

Tuberous sclerosis complex^{*}

Esclerose tuberosa

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Abstract: Tuberous Sclerosis Complex, also known as Epiloia or Bourneville-Pringle disease is an autosomal dominant neurocutaneous syndrome with variable clinical expression. It is a multisystem disorder that may be associated with hamartomas in multiple organs in an unpredictable manner. The dermatologist plays an essential role in the history of the disease, since skin manifestations represent the most prevalent clinical features, enabling early diagnosis and intervention in its natural course. This article aims to inform the scientific community about advances made in the study of genetics and molecular biology. Recent findings regarding stimulation of tumor growth have been changing the history of this condition, making therapeutic trials with topical and systemic drugs possible. Knowledge of these topics enables better management of the patients affected, since tissue replacement by tumors can result in significant morbidity and mortality.

Keywords: Dermatology; Diagnosis; Neurology; Sirolimus; Tuberous sclerosis

Resumo:

A Esclerose Tuberosa, também conhecida como Epilóia ou Facomatose de Pringle-Bourneville, é uma síndrome neurocutânea de caráter autossômico dominante com expressões clínicas variadas. É uma doença multissistêmica que pode cursar com hamartomas em diversos órgãos, de forma imprevisível. O dermatologista tem papel essencial na história da doença, uma vez que as afecções cutâneas representam as mais prevalentes apresentações clínicas, possibilitando assim o diagnóstico precoce da síndrome e intervenção na sua evolução natural. O presente artigo tem o objetivo de atualizar a comunidade científica sobre avanços alcançados no estudo genético e biologia molecular. Recentes descobertas sobre o estímulo do crescimento tumoral vêm mudando a evolução desta patologia, possibilitando ensaios terapêuticos com drogas tópicas e sistêmicas. O conhecimento destes aspectos possibilita melhor condução dos pacientes acometidos, dado que a substituição tumoral dos diversos tecidos pode resultar em relevante morbidade e mortalidade.

Palavras-chave: Dermatologia; Diagnóstico; Esclerose tuberosa; Neurologia; Sirolimo

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BACKGROUND

Tuberous sclerosis complex (TSC), also known as Epiloia or Bourneville-Pringle disease, is an autosomal dominant neurocutaneous syndrome with variable clinical expression. It is a multisystem disease that may be associated with hamartomas in various organs in an unpredictable manner. It most often affects the skin and central nervous system.¹

Centuries ago, isolated case reports described some of the various clinical manifestations resulting from a pathology which was then unknown. In the mid 19th century, Virchow and Von Recklinghausen identified hamartomas in the brain and heart, respectively.² The term "Tuberous" was coined after a post-mortem examination of the brains of patients who had seizures and cognitive impairment, due to the aspect of the tumors found, which resembled tuberous vegetables such as potatoes. Only in the late 19th century were the findings concomitantly described by Bourneville, who first reported the discovery of a new syndrome.³

Although cutaneous manifestations had been previously described by other authors, they started to be related to the disease described by Bourneville only in the early 20th century. The first to recognize this relationship were Campbell, in 1905, and Vogt, three years later, when the relationship between mental retardation, epilepsy, and sebaceous adenoma was established, forming the triad characterizing TSC.⁴

TSC is a complex clinical entity made up of many clinical manifestations, which require attention from various medical specialties. The dermatologist plays an essential role in the history of the disease, since cutaneous involvement represents the most prevalent finding, enabling early diagnosis of the syndrome and intervention in its natural course.

After years of studies limited to several clinical aspects and certain genetic aspects of TSC, the era of molecular biology started. The new objects of interest are the signaling pathways of hamartoma growth. Great success in the recognition of proteins, enzymes and signals involved in the etiopathological process of the syndrome has recently been obtained. These findings are used to understand diseases that have uncontrolled growth of tumor cells as a common causal factor, such as TSC. The advances that have been made in the area are relevant, and today, two centuries after the first description of tubers by Virchow and Von Recklinghausen, it is possible to perform clinical trials of new drugs that can alter the course of this disease that causes considerable morbidity and mortality.^{5,6}

EPIDEMIOLOGY

Studies assessing the incidence and prevalence of Tuberous Sclerosis Complex express different

results. It is a disease with great phenotypic variability, which sometimes hinders its recognition.⁷ It affects 1 in 10,000 newborns, and the majority of patients are diagnosed with the disease in the first 15 months of life.^{6,8} About 25% of the individuals diagnosed after that age had previously showed characteristic clinical signs that were overlooked during a previous medical evaluation.^{4,8} With the advent of new techniques for genetic study and the definition of new clinical manifestations, we have an estimated prevalence of 1:6,000 persons in the general population.⁶ Both sexes are affected in a similar frequency, but women may show more prominent signs. There are no reports showing disproportionate involvement in a particular ethnic group.⁹

The sign that most often leads to diagnosis of the syndrome is the presence of early-onset seizures.^{6,8} Involvement of the skin and mucous membranes also helps with the diagnosis; however, the set of characteristic skin manifestations tends to appear at later stages. The incidence of disorders of certain organ systems is variable, but neurological and renal complications are the leading causes of mortality and morbidity.¹⁰

ETIOPATHOGENESIS

Tuberous sclerosis complex is an autosomal dominant disease with high penetrance. It is caused by inactivating mutations of TSC1 and TSC2 tumor suppressor genes, located on chromosomes 9q34 and 16p13.3, respectively.¹¹ The TSC1 gene is responsible for encoding a protein called hamartin and TSC2 for encoding for tuberin. The hamartin-tuberin complex is an important inhibitor of tumor growth. Its absence triggers loss of inhibition on cell proliferation and migration.³

Numerous genetic changes are observed, such as deletions, insertions, nonsense, and missense mutations, basically involving all exons of the genes involved.⁶ In spite of verification of such changes, mutations are not identified in 15% of the cases.³ The familial forms of TSC arise from germline mutations and, although their transmission can be hereditary, 70% of the cases are a result of somatic mutations, especially when the mutant gene is TSC2. Somatic mutations are responsible for sporadic cases of the disease.⁶ The great variety of mutations and the possibility of involvement of different genes explain, in part, the phenotypic diversity of the disease. Another factor that may explain why clinical manifestations of TSC are unpredictable is the presence of mosaicism.^{12,13}

Studies show that changes in TSC2 are five times more frequent than changes in TSC1 in sporadic cases. This relationship becomes 1:1 in cases of familial transmission.⁶ Changes in the TSC2 gene result in more

severe pathology, when compared to TSC resulting from mutations in TSC1.¹⁴⁻¹⁶ Cases of familial transmission, which show higher frequency of changes in the TSC1 gene, result in mild to moderate disease, sometimes not meeting the various diagnostic criteria.¹⁶

For several years, the “two-hit” hypothesis, proposed by Knudson in the 70’s, explained the etiopathogenesis of hamartoma formation in TSC. According to that hypothesis, patients with TSC would already present a defective tumor suppressor gene in one of the alleles of TSC1 or TSC2 during germ-cell division. This stage would be the “first hit”. However, this previous change would not be enough to trigger phenotypic findings, since both alleles must be lost or deficient so that clinical manifestation occurs. Thus, a second change involving the normal allele and leading to loss of heterozygosity is necessary for the development of a hamartoma in TSC. This would be the “second hit”, which occurs during somatic cell proliferation. Knudson believes that the presence of the anomalous allele creates genomic instability or induces epigenetic phenomena (genetic changes caused by non-mutational factors, such as DNA methylation), which trigger loss of heterozygosity and disrupt the function of the tumor suppressor gene. This genetic change would lead to absence of the hamartin-tuberin complex, resulting in uncontrolled cell growth.^{18,19} Some studies have recently challenged this hypothesis, due to the finding that tumors have been developed in spite of an intact normal allele.²⁰

The mechanism through which these mutations lead to cellular hyperproliferation and appearance of numerous hamartomas anywhere in the human body is not fully understood. Some of the stages of this proliferation pathway have already been discovered. The cells of the human body continuously respond to a wide variety of integrated biological stimuli. Defects in this signaling mechanism result in proliferative diseases such as cancer and TSC. The TSC1 and TSC2 genes have an important role in regulating cell growth, via the phosphoinositide 3-kinase signaling pathway, inhibiting the mammalian target of rapamycin (mTOR). mTOR is a major sensor of energy and nutrient availability, thus regulating cell growth, differentiation and proliferation.^{5,21} As mentioned above, the TSC1 gene encodes for a 130Kda protein known as hamartin and TSC2 encodes for a 200Kda protein called tuberlin.²² The hamartin-tuberin complex forms a heterodimer that inhibits the signaling protein, known as “RAS homolog enriched in brain” (Rheb).⁶ mTOR, in turn, following stimulation by Rheb, regulates the phosphorylation of ribosomal protein S6 kinase 1 and 2 (S6K1 and S6K2) isoforms and of the protein inhibiting translation initiation, 4E-BP1 (also known as PHAS-1).^{21,23-25} The Loss of inhibitory function of the hamartin-tuberin

complex on Rheb allows mTOR to stimulate the S6K and 4E-BP1 proteins, leading to an increase in ribosomal biogenesis, with increased production of proteins, which ultimately culminates in uncontrolled cell proliferation and tissue growth, with the emergence of tumors observed in tuberous sclerosis.²⁶⁻²⁹

The role of TSC1 and TSC2 in regulating biological processes is not yet fully understood, and some of its properties are the subject of considerable interest. One example is the finding that the hamartin-tuberin complex acts in the biology of the cell cycle by regulating cyclin-dependent kinase inhibitor p27, playing a major role in the stages of cell differentiation.³⁰ Loss of inhibition of the mTOR signaling pathway also has an important role in the insulin-dependent cellular metabolism. Activation of mTOR induces endoplasmic reticulum stress, resulting in severe insulin and IGF1 resistance, besides making the cell more susceptible to apoptosis.⁵

Other clinical manifestations can be explained by genetic changes different from alterations in the TSC1 and TSC2. The best example is the concomitant occurrence of TSC and polycystic kidney disease, an important cause of end-stage renal disease in these patients. They may be considered contiguous gene syndromes, due to the proximity of the two mutant genes responsible for the two diseases. The concomitant occurrence of both diseases results from two large deletions in the TSC2 gene, leading to mutation, by contiguity, of the PKD1 gene, which is responsible for polycystic kidney disease. Both genes are located on chromosome 16.³¹⁻³⁴

CLINICAL ASPECTS

Tuberous sclerosis presents clinical manifestations resulting from the formation of hamartomas in various organs. These lesions are dependent on the different types of genetic changes found in the pathophysiology of the disease, a fact which contributes to the existence of various forms of phenotypic TSC.³⁵

Skin Manifestations

According to a study that examines clinical signs on the skin based on age group, skin clinical manifestations represent the most frequent findings in TSC, although some patients do not show skin involvement.³⁶ Among these skin clinical manifestations, the most prevalent is the presence of hypomelanotic macules (Figure 1). Hypochromic/achromic macules are found in 90 to 98% of the patients, especially before puberty and may be the only manifestation in children.^{3,36} Parents report the presence of such macules at birth or in early life, affecting mainly the trunk and limbs, usually sparing the face. These macules tend to increase in number and size through-

hout life, becoming less prominent in adults, when they become more pigmented, and may even disappear. When the achromic macules affect the scalp, there may be poliosis.^{36,37}

The most characteristic hypochromic/achromic macules are those that have the shape of leaves, rounded at one end and tapered at the other, and therefore, called "ash-leaves" (Figure 2).³⁶ They can also be rounded, "confetti-like", in 28% of the cases. These may be multiple, with 1-2mm in diameter, symmetrically affecting the distal part of the limbs, along their entire circumference (Figure 3). The "confetti-like" hypomelanosis is often underdiagnosed due to lack of routine use of ultraviolet light, which shows dyschromia more easily. A histopathological evaluation of achromic macules shows a normal number of melanocytes, but that melanosomes are reduced in number, size, and melanization. There may be "café-au-lait" macules, but some studies consider their prevalence the same as that found in the general population.³⁶

Angiofibromas are characterized by skin-colored to violaceous papules, depending on the higher proportion of fibrous or angiomatous tissue, respectively. They are present in 80% of affected children who are older than 5.³ They primarily affect the nasolabial folds, cheeks and chin, bilaterally and symmetrically, sparing the upper lip (Figures 4, 5 and 6). When they occur unilaterally, there may be mosaicism.³⁶⁻³⁸ Clinical observations report excessive malar erythema before the onset of angiofibromas.³⁶

Shagreen patch is a skin-colored to brown fibrotic plaque which appears at around age 3, but may already be present at birth (Figure 7).^{37,38} It occurs in

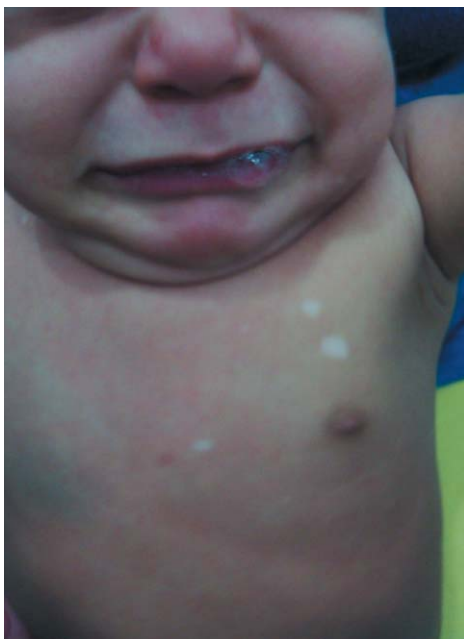


FIGURE 1: Early Findings - hypomelanotic macules

54% of affected children over 5 years old, usually at puberty, and almost always occurs in the lower dorsal surface, with multiple satellite papules.³ Skin-colored papules grouped at the characteristic site of the plaque may be considered equivalent.³⁶⁻³⁸

Forehead fibrous plaques, although not as prevalent, are considered pathognomonic for TSC. They present as a unilateral plaque with a fibrotic aspect in the frontal region and may be skin-colored or brown (Figure 8).³⁸

Periungual fibroma or Koenen's tumor is one of the last changes to occur in TSC and its incidence tends to increase with age (Figure 9).³⁹ Tumors tend to be multiple over the years, affecting mainly females, especially the nails of the toes. In some cases, there is only a longitudinal depression in the nail, corresponding to the fibroma still in the nail matrix (Figure 10) or to the remnant of the tumor, after being excised by the patient himself.³⁶

ORAL CAVITY

The teeth and gum tissue may be affected in TSC. Gingival fibromas affect about 36% of adults with TSC and are rarely found in children younger than 11 years old. They are usually detected in the anterior gingiva and may result in flesh-colored or erythematous lesions.^{36,40} Enamel pits have also been described, but they are not considered pathognomonic for TSC and are often underdiagnosed on examination.⁴¹ Therefore, a detailed assessment of the oral cavity is crucial, including examination of the gingiva under dentures, for the detection of these changes.

RENAL MANIFESTATIONS

Renal changes are the main cause of morbidity and mortality in TSC. Among them, the most common



FIGURE 2: "Ash-Leaf" hypomelanotic macule



FIGURE 3: "Confetti-like" hypomelanotic macules on the anterior surface of legs

are renal angiomyolipomas, which appear before adolescence and are present in 93% of the cases.³ They are usually bilateral and asymptomatic. They may be the cause of intense hematuria, which is more common in tumors larger than 4 cm, and may lead to loss of renal function. Their growth is slow, but in rare cases, their size may increase by up to 4 cm every 2 years.^{37,38}

Concomitant polycystic kidney disease occurs due to the proximity of the polycystic kidney disease 1 (PKD1) gene in relation to TSC2 gene, both located on chromosome 16. This disease affects mainly children, resulting in progressive loss of renal function and may culminate in chronic renal failure.^{37,38}

Patients with TSC have an estimated incidence of renal cell carcinoma close to that of the general population. However, these tumors develop early, increasing morbidity and mortality of the patients affected by TSC.

PULMONARY MANIFESTATIONS

In TSC, the expression of lung disease seriously affects the function of the organ, due to replacement of alveolar tissue by numerous cysts and proliferation of smooth muscle, called pulmonary lymphangiomyomatosis (LAM).⁴² It occurs in 1 to 3% of the cases, preferably in women during premenopause. Pulmonary involvement is rare in males. This predilection for females may be explained by the regulatory action of estrogen on cellular signaling pathways involved in TSC and on the migration of deficient cells of TSC2. The symptoms are cough and progressive dyspnea, and may also include hemoptysis and pneumothorax. Besides presenting therapeutic difficulty, the evolution of LAM is progressive, which offers a guarded prognosis, and may lead to respiratory failure.³



FIGURE 4: Facial angiofibromas at early stage



FIGURE 5: Facial angiofibromas

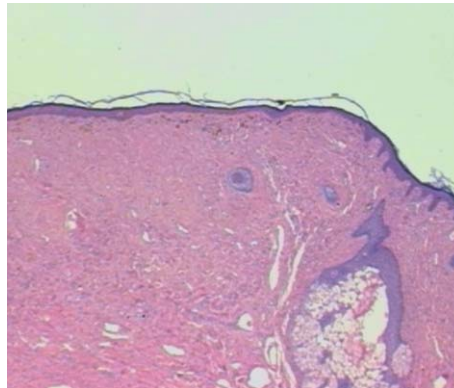


FIGURE 6: Histopathological examination of facial angiofibroma: HE. 25X

Heart changes

Rhabdomyoma is the most common cardiac tumor in TSC. Since it is more prevalent early in life, it is the most frequent clinical change in fetuses and newborns.⁴³ They are usually located in the wall of the ventricles and, depending on size, number and location, can result in cardiomegaly, heart murmurs, altered blood flow, arrhythmias, non-immune hydrops fetalis and death. They usually regress completely in the first years of life, due to lack of maternal hormone stimulation.⁴⁴ Despite the variety of symptoms resulting from rhabdomyoma, most cases



FIGURE 7: Shagreen patch



FIGURE 8: Fibrous forehead plaque



FIGURE 9: Koenen's tumor

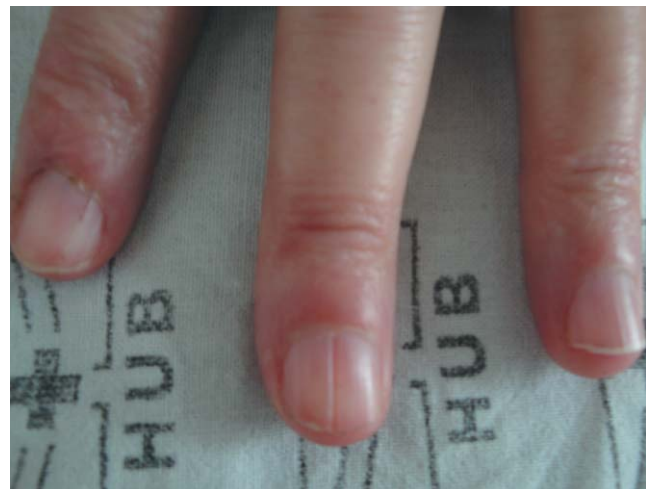


FIGURE 10: Longitudinal canalicular nail depression, corresponding to unguis fibroma in the nail matrix

are asymptomatic.⁴³

In a recent study, Adriaensen et al. evaluated chest CT of 55 patients with TSC and found foci of fat attenuation in 64% of the cases. The authors suggest that such findings may be part of the characteristics of TSC; however, its true clinical significance remains uncertain.⁴⁵

Neurological Changes

The most common neurological clinical manifestations in TSC are epilepsy, cognitive delay and autism.⁴⁶ Seizures are routine in the childhood of patients with TSC, and infantile spasm is considered to be the most commonly diagnosed subtype in the first year of life.³⁷ Epilepsy may be present in up to 90% of the cases. Its early onset is associated with its refractoriness and more severe cognitive delay.⁴⁶

Epileptogenesis in TSC can be explained by decreased neuronal inhibition secondary to molecular alterations in GABA receptors, which are present in giant cells and dysplastic neurons. GABAergic deficiency may explain early onset and severity of seizures.³ An explanation suggested for refractory seizures in TSC, after immunohistochemical evaluation of surgical specimens from epileptic patients with TSC, is the overexpression of P-glycoprotein, encoded by MDR1 gene, in the epileptogenic tissue. This glycoprotein could be responsible for clearance of antiepileptic drugs, and would be increased in these cases, leading to poor therapeutic response.⁴⁷

In a study carried out by means of serial analysis of interictal electroencephalogram (EEG) records of patients with TSC, it was found that patients with more than three interictal epileptogenic foci tend to

have poorer cognitive development. It was also shown that the earlier the onset of seizures, the greater the number of interictal epileptogenic foci.⁴⁸

An important datum in clinical practice is that West syndrome, which comprises spasm-type seizures, delayed psychomotor development and hypsarrhythmia in the electroencephalogram, is the most frequent epileptic encephalopathy in the first year of life and that, after severe neonatal asphyxia and congenital brain malformations, TSC is the most frequent cause of West syndrome. Hence the need to diagnose these pathologies, which can be associated, since 30% of children under 1 year of age with TSC and epilepsy will develop West syndrome.⁴⁹

Neuroimaging studies are altered in 90 to 95% of cases of TSC, with the description of tubers in the cerebral cortex, subependymal nodules in the walls of the lateral ventricles and subependymal giant cell tumors.³⁶ Serial studies that have evaluated the relationship between imaging and clinical manifestations of TSC have identified that a greater number of tubers, their bilateralism and location in the temporal lobe are directly related to greater severity of neurological involvement.^{50,51}

On histopathological examination, cortical tubers in the brain show absence of normal laminated architecture. There is also presence of large cells resembling astrocytes but positive for neuronal and glial markers. Subependymal nodules present vascular stroma and astrocyte-like cells.³⁶

Ocular changes

Calcified retinal astrocytic hamartoma can be present in 50% of patients.^{37,52} They tend to be bilateral and become evident at the age of 2. They are asymptomatic in most cases, in which case they do not affect the optic nerve or macula. Patients may also present hypochromic macule in the retina, corresponding to skin macules.³

Liver changes

Multiple hepatic angiomyolipomas have been reported in rare cases of TSC, and this prevalence may be the result of underdiagnosis, for they are usually asymptomatic. Ultrasonographic evaluation of patients with TSC shows higher prevalence of hepatic hamartomas in adulthood (23-45%). There is some predilection for females.³

Diagnosis

Diagnosis of tuberous sclerosis is initially based on clinical findings. The disorder should be considered in cases of children with seizures and hypomelanotic macules.

Due to the clinical variability of TSC, clinical

and radiological diagnostic criteria were revised in 2000. Diagnosis can be definitive, probable or possible, depending on the number of major and minor criteria present (Table 1).^{37,53} Definitive diagnosis is considered when there is presence of at least two major criteria or one major and two minor criteria. Probable diagnosis is considered when there is presence of one major and one minor criterion. Possible diagnosis refers to the presence of one major criterion or two or more minor criteria.^{36,37,53} Some considerations regarding TSC diagnostic criteria should be stressed. When cortical dysplasia and cerebral white matter radial migration occur together, they shall be considered as only one criterion. When LAM and renal angiomyolipomas occur concomitantly, other criteria for TSC must be present, before confirming the diagnosis. It is suggested that hamartomatous rectal polyps, multiple renal cysts and nonrenal hamartomas be histologically confirmed. Identification through imaging examinations is sufficient for the diagnosis of cerebral white matter radial migration and bone cysts.⁵³

Earlier at the onset of clinical manifestations of TSC, some additional tests should be performed in order to confirm the diagnosis and to elucidate the causes of symptoms. Thus, before the diagnostic possibility of TSC, cranial computed tomography (CT) or magnetic resonance imaging (MRI) must be requested; electroencephalogram must be requested in case of seizures; renal ultrasound must be performed in all suspected patients; echocardiography, electrocardiogram, ophthalmoscopy and pulmonary CT must be requested for women; pulmonary function tests should be performed in women with respiratory symptoms; renal function tests should be requested in cases of children with polycystic kidneys and of adults with extensive renal involvement. Neuropsychomotor development and behavior should also be assessed in an attempt to establish the presence of autism, hyperactivity and mental retardation.³⁷

Echocardiography may be altered due to the presence of rhabdomyomas, even before neurological and skin lesions become noticeable.⁴⁴ Cranial CT scanning shows subependymal nodules, often calcified, present in the walls of the lateral ventricles and which may be protruding into the ventricular cavity (Figure 11).^{3,36} For evaluation of cortical tubers, MRI of the brain, using FLAIR sequences, shows to be superior to other neuroimaging studies. With this method, tubers may be associated with white matter abnormalities, such as radial migration lines.^{36,37,52} Fetal MRI shows alterations from the 26th week of pregnancy, when there are tubers in the central nervous system.³

Although it is not part of the classic diagnostic criteria due to its low availability, a genetic study may be asked for confirmation and detection of the mutation trig-

gering TSC. This test may also be useful in evaluating and counseling healthy relatives of patients with TSC.

MONITORING

Brain MRI or cranial CT scan should be performed every 1 to 3 years in children and less frequently in adults. Early diagnosis of intracranial changes enables complete removal of tumors, when indicated.³⁷

Chest CT scan and pulmonary function tests should be performed every 6 to 12 months in symptomatic women with pulmonary LAM.³⁷ Renal ultrasound should be obtained every 1 to 3 years in adolescents and adults for monitoring the emergence of renal angiomyolipomas.^{3,37}

GENETIC COUNSELING

The active search for cases of TSC in undiagnosed relatives, due to a less prominent clinical manifestation, is important for the establishment of early treatment of possible complications caused by tumors and also for raising awareness of the possible transmissibility of TSC to future generations. It is known that a patient with TSC has a 50% chance of having a child affected by the disease, and the risk of a healthy

couple who had a child with TSC to have another child with the disease is 2%.³⁷

Medical evaluation of healthy family members who are planning to have children should be performed by means of a dermatological examination, due to the delayed onset of facial angiofibromas and unguis fibromas in some cases, in addition to renal ultrasonography and cranial CT scan.³⁶

Genetic testing, as mentioned above, help clarify mutations responsible for cases of TSC, in addition to evaluating changes in healthy relatives so that the risk of another child being born with the disease is established. In spite of this, about 2% of healthy parents of children with TSC present gonadal mosaicism. Thus, such mutations would not be diagnosed during genetic evaluation, which means that the risk of the next child to be affected by TSC would remain.³

Genetic evaluation is not routinely indicated for monitoring of patients affected by TSC. Before an uncertain clinical and radiological diagnosis, the need for evaluation of family members and prenatal diagnosis of the disease, molecular genetic testing helps the physician in clinical practice. According to the Tuberous Sclerosis Alliance, genetic testing for Tuberous sclerosis complex can be performed by means of polymerase chain reaction, DNA sequencing and TSC1 and TSC2 dosage.^{54,55}

TREATMENT

Treatment of TSC consists in addressing the symptoms caused by hamartomas and in prophylactic measures to prevent loss of function of the affected organ. Since it is a systemic disease, a multidisciplinary approach is mandatory.

Facial angiofibromas may be removed by derma-

TABLE 1: Diagnostic Criteria for Tuberous sclerosis complex.⁵³

Major criteria:

Facial angiofibromas or forehead plaques;
Nontraumatic unguis or periunguis fibroma;
Hypomelanotic macules (more than three);
Shagreen patch;
Multiple retinal nodular hamartomas;
Cortical tubers;
Subependymal nodules;
Subependymal giant cell astrocytoma;
Cardiac rhabdomyoma (single or multiple);
Pulmonary lymphangioleiomyomatosis;
Renal angiomyolipoma.

Minor criteria:

Multiple pits in dental enamel;
Hamartomatous rectal polyps;
Bone cysts;
Cerebral white matter radial migration lines;
Gingival fibromas;
Nonrenal hamartomas;
Retinal achromic patch;
"Confetti-like" hypomelanotic macules;
Multiple renal cysts.

1. Definite diagnosis: two major criteria or one major and two minor criteria;
2. Probable diagnosis: one major criterion and one minor criterion;
3. Possible diagnosis: a major criterion or two or more minor criteria.



FIGURE 11: Cranial computed tomography scan: calcification in the ventricular walls

brasion, surgical excision, electrocautery and argon laser therapy, and their recurrence is common.^{36,37} Fibrous tumors are best treated with CO₂ laser.³⁷ Due to the recurrent and progressive growth of facial tumors, surgical treatment may be delayed until after adolescence, when their growth is at maximum peak.³⁶ Ungual fibromas that present frequent bleeding or are painful may be surgically excised, treated with electrocautery or argon laser, but recurrence is not uncommon.^{36,37}

Renal angiomyolipomas that cause persistent hematuria should undergo arterial embolization. In tumors larger than 4 cm, there should be close monitoring, with evaluation of the need for prophylactic embolization, since these are the ones most likely to cause severe hematuria.³⁷ This procedure should also be performed in centrally located tumors, when surgical treatment poses greater risks. Angiogenesis inhibitors may be used to prevent the development of angiomyolipomas and may improve the prognosis of TSC.³

Cardiac rhabdomyomas should be surgically removed if symptomatic. Cardiac arrhythmias are treated clinically.³⁷

Anticonvulsants should be used in patients with epilepsy, and the most effective drug is vigabatrin. In cases of infantile spasms, the use of corticotropin or prednisolone is recommended.³⁷ In patients with TSC and refractory epilepsy, surgical resection of epileptogenic foci has decreased drug resistance in these patients by 57%. Surgery can reduce the deterioration of cognitive function and behavioral disorders.³⁷ In case of subependymal astrocytoma, surgical resection is preferred over radiotherapy, since response to the latter is unsatisfactory and since it increases the occurrence of glioblastomas.³⁷

After the discovery that regulation of the mTOR pathway is associated with the development of tumors in TSC, some promising studies have been receiving great attention. Interferon-gamma and -alpha interact with the mTOR pathway, leading to deactivation of 4E-BP1, which could be very helpful in the treatment of TSC.³

Inhibitors of the mTOR pathway, such as rapamycin, also known as sirolimus, have an immunosuppressive and antiproliferative action. They are responsible for normalizing the functioning of this pathway in cells deficient in TSC1 or TSC2. This drug is effective in reducing the volume of tumors in patients with TSC, such as renal angiomyolipoma, subependymal giant cell astrocytoma and sporadic LAM. Patients with mutations in TSC2 presented learning improvement and patients with LAM showed recovery of the pulmonary function after using rapamycin. Despite the satisfactory therapeutic effect in the treatment of renal angiomyolipomas, recurrence of uncontrolled tumor growth after discontinuation of the drug was observed.⁵⁶ Topical therapy with rapamycin was shown to be feasible and safe in a clinical study conducted with patients with psoriasis.⁵⁷ The real role of this route of administration is promising, due to the possibility of reduced side effects and greater effect on the skin. However, there is no consistent scientific evidence to date.⁵⁸

It is believed that, in the future, gene therapy will make it possible to treat mutations that cause TSC through reintroduction of defective genes, leading to induction of apoptosis of mutated cells, or through reintroduction of the lost gene, enabling the cell to present normal phenotype and avoiding the clinical changes of TSC.^{59,60} □

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QUESTIONS

1. **Tuberous Sclerosis Complex is a condition which results in various skin changes and which was the subject of numerous historical descriptions. It is possible to state the following about TSC, except:**
 - a. Epiloia, Bourneville's disease, and Pringle-Bourneville disease are synonymous with Tuberous Sclerosis Complex;
 - b. Vogt's triad consists of mental retardation, epilepsy, and sebaceous adenoma;
 - c. Although associated with frequent systemic complications, the dermatologist plays an essential role in the diagnosis and monitoring of these patients;
 - d. Diagnosis of the disease is subject to clinical criteria, and advances in genetics and molecular biology have contributed little to the diagnosis and treatment of these patients.
2. **Regarding the epidemiology of Tuberous Sclerosis Complex, it is incorrect to state that:**
 - a. There is no difference in incidence between the sexes;
 - b. Diagnosis is made around the first year of life in most cases;
 - c. The disease most commonly affects the black race;
 - d. The main causes of morbidity and mortality associated with the disease result from neurological and renal involvement.
3. **Considering the etiopathogenesis of Tuberous Sclerosis Complex, it is correct to state that:**
 - a. It is an autosomal recessive disease;
 - b. It is the result of mutations occurring in the TSC1 and TSC2 genes, located on chromosomes 9 and 16, respectively;
 - c. It is most commonly triggered by mutations transmitted through genetic inheritance;
 - d. Depending on the gene affected, clinical changes are predictable, resulting in clinical homogeneity in most affected patients.
4. **TSC1 and TSC2 genes encode for the following signaling proteins, respectively:**
 - a. Cathepsin and tuberlin;
 - b. Cathepsin and hamartin;
 - c. Tuberlin and hamartin;
 - d. Hamartin and tuberlin.
5. **The clinical finding that most often leads to a diagnosis of Tuberous Sclerosis Complex is:**
 - a. Polycystic kidney disease;
 - b. Facial angiofibromas;
 - c. Heart failure;
 - d. Early-onset seizures.
6. **Studies have shown that mutations occurring in the TSC2 gene are more frequent and characterized by:**
 - a. Association with polycystic kidney disease, due to adjacent genetic mutations;
 - b. Resulting in milder disease;
 - c. Taking greater proportions in cases of familial transmission;
 - d. Association with other phakomatoses.
7. **The TSC1 and TSC2 genes, by encoding signaling proteins, play an important role in regulating cell growth and tumor development through inhibition of (a):**
 - a. Dihydrofolate reductase enzyme;
 - b. Mammalian target of rapamycin (mTOR);
 - c. Collagen synthesis;
 - d. TNF - α .
8. **The role of TSC1 and TSC2 genes in the regulation of biological processes is not fully understood. It is known that these genes play an important role in (a):**
 - a. Insulin-dependent cellular metabolism;
 - b. Activation of atheromatous vascular disease;
 - c. Vascular remodeling;
 - d. Conduction of nerve stimuli.
9. **According to the NSTA, the following are major diagnostic criteria, except:**
 - a. Facial angiofibromas;
 - b. Cortical tubers;
 - c. Retinal hamartomas;
 - d. Multiple renal cysts.
10. **Regarding the cutaneous manifestations of tuberous sclerosis complex, it can be stated that:**
 - a. They are present in all affected patients;
 - b. Hypomelanotic macules are the most prevalent findings;
 - c. Facial angiofibromas tend to appear in the first years of life, facilitating early diagnosis;
 - d. Ungual fibromas tend to disappear with age.

11. About periungual fibroma or Koenen's tumor, it is correct to state that:

- a. They are invariably presented as exuberant lesions that can be easily diagnosed;
- b. They are single, in most cases;
- c. It is a common abnormality at birth;
- d. They are usually multiple and more common in the toes and in female patients.

12. Regarding the systemic manifestations of Tuberous Sclerosis Complex, it can be stated that:

- a. Retinal hamartomas are responsible for late-onset amaurosis, observed in most patients;
- b. No changes are described in the oral cavity;
- c. Patients may develop renal cell carcinoma at an early stage, increasing morbidity and mortality;
- d. Neuroimaging studies reveal changes in only 10% of affected patients.

13. Patients diagnosed with Tuberous Sclerosis Complex and symptoms of persistent hematuria should be evaluated carefully, primarily considering the diagnostic possibility of:

- a. Polycystic kidney disease;
- b. Renal cell carcinoma;
- c. Angiomyolipomas;
- d. Nephrolithiasis.

14. It is considered the most common cardiovascular change in Tuberous Sclerosis Complex:

- a. Rhabdomyomas;
- b. Mitral stenosis;
- c. Coarctation of the aorta;
- d. Rhabdomyosarcomas.

15. Pulmonary lymphangiomyomatosis is the proliferation of smooth muscle, which affects the lung tissue. It is correct to state the following:

- a. It affects all patients with Tuberous Sclerosis Complex;
- b. It is more common in males;
- c. It mainly affects elderly patients;
- d. It mainly affects premenopausal patients.

16. About regular monitoring of patients diagnosed with Tuberous Sclerosis Complex, it is correct to state that:

- a. Neuroimaging tests only serve purposes of documentation, since surgical treatment is ineffective and risks preclude its implementation;
- b. Ultrasound of the urinary system should be performed only in those patients with persistent hematuria;
- c. Cranial imaging studies should be performed every 1 to 3 years in children and less often in adults;
- d. Pulmonary function tests and chest tomography should be performed every five years in symptomatic patients with pulmonary lymphangiomyomatosis.

17. Genetic counseling is an important tool for managing patients with Tuberous Sclerosis Complex and their family members. It is correct to state that:

- a. Dermatological examinations are useful in the evaluation of healthy relatives and may detect later-onset skin changes;
- b. For ethical reasons, active search in relatives of affected patients should not be performed;
- c. A patient with Tuberous Sclerosis Complex has 25% chance of having a child affected by the disease;
- d. Genetic tests are not suitable for assessing healthy relatives of patients with Tuberous Sclerosis Complex due to the high frequency of gonadal mosaicism.

18. Regarding treatment of skin lesions, it is correct to state that:

- a. Facial angiofibromas may be removed through dermabrasion, excision, electrocautery and laser therapy, with low recurrence rates;
- b. Fibrous tumors may be treated with CO2 laser;
- c. Facial tumors exhibit maximum growth in the first five years of life;
- d. Ungual fibromas are not very painful, do not bleed and may be surgically excised without recurrences.

19. The use of drugs such as sirolimus is justified in Tuberous Sclerosis Complex by its:

- a. mTOR pathway inhibiting action;
- b. Immunomodulatory action;
- c. Immunosuppressant action;
- d. Anti-inflammatory action.

20. It is the most effective anticonvulsant drug in cases of Tuberous Sclerosis Complex:

- a. Valproic Acid;
- b. Phenobarbital;
- c. Carbamazepine;
- d. Vigabatrin.

Answer key of the quiz on Tuberous Sclerosis Complex

HLA and skin cancer. *An Bras Dermatol.* 2012;87(1):9-18.

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|------|-------|-------|-------|
| 1. c | 6. a | 11. c | 16. b |
| 2. a | 7. d | 12. c | 17. c |
| 3. d | 8. b | 13. c | 18. d |
| 4. b | 9. d | 14. d | 19. b |
| 5. d | 10. d | 15. d | 20. b |

Papers

Information for all members: The EMC-D questionnaire is now available at the homepage of the Brazilian Annals of Dermatology: www.anaisdedermatologia.org.br. The deadline for completing the questionnaire is 30 days from the date of online publication.