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Case Report

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Tuberous sclerosis: a review of 18 cases

Abstract

Introduction: Tuberous sclerosis (TS) is a phacomatosis characterized by the development of benign tumors of the skin, kidney, heart, eye and brain .The objective of this paper is to discuss the clinical and evolutionary aspects of this condition using 18 representative cases.

Materials and methods: This is a retrospective study of 18 cases of children with TS compiled in the Neuro-Pediatrics unit of the Children's Hospital of Rabat during the period from 2004 to 2012.
Results: The 18 cases included 8 boys and 10 girls and their ages ranged from 17 months to 16 years. Neurological involvement was present in 17 patients; 4 patients had West syndrome, and 13 patients had partial or generalized seizures. Mental retardation was noted in 7 patients and autism in 4. Brain imaging noted 12 cases of parenchymal calcifications, 4 cases of subependymal nodules and 2 cases of tubal cortical. Achromic or angiofibromatous lesions were found in 11 patients. Renal ultrasound was performed in 12 patients and 9 cases of parenchymal abnormalities such as angiomyolipoma and polycystic kidney disease were discovered. Cardiac involvement with intracardiac hamartoma was noted in one patient. Patient outcome was variable depending on the organs affected.

Conclusion: TS is a rare phacomatosis. Renal and cardiac evaluations are needed to rule out the risk of associated life-threatening illness. Timely multidisciplinary care is necessary to mitigate severe impact of this debilitating disease.

Keywords: phacomatose, multiorgan, epilepsy, multidisciplinary care

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Abbreviations: TS, tuberous sclerosis; TSC, tuberous sclerosis complex

Introduction

Tuberous sclerosis (TS) is an ectodermatosis of neuro-genetic origin with variable neurological, cutaneous and visceral manifestations. TS is due to the development of benign tumors of the hamartomatous type. First described by Bourneville in 1880, the classic triad characterizing the TS was described by Vogt in 1908 including epilepsy, mental retardation and sebaceous adenomas. The prevalence is estimated between 1/6000 and 1/10000 population.

Aim of the Study

The aim of this paper is to discuss the clinical presentation of this disease as well as potential associated life threatening illness which are found by in depth screening using 18 representative cases.

Patients and Methods

This is a retrospective study of 18 cases of children with TS compiled in the neuro-pediatric unit of the Children's Hospital of Rabat during the period of 2004-2012. We collected data related to the personal and familial history of the patient, type of seizures, results of clinical examination, imaging and electrophysiological examination as well as treatment and prognosis.

Results

The 18 cases were reviewed and included 8 boys and 10 girls and their ages ranged from 17 months to 16 years with a mean age of 9 years.

Neurologically, 23% of our patients had a history of prematurity, neonatal distress and febrile convulsions and 20% of them were previously treated for an epileptic encephalopathy known as "West Syndrome". Seizures were noted in 90% of our patients and neurological impairment in 89% of them. Behavioral problems arose 25% of children of which two thirds of them were autistic. Intellectual disability affected 40% of patients with specific language delay, apraxia and dyscalculia in about 11% of cases. Skin involvement was present in 81% of cases, 96% of our patients had depigmentation of some skin areas named achromic patches, 34% had rounded fleshy and rose nodules on the nose and cheeks like "butterfly wings" named facial angiofibroma and 12% had nail fibromas also known as Koenen tumors.

Brain CT and MRI showed ependymal nodules of the CNS in 87% of cases of which 82% of them were calcified and cortical tubers in 78% of cases. Seventy seven percent of EEG recordings showed various electroencephalographic abnormalities including hypsarrhythmia in 6% of them. Renal ultrasound was performed for 12 patients and showed angiomyolipoma either alone or accompanied by polycystic kidney disease in 50% of cases with a female predilection. One of our patients had cardiac tumor that became evident after palpitations and chest pain and diagnosed by echocardiography and cardiac MRI. The clinical course was variable from one patient to another and was dependent primarily to renal, neurological or cardiac impairment. We recorded one death by renal failure in a patient with renal angiomyolipoma.

Discussion

TS is a genetic disorder with a prevalence of sporadic cases and high genetic heterogenicity. Two major tumor suppressor genes have been identified: TSC1 and TSC2, respectively which located on chromosome 9q34 and 16p13.3. A mutation in one of these two genes is found in 90% of cases.[1] These mutations are responsible of the occurrence of tumors named hamartomas that could be localized in the central nervous system CNS, skin, kidney, retina, heart and bone.

The central nervous system CNS is most frequently affected in the TS. These neurological abnormalities are the leading cause of morbidity and mortality and are associated with benign cerebral

hamartomas of 3 types: cortical tubers and subependymal nodules found in 80% to 95% of patients and giant cell astrocytomas present in 6 to 14% of the patients.[1,2] Cortical tubers are smooth and firm masses located at the top of the cerebral convolutions. The subependymal nodules lie on the surface of the lateral ventricles and their number increases with age until the age of 10 years when they stabilize, malignant transformation of these lesions is possible. Giant cell astrocytomas are located in the walls of the lateral ventricles and their volume increases over time resulting a high risk of hydrocephalus. Clinically, neurological manifestations include epilepsy, mental retardation and behavioral disorders like autism. Epilepsy is the most common symptom and seizures occur in 70-90% of cases in the first year of life. In 60% of cases, the disease progresses to an epileptic encephalopathy known as "Lennox-Gastaut syndrome". Cognitive prognosis is closely related to the age of onset of epilepsy with the prognosis being poorer if the disease onset occurs before the age of one year, its severity based on the degree of epilepsy management and the type of epilepsy. Intellectual impairment affects 50-60% of children with TS; and is consistently associated with epilepsy. Partial-onset epilepsy and transient occurrence of infantile spasms are the only two types of epilepsy associated with TS which have been associated with normal intelligence. Except epilepsy, other factors of intellectual disability have been reported including the number of cortical tubers with the risk being greater beyond 7 to 10 tubers and the total volume and locations including front and temporal locations. In our study, 90% of our patients had seizures and only 20% of them manifested seizures during the first year of life, these patients were treated as West syndrome and progressed to Lennox Gastaut syndrome with a poor cognitive prognosis.

Autistic-like behavior was observed in 17-68% that seems to be improved by the use of Vigabatrin (Sabril®) in order to control spasms. Sleep disorder is noted in 60% of patients, as well other abnormalities such as weaknesses of memory, language delay, dyscalculia, visuospatial difficulties and apraxia. In our study behavioral disorders were found in 25% of patients, with intellectual disability affected 40% of patients with language delay, apraxia and dyscalculia in about 11% of cases. Neuroradiological signs are a key element for diagnosis. CT scan is useful for detecting calcified subependymal nodules, however MRI is more appropriate to specify the number and location of hamartomatous brain lesions. Imaging may be normal during childhood and the lesions may appear later. Rarely, the TS might be present in the fetal period and could be detected by fetal MRI.

The cutaneous manifestations are the second most frequent manifestations and are present in 96% of patients with TS. Their occurrence changes according to age: hypopigmented macules are usually the earliest manifestations, followed by fibrous plaques on the forehead, while fibroids facial angiomas and peri-ungual fibromas occur later. The achromic patches are present in 90-98% of cases with a distribution possible over the entire body with a predilection for the trunk and buttocks. The angio-fibroids are found primarily on the face, they are pathognomonic of the TS and appear after the age of 3 or 4 years. Affecting 50 to 75% of cases, they are distributed bilaterally and symmetrically in the nasolabial folds. The Koenen tumors are pathognomonic and are present in 15-20% of patients especially at feet.[2,3] In our study only 81% of our patients had cutaneous manifestations consisting on achromic patches in 96% cases, fibroids facial angiofibroma in 34% of our cases and nail fibroma in 12% of cases.

The renal manifestations are detected in 94% of patients with TS and they are the second cause of death after neurological impairment. Angiomyolipoma consists the most common tumor found in 40-80% of cases followed by the cystic lesions in 25% of cases and the renal cell carcinoma. However, some studies have shown that the risk of renal cell carcinoma is the same as that of the normal population, but occur at a younger age. Angiomyolipomas are not pathognomonic of the TS and they remain asymptomatic for a long time.[1,4] In our study, half of patients presented renal lesions, 65% of them were angiomyolipoma with a female predilection and resulting a renal failure that caused the death of the children.

Studies have shown the existence of cardiac rhabdomyomas in 66% of TS. The diagnosis is suggested by the presence of polypoid masses embedded in the cardiac chambers, clogging atrioventricular orifices and especially aortic and pulmonary outflow tract. They may be single but are mainly multiple, scattered in the myocardium or in the interventricular septum, or in the free walls of the ventricles in the atrial walls.[5] The usual presentation is an obstructive syndrome or rarely a disorder of rhythm, however, syncope or sudden death may be the initial presentation. The diagnosis is provided by Doppler echocardiography and cardiac MRI. Cardiac rhabdomyomas can be asymptomatic and have the capacity for spontaneous regression, requiring a simple regular echocardiographic monitoring.[6] Antiarrhythmic treatment or surgical excision may be performed as appropriate. In our case series one patient presenting with palpitations and chest pain symptoms demonstrated interventricular rhabdomyoma that required medical thump.

TS is a phacomatosis which essentially combines eye, brain and skin lesions. Other organs may be affected as kidney, heart or lungs. Timely multidisciplinary care is necessary to mitigate the vital and cognitive impact of this often disabling disease.[7]

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Conflicts of Interest

There is no conflict of interest.

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