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Esclerosis tuberosa infantil: caso clínico

Tuberous sclerosis of infancy: case report

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Palabras claves:
Esclerosis tuberosa, pacientes pediátricos, epilepsia, enfermedad autoinmune

Resumen

Introducción: La enfermedad autosómica dominante multisistémica conocida como complejo de esclerosis tuberosa (CET) es causada por mutaciones en los genes supresores de tumores TSC1 o TSC2. **Objetivo:** Investigar un caso clínico de un paciente pediátrico con Esclerosis Tuberosa con el fin de revelar nuevos aspectos o indicaciones de la enfermedad. **Metodología:** se realizó un análisis de casos clínicos de tipo descriptivo retrospectivo. Para obtener información, se revisó la historia clínica y se buscó información sobre la enfermedad en bases de datos conocidas a nivel mundial dentro de la rama de las ciencias de la salud. **Resultados.** En el caso clínico expuesto se presenta a un paciente pediátrico de 5 años con diagnóstico de esclerosis tuberosa debido a la presencia de hamartomas subependimarios y tubers corticales laterales. Con actividad psicomotriz disminuida, piel con presencia de cambios anormales en todo el cuerpo, miembro inferior derecho con deformidad. Vigil, orientado en tiempo, espacio y persona, lenguaje con retraso en el habla, fuerza muscular levemente disminuida, paciente dismétrico, discronométrica. **Conclusión:** La tríada clínica, también conocida como tríada de Vogt, consiste en retraso mental, convulsiones y lesiones en la piel (adenoma sebáceo) es un signo de la enfermedad neurocutánea conocida como esclerosis tuberosa. El diagnóstico se basa en los hallazgos intracraneanos comunes. **Área de estudio general:** medicina. **Área de estudio específica:** neurología. **Tipo de estudio:** Casos clínicos.

Keywords:
Tuberous sclerosis, pediatric patients, epilepsy, autoimmune disease

Abstract

Introduction:tuberous sclerosis complex (TSC) is a multisystem autosomal produced by mutated cells in the tumor suppressor genes TSC1 or TSC2. Objective: To analyze the clinical case of a pediatric patient with tuberous sclerosis, to present new or instructive aspects of the disease. Methodology: Analysis of a retrospective descriptive clinical case, for the collection of information a review of clinical history was performed; for the description of the disease a complication of information in recognized databases such as: Scopus, Pubmed, web of Science, Lilacs was performed. Results. The clinical case presented is a 5-year-old pediatric patient with a diagnosis

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of tuberous sclerosis due to the presence of subependymal hamartomas and lateral cortical tubes. With decreased psychomotor activity, skin with presence of abnormal changes all over the body, right lower limb with deformity. Vigilant, oriented in time, space and person, language with speech delay, slightly decreased muscle strength, dysmetric patient, dyschronometric. Conclusion: Tuberous sclerosis is a neurocutaneous disease, characterized by the appearance of a clinical triad (Vogt's triad): mental retardation, seizures and skin lesions (sebaceous adenoma). It presents typical intracranial findings that allow to guide its diagnosis.

Introduction

Tuberous sclerosis is thought to be a multisystem disorder with complete penetrance. Therefore, it is difficult to make a diagnosis in some families, especially those with subtle features (1). Tuberous sclerosis is found in 1 in 6,000 to 10,000 births, regardless of sex or ethnicity. TSC1 (hamartin) on chromosome 9q and TSC2 (tuberin) on chromosome 6p are the two genes involved in this disease, which is transmitted in an autosomal dominant manner; some people have signs and symptoms so mild that they are not diagnosed until adulthood (2).

It is a disease that causes benign non-cancerous tumors, identified by the growth of tumors in the brain, eyes, skin, kidneys, heart and lung, abnormal neoplasms in the brain and skin alterations. A protocolized follow-up helps us confirm the diagnosis, as well as identify clinically significant complications (3). Intrauterine tubes can be diagnosed by fetal magnetic resonance imaging (4).

The loss of these proteins causes cell growth and proliferation in a variety of organs (5). Central nervous system complications occur in 85% of children and adolescents with tuberous sclerosis, the most frequent symptoms occur in the first year of life, which are epilepsy (50-96%), seizures (20-30%), cognitive disorders (50-70%), behavioral changes (50-60%), autism (10%) and learning difficulties, also generating brain lesions such as cortical tubules and subependymal nodules (5).

Rhabdomyomas, which appear as benign cardiac tumors and are more common in childhood and the prenatal period, are the most frequent pathological forms, renal angiomyolipoma, facial angiofibromas, hypochromic macules and pulmonary

lymphangioleiomyomatosis, cortical tubers in the brain appear in the frontal lobes, parietal, occipital and temporal lobes the identification of these lesions can be observed through a computed tomography and magnetic resonance imaging (6). Not much data has been recorded on the prevalence in Latin America, but some cases have been recorded, such as that of Brazil, where a prevalence of between 1 and 50 live births is estimated. For every 100,000 live births, in Costa Rica there are 3.09 patients (6).

Tumors caused by this disease are called hamartomas because they resemble embryonic cells and are thought to have very early mutational effects (7). TSC is autosomal dominant and is caused by mutations in the genes TSC1, located on chromosome 9q34, and TSC2, located on chromosome 16p13, which are encoded by the proteins hamartin and tuberin, respectively (7). These two proteins are essential for the PI3K/PKB (Akt)/mTOR/S6K signaling cascade, which regulates nutrient uptake, cell size, and proliferation (7, 8).

Through a consensus among experts, the American Association on Intellectual and Developmental Disabilities (AAIDD) grouped several potential causes, including the most common: genetic factors, such as multigene abnormalities of variable expression, autonomic recessive genes, or chromosomal aberrations; problems related to mental disorders, such as psychosis; and problems that arise during pregnancy, childbirth, or the postpartum period. Autism has a variety of clinical manifestations and develops mainly in childhood, usually before 10 years of age. Typical clinical manifestations include epilepsy, autism, and heart failure. Due to its progressive evolution, its life expectancy is 35 years in most cases (9).

Symptoms and signs vary greatly depending on the location of the tumor and the severity of the disease. The organ most affected is the brain, which can cause seizures, autism, delay in motor and language skills, and also cause learning and behavioral problems such as hyperactivity and aggression (4). The main clinical manifestations in order of frequency are the following: Skin lesions represent more than 90% of brain damage, renal abnormalities in 70-90%, retinal hamartoma in 50% and rhabdomyoma in approximately 40%. 60%. of patients (10).

With an incidence of 1 in 5,800 births and approximately 6.8 to 12.4 cases per 100,000 inhabitants, the disease affects both sexes and different ethnic groups. This pathology can be presented from the seventh month of gestational age through an MRI (10). TSC mainly affects the central nervous system. The second manifestation is the renal one, which could be the most dangerous, is the renal one. Younger patients than the general population are more likely to develop malignant renal tumors (1).

The symptoms of tuberous sclerosis affect the brain, the most common are infantile spasms called seizures, followed by intellectual disability, autism, delayed motor development, learning problems, the skin is affected by the appearance of light-colored

spots in the form of a leaf that occurs during the lactation period, there is also the growth of small fleshy protuberances called angiofibromas (4). Benign non-cancerous tumors can be detected in the brain, heart, lungs, kidneys, eyes and skin, these tumors can cause heart failure or various disabilities, this can occur in childhood or adulthood (11).

Tuberous sclerosis can be caused by two variants, the first is caused by cell division through the TSC1 or TSC2 genes, which can be altered by a family history of having this disease. It has been determined that one third of patients can test positive for tuberous sclerosis through a clinical diagnosis (12). The disease can be severe or mild. A parent's tuberous sclerosis can be milder or more severe in their child, and it also occurs due to a random error in cell division without having a genetic or family history (13).

Cell proliferation, cell size and nutrient uptake are crucial regulations performed by these two proteins (4). The disease is diagnosed through the symptoms, signs that patients present depending on the affected organs are often combined Tuberous sclerosis syndrome (TSC), a peripheral blood test and a regional analysis of the hamartin and tuberin genes, which are involved in coding the disease, are performed (4,14).

TSC primarily affects the central nervous system. The second symptom is the kidneys, which can be very dangerous. Common kidney diseases include angiolipomas, kidney cysts, and often kidney tumors, many of which are benign (4). Both magnetic resonance imaging (MRI) and computed tomography (CT) scans can be used to image the brain to look for calcifications (cortical tubers) and other abnormalities in the brain (15).

Because of its rapidity, safety, and high sensitivity and specificity, lung ultrasound has become an important tool in neonatal units to evaluate neonates with respiratory problems. However, there are imaging challenges (1). In a patient with Bourneville tubercle multiple sclerosis type II (geneTSC2), cranial MRI shows white matter cysts, radial tracts, subependymal nodules (core criteria), and subependymal tubercles and nodules. The diagnosis of cardiac tubercles was confirmed by echocardiography and cranial MRI (1). Most individuals do not have tuberous sclerosis in their family. This is a genetic change that is passed down through family members (16).

The presence of a mutation in TSC1 or TSC2 in 85% of cases and mosaicism in the remaining 15% confirms the diagnosis. In case of isolated disease, a separate diagnosis should be made at another pigmentation center (17). Cerebral or hamartomatous development depending on the case, comprehensive studies of the disease in other areas (brain, eyes, heart, kidneys and lungs), investigation of variable characteristics that allow clinical evaluation and early diagnosis in some cases, and prenatal and preimplantation tests help to obtain results from parents (18).

The prognosis of tuberous sclerosis is based on the severity of signs and symptoms may be mild children usually develop the best or severe children may get disabilities, in most cases seizures occur, protuberances in the brain and kidney, appearance of subependymal nodules are formed in the walls of the ventricles are filled with fluid or can block the flow of fluid from the brain causing death (4). Patients with AML and TSC have high rates of rupture and hemorrhage as well as high morbidity rates10. Patients at risk of bleeding greater than 4 cm or microaneurysms greater than 5 mm are candidates for treatment (19).

Treatment for tuberous sclerosis depends on the symptoms: For spasms: anticonvulsants (mainly vigabatrin for spasms in children). More information) or occasionally, surgical intervention for epilepsy. For skin lesions, dermabrasion or laser (19). In case of severe bleeding, the emergency treatment is transarterial embolization, which is 93% effective. This treatment causes post-embolization syndrome (nausea, fever and pain lasting 72 hours) in 35% of patients. Nephrectomy increases the risk of kidney failure sevenfold, but both nephrectomy and embolization can solve the problem (20).

Multidisciplinary treatment is required for the various manifestations of the disease, ranging from epilepsy to possible renal or respiratory failure. The pathway inhibitor everolimus has been approved for use to slow the growth of subependymal cell tumors, giant brain tumors, and renal angiomyolipomas, and it is hoped that its use may be expanded in the future to treat other manifestations of the disease (21). Treatment for tuberous sclerosis in children depends on the symptoms they have and may include medications to control seizures, therapy to treat learning or behavioral problems, and surgery to remove tumors that may be affecting organs in the body. It is important for children with tuberous sclerosis to receive medical care to monitor the progression of their disease and prevent possible complications (22).

Tuberous sclerosis is a lifelong disease that requires careful monitoring and control, as many symptoms may appear for years. Attending medical appointments and check-ups at least 4 times a year in order to obtain early detection and treatment of problems can help prevent complications (16). Nephrectomy should be avoided if the emergency situation allows it and radiological techniques are available due to the risk of kidney failure. Embolization remains the preferred treatment in case of acute pregnancy-related rupture. In some cases, an urgent caesarean section and subsequent embolization can be performed.

Non-urgent treatment can be performed by selective embolization, cryoablation, radiofrequency or microwave, surgery and active surveillance (23). However, once treatment is stopped, lesions recur (24). Patients receiving everolimus, due to its immunosuppressive action, should be monitored with special attention in case of recurrent infections (25).

In Ecuador, a study was conducted in pediatric hospitals. 22.5% of patients with TSC had a family history, 61.3% were diagnosed with the disease before the age of 2 years and the most common clinical feature at diagnosis was seizures in 74.1%, of which 39.1% of these patients were diagnosed with refractory epilepsy (1). Currently, there are 21 cases in Ecuador with problems that involve 67.74% of patients presented some type of cognitive impairment and half (51.6%) presented behavioral disorders (26).

Methodology

This paper presents a clinical case based on a retrospective literature review on sinoatrial nodal block disease. The clinical history was reviewed and analyzed to obtain information about the case. The Vancouver style was used in writing, and the following structure was used to describe the pathology: define the disease, the causes, the triggering factors, the clinical diagnosis, clinical manifestations, consequences and/or complications, the nursing care plan and the medical treatment. To do this, articles from high-impact databases with health-related topics were used.

Case data were systematically collected from the patient's medical record (secondary database), including reason for presentation, patient's current illness, diagnostic impression (DIX), personal and family history, medications taken by the patient, physical examination and health status of the patient, initial laboratory tests, treatment plan, additional tests and results. In the last section, knowledge about the characteristics that comprehensively affect the patient's outcome was discussed and synthesized.

Results

A 5 year and 7 month old pediatric male patient diagnosed with tuberous sclerosis due to the presence of subependymal hamartomas and right and left lateral cortical tubers measuring between 1 mm and 5 mm in the frontal and parietal cortical tubers, found in an MRI scan, comes to the consultation with a family member (mother), who reports that the seizures are intermittent and mild, he stays awake during the day and manages to fall asleep at night without interruption, he has a slight delay in speech and motor skills, which improved after the consultation with the neurologist a month ago due to constant seizures.

On physical examination, the patient showed decreased psychomotor activity, abnormal skin changes throughout the body, and a deformed lower limb. Neurological: he was awake, oriented in time, space, and person, language was delayed, and muscle strength was slightly decreased. The patient was dysmetric and dyschronometric. After a medical evaluation and observing the changes in the skin, it was decided to perform additional tests: an abdominal ultrasound, which showed no abnormalities, a poorly performed electroencephalogram, and magnetic resonance imaging, which confirmed tuberous sclerosis.

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The patient's medical history includes a diagnosis of cardiac rhabdomyoma at birth, for which he underwent surgery on the second day after birth and was admitted to the neonatal unit for 18 days after his surgery.

Patient remains on the following treatment medication:

- Ceumid: 2 ML in the morning and 3 ML at night.
- Valcote: 100 mg at 6 am and 300 mg at night.
- Neuryl: 6 drops (0.8 mg) every 12 hours.
- Keppra: 3 ML (40mg/kg) in the morning and at night.
- Lacosamide: 25 mg at 7 am and 50 mg at 7 pm.

Figure 1: Dermatological symptoms of tuberous sclerosis

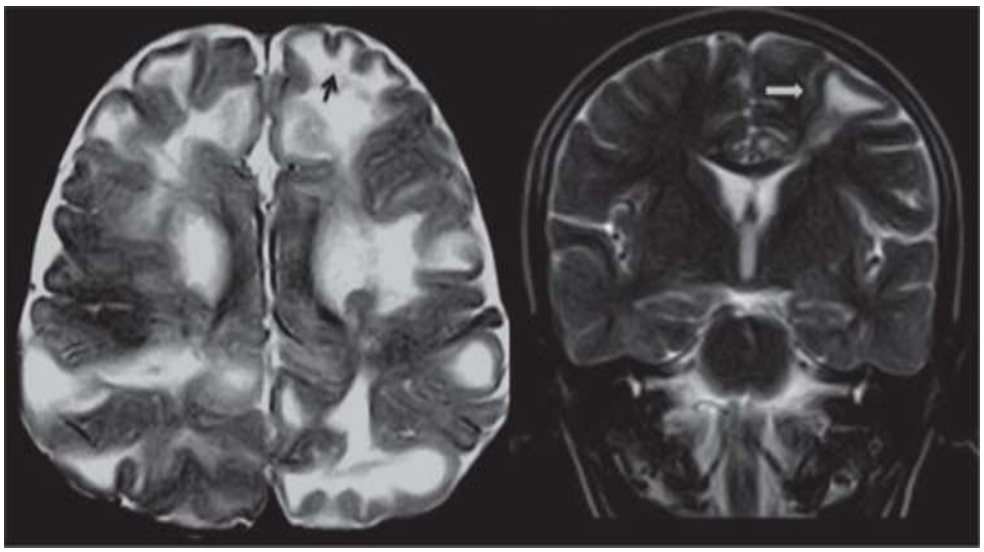

Figure 2: Evaluation of intracranial lesions: tuberous sclerosis

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In the research carried out by (27), it indicates that Multiple sclerosis is a hereditary multisystem disease that affects a large number of people at national and global level, characterized by the development of symptoms in various organs. Thus agreeing with what was indicated by (28, 29), which indicates that Pediatric multiple sclerosis is an autoimmune, demyelinating and neurodegenerative disease of the central nervous system that occurs in people under 18 years of age and is caused by immune responses and secondary axonal damage.

Rubilaraet al. (30) reported a worldwide incidence of 6.8 to 12.4 per 100,000 people, with an incidence of 1 in 5,000 to 10,000 live births, regardless of sex or ethnicity. To complement thisOrtizet al. (31), in their research indicated that the main reasons for this diagnosis were epilepsies and rhabdomyomas. Thus, in the present case, the pediatric patient was diagnosed with infantile tuberous sclerosis because hamartomas were found in the brain in his imaging studies, which agrees with the aforementioned authors.

In a study conducted by theFieldset al. (35), indicates that the cutaneous clinical manifestations are observed in approximately 90% of patients with TSC. Among which we have: Hypopigmented macules, angiofibromas, collagen plaques, shagreen patch (or sandpaper skin), nail fibromas, confetti-type lesions, lesions in the oral cavity. While in non-cutaneous ones there are clinical and cardiological manifestations. Likewise (32) they point out that currently, less than a third of patients have mental retardation, epilepsy and sebaceous adenoma, and up to 6% of cases do not have any of the mentioned characteristics.

Navarreseet al. (37) adds that 20% of patients develop a subependymal giant cell astrocytoma, which can generate hydrocephalus due to obstruction of the foramen of Monro. In the present study, the patient presented some of the symptoms that were previously mentioned by other authors. In the pediatric patient, the following were evident: decreased psychomotor activity, skin with abnormal changes throughout the body, right lower limb with deformity. In the Neurological: alert, oriented in time, space and person, language with speech delay, slightly decreased muscle strength, dysmetric, dyschronometric patient, thus agreeing with the aforementioned theory.

BesidesMonteiroet al. (38), points out that tuberculous sclerosis, in addition to affecting the processes of cell proliferation and differentiation, causes damage to the brain, skin, heart, kidney and other organs, thus generating different types of symptoms in the person. While in the study ofRubilaret al. (33) 73% of the cases presented seizures and 17% found cardiac rhabdomyomas as the most common symptomatology, which were the first manifestations of TSC. All patients showed signs of neurological involvement throughout their treatment.

28.6% of the patients developed autistic behaviors and 92.9% developed epilepsy in the future. It is consistent with what has been described in the literature that the coexistence of early-onset and difficult-to-manage epilepsy was associated with the presence of autistic behaviors (34). In the pediatric patient studied in the present case, it was observed that he presented convulsive crises, in addition to that the presence of decreased speech and a slight decrease in body mobility, therefore, the complications shown in the pediatric patient are similar to those mentioned by these authors.

According toBoronatet al. (39) points out that both their study and others developed previously have associated vitamin D deficiency with multiple sclerosis, which has led to the question of its potential role in the immune response. In this regard, Navarro et al. (37) mentions that vitamin D can be obtained from a wide variety of foods such as: codfish oil, salmon, mackerel, sardines, tuna oil, milk, orange juice, yogurt, margarine, cereals, eggs, cheese, among others. In the present study, the child was eating correctly, ingesting all kinds of foods, thus ruling out the possibility that his health problem is caused by a vitamin D deficiency.

According toWarrioret al. (41), it was found that between 60% and 89% of patients with ET who met the diagnostic criteria had a causative mutation. Approximately 50% of these patients are believed to have the TSC2 mutation and 17% have the TSC1 mutation. Reinforcing this concept according to the clinical guidelines of Boronat et al. (39) for example, a difference whose significance is unknown.

If mentioned above the inclusion criteria for an effective diagnosis of infantile tuberous sclerosis.Sourceset al. (36) in their scientific work points out the most important ones as: Facial angiofibromas or spots on the forehead, periungual myomas, hypochromic spots, irritation spots, cortical nodules, subependymal nodules and subependymal giant cell astrocytomas. Coinciding with what was expressed by,Sourceset al. (42) who, in addition to the above, also points out hypopigmented macules larger than 5 mm in diameter, multiple retinal nodular hamartomas, among others. There are also minor criteria for a diagnosis of tuberous sclerosis such as those indicated by Barboza et al. (43). Enamel hypoplasia, hamartorectal polyps, bone cysts, radial migration lines in the white matter, gingival fibromas, non-renal hamartomas, retinal achromatic spots, hypochromic multicolor spots, and multiple renal cysts. Speaking of the Shagreen patch for Ballesteros et al. (16), another significant dermatological finding is that it appears as an extensive plaque on the lower back during the first decade of life, with an orange peel appearance, yellowish-brown in color, and is believed to be a type of connective tissue hamartoma. Diagnostic evaluation of tuberous sclerosis complex requires a family history and a multidisciplinary evaluation, as well as imaging studies and functionality of internal organs depending on the age of the patient (38). In the fetal period, cardiac rhabdomyomas are the first clinical manifestations of tuberous sclerosis and can be

identified by ultrasound examination in the second trimester (39). In this case, the pediatric patient presented signs of dermatological lesions, which were originally from tuberous sclerosis.

The left ventricle and the ventricular septum are the most frequent locations, although up to 30% can be found in the atrial wall or in the right ventricle (40). Most of the time it starts spontaneously before the age of four, and because our patient did not present symptoms at the time of the evaluation, a clinical and ultrasound control was chosen (41). Likewise, in agreement with the theory stated by the authors, the patient was diagnosed with a cardiac rhabdomyoma at birth for which he underwent surgery, which was resolved.

Standardized diagnostic criteria only include ocular manifestations. Retinal features are the main retinal problems and appear in approximately 50% of affected individuals (44), but these lesions usually affect visual function only minimally (45). In the following case, no ocular signs or symptoms were present, so this does not agree with the authors' statement.

Conclusions

- Clinical signs develop gradually. Neurological and dermatological symptoms were most frequently present in patients with TSC. Depending on the age of the patient, TSC requires a diagnostic evaluation, including family history, neuropediatrics, dermatology, ophthalmology, dentistry, cardiology, pulmonology, nephrology, oncology, and medical genetics evaluation, including imaging studies and evaluation of visceral function.
- TSC is mainly diagnosed due to neurological and dermatological problems. Because it is a multisystem disease, interdisciplinary management is required in these patients.

Conflict of interest

The authors declare that there is no conflict of interest in relation to the submitted article.

Authors' contribution statement

Author 1: I actively participated in the planning and design of the literature review. I also carried out a critical evaluation of the selected studies, analyzing both the methodological quality and the validity of the results.

Author 2: Significantly contributed to the interpretation and discussion of the findings obtained in the clinical case. He/she also played an important role in the writing and revision of the content of the manuscript.

Author 3: Provided valuable input by providing comments that improved the clarity and coherence of the work. Actively participated in the development of the results and conclusions of the study.

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