International Journal of Medical Science and Clinical Research Studies

ISSN(print): 2767-8326, ISSN(online): 2767-8342

Volume 05 Issue 04 April 2025

Page No: 549-552

DOI: https://doi.org/10.47191/ijmscrs/v5-i04-08, Impact Factor: 8.188

Infantile Epileptic Spasm Syndrome and Tuberous Sclerosis Complex: About Five Cases

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ABSTRACT

Epileptic spasms associated with tuberous sclerosis complex (TSC) are associated with poor epileptic and cognitive prognosis [1,2]. Knowledge of prognostic factors makes it possible to improve its management. We report the clinical, electrical, renal ultrasound, brain MRI and neurocognitive profile of this drug-resistant epilepsy. During the 5-year study period, five patients were diagnosed with TSBdue to the association of epilepsy with Infantile Epileptic Spasm Syndrome (IESS), achromic spots, cortical tubes and renal cysts in all patients. The clinical symptoms of seizures with types of epileptic spasms, associated with partial or generalized seizures and the EEG: atypical hypsarrhythmia or focus of spikes and slow waves localized to lesional foci of the tubers. Brain MRI shows cortical tubes with subependymal nodules. Two out of five patients, late onset of epilepsy at 18 and 2 years old, had good electro-clinical control of epilepsy with a better cognitive and behavioral score. The others started their epilepsy before a year or unsuitable treatment of spasms. evolved into drug-resistant epilepsy, with a neuro-cognitive-behavioral deficit, an 8-year-old patient with drug-resistant epilepsy had a spectacular improvement under Rapamycin. Our conclusion is that early diagnosis and treatment, Rapamycin and Antenatal and neonatal diagnosis with antiepileptic drugs in front of a pathological EEG, could improve epilepsy and associated comorbidities.

KEYWORDS: Epileptic spasms, partial seizure, Tuberous Sclerosis Bourneville, Achromic spots, Epileptic and cognitive-behavioral score..

ARTICLE DETAILS

Published On:
07 April 2025

Available on:
https://ijmscrs.com/

INTRODUCTION

Tuberous sclerosis complex (TSC), is an autosomal dominant genetic disorder (Mutations of the TSC1,TSC2 genes encoding the Tuberine and Hamartine proteins on chromosomes 9q34 and 16p13,) [4]. Of the phacomatosis and neuroectodermosis family, its frequency is 1/6000 [2]. It is a multi-systemic disease of variable expressions, affecting in particular the brain and skin [3]. Epilepsy is the neurological manifestation common to tuberous sclerosis [5] . Infantile epileptic spasm syndrome (IESS) associated with achromic skin spots, occurring in the 1st$^{year\ of}$ life is almost the signal of the disease (STB)

Epilepsy is of the infantile spasm syndrome type with an onset between 3 months and 2 years of age, or epileptic spasms associated with a partial seizure, EEG is rarely hypsarrhythmic typical Husein 2009 [1]. Neurocognitive abnormalities such as intellectual and attentional deficit, as well as impaired quality of life [2,7] are associated with epilepsy in TSC and are correlated with the level of epilepsy control, with a better neurocognitive-developmental score in well-controlled clinical and electrically controlled seizures [5,6,7]. Vigabatrin is the 1st$^{line\ treatment}$ in SSEI associated with STC with better electro-clinical seizure control and a better neurocognitive score as demonstrated by chiron in 1997, and adopted by subsequent studies with statistically significant results [5,6,8]. m'TOR pathway inhibitors are used in the treatment of kidney cysts, angiomyolipoma, and drug-resistant epilepsies, as an alternative to surgery in cases of bilaterality of the tubers [3]

Objectives of the study to study the clinical, electrical and psychomotor profiles of infantile epileptic spasm syndrome in TSC, to identify the risk factors for drug resistance. To emphasize the importance of better clinical and electrical

control by vigabatrin correlated with a better neurocognitive prognosis.

Patients and Methods: We conducted a retrospective study of 5 cases, followed in pediatric neurology consultations for epilepsy with TSC. We noted on patients' files: the inbreeding of the parents, the involvement of siblings, the age of onset of infantile spasms, psychomotor development before the onset of spasms, the electro-clinical and neuroradiological characteristics of the spasms, psychomotor regression, the diagnostic criteria for TSC, the therapeutic and evolutionary modalities, as well as the prognostic factors of this pathology.

Results During the study period, five patients (4 girls and one boy) were diagnosed with epilepsy associated with TSC. The mean age of consultation is 12 months [4-24 months], Epilepsy was the call sign or reason for consultation that led to the diagnosis of the diagnosis in all cases, and the association with the skin examination of achronic spots that guided the diagnosis, confirmed by brain MRI which found the 2nd major cortical tuber criterion.

The type of epilepsy recovered: epileptic spasms, partial seizure, EEG finds a disorganized trace, typical hypsarrhythmia in 2 cases, in the remaining 3 atypical hypsarrhythmias with slow-wave foci linked to cortical tubers The epilepsy defined was of the type focal epilepsy, infantile spamses, generalized epilepsy. The evolution was favorable on levetiracetam and Vigabatin for the 3 cases with late onset of spasms, defavrable in early onset spasms progressing to LGS, cognitive and behavioral retardation Everolimus was put in a case

Tab 1: Demographic characteristics of the cases studied

	Age/Sex/Inbreeding	Early epilepsy	Diagnosis	Type of Mutation?	Other Impairments
Case 1	4A/M/C	2 months	4 months	2	Achromic spots, Cortical tubers Renal cysts
Case 2	5M/F/C	3 months	2 months	1	Cortical tubers
Case 3	19m/F/C	19 months	1 month	2	Renal Cysts,Cortical Tubers
Cas4	7A/F/C	8 months	16 months	2	MRI cortical tubers
Case 5	2A/F/NC	23months	1 month	1	Achromic spots,Cortical tubers

M:Male,F: Female Inbred NC:Non-Inbred

Case 1: ANIS 4 years old, of 1st degree consanguineous parents, pregnancy and normal childbirth, and normal psychomotor development, the 3rd of a sibling of 3 healthy living children. The onset of epilepsy at 2 months, type of partial motor seizure, bursts of spasms, on waking at 4 months: 8 in number, diurnal and nocturnal, asymmetrical, with EEG: predominant spikes on temporal territories, asynchronous, during wakefulness, becoming synchronous during sleep. A neurocognitive degradation II area intellectual and attentional deficit and language. The diagnosis of TSC is certain in the face of two major criteria :p more than 6 achromic spots, bilateral cortical tubers, and subependymal nodules, renal cysts: the patient received different molecules of which vigabatrin was the most effective. Follow-up at 4 years: the spas have evolved into Lennox Gastaut syndrome with atonic seizures, and atypical absences motivating the addition of Repanide with comorbidities: cognitive and behavioral, the child is still waiting for the surgical act or Everolimus (age does not allow the use of everolimus for his drug-resistant epilepsy.

Case 2 Amira, 2 years old, of non-consanguineous parents, normal pregnancy and childbirth normal psychomotor development. The onset of epilepsy at 2 years of age, marked by a single partial, secondarily generalized seizure, without spasms, but his EEG showed multifocal, asynchronous spikes, predominant on the temporo-occipital regions. This child is treated with levetiracetam, secondarily associated with vigabatrin with EEG normalization. The diagnosis of TSS associated with partial epilepsy was made in the face of 2 major criteria: 6 achromic spots, plus cortical tubers, and subependymal nodules of the white matter. This child is currently 5 years old, in preparatory school, with a better performance, and a normal neurocognitive assessment.

Case 3: Tasnim born on 03/07/2016, of non-consanguineous parents, of pregnancy and a normal delivery, the 2nd of a sibling of 2EVBP, to the ATCD of an epileptic paternal uncle, initial psychomotor development normal, presented to a

neuropaediatric consultation at the age of 7 for drug-resistant epilepsy. The onset dates back to the age of 8 months marked by grimaces at the level of the Face, with an EEG showing multifocal waves, asynchronous, predominant on the temporo-occipital regions. Between one and 2 years of age, the attacks became frequent, the patient was treated respectively with valproate, tegretol, keppra at 3 months interval between the introduction of each molecule. The EEG showed a persistence of seizures with aggravation. then cognitive and behavioral degradation: intellectual, language and attention deficits. Brain MRI showed a T2 hypersignal of the white matter with bilateral cortical tubers, the patient improved on a ketogenic diet, with recurrences of seizures. Therapeutic readjustment with the introduction of Rapamycin transformed his prognosis with a better cognitive and behavioral score.

Case 4: Watine, 5 months old, of consanguineous marriage, the youngest of 2 children, of pregnancy and of a normal childbirth, with normal psychomotor development, presents to the consultation for a refractory epilepsy with the type of infantile spasms, whose 1st seizure with the epileptic spasm type dates back to 3 months to type two bursts of spasms per day of 4 to 5 spasms per day. The intercritical EEG does not find spindelesse, nor vertex spikes, with subcontinuous diffuse wave spikes evoking a fragmented sleep hypsarrhythmia. The clinical examination found a good interaction, axial hypotonia with loss of head hold. The management of epilepsy consists of the administration of sabril, combined with Leviracatam.

Case 5: Soudjoud, 19 months old, of consanguineous parents, with a normal neonatal history, normal staturoweight and psychomotor development, consults for a partial tonic crisis secondarily generalized, the clinical examination finds achromic spots more than 3 spots on the limbs and trunk. The definite diagnosis of tuberous sclerosis of bourneville was made in the face of the association of 2 major criteria and more: achonic spots and cortical tubers, the subependymal nodule on brain MRI, and renal cysts on renal ultrasound. Currently, she is 7 years old, she has only had two partial seizures from the age of 19 months, until the age of 7, she keeps a good cognitive and behavioral posture.

DISCUSSION

TOSCA with the international registry of STC has made it possible to raise awareness for the management of infantile spasms on STC, with a better knowledge of the clinical and electrical characteristics of epileptic spasms, deficits neurocognitifs.il has also allowed a standardization of treatments with the choice of the best molecules such as Vigabatrin, the ketogenic diet, surgery, and inhibitors of the MTOR pathway: Rapamycin with a better neurocognitive score, and behavioral[].

Most authors report that epilepsy in TSC is predictive of drug-resistant epilepsy and poor neurocognitive disorders: intellectual deficit, attentional drug-resistant epilepsy [1,2,11]. However, surgical resection of the tubers improved the development of 3 patients [12]. Rapamycin could be an alternative to surgery in the presence of drug-resistant epilepsy and bilateral cortical tubers inaccessible to surgery

Since 2011, molecules inhibiting the voice of mTORs have been authorized for the treatment of drug-resistant epilepsies [14] and we have introduced rapamycin in five of our patients with infantile epileptic spasm syndrome and TSC

Our findings regarding our patients are: Epilepsy in TSC is not always accompanied by a poor prognosis as has been described by some authors [8,11]. The age at which epilepsy begins is decisive, in fact when the onset is at 2 years of age, seizures are infrequent and easily controlled by a Vigabatrin associated or not with another antiepileptic drug [6]. The 2 patients with onset of spasms at 2 years old had better epilepsy control and kept a good psychomotor development. One of the 2 patients had a vegetative seizure but his EEG was pathological, His treatment had prevented other attacks and better development (Hsier and preventive treatment).

Patients who started their epilepsy in the 1st year of life did not all have the same phenotype: the epileptic and neurocognitive prognosis depends on an early diagnosis and an appropriate treatment: in fact, the 5-month-old patient had started these epileptic spasms at 3 months was rescued with rectification of his treatment with vigabatrin at 5 months with a good control of epilepsy and his psychomotor development. The girl seen at 8 years old (having started her epileptic spasms at 8 months) for drug-resistant epilepsy (on 4 antiepileptics) partially improved her epilepsy by the ketogenic diet with electro-clinical disappearance of epileptic spasms and improvement of her neurocognitive score.

Some risk factors are correlated with drug resistance, such as age of onset of spasms, type of epilepsy (infantile spasms are recognized by their resistance), pathological MRI, hypsarrhythmia, TSC2 mutation [shier, elnok,]Our patients all had common elements of poor prognosis, namely; the age of early onset of spasms before one year, the TSC2 mutation, the type of epilepsy 3 had a symptomatic West syndrome recognized by its pharmacoresiatnce, the intercritical EEG tracing, the bilaterality of the tubers. Despite these common points, the evolution is not the same for all patients, the suppression of seizures by Vigabtrin[5,6], the ketogenic diet is predictive of good development while waiting to institute surgical resection of the tubers or inhibitors of the mTOR pathway, Rapamycin [2,14].

Screening of sick siblings allows EEG monitoring and treatment as soon as electrical abnormalities appear, before seizures appear, delays the onset of the 1st seizure and prevents RA and improves development [9].

CONCLUSION

Infantile epileptic spasm syndrome on Tuberous sclerosis complex (TSC), obeys the criteria of classic West syndrome and infantile epileptic spasm syndrome. Skin examination for

achromic spots in Wood's light is essential in the face of any epileptic seizure such as epileptic spasms in search of TSC, to be completed by the search for other systemic damage: renal, ocular, and cerebral tubes. Rapamycin is an effective treatment where surgery is inaccessible. Prenatal diagnosis and EEG screening of asymptomatic cases allows for correct and early management of drug-resistant epilepsy with a better neurocognitive and developmental score.

CONFLICT OF INTEREST

None of the authors has an interest with any party

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