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A Review on Tuberous Sclerosis

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Abstract: *Tuberous sclerosis is a genetic disorder characterized by the growth of non- cancerous tumour in various organs, including the brain, skin, kidney, heart, and lungs. It results from mutations in the TSC1 or TSC2 genes, which are responsible for regulating cell growth and division. The condition can lead to a range of symptoms, such as seizures, development delays, skin abnormalities (like facial angiofibroma), and various organ dysfunctions. Diagnosis is often made through imaging studies and clinical evaluation of symptoms. Management of tuberous sclerosis typically involves a multidisciplinary approach, focusing on treating the symptoms and complications asscociated with the disorders, as there is currently no cure. Early diagnosis and intervention can significantly improve the quality of life for affected individuals.*

Keywords: Tuberous sclerosis.

I. INTRODUCTION

Introduction Tuberous sclerosis complex (TSC) is a genetically inherited disorder of autosomal dominant form, with high but incomplete penetrance, which can affect organs such as the brain, skin, eyes, heart, lungs, liver and kidneys. [1, 2] This tuberous sclerosis complex was first described in part by Von Recklinghausen in 1862, who at that time found cardiac lesions (cardiac rhabdomyoma and cortical tubercles) in a newborn patient who died in his first days.[3]The first detailed descriptions of the clinical and neuropathological features of tuberous sclerosis were made and described by the French neurologist Désiré-Magloire Bourneville in 1880, therefore, the disease at that time was named "Bourneville's disease" in his hono.[4, 5]In the year 1908, Heinrich Vogt described the classic triad or "Vogt's triad", which was characterized by a clinical picture of clinical manifestations such as: epilepsy, intellectual disability and angiofibromas usually located in the mid-facial third commonly around the nose, cheek, and chin.[6,7] This condition is known to affect approximately 1 in 10,000 people and has been found to have no gender preference, it has a great phenotypic variability, which can sometimes make it difficult to diagnose and can be confused with other neurological diseases. Many cases may remain undiagnosed for several years due to mild symptoms in some patient.[8] Although it is considered a rare disease, it is listed among the genetic conditions that most affect the population worldwide.[9] Tuberous sclerosis complex (TSC) was first fully clinically detailed by Bourneville.[10]

TSC is a multisystem disorder associated with hamartomas or benign tumor growths in the brain, heart, lung, eye, or kidney.[11] Over the past 25 years, knowledge about genetic and cell signaling abnormalities in TSC has rapidly advanced, based on both animal model and clinical research, culminating in 2012 in the US Food and Drug Administration approval of a targeted therapy for renal and central nervous system involvement in TSC. Currently, TSC is estimated to affect one in 50,000 individuals worldwide and to occur in one in 6,000 to one in 10,000 live births across all ethnic demographies.[12] This review summarizes some of the recent developments in TSC genetics, diagnostic criteria, evaluation, and surveillance, as well as evaluates some of the salient cell biology of the TSC-mechanistic target of rapamycin (mTOR) pathway. The vast majority of patients show central nervous system (CNS) manifestations including epilepsy, cognitive impairment and autism spectrum disorders. [13,14]

Tuberous sclerosis complex (TSC) is a rare autosomal dominant disorder characterized by skin abnormalities (hypomelanotic macules, facial angiofibromas, shagreen patches, fibrous facial plaques, ungual fibromas), brain involvement [cortical tubers, subependymal nodules (SENs) and subependymal giant cell astrocytoma (SEGA), seizures, intellectual disability], also affecting other organs, such as: kidneys [angiomyolipomas (AMLs)], cysts, renal cell carcinomas), heart (rhabdomyomas), lungs [lymphangioleiomyomatosis (LAM)], etc.[15] Vascular involvement is rare and therefore less known and studied. Central and peripheral aneurysms and large and medium size arterial stenotic-

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occlusive disease have been reported in patients with TSC, as well as dysplasia of small vessels [16], including fibromuscular dysplasia.[17]

HISTORY

Patient information:

The female patient 35year old female admitted to AVBRH on date 25/11/2021 with the chief Complaint of fever chills, nausea, vomiting and itching and back skin over mouth and eye surrounding area since in 10 days. All investigations were completed after admission to the Intensive care unit, including CBC, KFT, LFT, MRI, C T Scan, EEG, ECG, Vision test, skin test, Developmental or psychiatric evaluation, screening, and genetic testing. (18)

- Past Medical History: The patient was having a history- she is known case of seizures disorder Since in 12 year and tuberous sclerosis disease for 2 years. And she is no history of HIV and Asthma and hypertension and DM.
- Psychosocial history: Patient maintains interpersonal relationship with family, friends and Relatives.
- Family history: A 35year old female is a known case of Tuberous sclerosis complex. There is No other family history of illness.
- Nutritional status: They consume mixed diet.
- Personal history: Patient is having disturbed sleeping pattern. Hygiene is well maintained.[19]

SYMPTOMS OF TUBEROUS SCLEROSIS

Tuberous sclerosis symptoms are caused by noncancerous growths in parts of the body, most commonly in the skin, brain, eyes, kidneys, heart and lungs. But any part of the body can be affected. Symptoms can range from mild to severe, depending on the size or location of the growths.

Although symptoms are different for each person with tuberous sclerosis, they can include:

- **Skin changes.** Skin changes are most common. These include patches of lighter skin and small areas of thickened, smooth or bumpy skin. On the forehead, skin can have raised, discolored areas. Small soft bumps under or around the nails may occur. Growths on the face that start in childhood and look like acne are common.
- **Seizures.** Growths in the brain may be linked with seizures. A seizure is often the first symptom of tuberous sclerosis. In small children, a common type of seizure called infantile spasm involves stiffening of the arms and legs and arching the back and head.
- **Problems in thinking, reasoning and learning.** Tuberous sclerosis can result in developmental delays. Sometimes it limits the ability to think, reason and learn. Mental health conditions, such as autism spectrum disorder or attention- deficit/hyperactivity disorder (ADHD), also can occur.
- **Behavior problems.** Common behavior problems may include hyperactivity, self- injury or aggression, or issues with social and emotional adjustment.
- **Kidney problems.** Growths on the kidneys are common, and more growths may develop with age.
- **Heart issues.** Growths in the heart, if present, are usually largest at birth and shrink as a child gets older.
- **Lung problems.** Growths that develop in the lungs may cause coughing or trouble breathing, especially with physical activity or exercise. These lung tumors occur more often in females than in males.
- **Eye problems.** Growths can appear as white patches on the light-sensitive tissue at the back of the eye called the retina. These growths usually don't interfere with vision.
- **Dental changes.** Teeth may have pits in the surface. Small growths may appear on the gums, inside of the cheeks and on the tongue.

DIAGNOSIS OF TUBEROUS SCLEROSIS

Comprehensive and reliable screens for TSC1 and TSC2 mutations are well- established, and many pathogenic mutations have been identified he recommendation of the Genetics Panel was to make identification of a pathogenic mutation in TSC1 or TSC2 an independent diagnostic criterion, sufficient for the diagnosis or prediction of TSC

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regardless of the clinical findings. This will facilitate the diagnosis of TSC in some, particularly young individuals, allowing earlier implementation of surveillance and treatment with potential for better clinical outcomes. A "pathogenic" mutation was defined as a mutation that clearly prevents protein synthesis and/or inactivates the function of the TSC1 or TSC2 proteins (e.g., nonsense mutation or frameshift mutations, large genomic deletions) or is a missense mutation whose effect on protein function has been established by functional assessment.[20] TSC1 and TSC2 genetic variants whose functional effect is less certain are not definitely pathogenic and would not be considered a major diagnostic criterion. A significant fraction (10-25%) of TSC patients have no mutation identified by conventional genetic testing. Therefore, a normal result does not exclude TSC. Nonetheless, if the mutation in an affected relative is known, testing for that mutation has very high predictive value for family members. Assembled experts at the Consensus Conference agreed with the recommendation that identification of a pathogenic mutation in TSC1 or TSC2 is an independent diagnostic criterion.[21]

Clinical diagnostic criteria

In addition to diagnosis by genetic analysis, the clinical diagnostic criteria used to establish the diagnosis of TSC were also reviewed at the conference. Updated diagnostic criteria for tuberous sclerosis complex 2012 A. Genetic diagnostic criteria The identification of either a TSC1 or TSC2 pathogenic mutation in DNA from normal tissue is sufficient to make a definite diagnosis of tuberous sclerosis complex (TSC). A pathogenic mutation is defined as a mutation that clearly inactivates the function of the TSC1 or TSC2 proteins (e.g., out-of-frame indel or nonsense mutation), prevents protein synthesis (e.g., large genomic deletion), or is a missense mutation whose effect on protein function has been established by functional assessment (www.lovd.nl/TSC1, www.lovd/TSC2, and Hoogeveen- Westerveld et al., 2012 and 2013). Other TSC1 or TSC2 variants whose effect on function is less certain do not meet these criteria, and are not sufficient to make a definite diagnosis of TSC. Note that 10% to 25% of TSC patients have no mutation identified by conventional genetic testing, and a normal result does not exclude TSC, or have any effect on the use of clinical diagnostic criteria to diagnose TSC.

B. Clinical diagnostic criteria

Major features 1. Hypomelanotic macules (3, at least 5-mm diameter) 2. Angiofibromas (3) or fibrous cephalic plaque 3. Ungual fibromas (2) 4. Shagreen patch 5. Multiple retinal hamartomas 6. Cortical dysplasias* 7. Subependymal nodules 8. Subependymal giant cell astrocytoma 9. Cardiac rhabdomyoma 10. Lymphangioleiomyomatosis (LAM)y 11. Angiomyolipomas (2)y Minor features 1. "Confetti" skin lesions 2. Dental enamel pits (>3) 3. Intraoral fibromas (2) 4. Retinal achromic patch 5. Multiple renal cysts

6. Nonrenal hamartomas Definite diagnosis: Two major features or one major feature with 2 minor features Possible diagnosis: Either one major feature or 2 minor features * Includes tubers and cerebral white matter radial migration lines. y A combination of the two major clinical features (LAM and angiomyolipomas) without other features does not meet criteria for a definite diagnosis. 244 H. Northrup, D.A. Krueger / Pediatric Neurology 49 (2013) 243e254 given to evaluate the sensitivity and specificity of clinical findings with respect to TSC diagnosis.

Panels were assigned to the following focus areas for this process, and specific attempts were made to refine and simplify the clinical diagnostic criteria that included 11 major features and nine minor features according to the 1998 Conference. The individual panels were organized as follows: (1) dermatology and dentistry; (2) ophthalmology; (3) brain structure, tubers, and tumors; (4) epilepsy; (5) TSC-associated neuropsychiatric disorders; (6) cardiology; (7) pulmonology; (8) nephrology; (9) endocrinology; (10) gastroenterology; and (11) care integration. The recommendations of each panel were presented to the entire congress for discussion, modification if necessary, and final approval. The new, updated diagnostic clinical criteria now include 11 major features and six minor features (Table part B). Dermatologic and dental features The dermatology and dental panel recommended retaining the existing mucocutaneous criteria and suggested minor changes regarding their number, size, or nomenclature. The major features (with changes italicized) include: (1) hypomelanotic macules (3, at least 5-mm diameter), (2) on physical examination. It is therefore important that these features be highlighted to aid in bringing TSC patients to medical attention. angiofibromas (3) or fibrous cephalic plaque, (3) ungual fibromas (2), and (4) shagreen patch. The revised minor

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features include: (1) "confetti" skin lesions, (2) dental enamel pits (3), and (3) intraoral fibromas (2). Nearly 100% of individuals affected with TSC have skin or dental findings of the disease that are easily detectable.[22]

Dermatologic and dental features

Hypomelanotic macules

Hypomelanotic macules are a significant feature because they are observed in about 90% of individuals with TSC, they typically appear at birth or infancy, and they may be a presenting sign of TSC (Fig 1).[23] At the 1998 Consensus, it was stipulated that an individual must have three or more hypopigmented macules, because one or two lesions are relatively common in the general population.[24]In the updated criteria, it was recommended that hypomelanotic macules meet a size requirement of at least 5-mm diameter to distinguish hypomelanotic macules from smaller and more numerous "confetti" lesions. In addition, it was suggested that poliosis, circumscribed areas of hypomelanosis of hair, be included in the count of hypomelanotic macules.[25]

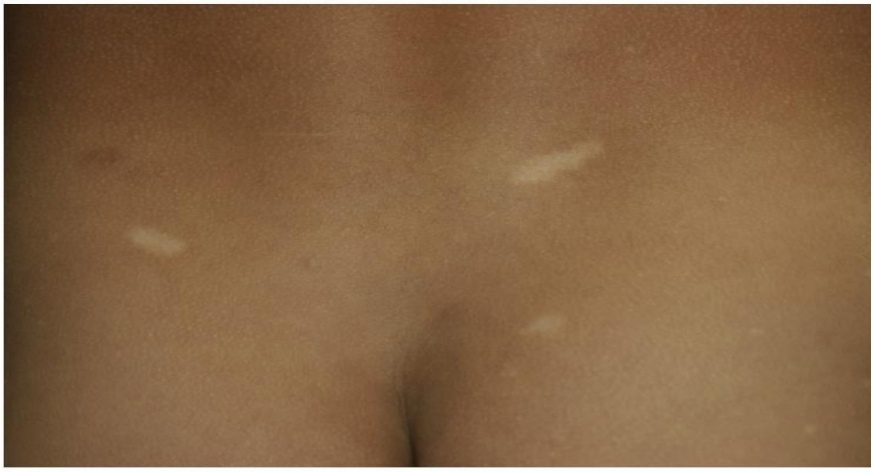

Figure 1: Three hypopigmented macules the lower back/upper buttocks

Angiofibroma or fibrous cephalic plaque

Facial angiofibroma occur in about 75% of TSC patients, [26,27,28,29] with onset typically between ages 2 and 5years. [30] Although most TSC patients have several facial angiofibromas, milder cases of TSC with limited facial angiofibromas have been described. However, because one or two isolated sporadic lesions may be observed in the general population, (25) the presence of at least three facial angiofibroma lesions is now recommended to meet this major criterion for TSC. Multiple facial angiofibromas have also been observed in Birt-Hogg-Dubé (BHD) syndrome, and multiple endocrine neoplasia type 1 (MEN1).[31] In these conditions, the age of onset of angiofibromas is later than in TSC. Therefore, multiple facial angiofibromas remains a major feature for diagnosis when their onset occurs in childhood. In the unusual circumstance when angiofibromas have their onset in adulthood, they should be considered as a minor feature and the differential diagnosis expanded to include BHD and MEN1. When angiofibromas are few or later in onset, a skin biopsy may be required to confirm the clinical diagnosis. The forehead plaque is observed in about 25% of TSC patients and this feature was paired with angiofibromas for the diagnostic criteria in 1998 The panel recommended changing the terminology from forehead plaque to fibrous cephalic plaque. This term was created to increase awareness that these fibrous plaques, although often located unilaterally on the forehead, may occur on other parts of the face or scalp Fibrous cephalic plaques, which are histologically similar to angiofibromas, may be the most specific skin finding for TSC.[32]

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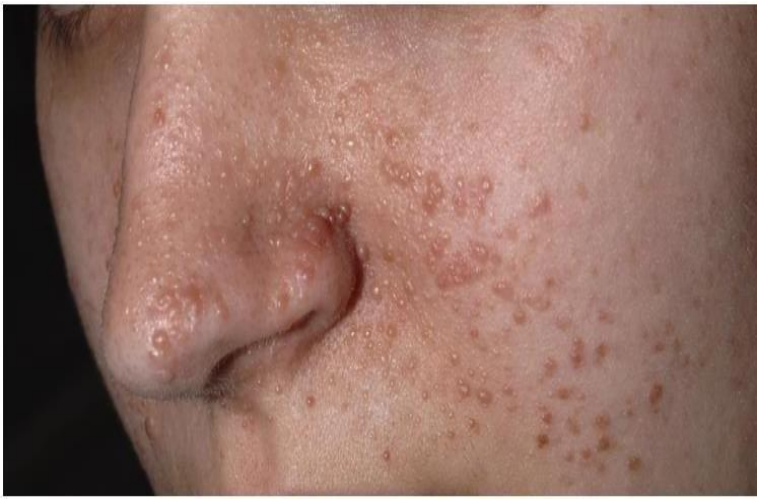

Figure 2: Facial angiofibroma

Dental enamel pits

Dental enamel pits, previously included as a minor feature listed as "multiple, randomly distributed pits in dental enamel" were again included as a minor feature. The designation was simplified to dental enamel pits (3) for the entire dentition. Dental pits are much more common in TSC patients than the general population, with Mlynarczyk reporting 100% of adult TSC patients (n ¼ 50) as having pitting compared with 7% of 250 adult control subjects. [33] Because they are relatively common in the population, they are listed as a minor feature.[34]

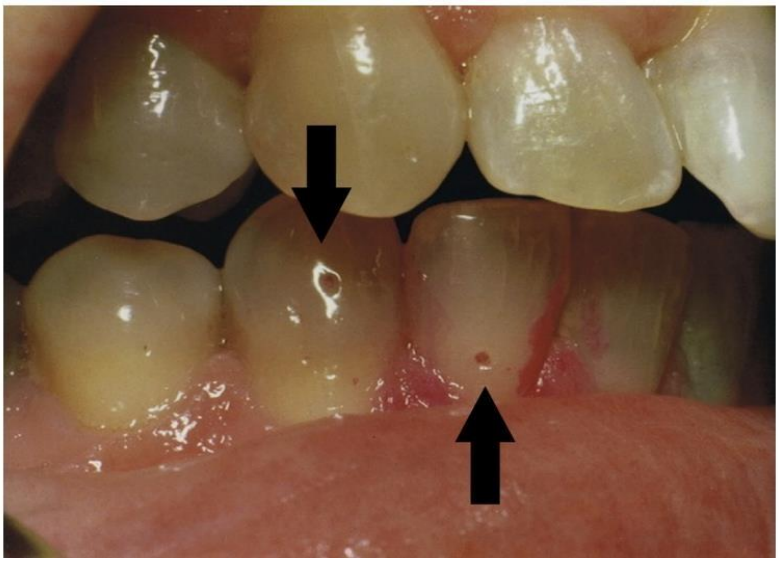

Figure 3: Dental pits indicated by arrow

Ophthalmologic features

A) Multiple retinal hamartomas

The finding of more than one retinal hamartoma was determined to be significant and specific enough to retain as a major feature. These lesions have similar histologic features to the tubers located in the brains of TSC patients. They are observed in 30-50% of TSC patients and it is not unusual to have multiple lesions in the same.[34]The prevalence of retinal hamartomas in non-TSC populations is not known, but rare case reports have been made and a recent series of 3573 healthy term newborns identified only two cases of astrocytic hamartomas in that population.[35] Fortunately, these

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lesions in TSC usually do not cause problems with vision and are a good marker for the disease, particularly in young children who might not yet have many other features.[36]

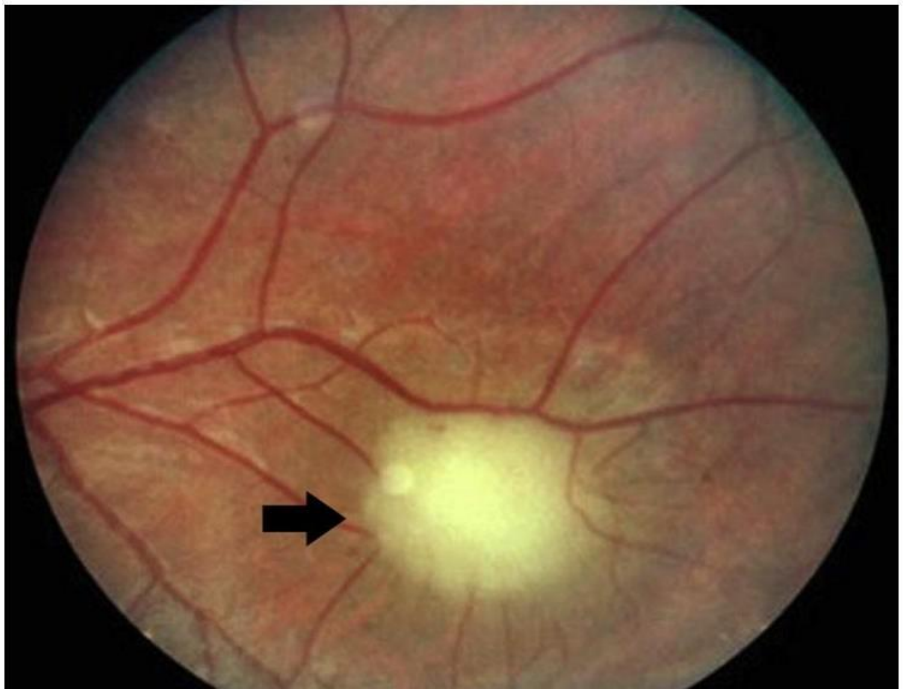

Figure 4: Retinal hamartoma indicated by arrow

Retinal achromic patch

The presence of a retinal achromic patch was determined at the 1998 conference to constitute a minor feature. The assembled experts at the 2012 conference concurred with the previous recommendation. Retinal achromic patches are basically areas of hypopigmentation on the retina. These patches have been noted to occur in 39% of TSC patients. [37-38] Incidence in the general population is estimated at 1 in 20,000.
[39]

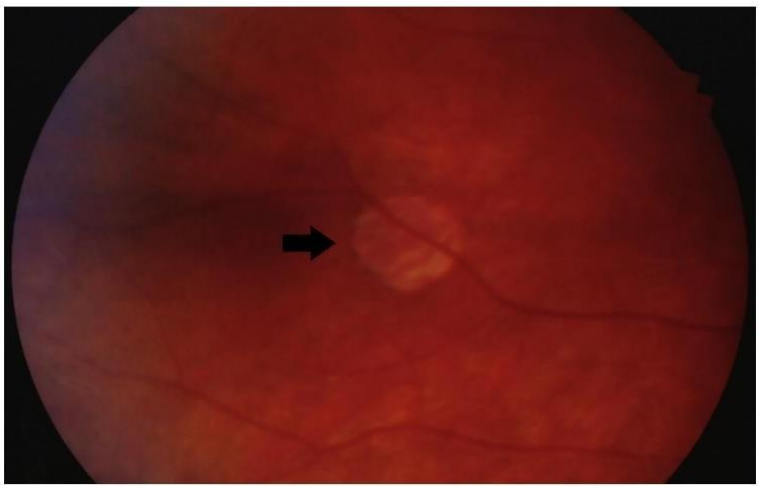

Figure 5: Retinal archromic patch indicated by arrow.

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Intraoral fibromas

Gingival fibromas have long been associated with TSC and were listed as a minor feature in the 1998 consensus document. They occur in about 20-50% of individuals with TSC, with greater frequency in adults than children. [39,40]

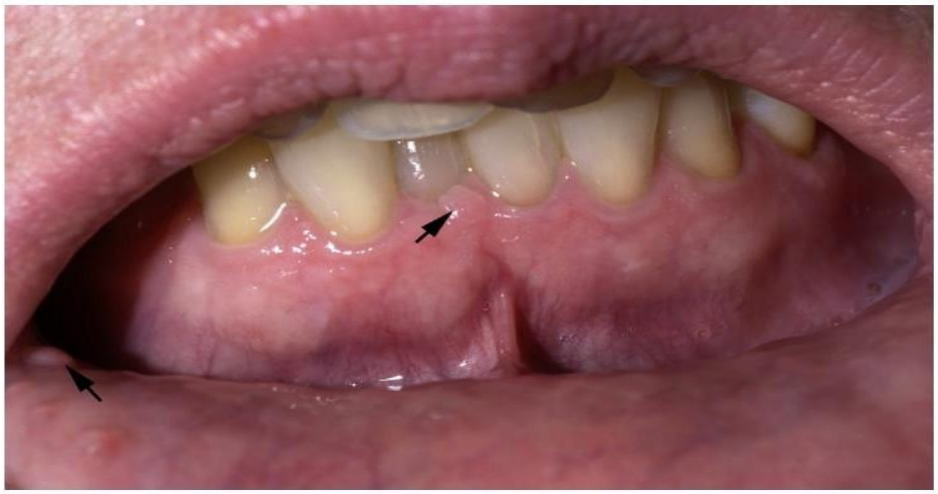

Figure 6: Intraoral fibromas (gingival and labial indicated by arrows).

Cortical dysplasia

Cortical dysplasia are congenital abnormalities caused, at least in part, when a group of neurons fail to migrate to the proper area of the brain during development. The cortical tubers observed in w90% of TSC patients and the pathologic finding for which the disorder is named, are a type of focal cortical dysplasia. Cerebral white matter radial migration lines arise from a similar pathologic process as cortical tubers and other forms of cortical dysplasia and in TSC it is not unusual to find tubers and white matter migrational abnormalities together. Both types of cortical dysplasia in TSC are commonly associated with intractable epilepsy and learning difficulties in TSC. The pathologic and clinical overlap between "cortical tuber" as a major feature and "cerebral white matter radial migration lines" as a minor feature in the 1998 diagnostic criteria were felt to no longer represent separate processes and are replaced with a single major feature in the new classification "cortical dysplasia." However, it is appreciated that a single area of focal cortical dysplasia or even two can be observed in an individual who does not have TSC; thus, in the new diagnostic criteria, multiple areas of focal cortical dysplasia count only as one major feature and additional clinical features are necessary to establish a definite diagnosis of TSC.[41]

1 Subependymal nodules and subependymal giant cell astrocytoma

Subependymal nodules (SEN) and subependymal giant cell astrocytoma (SEGA) will continue to represent two separate major features. Both of these lesions were also included in the 1998 Consensus Conference Criteria as major features. Histologically, the two lesions are similar and both are relatively specific to TSC although not exclusive to the disorder. Subependymal nodules are benign growths that develop along the wall of the ependymal lining of the lateral and third ventricles. They are observed in 80% of TSC patients and often prenatally detected or at birth.[42] SEGAs have an incidence of 5-15% in TSC and may also be detected prenatally or at birth, although they are much more likely to arise during childhood or adolescence and it would be unusual for one to occur after the age of 20 years if not already previously present.[43]

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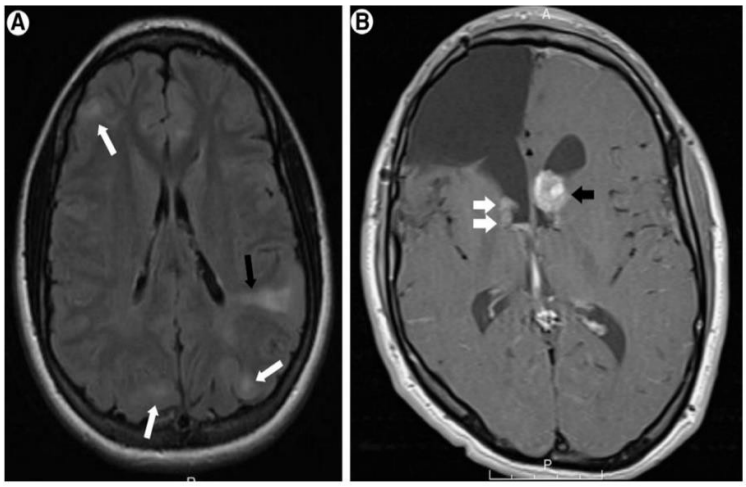

Figure 7: a) axial magnetic resonance imaging (MRI) T2 fluid-attenuated inversion recovery) of the brain.

B) Axial MRI (T1+contrast) of the brain, demonstrating subependymal nodules (left two white arrows

Cardiac rhabdomyoma

Cardiac rhabdomyomas are benign tumors of the heart that are rarely observed in non-TSCeaffected individuals. These lesions usually do not cause serious medical problems, but they are highly specific to TSC and often the first noted manifestation of disease, and therefore remain a major feature. Tumors are most frequently located in the ventricles, where they can compromise ventricular function and on occasion interfere with valve function or result in outflow obstruction.[44] These tumors are frequently observed in TSC-affected individuals during fetal life but after birth, they often regress and, in some individuals, may no longer be detectable by echocardiographic examination.[45-46]

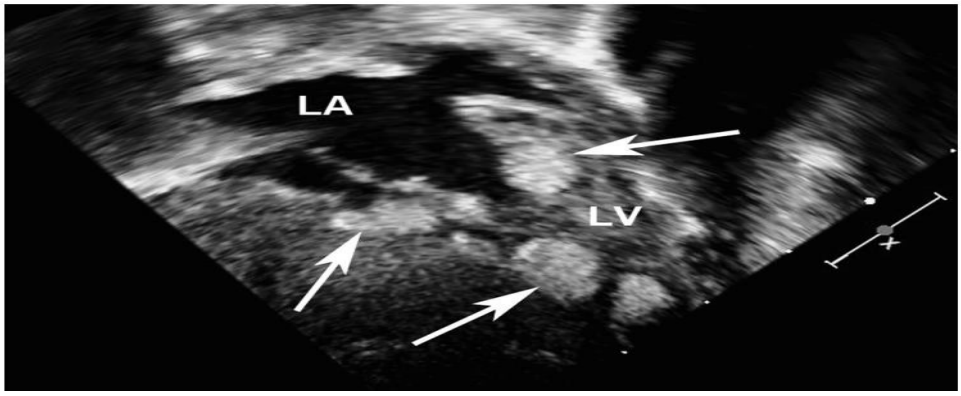

Figure7: Echocardiographic indicating cardiac rhabdomyomas (arrows).

TREATMENT OF TUBEROUS SCLEROSIS

The first diagnostic criteria for tuberous sclerosis were established by neurologist Manuel Rodriguez Gomez in 1979. The first update date of the diagnostic criteria dates back to 1998, these diagnostic criteria were updated in 2012, where the genetic diagnostic criterion is the pathogenic mutation of the TSC1 OR TSC2 gene.

[47]Within the dermatological clinical diagnostic criteria are: hypomelanotic macules, angiofibromas and nail fibromas. In odontology, this condition presents clinical features, such as: dental enamel pits and intraoral fibromas in most patients. [48]Diagnostic evaluation may be initiated due to positive family history or due to clinical signs or symptoms.[49]

Identification of a variant pathogenic gene in TSC1 or TSC2 is sufficient for diagnosis or the disease, this is of utmost importance, because clinical manifestations of tuberous sclerosis are known to emerge over time at various ages. [50]

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II. CONCLUSION

Tuberous sclerosis is a neurocutaneous syndrome, the most accepted etiology of this condition is a mutation in the tuberous sclerosis genes identified as TSC1 or TCS2, which generate two proteins that cause this neuronal disorder. The identification of a genetic mutation in these genes is required to establish the diagnosis, within the treatment different therapies and medications are proposed to control the neuropathologies present as medications used in autism spectrum disorders. Within the clinical manifestations, dermatological and neuronal manifestations can be observed as the most common, but different organs such as the heart, lung, liver, and pancreas can also be affected. Dental consultation is essential for the diagnosis and treatment of tuberous sclerosis as oral manifestations such as enamel pits and oral fibromas and gingival hyperplasia can be observed during consultations. This genetic disorder is uncommon where the prevalence is estimated at an average of 1 in 6000 births, so it is currently considered within the list of rare diseases according to WHO.

In recent years, mTORi have been more and more widely used in the treatment of various TSC manifestations. Although there is evidence for the effectiveness and safety of mTORi in the treatment of CRs, currently, due to the lack of high-quality studies, the evidence is not sufficiently robust to unequivocally recommend this therapy in every patient. However, based on the available data and considering the tendency to spontaneous regression of CRs in most patients, mTORi may be considered as a temporary therapeutic option for symptomatic CRs in children with TSC, especially when the risk of surgical intervention is significant. Due to the immaturity of liver enzymes, it is important to slowly introduce mTORi and frequently check the drug serum concentration in neonates and young infants. The upcoming randomized trial (ORACLE) may provide more reliable, evidence-based results on the effectiveness of mTORi in the treatment of CRs among children with TSC

REFERENCES

[1]. Salussolia CL, Klonowska K, Kwiatkowski DJ, Sahin M. Genetic Etiologies, Diagnosis, and Treatment of Tuberous Sclerosis Complex. Annu Rev Genomics Hum Genet. 2019;31;20:217-240.
[2]. Kaneda M. [Tuberous Sclerosis Complex]. Brain Nerve. 2019;71(4):374-379
[3]. Hasbani DM, Crino PB. Tuberous sclerosis complex. Handb Clin Neurol. 2018;148:813-822.
[4]. Uysal SP, Şahin M. Tuberous sclerosis: a review of the past, present, and future. Turk J Med Sci. 2020;50(SI2):1665-1676.
[5]. Brigo F, Lattanzi S, Trinka E, Nardone R, Bragazzi NL, Ruggieri M, et al. First descriptions of tuberous sclerosis by Désiré-Magloire Bourneville (1840- 1909). Neuropathology. 2018;38(6):577-582.
[6]. Brigo F, Lattanzi S, Trinka E, Nardone R, Bragazzi NL, Ruggieri M, et al. First descriptions of tuberous sclerosis by Désiré-Magloire Bourneville (1840- 1909). Neuropathology. 2018;38(6):577-582
[7]. Sánchez-Meza E, Ancer-Arellano J, Villarreal-Villarreal CD, Cárdenas-de la Garza JA, et al. Características clínicas y epidemiológicas de esclerosis tuberosa en un centro de referencia dermatológico del noreste de México. Dermatol Rev Mex. 2018;62(6):475-485.
[8]. 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):323-331.
[9]. Peron A, Northrup H. Tuberous sclerosis complex. Am J Med Genet C Semin Med Genet. 2018;178(3):274-277.
[10]. Bourneville DM. Sclerose tubereuse des circonvolutions cerebrales. Arch Neurol. 1880;1:81–91. French.
[11]. Orlova KA, Crino PB. The tuberous sclerosis complex. Ann N Y Acad Sci. 2010;1184:87–105.
[12]. Northrup H, Krueger DA. Tuberous sclerosis complex diagnostic update: recommendations of the 2012 international tuberous sclerosis complex consensus conference. Pediatr Neurol. 2013;49(4):243–254
[13]. Curatolo P, Bombardieri R, Jozwiak S. Tuberous sclerosis. Lancet. 2008;372: 657–68
[14]. Curatolo P, Moavero R, de Vries PJ. Neurological and neuropsychiatric aspects of tuberous sclerosis complex. Lancet Neurol. 2015;14:733–45
[15]. Northrup H, Krueger DA; International Tuberous Sclerosis Complex Consensus Group. Tuberous sclerosis complex diagnostic criteria update: recommendations of the 2012 Inter-national Tuberous Sclerosis Complex

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Consensus Conference. Pediatr Neurol, 2013, 49(4):243–254. https://doi.org/10.1016/j.pediatrneurol.2013.08.001 PMID: 24053982 PMCID: PMC 4080684

[16]. Beltramello A, Puppini G, Bricolo A, Andreis IA, el-Dalati G, Longa L, Polidoro S, Zavarise G, Marradi P. Does the tuberous sclerosis complex include intracranial aneurysms? A case report with a review of the literature. Pediatr Radiol, 1999, 29(3):206– 211.https://doi.org/10.1007/s002470050573 PMID: 10201041

[17]. Paraf F, Bruneval P. Dysplasie fibromusculaire artérielle et sclérose tubéreuse de Bourneville [Arterial fibromuscular dysplasia and Bourneville's tuberous sclerosis]. Ann Pathol, 1996, 16(3):203–206. PMID: 8766180

[18]. Shrestha S, Shrestha S, Ojha AR. Case report on tuberous sclerosis. J Kathmandu Med Coll. 2013;2:208–10. [Google Scholar]

[19]. Jankar AN, Palange PB, Purandare VC. Tuberous sclerosis – A case report. Int J Biomed Res.2014;5:649–50. [Google Scholar]

[20]. Hoogeveen-Westerveld M, Ekong R, Povey S, et al. Functional assessment of TSC2 variants identified in individuals with tuberous sclerosis complex. Hum Mutat. 2013;34:167-175.

[21]. Hoogeveen-Westerveld M, Ekong R, Povey S, et al. Functional assessment of TSC1 missense variants identified in individuals with tuberous sclerosis complex. Hum Mutat. 2012;33:476-479.

[22]. Au K, Williams A, Roach E, et al. Genotype/phenotype correlation in 325 individuals referred for a diagnosis of tuberous sclerosis com.

[23]. Webb D, Clarke A, Fryer A, Osborne J. The cutaneous features of tuberous sclerosis: a population study. Br J Dermatol. 1996;135:1-5.

[24]. . Alper J, Holmes L. The incidence and significance of birthmarks in a cohort of 4,641 newborns. Pediatr Dermatol. 1983;1:58-68.

[25]. 23. Vanderhooft S, Francis J, Pagon R, Smith L, Sybert V. Prevalence of hypopigmented macules in a healthy population. J Pediatr. 1996; 129:355- 361.

[26]. . Au K, Williams A, Roach E, et al. Genotype/phenotype correlation in 325 individuals referred for a diagnosis of tuberous sclerosis complex in the United States. Genet Med. 2007;9:88-1000.

[27]. Dabora SL, Jozwiak S, Franz DN, et al. Mutational analysis in a cohort of 224 tuberous sclerosis patients indicates increased severity of TSC2, compared with TSC1, disease in multiple organs. Am J Hum Genet. 2001;68:64-80.

[28]. Jozwiak S, Schwartz RA, Janniger CK, Michalowicz R, Chmielik J. Skin lesions in children with tuberous sclerosis complex: their prevalence, natural course, and diagnostic significance. Int J Dermatol. 1998;37:911-917

[29]. Webb D, Clarke A, Fryer A, Osborne J. The cutaneous features of tuberous sclerosis: a population study. Br J Dermatol. 1996;135:1-5.

[30]. Jozwiak S, Schwartz RA, Janniger CK, Bielicka-Cymerman J. Usefulness of diagnostic criteria of tuberous sclerosis complex in pediatric patients. J Child Neurol. 2000;15:652-659.

[31]. Bansal C, Stewart D, Li A, Cockerell C. Histologic variants of fibrous papule. J Cutan Pathol. 2005;32:424-428.

[32]. Darling TN, Skarulis MC, Steinberg SM, Marx SJ, Spiegel AM, Turner M. Multiple facial angiofibromas and collagenomas in patients with multiple endocrine neoplasia type 1. Arch Dermatol. 1997;133:853-857.

[33]. Toro J, Glenn G, Duray P, et al. BHD mutations, clinical and molecular genetic investigations of Birt-Hogg-Dubé syndrome: a new H. Northrup, D.A. Krueger / Pediatric Neurology 49 (2013) 243e254 251 series of 50 families and a review of published reports. J Med Genet. 2008;45:321-333.

[34]. Aronow M, Nakagawa J, Gupta A, Traboulsi E, Singh A. Tuberous sclerosis complex: genotype/phenotype correlation of retinal findings. Ophthalmology. 2012;199:1917-1923.

[35]. Rowley S, O'Callaghan F, Osborne J. Ophthalmic manifestations of tuberous sclerosis: a population based study. Br J Ophthalmol. 2001; 85:420-423.

[36]. Li N, Zhao J, et al. Findings of perinatal ocular examination performed on 3573, healthy full-term newborns. Br J Ophthalmol. 2013;97:588-591.

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[37]. Rowley S, O'Callaghan F, Osborne J. Ophthalmic manifestations of tuberous sclerosis: a population based study. Br J Ophthalmol. 2001; 85:420-423.
[38]. Franz D. Non-neurologic manifestations of tuberous sclerosis complex. J Child Neurol. 2004;19:690-698.
[39]. Northrup H, Wheless J, Bertin T, Lewis R. Variability in expression in tuberous sclerosis. J Med Genet. 1993;30:101-103.
[40]. Au K, Williams A, Roach E, et al. Genotype/phenotype correlation in 325 individuals referred for a diagnosis of tuberous sclerosis complex in the United States. Genet Med. 2007;9:88-1000.
[41]. Webb D, Clarke A, Fryer A, Osborne J. The cutaneous features of tuberous sclerosis: a population study. Br J Dermatol. 1996;135:1-5.
[42]. Lygidakis N, Lindenbaum R. Oral fibromatosis in tuberous sclerosis. Oral Surg Oral Med Oral Pathol. 1989;68:725-728.
[43]. Sparling J, Hong C, Brahim J, Moss J, Darling T. Oral findings in 58 adults with tuberous sclerosis complex. J Am Acad Dermatol. 2007; 56:786-790.
[44]. Crino P, Mehta R, Vinters H. Pathogenesis of TSC in the brain. In: Kwiatkowsi D, Whittemore V, Thiele E, eds. Tuberous Sclerosis Complex: Genes, Clinical Features, and Therapeutics. Weinheim: Wiley-Blackwell; 2010:285-309.
[45]. Freedom RM, Lee KJ, MacDonald C, Taylor G. Selected aspects of cardiac tumors in infancy and childhood. Pediatr Cardiol. 2000;21: 299-316.
[46]. Tworetzky W, McElhinney DB, Margossian R, et al. Association between cardiac tumors and tuberous sclerosis in the fetus and neonate. Am J Cardiol. 2003;92:487-489.
[47]. Pfirmann P, Combe C, Rigothier C. [Tuberous sclerosis system: A review]. Rev Med Interne. 2021:S0248-8663(21)00061-8.
[48]. Daphna Marom. Genetics of tuberous sclerosis complex: an update. Childs Nerv Syst. 2020;36(10):2489-2496.
[49]. Heske EP, Jóźwiak S, Kingswood JC, Sampson JR, Thiele EA. Tuberous sclerosis complex. Nat Rev Dis Primers. 2016;2:16035.
[50]. Northrup H, Aronow ME, Bebin EM, Bissler J, Darling TN, de Vries PJ, et al. International Tuberous Sclerosis Complex Consensus Group. Updated International Tuberous Sclerosis Complex Diagnostic Criteria and Surveillance and Management Recommendations. Pediatr Neurol. 2021;123:50-66.