottin V. Tuberous sclerosis complex for the pulmonologist. Eur Respir Rev. 2021;30(161):200348.
31. Han Z, Xue X, Wang J, Lu D. Tuberous sclerosis complex associated lymphangioleiomyomatosis. QJM. 2023;116(10):873-4.
32. Ebrahimi-Fakhari D, Meyer S, Vogt T, Pföhler C, Müller CSL. Dermatological manifestations of tuberous sclerosis complex (TSC). J Dtsch Dermatol Ges. 2017;15(7):695-700.
33. Northrup H, Koenig MK, Pearson DA, Au KS. Tuberous Sclerosis Complex. In: Adam MP, Feldman J, Mirzaa GM, eds. GeneReviews®. Seattle (WA): University of Washington, Seattle; 1993-2024.
34. Dulamea AO, Arbune AA, Anghel D, Boscaiu V, Andronesi A, Ismail G. Neurological and Dermatological Manifestations of Tuberous Sclerosis Complex: Report from a Romanian Tertiary Hospital Cohort. J Clin Med. 2023;12(20):6550.
35. Kotulska K, Kwiatkowski DJ, Curatolo P, Weschke B, Riney K, Jansen F, et al. Prevention of Epilepsy in Infants with Tuberous Sclerosis Complex in the EPISTOP Trial. Ann Neurol. 2021;89(2):304-14.
36. Uliel-Sibony S, Chernuha V, Meirson H, Fattal-Valevski A. Medical treatment of tuberous sclerosis-related epilepsy. Childs Nerv Syst. 2020;36(10):2511-7.
37. Nabbout R, Belousova E, Benedik MP, Carter T, Cottin V, Curatolo P, Dahlin M, et al. Epilepsy in tuberous sclerosis complex: Findings from the TOSCA Study. Epilepsia Open. 2018;4(1):73-84.
38. Specchio N, Pavia GC, de Palma L, De Benedictis A, Pepi C, Conti M, et al. Current role of surgery for tuberous sclerosis complex-associated epilepsy. Pediatr Investig. 2022;6(1):16-22.

39. Kingswood JC, d'Augères GB, Belousova E, Ferreira JC, Carter T, Castellana R, et al. TuberOus SClerosis registry to increase disease Awareness (TOSCA) - baseline data on 2093 patients. Orphanet J Rare Dis. 2017;12(1):2.
40. Sugalska M, Tomik A, Jóźwiak S, Werner B. Treatment of Cardiac Rhabdomyomas with mTOR Inhibitors in Children with Tuberous Sclerosis Complex-A Systematic Review. Int J Environ Res Public Health. 2021;18(9):4907.

Cite this article as: Bonilla NC, Ceja AAR, Santiago GG, Gonzalez GA, Castro AA, Suárez JL. The tuberous sclerosis complex: a review of the literature. Int J Contemp Pediatr 2024;11:616-24.