ARTÍCULO
DE REVISIÓN

A CLUE TO THE DIAGNOSIS: HYPOPIGMENTED MACULES AND INFANTILE SPASMS AS COMMON NEUROCUTANEOUS MANIFESTATIONS OF TUBEROUS SCLEROSIS COMPLEX.

Una pista hacia el diagnóstico: máculas hipopigmentadas y espasmos infantiles como manifestaciones neurocutáneas comunes del complejo de esclerosis tuberosa.

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INTRODUCTION

Tuberous sclerosis complex (TSC) is an autosomal dominant genetic disorder with complete penetrance and variable phenotypic expression. The condition affects 1 in every 6,000 to 10,000 individuals and is characterized by multiple benign hamartomas that affect various organs, including skin, central nervous system, heart, lungs, eyes, and kidney[1]. The majority of patients affected by TSC seek medical attention due to seizures or skin lesions. The importance of clinical features of tuberous sclerosis complex for diagnosis is highlighted in the Tuberous Sclerosis Consensus Conference updated diagnostic criteria **(Table 1)**. Accordingly, up to 100% of patients with TSC have characteristic skin or dental findings[2]. Similarly, seizures are the most common neurologic manifestation of TSC. In this sense, infantile spasms (IS) are the most commonly reported seizure type initially in up to 69% of patients with TSC. Conversely, TSC has been found in up to 25% of children with IS3. The importance of physical examination findings in guiding potential differential diagnoses in an infant with seizures is highlighted in this case report.

TABLE 1. *Diagnostic criteria for TSC- Adapted from the 2012 International Tuberous Sclerosis Complex Consensus Conference (2)*

Major Criteria	• Cortical dysplasias + • Subependymal nodules • Subependymal giant cell astrocytoma • Cardiac rhabdomyoma • Hypomelanotic macules (≥3, at least 5 mm diameter) • Angiofibromas (≥ 3) or fibrous cephalic plaque • Ungual fibromas (≥2) • Shagreen patch • Angiomyolipomas (≥2)* • Lymphangioleiomyomas * • Multiple retinal hamartomas
Minor criteria	• "Confetti" skin lesions • Dental enamel pits (> 3) • Intraoral fibromas (≥2) • Multiple renal cysts • Retinal achromatic patch • Nonrenal hamartomas • Multiple retinal hamartomas
Genetics	Identification of either a TSC1 or TSC2 pathogenic mutation in DNA from normal tissue

Definite diagnosis: Two major features, or one major feature with ≥2 minor features, or the presence of a TSC1 or TSC2 mutation (of confirmed pathogenicity).

Possible diagnosis: Either one major feature or ≥2 minor features.

+ Includes tubers and cerebral white matter radial migration lines.

* A combination of the two major clinical features (lymphangioleiomyomatosis and angiomyolipomas) without other features does not meet criteria for a definite diagnosis

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CASE PRESENTATION

A 6-month-old male was brought to the emergency department (ED) presenting with brief tonic spasms, occurring in clusters of 10 spasms at a rate of approximately 10 times per minute multiple times per day. In the ED such spasms were witnessed, which were remarkable for marked bilateral and involuntary symmetric and synchronic extension of all extremities along with upward head deviation.

The patient was the first child of healthy consanguineous parents (cousins), with no family history of TSC. He was born at term by spontaneous vaginal delivery, after a normal pregnancy. Birth and postnatal period were uneventful. Somatotropic parameters and developmental milestones were within normal limits. Important physical findings showed multiple small hypopigmented macules on the back **(Figure 1)**. No psychomotor retardation was noted. Based on the clinical presentation, an initial diagnosis of infantile spasms (West Syndrome) was presumed. Supportive clinical and dermatologic physical findings raised concern for tuberous sclerosis, for which a brain magnetic resonance imaging (MRI) and electroencephalogram (EEG), were ordered as an outpatient to further assess the diagnosis further. Treatment was started with daily vigabatrin 80mg/kg and magnesium valproate 19mg/kg.

On follow-up visit, the patient's parents reported complete resolution of spells around 1 week after treatment initiation. Routine awake and sleep EEG revealed paroxysmal left frontotemporal epileptiform discharges, theta waves and multifocal spikes with a tendency to secondary generalization consistent with hypsarrhythmia. Given EEG findings and clinical history, a diagnosis of infantile spasms was made.

The brain MRI showed multiple intraventricular tubers, bilaterally diffuse demyelinating zones in the frontotemporal and parietal white matter, and a tuber with cystic degeneration in the posterior parietal lobe **(Figure 2)**. The

FIGURA 1. *Hypopigmented macules on the back*

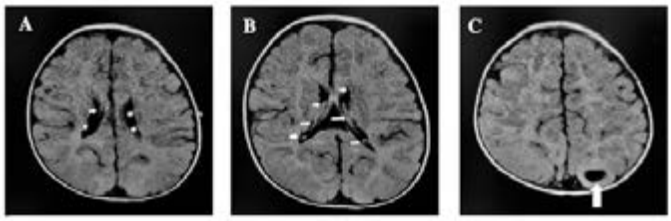

FIGURA 2. *A fluid-attenuated inversion recovery sequence image shows multiple intraventricular tubers as well as bilateral diffuse demyelinating zones in the frontotemporal and parietal white matter (Panel A and B). A tuber with cystic degeneration in the posterior parietal love (Panel C)*

diagnosis of infantile spasms as a clinical manifestation of Tuberous Sclerosis Context (TSC) was made. To complete the evaluation, an abdominal ultrasound was ordered to assess abdominopelvic lesions and a transthoracic echocardiogram to exclude rhabdomyomas.

DISCUSSION

TSC is a neurocutaneous disorder characterized by the development of hemartoumous tumors in diverse organs. The presented case diagnostic criteria according to the recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference[2]. The three major features presented include the 4 hypomelanotic macules with diameters exceeding 5 mm and the cortical tubers seen on brain MRI. The presence of hypomelanotic macules are an elemental feature, thus they are observed in up to 90% of patients with TSC4. This case highlights the importance of complete physical examination and the syndromic integration in an infant presenting with seizures. Particularly, when such typical skin lesions are observed, it is indispensable to review the case history thoroughly and complete pertinent imaging studies[5]. The hypopigmented macules observed in this patient, along with the infantile spasms and positive family history for consanguinity, favored a presumed clinical diagnosis for TSC, which was further confirmed with additional workup.

Current recommendations confirm vigabatrin as the most effective drug and suggest its use as a first-line antiepileptic treatment for infantile spasms associated with TSC6,7,8. Such treatment was initiated in our patient based on clinical suspicion and was maintained once the diagnosis was confirmed with further workup. Valproic acid was started as part of initial management as well in order to assure optimal seizure control. Taking into account that delayed treatment initiation delays seizure control, brain damage secondary to seizure activity can also be prevented when treatment is promptly started. In this sense, remission of seizures has been associated with higher

intellectual coefficient scores in children with TSC[7].

CONCLUSION

Tuberous sclerosis complex (TSC) is a neurocutaneous genetic syndrome characterized by the development of multiple benign hamartomas involving many organ systems. The importance of the classic dermatological findings can serve as a diagnostic clue in an infant presenting with first time seizures. It is optimal to never underlook the importance of physical examination as an aid to diagnosis of an underlying complex syndrome even prior to further diagnostic workup. Along with relevant family history, a thorough physical examination can guide clinicians to initiate prompt management and thus decrease patient morbidity, as well as provide trainees with the clinical reasoning skills necessary to implement clinical knowledge into practice by recognizing a constellation of signs and symptoms that may represent a syndrome.

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