Self-limited Non-Familial Neonatal Seizure: A study of 40 Argentinian patients

Alberto Luis Espeche[1,*], Marina Laura Hoffmann[1], Roberto Horacio Caraballo[2]

[1]Department of Neurology, Hospital Público Materno Infantil, Sarmiento 1301, Salta, Argentina
[2]Department of Neurology, Hospital Nacional de Pediatría 'J. P. Garrahan' Pichincha 1881, Buenos Aires, Argentina

*Correspondence: Alberto Luis Espeche, Department of Neurology, Hospital Público Materno Infantil, Sarmiento 1301, Salta, Argentina
Email: albertoespeche@yahoo.com.ar
http://orcid.org/0000-0003-2631-6698

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Background

Self-limited non-familial neonatal seizures (SLNFNS) represent a recognised epileptic syndrome that is heterogeneous in its presentation. The objective of this study was to analyse age of onset, electroclinical characteristics, treatment, and progress of patients diagnosed with SLNFNS.

Methods

Retrospective study of 40 cases that met inclusion criteria for SLNFNS from July 1996 to February 2016.

Results

Forty patients (21 female, 19 male) were examined, with a follow-up time ranging from one year and 10 months to 16 years. Age of onset: 17 days, 30/40 (75%); 8-20 days, 10/40 (25%); mean: 6 days; median: 3.5 days. All patients presented focal clonic seizures (unifocal or alternating; isolated or clustered), and four of them evolved into status epilepticus. The interictal electroencephalogram (EEG) was normal in 37 cases; three showed sharp focal or multifocal waves. An ictal EEG was performed in a patient and initial spike-wave activity was noted in the temporal area, which quickly

spread to the homologous hemisphere. Phenobarbital was the initial drug in all infants; 10/40 cases required combination with carbamazepine. In their evolution, two patients with a history of status epilepticus presented intellectual disability; seven children had afebrile seizures in the first year of life; and two patients evolved into focal epilepsy in childhood. Of all the patients, 95% are seizure-free at the moment and do not receive antiepileptic treatment.

Conclusions

In infants with clonic focal seizures, in whom history and investigations reveal no aetiology factors, SLNFNS should be considered. Although the majority of our patients evolved favourably, some presented epilepsy and intellectual disability during their follow-up.

Introduction

Seizures that start in the neonatal period are a frequent manifestation of a central nervous system (CNS) impairment [1]. Neonatal seizures are defined as seizures that occur between birth and 44 weeks of postconceptional age [2,3].

The International League Against Epilepsy (ILAE) report from 2010 suggests that neonatal seizures should no longer be considered as a separate entity. Therefore, after excluding acute reactive and symptomatic causes of neonatal seizures, initial neonatal epilepsies could be included in the etiologic classification proposal [4].

Two neonatal idiopathic epilepsy syndromes have been recognised until now: self-limited familial neonatal seizures (SLFNS), included within the recognised initial neonatal stage epilepsy syndromes, and self-limited non-familial neonatal seizures (SLNFNS), which belong to a sub-group characterised by epileptic seizures that are not traditionally diagnosed as a form of epilepsy *per se* [4-6].

SLFNS and SLNFNS are characterised by seizures in neonates with normal neurological examination prior to the onset of the seizures, absence of pathological prenatal and perinatal history, normal investigations, normal or non-specific interictal electroencephalogram (EEG), and favourable evolution. The main difference between these two entities lies in the presence of a family history of seizures with an onset at the same age in SLFNS, and the identification of mutations in two genes, *KCNQ2* and *KCNQ3*, located in chromosomes 8 and 20 [7,8]. However, a *novo KCNQ2* mutation has been detected in one family with SLNFNS [9]. Seizures that occur at neonatal and infantile stages in the same family have also been described and they are called self-limited familial neonatal-infantile seizures (SLFNIS) [10,11]. Subsequently, the association with a channelopathy that affects sodium channels and which encodes a mutation in the *SCN2A* gene was recognised in five families with SLFNIS [12].

SLFNS, also known variously as ‘fifth day fits’, benign neonatal convulsions, benign idiopathic neonatal convulsions, benign neonatal epilepsy, or benign non-familial neonatal seizures were initially reported in 1977 by Dehan and colleagues [13]. Their prevalence has been estimated at between 27% of all neonatal seizures, and they are characterised by clonic seizures (frequently focal and associated with sleep apnoea or status epilepticus in some cases), with normal interictal EEG, and favourable evolution [13,14].

The objective of our study was to analyse electroclinical characteristics, treatment, and evolution of neonates who presented SLNFNS in two different hospitals in Argentina.

Materials and methods

Retrospective study

Forty cases that met inclusion criteria for SLNFNS were evaluated from July 1996 to February 2016. We analysed patients of two centres with different characteristics. The *Hospital Público Materno Infantil* is a maternity unit and has a Paediatrics Department and a Neonatal Intensive Care Unit (NICU). The Hospital Nacional de Pediatría ‘J. P. Garrahan’ is a paediatric hospital with a NICU, and only receives babies referred to the emergency department.

Inclusion criteria: full-term infants that presented neonatal seizures with normal perinatal history, laboratory tests and neuroimaging, and normal or non-specific interictal electroencephalography.

Exclusion criteria: acute symptomatic seizures; metabolic origin, structural or genetic epilepsies; family history of neonatal seizures.

The analysis included medical records, age at onset of seizures, clinical characteristics and number of seizures, complementary tests, treatment received, and duration and evolution. All patients were studied using laboratory tests, EEGs and neuroimaging (ultrasound, computerised tomography [CT] and/or magnetic resonance imaging [MRI] of the brain).

A genetic panel of neonatal seizures was not carried out in any patients. Metabolic disorders were ruled out in all cases by clinical presentations, investigations, and therapeutic tests.

Results

General aspects

Forty patients (21 female, 19 male) presented with SLNFNS, with the first seizure occurring on average six days after birth (Table 1); the median was 3.5 days. Thirty patients (75%) presented with the first seizures within the first week of life: it appeared between the first and second day in 20 patients (50%), and between the third and fifth day in 10 patients (25%). With the remaining 10 patients (25%), the first seizures presented on the second and third week of life. No patient had their first seizures after the third week of life.

The time of the follow-up ranged from one year and 10 months to 16 years of age (average of 10 years and four months).

Clinical characteristics

In all cases, the type of epileptic seizures observed were focal clonic seizures. In 20 patients (50%), only unilateral focal clonic seizures were recognised as a clinical manifestation; in 14 patients (35%) it was observed that focal clonic seizures were associated with fixity of gaze or eye, or cephalic deviation; and in three cases (8%), apnoea episodes appeared along with the focal clonic seizures.

Twenty-five patients had unilateral clonic seizures affecting face and limb that remained on the same side, 10 started with seizures on one side with the seizures spreading to the same half of the body, and five cases alternated sides, beginning with unilateral clonic seizures, which then continued on the other side of the body.

There were clusters of seizures in 31 cases (78%), while a unique and isolated seizure was observed in nine neonates (23%). The number of seizures during clusters were 2–5, and the clusters lasted 1–3 days; the duration of isolated seizures was 1–3 minutes. In 18 cases (45%), seizures occurred while being awake; in 12 (30%) while asleep; and in eight (20%) while half-asleep, indistinctively. Four cases (10%) presented status epilepticus, characterised by brief or extended seizures without recovery of consciousness with a duration of 3–20 hours.

Electroencephalographic characteristics

The interictal EEG was normal in 37 cases (93%), and in the remaining three patients (8%), a record of temporal sharp focal waves with low-frequency discharge was noted.

Four patients (10%) had status epilepticus. In two of these, an interictal EEG was performed in the first day prior to status epilepticus, showing a temporal sharp wave. In the other two cases, the interictal EEG was done two days after the presentation of seizures, and it showed no changes. An ictal video-EEG was performed in one patient, showing spike-wave activity that started in the left temporal area and quickly spread to the homologous hemisphere (Figure 1 and 2).

Neuroimaging

CT scans were normal in all patients. The brain MRI was obtained, and it was normal in 16 children (40%).

Treatment

In all neonates, phenobarbital was administered as a maintenance drug at the onset of epilepsy. A change in medication was necessary in 10 patients, who received carbamazepine.

Patients who showed status epilepticus required the association of antiepileptic drugs (AEDs), diphenylhydantoin, phenobarbital and pyridoxine.

Forty patients were treated with AEDs. The medication was discontinued before the sixth month of life in 28 cases; before the age of 18 months, 10 patients stopped receiving the treatment, seven of them because of infantile seizures during the evolution. Two patients that evolved with intellectual disability remained medicated – one with valproic acid and the other one with topiramate, because they presented with childhood epilepsy.

Evolution

Normal neurodevelopment was observed during the follow-up period in 37 children (92.5%). Seven children presented epilepsy during follow-up with all the afebrile seizures occurring during the first year of life; five resolved spontaneously with suspension of treatment with AEDs; and two cases evolved into afebrile seizures in the first year of life, complex febrile seizures and learning difficulties (these last two cases had epileptic status at the onset of the neonatal epilepsy). One child presented with simple febrile seizures.

Thirty-eight of the 40 cases are currently not treated with AEDs. Two patients with intellectual disability are seizure-free and continue with AEDs.

Electroclinical sub-groups

The electroclinical evolution of our patients could be divided into three groups:

Group 1: would correspond to the classical form of presentation initially described, with more self-limited seizures and normal neurodevelopment (n = 33).

Group 2: epilepsy in the first year of life, self-limited and normal neurodevelopment (n = 5).

Group 3: has the worse prognosis, in which the status epilepticus would cause a predisposition for intellectual disability and epilepsy (n = 2). These patients developed epilepsy in infancy and childhood, and intellectual disability.

Discussion

All our patients met the SLNFNS criteria, had normal neurological tests prior to the onset of the seizures, and had no pathologic history of relevance.

SLNFNS represents an idiopathic epileptic syndrome of rare appearance. In a prospective study of neonatal seizures in the Neonatology Unit of the Hospital Público Materno Infantil in Salta, there was a frequency of 2.4% (54/2243) of all in-patients. Two of 54 patients (4%) with neonatal seizures presented with SLNFNS [15]. This figure is similar in Plouin and Neubauer [14], who reported that the frequency of SLNFNS would be approximately 4% of all neonatal seizures.

Epileptic seizures in SLNFNS have been described as seizures with an onset within the first seven days of life in all cases, most frequently between the fourth and sixth day [12]. All our patients had neonatal onset but, when compared with the reported series, many patients presented with the first seizures between the first and the third day, most patients in the first week, and some within 8–21 days from birth.

The type of seizures observed most frequently was clonic with focal characteristics, most of them brief or self-limited. None of the patients presented with tonic seizures. The majority of our patients presented with clustered seizures, with recovery of consciousness between each episode. Four cases presented status epilepticus. The association with apnoea in our series was lower when compared to other studies [16]. Nonetheless, the clinical characteristics of the seizures are similar to those reported by other authors [13, 14, 16–19].

Dehan and colleagues described in 1977 an electroencephalographic pattern in patients with BNFNS, characterised by dominant theta activity, alternating or discontinuous with sharp waves in Rolandic areas, the *theta pointu alternant* [13]. However, in 1981, Navelet concludes that this path is non-specific and should not be considered characteristic of this epileptic syndrome [20]. We observed the predominance of normal sleep EEG recordings, while focal alterations found in the EEG corresponded mostly to patients who presented status epilepticus. Ictal EEG have been recorded in some patients, characterised by rhythmic spikes or rhythmic slow waves, localised in all areas, but most frequently in Rolandic areas [14]. In one patient with critical EEG, the onset of the seizures was in Rolandic temporal areas, as has previously been reported [14].

Since most seizures subside spontaneously without medication, some authors suggest keeping a period of watchful waiting for the treatment with AEDs, and if treatment is started, they recommend it should last for just a short period of time [14, 21]. We believe that it is difficult not to administer treatment in neonates, specifically in those who present recurrence of seizures or status epilepticus. Two cases with status epilepticus presented a poor outcome with intellectual disability and it could be a consequence of the status epilepticus or an unknown etiology. On the other hand, it is important to acknowledge this syndrome, because it would allow the early suspension of AEDs during the follow-up period. AEDs have been indicated in SLNFNS as a single or combined treatment [14]. However, treatment with medication has not been shown to modify the course of epilepsy, because the majority of the seizures were self-limited, regardless of the AED [14, 21]. We observed that the majority of the patients responded well to phenobarbital and that some patients who continued having seizures responded favourably to carbamazepine. Because carbamazepine is usually chosen to treat focal onset seizures, we believe that it should be an alternative to onset treatment when this epileptic syndrome is suspected.

The prognosis is favourable, although there are cases of intellectual disability and microcephaly [16, 22, 23]. Two children in our study developed an intellectual disability, both with a history of having suffered prolonged epileptic seizures.

The estimated risk of presenting with subsequent epilepsy has been rarely reported [16, 22]. Some authors even consider that it is less frequent when compared with the incidence of SLFNS [10, 21,24]. Nevertheless, of the cases we analysed, seven children presented with seizures in the first year of life and two of them developed focal epilepsy of unknown cause in childhood during their follow-up.

Once non-epileptic paroxysmal disorders, symptomatic causes, and secondary epilepsies have been ruled out, SLNFNS must be considered, so diagnosis is made by exclusion. The main entity from which they must be differentiated is SLFNS [25]. Three genetic mutations associated with benign familial neonatal seizures (BFNS) have been found: *KCNQ2*, *KCNQ3* and *SCN2A* [26]. The *KCNQ2* mutation is the most frequently-found association; however, there are families in which these mutations were not found, so it is suspected that there is probably another unknown gene related to this syndrome of familial presentation. Regarding SLNFNS, an association with KCNQ2 has been reported in one family, but most patients have unknown etiology [9]. Also in non-familial forms of nursing infant self-limited seizures, new *PRRT2* gene mutations – described in self-limited familial infantile epilepsy – were observed in some cases [27].

Acute deficiency of zinc concentration in cerebrospinal fluid [28] and rotavirus infection [29] were referred to as probable causes of SLNFNS. However, this has not been supported by another study [14].

The electroclinical evolution of our patients was divided into three groups. Group 1 would correspond to the classical form. Group 2 (neonatal seizures, infantile seizures and normal neurodevelopment) would correspond to a particular form of SLNFNS – a neonatal-infantile seizures sub-group in which we could not record a family history of childhood focal epilepsy [10-12], or new mutations of neonatal-infantile seizures. And Group 3, with the worst form of SLNFNS, in which the status epilepticus would cause a predisposition for intellectual disability and epilepsy. Otherwise, it could be

a distinct syndrome of neonatal onset with personal predisposition for early onset seizures and intellectual disability.

From the initial descriptions of SLNFNS, several reports have been presented confirming the particular electroclinical evolution with early onset crisis with good evolution. However, in recent years, there have been few publications about the new series of this epileptic syndrome. Despite having been recognised as an epileptic syndrome by the ILAE working group, the issue of whether or not this syndrome is a form of epilepsy is still under debate. Our work includes new cases of SLNFNS confirming the existence of the syndrome, which should be viewed as a focal idiopathic, self-limited epileptic syndrome, with an electroclinical spectrum that is close to familial and non-familial forms of neonatal or neonatal-infantile onset.

The clinical approach in neonates with seizures is to rule out any form of acute symptomatic seizures and their etiology, to correct the underlying abnormality, and to treat the seizures with the appropriate medications [30]. Once we have ruled out the acute symptomatic causes of the seizures, we may consider an epileptic syndrome. In the neonatal period, the epileptic syndromes may include a broad clinical spectrum, ranging from self-limited seizures to severe forms of epilepsy [30]. The most common self-limited seizures are the SLFNS, which may be associated with self-limited familial infantile seizures in the same patient and in the same family. This neonatal-infantile familial form corresponds to a clinical spectrum of a heterogeneous genetic origin. We believe that SLNFNS should be considered as a well-defined self-limited epileptic syndrome or electroclinical pattern similar to the familial form of neonatal seizures. From a broader perspective, and taking into account the relationship between familial neonatal and infantile seizures, the similarities regarding clinical features, course and outcome, we could speculate that the non-familial forms of neonatal and infantile seizures follow a similar pattern. Of interest, we studied patients with self-limited non-familial seizures that started on day 28 of life, a time threshold between both forms [31].

The current management and the definition of neonatal seizures are a challenge [32]. Prospective studies including genetic investigations would be necessary to better define the electroclinical features, nosological place, etiology, and outcome of this type of neonatal seizures.

Conclusions

In infants with clonic focal seizures, with no abnormal medical history, and normal complementary tests, SLNFNS should be considered. The recognition of this entity is important to avoid unnecessary complementary studies and to shorten the duration of the treatment. A group of SLNFNS is recognised, in which the presentation of epilepsy and intellectual disability develop in some of the patients and question the favourable prognosis of this syndrome. SLNFNS may correspond to *de novo* mutations or they might be sporadic cases of SLFNS. Future genetic studies could improve understanding of these types of seizures.

Competing interests

The authors have declared that no competing interest exists.

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Table 1. Electroclinical manifestations										
Case	**Sex (M/F)**	**Age of onset (days)**	**Seizure semiology**	**Status epilepticus**	**Interictal EEG**	**1st AED**	**2nd AED**	**Treatment duration (months)**	**Follow-up (years, months)**	**Outcome**
1	M	8	FCS		Normal	PB		4	1y, 10m	ND
2	F	2	FCS + FG	yes	Normal	PB	DFH, CBZ	18	7y, 1m	ND, SLIS
3	M	2	FCS + FG	yes	Normal	PB	DFH, CBZ	Remain on AED	8y, 3m	ID, IS, FE in childhood
4	F	1	FCS + FG + OD	yes	TSW	PB	DFH, CBZ	Remain on AED	7y, 2m	ID, IS, FE in childhood
5	M	2	FCS		Normal	PB		4	10y, 7m	ND
6	F	4	FCS		Normal	PB		2	10y	ND
7	M	2	FCS + FG		Normal	PB		6	8y	ND
8	F	8	FCS + FG		Normal	PB		6	7y, 10m	ND
9	F	5	FCS		Normal	PB		6	5y, 1m	ND
10	F	2	FCS		Normal	PB	CBZ	8	13y	ND, SLIS
11	M	2	FCS		Normal	PB		3	3y, 7m	ND
12	M	20	FCS + FG		TSW	PB	CBZ	18	5y	ND, SLIS

13	M	15	FCS		Normal	PB	CBZ	18	5y, 1m	ND, SLIS
14	F	3	FCS		Normal	PB		6	4y, 4m	ND
15	M	10	FCS		Normal	PB		2	10y, 9m	ND
16	F	3	FCS		Normal	PB		4	6y, 7m	ND
17	M	5	FCS + AP		Normal	PB		18	4y, 5m	ND, SLIS
18	M	11	FCS		Normal	PB		4	1y, 10m	ND
19	F	2	FCS + FG	yes	TSW	PB	DFH, CBZ	3	5y, 7m	ND
20	M	5	FCS		Normal	PB		3	5y, 6m	ND
21	F	2	FCS + AP		Normal	PB		9	3y, 9m	ND
22	F	18	FCS + AP		Normal	PB		3	5y	ND
23	M	2	FCS		Normal	PB		6	16y	ND
24	F	2	FCS		Normal	PB		5	2y	ND
25	M	5	FCS		Normal	PB	CBZ	3	9y	ND
26	F	1	FCS		Normal	PB	CBZ	4	3y	ND
27	F	3	FCS		Normal	PB		4	1y	ND
28	M	2	FCS		Normal	PB		3	5y	ND
29	F	7	FCS		Normal	PB		3	7y	ND
30	M	1	FCS		Normal	PB		2	2y	ND
31	F	1	FCS + FG		Normal	PB		1	9y	ND

32	M	7	FCS + OD		Normal	PB		3	6y	ND
33	F	2	FCS + OD		Normal	PB		2	2y	ND
34	F	2	FCS + FG		Normal	PB	CBZ	2	8y	ND
35	F	1	FCS + FG		Normal	PB		1	3y	ND
36	F	1	FCS + OD		Normal	PB		4	10y	ND
37	M	2	FCS + FG + OD		Normal	PB		11	4y	ND
38	M	3	FCS + FG		Normal	PB		12	11y	ND
39	F	9	FCS + FG + OD		Normal	PB		14	5y	ND
40	M	10	FCS + OD		Normal	PB		9	2y	ND

Abbreviations: *AED, antiepileptic drug.* ***Seizure semiology:*** *AP, apnea; FCS, focal clonic seizures; FG, fixity of gaze; OD, ocular deviation.* ***Interictal EEG:*** *TSW, temporal sharp wave.* ***AEDs:*** *CBZ, carbamazepine; DFH, diphenylhydantoin; PB, phenobarbital.* ***Outcome:*** *SLIS, self-limited infantile seizures; FE, focal epilepsy; ID, intellectual disability; IS, infantile seizures; ND, normal neurodevelopment.*

Figure 1. Ictal Video-EEG. Right-hand clonic jerks recorded with spike-wave activity that started in the left temporal area and quickly spread to the homologous hemisphere.

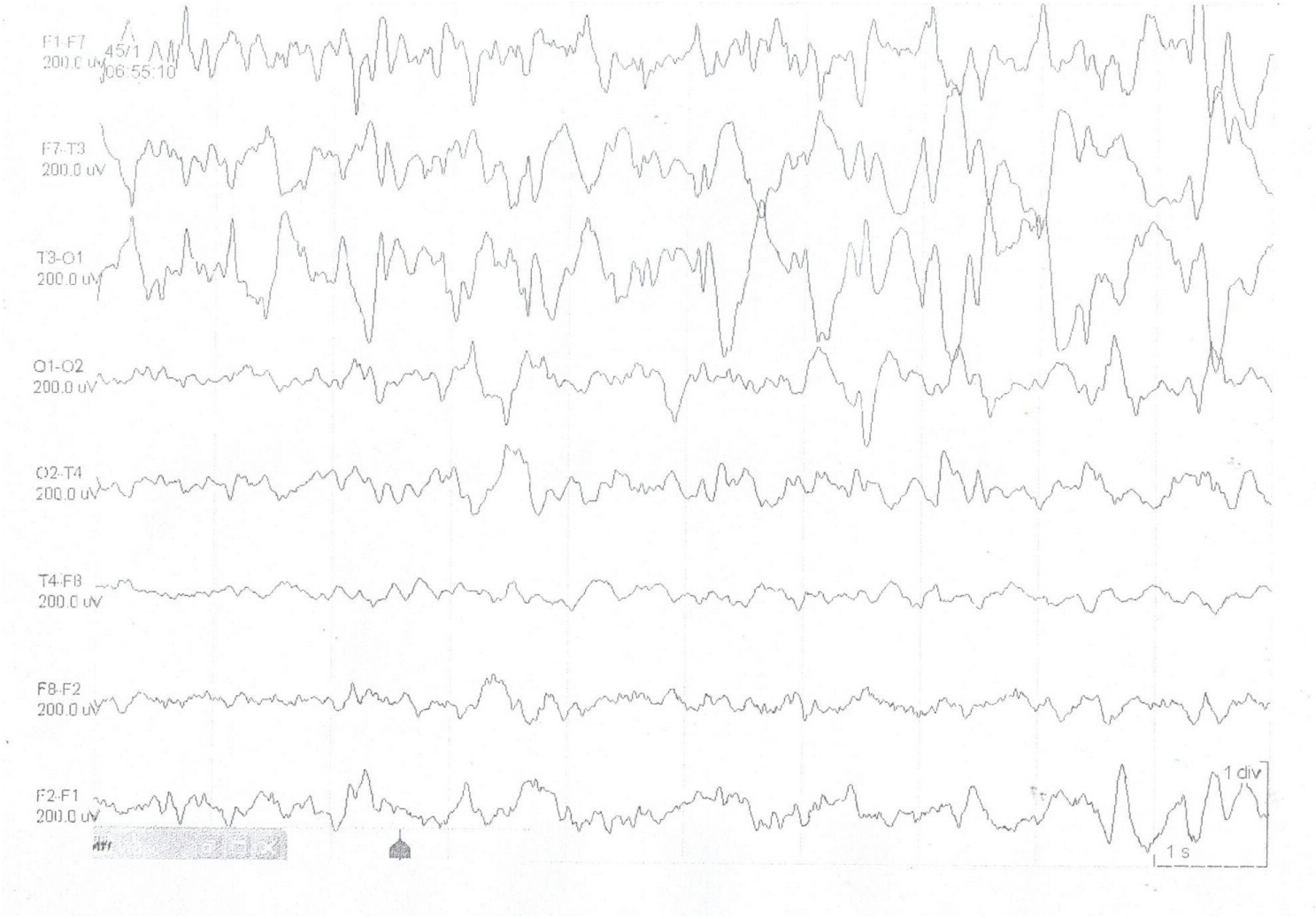

Figure 2. Same case as Figure 1. Ictal video-EEG. After more than one minute, the patient presented impairment of the consciousness and hypotonia and the EEG showed rhythmic dominant theta activity in the left hemisphere.