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Review Article

An approach to the tuberous sclerosis complex

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ABSTRACT

Tuberous sclerosis is an autosomal dominant disorder with complete penetrance that is characterized by the formation of benign tumors in multiple organs, such as hamartomas in the skin, angiomyolipoma in the kidney, retina, heart, lungs and infratentorial brain tumors, conditioning alterations of neurological type, which condition repercussion on the quality of life of patients.

Keywords: Tuberous sclerosis, Bourneville pringle, Epiloia, Hamartoma, Angiomyolipoma

INTRODUCTION

Pierre François Rayer in 1835 described the first typical lesions of disease in 1862, Friedrich Daniel Von Recklinghausen reported the presence of cardiac rhabdomyomas and cortical tubers. In 1879, Désiré-Magloire Bourneville described the autopsy of a 15-year-old woman who had skin lesions compatible with angiofibromas described as confluent lesions of the vesicular-papular type in the nose, which would later be associated with the tuberous sclerosis complex, which included history mental retardation as well as history of seizures. John James pringle describe the lesions as angiofibromas, Heinrich Vogt reported a triad composed of persistent seizures, mental disability and sebaceous adenoma later these characteristics would be used as clinical criteria for the diagnosis of tuberous sclerosis complex.[1-6]

Tuberous sclerosis complex (Pringle Bourneville phacomatosis) is an autosomal dominant disorder, in which an inactivating variant in the TSC 1 gene located on chromosome 16, derived from multiple organs, mainly to the brain, causing developmental abnormalities, epilepsy, neuropsychiatric and neurobehavioral disorders.

Specifically, the TSC 2 gene is more associated with severe neuronal damage; through hyperactivation of the mTOR pathway, causing deregulated signaling which causes greater cell growth and potentiation; being the brain, the skin and the kidney the most affected organs up to 80-90%.[7-12]

Epidemiology

It has an incidence of 1/6000-10,000 newborns annually, affects two million people in the world, without predilection for gender and ethnicity.

In a recent study conducted in Germany with the updated diagnostic criteria, an incidence of 1:6760 to 1:13,520 live births wart estimated.[13-18]

Etiopathogenesis

The inactivation of tumor suppressor genes TSC1 and TSC2 cause the translation of abnormal proteins called hamartin and tuberin, which are linked to a third protein known as TBC1D7. This has a role in the regulation of cell growth through phosphatidylinositol 3 kinase, causing inhibition of mTOR receptors, inhibiting apostosis.[18-23]

The cortical tubers of the tuberous sclerosis complex present an elevated expression of genes involved in the development of the innate immune system, such as the complement system, associated with a decrease in the predominant gene expression associated with normal cellular pathways such as neurogenesis and the signaling pathway of glutamate.[24]

Sirolimus manipulates the mTOR pathway through rapamycin, which binds to FKPB12 and causes the mTORC1 complex to dissociate, inhibiting the stimulation of anabolism; mTORC1 is also activated by tyrosine kinase growth factor receptors such as insulin, IGF1, brain-derived neurotrophic factor and epidermal growth factor.[25-27]

Clinical findings

Cutaneous manifestation

The skin is the organ most affected by this disease, presenting manifestations in 90% of which are found in Table 1 and they are illustrated in Figure 1.[28-31]

Table 1: Cutaneous manifestation of tuberous sclerosis complex and their percentage of presentation.

Manifestations	Presentations
Hypermelanocytic macules	They are observed in 90% of patients with TSC, being found as a major criterion when more than 3 macules of 5 mm are found or as a minor criterion when confetti lesions are found
Angiofibromas	They occur in 75% of patients between 2 and 5 years of age, they are distributed centrally in the face with a butterfly pattern, nasolabial región and chin
Fibrous cephalic plates	They occur on the forehead or in other craniofacial areas in 25%, they represent a more specific finding of dermatological lesions
Nail Fibroma	Also known as Koenen tumors, they are found in 20% of patients
Shagreen patch	Normally located in the trunk, they are found in 50% of patients

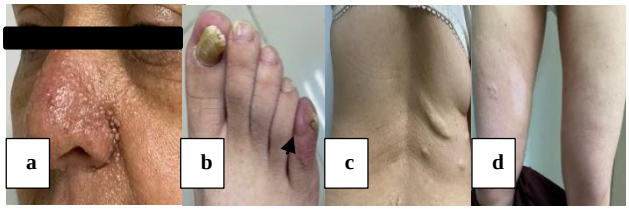

Figure 1: Cutaneous manifestations of tuberous sclerosis complex: (a) facial angiofibromas: multiple shiny dome-shaped papules on the nose and cheeks; (b) periungual fibromas: fibromas growing in the periungual area of the fifth toe of the right foot; (c) Shagreen's patch: slightly hypopigmented plaques located in the lumbar area; (d) hypopigmentation in ash leaf.

Among the main differential diagnoses of skin lesions are vitiligo, Alessandrini syndrome, Vogt-Koyanagi-Harada disease, scleroderma, autoinmune disease, Birt-Hogg: Dube syndrome and multiple endocrine neoplasia type 1.[28]

Neurological manifestations

Astrocytes

Astrocytes are support cells of the central nervous system responsible for metabolism, structural support, blood-brain barrier support, regulation, changes in neurotransmitters a gliotransmission (direct intercellular communication with other astrocytes); maintaining the balance, providing lactate and nutrients to the neurons. As well as the transport f neurotransmitters such as glutamate, helping to signal in synaptic termination and preventing excitotoxicity.[32-35]

Astrogliosis is a prominent feature of cortical tubers secondary to a change in morphology and increased glial fibrillary acidic protein staining. There are two types of astrocytes the first with elongated radial processes and astrocytes with abundant inner filaments and reactive presenting increased cell size and increased expression of vimentin causing giant cells, causing impairment of neuronal function and excitability preventing toxicity due to hyperexcitation, which occurs in patients with TSC, causing convulsive crises, alterations in behavior and neurodevelopment.[32-35]

Microglia

They are the cells responsible for mediating the innate and adaptive immune response in the central nervous system such as infections, neurodegenerative diseases and other brain injuries, in addition to their central role in immunity, they have activity in the regulation of neurogenesis, neuronal migration and synaptic contrary, excessive activation leads to brain damage; in patients with tuberous sclerosis, activation of microglia is found

in the tubers, with cortical tubers being found in difficult control epilepsy.[32,36-38]

Oligodendrocytes

It is the main cell responsible for the creation of myelin in the central nervous system, a decrease in the creation of the myelin sheath and the number of oligodendrocytes around the tuber has been found, being linked to a deficiency in oligodendrocyte progenitor cells and elevated mTOR activity.[39-41]

Epilepsy

About 80% of patients present epileptic seizures of variable types, clinically are presented as West syndrome during childhood and focal epilepsy, being in or adjacent to the cortical tuber, leading to difficult to control epilepsy.[42,43]

Neuropsychiatric disorders

Intellectual disability is present in more than half of the patients and autism spectrum disorder is identified in a large part of patients, even presenting behavioral, cognitive, and psychosocial problems in individuals with a normal intelligence level.[44]

Brain tumors

Subependymal giant cell astrocytoma (SEGA), a benign tumor of the lateral ventricle wall, is found in approximately 10% of patients, being a cause of increased intracranial pressure and hydrocephalus, requiring surgical treatment and sometimes chemotherapy with an mTOR inhibitor such as everolimus.[45]

Cortical tubers

They are predominantly supratentorial, with infratentorial cerebellar tubers presenting in 8-15% of patients; in adult patients, the tubercles appear hypointense on T1-WI and hyperintense on T2-WI and FLAIR46-47 (Figure 2).

Subependymal nodules

They occur along the surface of the ventricle, closer to the caudate nucleus, posterior to the foramen of Monro, appearing as irregular nodules with variable signals, generally hypointense to the white substance in T2 due to calcification.[46]

Subependymal giant cell astrocytoma

Located near the Monro foramen, they occur in 5 to 10% of patients, frequently calcifying, with a heterogeneous signal on magnetic resonance, enlarging over time, frequently causing obstructive hydrocephalus.[46-48]

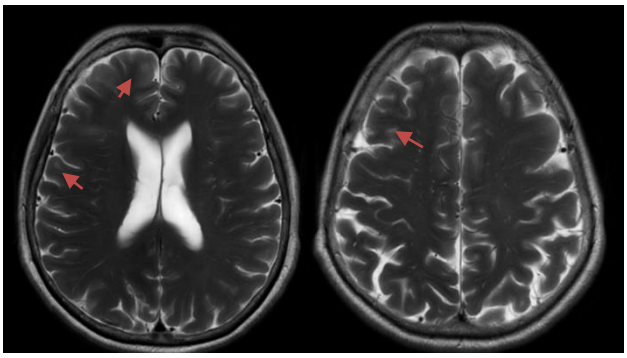

Figure 2. T2-weighted brain magnetic resonance imaging (PROPELLER) shows hyperintense lesions with diffuse limits in the subcortical región of the right frontal lobe suggestive of tubers; at periventricular level white matter, hyperintense lines are observed bilaterally that extend towards the cortex and correspond to lines of radial migration.

Renal manifestations

Renal angiomyolipoma is a rare benign mesenchymal neoplasm characterized by the presence of thin dysmorphic veins, smooth muscle in variable proportion and adipose tissue, presenting associated with tuberous sclerosis, associated with TSC1 and TSC2 with frequency of 65 to 80% of patients studied by ultrasound, with a predilection for the female sex from 2 to 1; it can be asymptomatic or present with symptoms such as flank pain, hematuria or Wunderlich syndrome, characterized by hypovolemic shock associated with flank pain with perirenal hematoma.[21,49]

Cardiac manifestations

Cardiac rhabdomyoma are benign tumors dependent of cardiac muscle fibers, being multiple, with a location of 70% in the left ventricle, with a tendency to decrease in size with spontaneous regression in 90% of cases, an association with tuberous sclerosis is described in 61-72%, sometimes causing mechanical obstruction, appearing during fetal age between 20 to 30 weeks of gestation, presenting regression in childhood in some cases, Kotulska et al found expressions of pro-apoptotic proteins in this type of tumors associated with tuberous sclerosis, fibromas were also found in 15.4% and myxomas in 5.8%, associated with tuberous sclerosis complex.[52-57]

The clinical impact varies depending on the location and number of lesions, however, in most cases they are asymptomatic. On the other hand, when they develop symptoms, they vary from cardiomegaly, murmurs, arrhythmias, hydrops fetalis and depending on the location, they can generate an obstruction gradient that can even result in the death of the patient. The average number of lesions is 3 from approximately 3 to 25 mm. Within the macroscopic characteristics are nodular lesions, grayish pink. Microscopically, they are

characterized by tumor cells of different degrees of vacuolization with a thin fibrous layer, Schiff positive with central nuclei with fine cytoplasmic fibers, distributed towards the periphery, called spider cells. Al Kindi et al found a high expression of autophagic proteins such as P62 and LC3b an apoptotic protein such as caspase 3 and 7 that are involved in the process of spontaneous regression of the lesion.[53,56,57]

On echocardiography lesions are found in the wall of the right or left ventricle, in the left ventricular outflow tract, being mural lesions, pedunculated, multiple, of variables size, and hyperechoic (Figure 3).

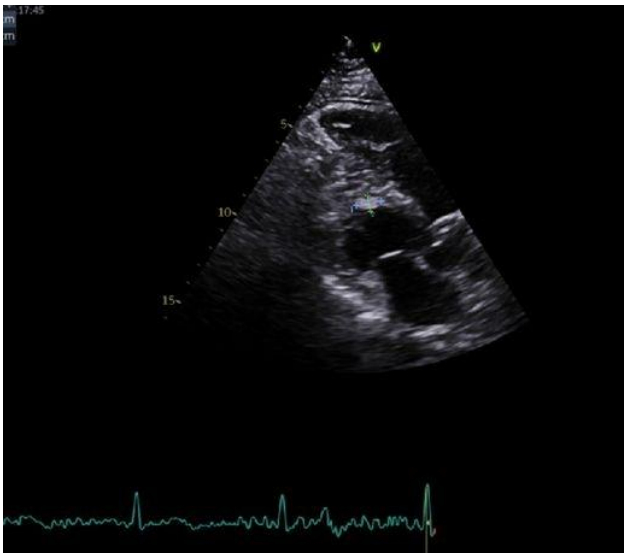

Figure 3: In long-axis parasternal projection 4-chamber projection a hyperechoic, homogeneous nodular mass of 6×9 mm with well-defined contours (red arrow) is observed in the interventricular septum, which protrudes intracavitary without generating an obstruction gradient.

Other studies can be used, such as cardiac tomography, finding hypodense lesions after contrast and in cardiac magnetic resonance, isointense or hyperintense lesions in the myocardium at T2.[53-57]

Based on international guidelines, if this type of injury is detected in the fetal period, it is suggested to intentionally seek data that predict heart failure at birth. Ebrahimi-Fakhari et al studied the maternal administration of sirolimus from 1 to 6 mg per day, observing a gradual decrease in tumor size. Follow up is suggested with an echocardiogram annually, and an electrocardiogram every 3 years to look for conduction abdormalities.[57,58]

Ophthalmological alterations

They present rare vision impairment, without requiring specific treatment, presenting in 50% of unilateral retinal hamartoma patients and in 25% of patients bilaterally.[59]

Hamartomas of the optic nerve

Are typically found in the retina, astrocytic hamartomas can also be found with optic nerve involvement causing papilledema, sometimes presenting bilaterally in patients with symptoms of intracranial hypertension and must be differentiated from other causes of papilledema such as edema in the central nervous system, infiltration optic nerve compression. Sometimes optic nerve hamartomas can cause drusen with a prevalence of 2% of the population, causing symptoms and visual fields defects, with reported complications such as retinal vascular occlusion and non-arteritis ischemic optic neuropathy. An ophthalmological follow-up should be carried out on patients with hamartomas of the optic nerve.[59,60]

Cranial nerve palsy

Infrequent neuro-ophthalmological disorder with involvement of the III and IV cranial nerves, with involvement of the VI nerve being common secondary to high ICP, on the contrary, the paralysis of the III nerve is more associated with intracranial aneurysm presenting as ptosis, mydriasis, ipsilateral abducted eye, it may be partial or incomplete.[61,62]

Cortical visual impairment

It is one of the most frequent manifestations in patients, including all visual dysfunction caused by damage and/or dysfunction of the retro chiasmatic pathways and brains structures in the absence of a significant ophthalmological disease.[63]

Diagnosis

Table 2 illustrates the diagnostic criteria to prove a definitive diagnosis with two major criteria or one major accompanied by two minor criteria or the presence of a mutation in the confirmed TSC1 or TSC2 gene or a possible diagnosis with one major criteria plus two minor criteria.

Treatment

Treatment in these patients requires a multidisciplinary approach in which neurology, dermatology, cardiology, nephrology, ophthalmology, dentistry, neurosurgery, neurodevelopmental pediatrics, pulmonology and genetics services must participate.

In the first instance, the organs and systems involved must be identified so that the injuries can be followed up to act in a timely manner in case they progress further compromising their health.

At the neurological level, it is recommended to carry out follow-up with brain magnetic resonance imaging every 1 to 3 years until the age of 25 and an electroencephalogram according to clinical need. For the

treatment of muscle spasms, there is strong evidence to support vigabatrin as a first-line treatment and some bibliographies suggest it as a treatment for epileptic seizures.[57]

Table 2: Diagnostic criteria according to the International Council of Tuberous Sclerosis Complex 2012.

Major criteria
Skin and oral cavity
Hypomelanocytic macules (>3 macules of at least 5 mm in diameter) Angiofibromas (>3) or cephalic fibrous plaque Nail Fibromas (>2) Shagreen patch
Central nervous system
Cortical dysplasia (tuber and radial migration lines of white matter) Subependymal nodules Giant subependymal astrocytoma
Heart
Cardiac rhabdomyoma
Lungs
Lymphangioleiomyomatosis
Kidneys
Angiomyolipoma (>2)
Eyes
Mutiple retinal hamartomas
Minor criteria
Skin and oral cavity
Confetti skin lesions, tooth enamel pits (>2), intraoral fibromas (>2)
Kidneys
Multiple kidney cysts
Eyes
Achromic retina patch
Other organs
No renal hamartomas
Genetics: Genetic mutation in DNA genes TSC1 o TSC2

In these patients, epilepsy may be difficult to treat, so surgical treatment may be useful. Due to the small number of patients with this syndrome, more studies are needed to address improvements in treatment and evaluate its impact on prognosis.

For the rest of the systemic manifestations, at the cutaneous, renal, cardiovascular, ophthalmological and pulmonary levels, constant screening should be carried out in search of new lesions and these may benefit from treatment with mTOR inhibitors and surgical treatment.[15]

DISCUSSION

Tuberous sclerosis is a disease in which the diagnosis is commonly made at a young age, mainly due to the presence of neurological manifestations. However, in patients with a mild degree of the disease, late diagnosis may be frequent. Being in adulthood commonly diagnosed by dermatological lesions, inquiring about hereditary family history due to its autosomal dominant heritability.[1]

Given that the involvement of the central nervous system causes the second most frequent manifestations of this entity, T2-weighted magnetic resonance imaging of the skull should be requested in search of multiple tuberomas or another characteristic neurological lesions.[46,47]

Within the visceral manifestations, an abdominal tomography should be performed in search of renal angiomyolipoma, which are associated with tuberous sclerosis with a frequency of 0.13% of the patients studied by ultrasound with a predilection for the female sex, a ratio of 2 to 1. Its presentation is variable and ranges from the absence of symptoms to flank pain, hematuria, or Wunderlich syndrome, which corresponds a hypovolemic shock due to the presence of a perirenal hematoma. When this entity is suspected, it should also be performed an echocardiogram looking for cardiac rhabdomyoma.[52]

CONCLUSION

Tuberous sclerosis is a rare disease, it is not considered one of the first diagnostic suspicions; however, knowing the diagnostic criteria and clinical manifestations such as the classic skin manifestations should increase suspicion of the disease, since these reveal the rest of the associated systemic alterations, allowing early recognition to provide genetic counseling and prevent treatable complications, start early management, improve the quality of life and the long-term prognosis of patients with the disease.

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