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Case Report

Combined targeted treatment in early onset epilepsy associated with tuberous sclerosis

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ABSTRACT

Tuberous sclerosis is associated with epilepsy in up to 85% of cases, and in 2/3, the onset is within the first year of life. An early antiepileptic treatment is crucial to minimize the consequences of epilepsy on cognition and behavior. We present a case report of a child with tuberous sclerosis who presented with infantile spasms at the age of 6 months, immediately treated with vigabatrin. Because of the presence of a subependymal giant cell astrocytoma, he also received everolimus since 18 months of age. We might wonder if an earlier treatment could have produced a better outcome; in fact, despite a targeted combined treatment, he continues to suffer from sporadic focal motor seizures, and at the age of 40 months, he presents severe developmental delay with autism-like behavior.

1. Introduction

Tuberous sclerosis complex (TSC) is a genetic multisystem disorder in which benign hamartomas develop in multiple organ systems [1]. The disorder has an estimated birth incidence of 1:5800 [2]. Epilepsy is the most frequent neurological manifestation in patients affected by TSC, involving up to 80% of subjects [3]. Epileptic seizures begin in the first year of life in about one-third of TSC patients, and sometimes in the very first weeks of life [4]. Focal seizures may be the first seizure type and may coexist or evolve into infantile spasms [5]. Children with TSC presenting an early seizure onset are at high risk of developing refractory epilepsy and/or an epileptic encephalopathy; by the age of 2 years, 42% of children with TSC will manifest drug-resistant seizures [4]. Early life seizures are also associated with a greater incidence of severe/profound cognitive impairment and autism-like behavior [4,6]. However, cognitive–behavioral disturbances might be present independently of seizures. Manifestations related to TSC are the consequence of the hyperactivation of the so-called mTOR (mammalian target of rapamycin) pathway, resulting from the loss of *TSC1* or *TSC2* gene, and leading to abnormalities in cell growth and differentiation, synaptogenesis, and impaired protein synthesis [7].

A definite clinical diagnosis of TSC can be made in the presence of two major features, but identification of either a *TSC1* or *TSC2* pathogenic mutation is sufficient to make a definite diagnosis too [8]. Cardiac rhabdomyomas, cortical tubers, subependymal nodules, and renal angiomyolipomas may be detected by prenatal imaging allowing an early diagnosis [9,10]. Today, TSC can be diagnosed prenatally, or early postnatally in a growing number of patients [11], and all the diagnosed infants should be considered at a high risk of developing early onset seizures [12]. Therefore, clinicians should educate parents to recognize subtle focal seizures or epileptic spasms as early as possible, thus, trying to reduce the gap between seizure onset and treatment initiation [13–15].

Similarly, all children should be considered at high risk for neurocognitive and behavioral impairments, and should be regularly evaluated in order to highlight early signs of deviation from the typical developmental trajectory so that an early intensive behavioral treatment program could be applied. In particular, there is still little evidence whether early treatment with everolimus or combined treatment with vigabatrin and everolimus is able to reduce the risk of epilepsy and neurodevelopmental disability.

In this paper, we report the case of a child with TSC and early onset epilepsy, treated with a combined targeted therapy of vigabatrin and everolimus, and followed up until the age of 40 months.

1.1. Case presentation

A 3-week-old male newborn came to our attention after the detection of cardiac rhabdomyomas at 28 weeks of gestational age, and the

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subsequent identification of cortical tubers and a subependymal nodule by fetal brain MRI. He was born at 32 gestation weeks after an uneventful pregnancy by healthy, nonconsanguineous parents. An early postnatal MRI confirmed the TSC diagnosis. Genetic molecular analysis revealed a de novo mutation on the *TSC2* gene (c.687_690del CTGC). Electroencephalogram monitoring was started at 3 weeks of life and was continued at 4-week intervals, for the first 6 months of life, and every 6–8 weeks, or as clinically needed thereafter, according to the recommendations from the European Consensus Conference on TSC-related epilepsy [14]. During the first evaluations, his neurologic examination and the wakefulness and sleep video-EEG were normal for his age (Fig. 1A). At the age of 2 months, some isolated sharp waves and spikes appeared on the left temporal region during sleep (Fig. 1B); this epileptic focus appeared to be in topographic concordance with a large left temporal tuber seen by MRI. At the age of 5 months, the epileptiform abnormalities became multifocal, and bilateral temporoparietal slow waves were also recorded (Fig. 1C). However, the background EEG activity showed a good organization, with regional differentiation and sleep spindles and K complex during NREM sleep. At the age of 6 months, the EEG was more active, showing recurrent multifocal slowing and epileptiform abnormalities, with a pseudo-periodism (Fig. 1D). Epileptiform abnormalities became more frequent and often generalized, with epileptic foci mainly localized in the right hemisphere. Starting from the age of 6 months, serial neuropsychological evaluations were performed every 6 months using the Griffiths Mental Developmental Scale (GMDS). All the single items have been analyzed in full detail to

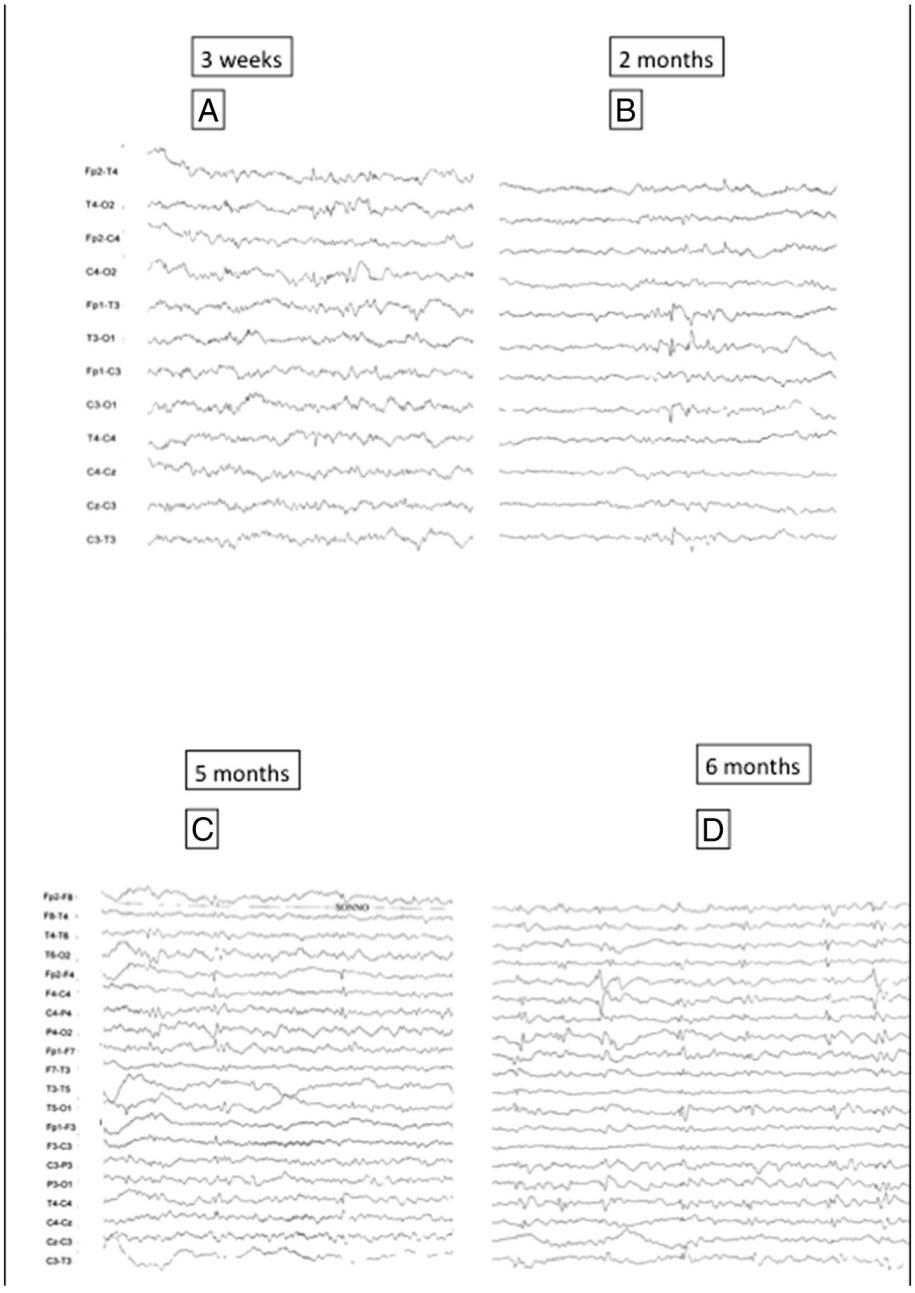

Fig. 1. Sleep EEGs of the patient at different timepoints. A. The first EEG at 3 weeks of life showed a good background organization with no clear epileptiform abnormalities. B. At the age of 2 months, sleep and awake EEG continued to show a good background organization. Very rare and isolated spikes appeared only during sleep on the left temporal region (T3). C. At the age of 5 months, the EEG pattern begins to change. Epileptiform abnormalities now become sustained and multifocal, with an initial tendency to spread, at least in the same hemisphere. This kind of EEG pattern might be considered as a "point of no return", after which, a progressive EEG deterioration with a significant increase of epileptiform abnormalities is likely to occur in a few weeks. D. Significant evolution of the EEG pattern, which now shows recurrent and sustained epileptiform abnormalities with spikes and spike and waves with a tendency to spread with a pseudo-periodism.