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Sleep EEG patterns in infants with congenital Zika virus syndrome

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HIGHLIGHTS

- First description of early EEGs from infants with microcephaly due to congenital Zika virus (ZikV) syndrome.
- Background abnormalities and epileptogenic activity were the most prominent findings.
- Frontal or occipital high voltage slow waves were another marker that may correlate to outcome.

ABSTRACT

Objectives: To describe sleep EEG patterns of neonates, and infants with microcephaly due to congenital Zika virus (ZikV) syndrome.
Methods: A descriptive case series of EEGs performed in a cohort of neonates with microcephaly monitored from October 2015 to February 2016 at a University Hospital in Northeast Brazil. Infants were investigated following an established protocol that includes EEG, neuroimaging studies, PCR and specific antibodies for ZikV detection.
Results: EEGs ($n = 37$) from 37 infants were reviewed. Age at investigation varied from 1 to 5 months (mean = 2.6). Diffuse low voltage ($n = 7$), background asymmetry ($n = 6$) and modified hypsarrhythmia with or without burst–suppression ($n = 11$), were the main background abnormalities identified. Interictal EEG abnormalities were identified in 23 recordings (62%) and localized as focal frontal ($n = 8$) or occipital ($n = 2$) spikes/sharp, multifocal spikes/sharp waves ($n = 13$). Electrographic seizures without clinical manifestation were identified in 4 recordings and characterized as focal pseudo rhythmic pattern. Further findings were focal high amplitude slow waves that were registered in the frontal ($n = 3$) or occipital ($n = 1$) regions.
Conclusions: Different types of EEG abnormalities were encountered with a predominance of interictal epileptogenic activity and hypsarrhythmia.
Significance: Sleep EEGs in congenital Zika virus syndrome are consistently abnormal even in infants who have not yet developed epilepsy.

1. Introduction

The recognition of a congenital Zika virus (ZikV) infection syndrome is very recent and few articles have been published with the aim of describing its clinical characteristics and diagnosis (Schuler-Faccini et al., 2016; de Fatima Vasco Aragao et al., 2016). Until the year 2015, it was unknown that this agent was the cause of an effective fetal disease. Zika virus is an RNA virus of the flaviviridae family and is transmitted primarily via vector (*Aedes aegypti* mosquito), therefore it presents clinical signs and epidemiology similar to other arboviruses such as dengue fever and chikungunya fever (Ioos et al., 2014). Formerly known in Africa and Asia to cause sporadic infections, it was an agent of at least two

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Table 1
Clinical information, sleep EEG and neuroimaging findings.

Case	Sex	GA (w)	ZV	HC (cm)	Time of infection	Neuroimage	EEG age[a]	EEG/description
1	F	37	+	29,5	No rash	Calcification of parietal lobes	3m	Bilateral sleep spindles. Background asymmetry (L<R)
2	M	39	+	29	No rash	Asymmetrical (+left) ventricular enlargement reduced cortical volume (temporal, parietal, and occipital). Parietal calcifications and basal ganglia	2m23d	Unilateral sleep spindles (right) Unilateral frontal spikes and sharp waves (left)
3	M	39	+	31	3rd month	Enlargement of the posterior lateral ventricles, frontal lobe calcifications	4m	Unilateral spiky sleep spindles (right)
4	M	36	NA	31	3rd month	Reduced cortical volume, enlarged ventricles, cortical calcifications.	2m (44 weeks)	Diffuse low voltage
5	F	37	+	31	5th month	Reduced cortical volume, enlarged ventricles, polymicrogyria, cortical and sub cortical calcifications.	2m7d	Diffuse low voltage
6	M	33	+	28	3rd month	Diffuse cortical calcifications	2m20d (44 weeks)	Bilateral frontal spikes, background with dysmature pattern
7	F	36	+	27	4th month	Pachygyria. Diffuse cortical and sub cortical (basal ganglia and thalamus) calcifications, reduced cortical volume, enlarged ventricles	3 m (48 weeks)	Diffuse low voltage
8	F	36	+	27	2nd–3rd month	Sub cortical and thalamic calcifications, reduced cortical volume, enlarged ventricles	3m (48 weeks)	Background asymmetry (L < R) Bilateral occipital sharp waves
9	F	38	+	29	No rash	Calcifications in the cortical–sub cortical junction. Discreet reduction of cortical volume	1m18d	EEG seizure, brief burst (5 s) left frontal rhythmic (3 Hz, 50 uV) activity
10	F	39	+	26	3rd month	Pachygyria	4days	EEG seizure (T3-O1) Low voltage
11	M	38	+	31	8th month	Sub cortical calcifications, reduced cortical volume, colpocephaly	3m	EEG seizure (O1) Rhythmic high amplitude (200 uV) slow waves (2 Hz) in the left occipital region spreading to the right hemisphere.
12	F	40	NA	32	2nd–3rd month	Reduced cortical volume, enlarged ventricles, pachygyria, cortical and sub cortical calcifications.	2m15d	EEG seizure (Fp1)
13	F	42	+	30	2nd–3rd month	Cortical and subcortical calcifications. enlarged ventricles, absence septum pellucidum, ectasy of lateral ventricles, proeminent cortical sulci (frontal-temporal region)	2m12d	Slow, high voltage bilateral occipital waves, asymmetric background (L < R)
14	M	40	+	33,5	4th month	Diffuse alteration of sulci and gyri (migration disorder), cortical and sub cortical calcifications	3m	Bilateral occipital high voltage, sharp and slow (2 Hz) waves
15	F	37	+	29	7 month	Subcortical calcifications (more frontal) reduced cortical volume	3m	Multifocal spikes and slow spike-waves, hypsarrhythmia
16	F	38	+	29,5	No rash	Cortical and subcortical calcifications. enlarged ventricles, reduced cortical volume.	1m16d	Bilateral frontal sharp waves Diffuse low voltage background
17	M	38	+	29,5	No rash	Subcortical calcifications, reduced cortical volume. Altered sulci and gyri.	2m	Bilateral frontal spikes Diffuse low voltage background
18	F	38	+	27	2nd month	Marked enlargement of ventricles. Thinning of cortical mantle, cerebellum cortex and brain stem. Assymetry of cular globe (left < right)	1m21d	Bilateral frontal high voltage spikes-slow waves. Asymmetric background
19	F	39	NA	30	No rash	Enlargement of lateral ventricles, agyria-pachygyria, cortical and subcortical fronto-parietal right schizencephaly	2m	Bilateral frontal high voltage slow waves
20*	M	39	+	33	No rash	Pachygyria (right temporal and parietal region), assymetry of hemispheres (right small), thinning of the corpus callosum, calcifications in the cortical–subcortical junction	1m	Bilateral frontal high voltage slow waves (1 Hz)
21	F	39	+	26	3rd month	Ventriculomegaly, periventricular calcifications	1m13d	Bilateral frontal spikes. Diffuse low voltage background
22	M	37	+	29,5	3rd month	Thinning of cortical layers and enlarged ventricles, cerebellar vermis hypoplasia. Agyria, pachygiria, Diffuse calcifications	2 m11 d	Bilateral frontal (50–70 uV) sharp waves
23	M	40	+	32	2nd–3rd month	Cortical and subcortical calcifications, enlarged ventricles, reduced cortical volume	1m	Frontal left high voltage spikes and independent slow waves (70–100 uV). Asymmetric background (L > R)
24	M	40	NA	31,5	No rash	Prominent lateral ventricles, cortical sub cortical calcifications (more posterior and left side)	5 m	Generalized bursts of polyspike waves and spike-waves, intermixed with focal slow waves at T3. Hypsarrhythmia
25	F	40	NA	29	3rd month	Sparse cortical and subcortical calcifications. enlarged ventricles, reduced cortical volume	2m9d	Generalized multifocal spikes and spikes waves (80 uV) with brief periods (1 s) of background attenuation. Hypsarrhythmia
26	M	41	–	31	No rash	Sparse subcortical calcifications, enlarged ventricles, reduced cortical volume.	3m	Slow background with multifocal spikes and generalized polyspikes-waves, followed by brief periods of background attenuation. Hypsarrhythmia
27	M	40	+	27	No rash	Pachygyria Cortical and subcortical calcifications. enlarged ventricles, reduced cortical volume	2m	Asymmetrical background with multifocal generalized spikes and spike-waves more prominent in the right hemisphere. Hypsarrhythmia
28	M	40	+	28,5	4th month	Lyssencephaly and subcortical calcifications	3m	Synchronic and asynchrony bursts of multifocal spikes and sharp waves followed by background attenuation (3 s). Hypsarrhythmia

(*continued on next page*)

Table 1 (*continued*)

Case	Sex	GA (w)	ZV	HC (cm)	Time of infection	Neuroimage	EEG age[a]	EEG/description
29	F	39	+	30	2nd month	Lyssencephaly and cortical–subcortical calcifications	4m	Multifocal spikes and spike-waves with brief (1 s) background attenuation. Hypsarrhythmia
30	F	38	+	31	3rd–4th month	Reduced cortical volume, agenesis of corpus callosum, small calcifications in the cortical–subcortical junction	1m	Multifocal spikes and spike-waves followed by background attenuation. Hypsarrhythmia
31	M	39	+	28,5	3rd–4th month	Reduced cortical volume, cortical–subcortical calcifications	5m	Generalized bursts of polyspike-waves followed by background attenuation, mulitfocal spike waves complexes. Hypsarrhythmia
32	F	38	+	31	2nd month	Reduced cortical volume, cortical–subcortical calcifications,	3m	Multifocal generalized bursts of polyspike-wave and spike-slow wave, followed by background attenuation. Hypsarrhythmia
33	M	39	+	28,5	No rash	Reduced cortical volume and enlarged ventricles, calcifications over internal capsule fibers.	4m	Frontal left sinusoidal activity and high voltage spikes
34	M	39	+	31	2nd month	Pachygyria Reduced cortical volume, enlargement of ventricles, cortical–subcortical calcifications (basal ganglia, periventricular)	4m	Multifocal spikes and sharp waves Unilateral right sleep spindles
35	F	38	+	28	NA	Cortical and subcortical (thalamic) calcifications, enlarged ventricles, reduced cortical volume.	3m	Multifocal spikes
36	F	39	+	29	2nd month	Lyssencephaly and cortical–subcortical calcifications (basal ganglia, mesencephalic peduncles, agenesys of corpus callosum, lateral ventricle enlargement, enlarged cisterna magna	2m10d	Right frontal spikes
37	F	39	+	28	No rash	Reduced cortical volume, ventricular enlargement, sparse cortical–subcortical calcifications	2m11d	Bursts of generalized polyspike and spike – waves followed by background attenuation and intermixed with sinusoidal theta rhythmic activity starting in right rolandic region and spreading to both hemispheres. Hypsarrhythmia

OBS: HC = head circumference, GA = gestational age, W = weeks, ZV = result of ZikV immunology, NA = not available. BS = burst-suppression. Time of infection = presumed time of infection based on the cutaneous rash reported during pregnancy.

[a] Age at EEG was expressed in months/days and plus in weeks (corrected age for preterm patients).

[*] Neuroimaging findings were based on computerized tomography scan, except for patient 20 who underwent magnetic resonance.

documented epidemics, one in Micronesia in 2007 and the other in French-Polynesia in 2013 (Duffy et al., 2009; Besnard et al., 2014).

In May 2015, Zika virus was confirmed to be circulating in Brazil (Campos et al., 2015; Cardoso et al., 2015; Bogoch et al., 2016), in two states of the Northeast region, an area considered endemic for arboviruses. In October 2015, the State Government of Pernambuco reported an unexpected increase in the number of cases of infants with microcephaly and with neuroimaging (CT scan) suggestive of congenital infection. Soon after, the virus genome was detected in a neonate in the state of Ceará, and in the amniotic fluid of two pregnant women with fetuses diagnosed with microcephaly and brain malformations. Anti-ZikV IgM antibodies were also detected in the last two cases (Brazilian Ministry of Health, 2015a,b). In 2016, a fetal autopsy identified the full genome of the virus in brain tissue (Mlakar et al., 2016). The Brazilian Ministry of Health, based on anatomical, pathological and epidemiological data have recognized the relationship between the increased occurrence of microcephaly and maternal infection by Zika virus, and have established protocols in order to monitor infected pregnant women and neonates with microcephaly (Brazilian Ministry of Health, 2015a,b). From that moment Zika virus was considered a global threat and an emergency situation was declared by the World Health Organization (PAHO/WHO, 2015).

The aim of this study was to describe sleep EEG patterns of neonates and infants with microcephaly due to congenital Zika virus (ZikV) syndrome.

2. Methodology

We described the sleep EEG patterns in a series of infants aged less than 6 months with microcephaly who diagnosed with congenital Zika virus infection. The infants were evaluated from October 2015 to February 2016 at the University Hospital Oswaldo Cruz in Recife – Northeast Brazil. This is a reference hospital for monitoring affected infants, and performing EEG studies.

Infants from the congenital ZikV syndrome cohort were investigated following an established protocol that included EEG, neuroimaging studies, blood tests to rule out other congenital infections, PCR and specific antibodies for ZikV detection. They were further submitted to a complete clinical and developmental evaluation, including ophthalmologic and audiology tests (de Fatima Vasco Aragao et al., 2016). Infants included in this study had extensive investigations to rule out other viral etiologies. They all had at least one sleep EEG before age 6 month.

EEGs were obtained through a NEUROTEC (Neuromap)® digital recorder, with a sensitivity of 7 uV/mm, low frequency 0.6 Hz filters and a high frequency of 70 Hz, and a speed of 1.5 cm/s. Electrodes were distanced with the 10–20 system modified for newborns, and the bipolar montage (Fp1-C3, C3-01, Fp1-T3, T3-01, Fp2- C4, C4-02, Fp2-T4, T4-02, Cz-Oz) was used (De Weerd et al., 1999). All patients were recorded during spontaneous sleep, and the duration of the exam was 20–30 min.

The recordings were part of the assistance protocol of the institution and followed the routine of the laboratory; video-EEG is not available in this facility. EEGs were first analyzed by a local neurophysiologist (MDCGC) and retrospectively reviewed by a specialist in neonatal EEG (MLN) blinded to the clinical aspects and neuroimaging findings.

The basal rhythm and abnormalities were described as suggested by Lombroso, according to gestational age and age when EEGs were performed (Lombroso, 1987).

Information regarding clinical data and neuroimaging studies were collected from the cohort database.

The study was approved by the Hospital Universitário Oswaldo Cruz ethics committee and is registered at Plataforma Brasil under the number 52803316.8.0000.5192. Parents signed an informed consent before neonates and infants were included in the main study.

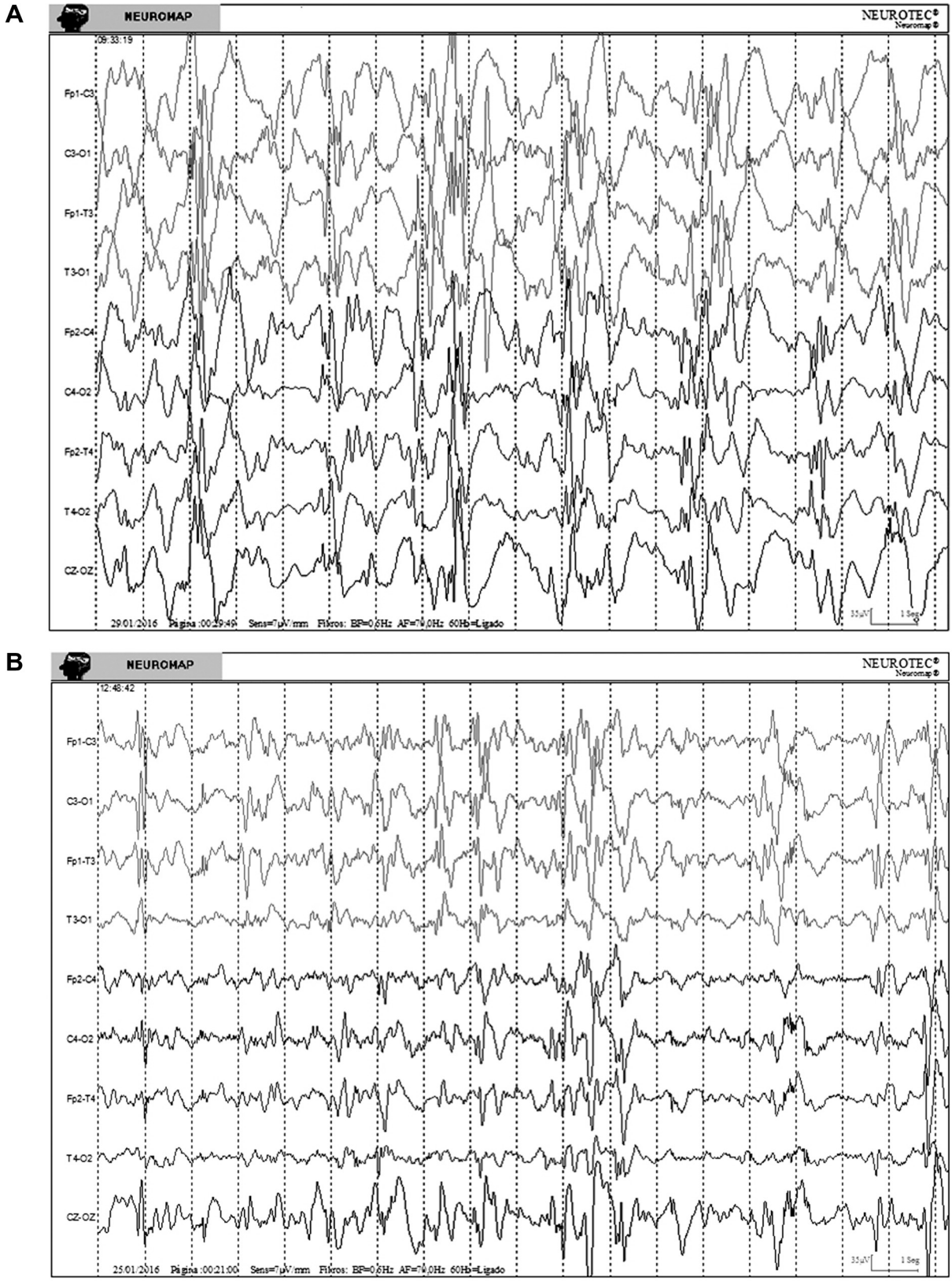


Fig. 1. (A–C) Modified hypsarrhythmic patterns recorded in patients 26, 29 and 32.

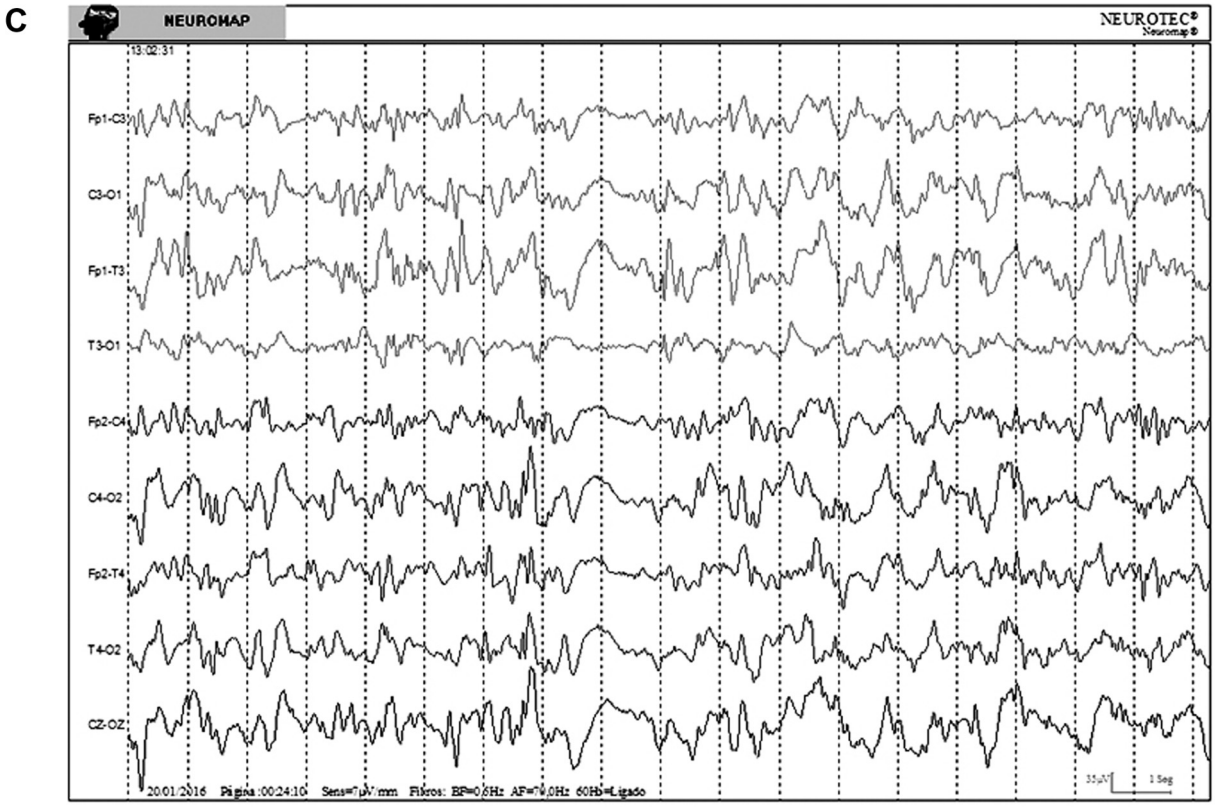


Fig. 1 (*continued*)

3. Results

The EEGs (n = 37) of 37 infants were reviewed. From the sample, 32 (86%) presented with positive results for Zika virus serology and the remaining were still under investigation. There were 20 male and 17 female infants. Head circumference at birth varied from 26 cm to 33.5 cm (mean 29.5 cm). Gestational age varied from 33 to 42 weeks (mean ± 38.5 weeks), and the majority of patients (89%) were born at term (between 37 weeks and 42 weeks). Irritability and irregular muscle spasms were the chief clinical complaints in 21% of the sample.

Table 1 presents a description of the sleep EEG findings together with the neuroimaging abnormalities and estimated time of infection during pregnancy.

From the 37 recordings, 7 were performed during the neonatal period, and 30 from the 2nd to the 5th month of life. Among the recordings obtained from the 2nd month of life onwards, it was only possible to identify sleep spindles in 4, 3 of which (Patients 2,3 and 34) presented with spindles in only one hemisphere during the entire recording.

Background activity was abnormal in the majority of recordings (59.5%). The main findings were diffuse low voltage (n = 7), asymmetrical voltage between hemispheres (n = 6) and hypsarrhythmia with or without burst–suppression (n = 11). Fig. 1.

Interictal EEG abnormalities, either focal or multifocal spikes, were identified in 22 recordings (62%). Focal frontal (n = 8) or occipital (n = 2) spikes/sharp, or multifocal spikes/sharp waves (n = 13). Electrographic seizures without clinical manifestation were identified in 4 recordings and characterized as focal pseudo rhythmic pattern. Fig. 2.

Another characteristic finding was focal high amplitude (>200 μV) slow waves (<1HZ) observed either in the frontal (n = 3) or occipital regions (n = 1) Fig. 3.

4. Discussion

In this article we present the first description of EEGs from a cohort of neonates and infants with microcephaly due to congenital Zika virus infection. All infants showed a variety of abnormal EEGs findings, such as background abnormalities, ictal and interictal epileptogenic activity as well as high amplitude focal slow waves mainly localized over frontal regions.

There is very little information available in the literature regarding EEG patterns in microcephaly. Fois and Rosenberg described the EEGs of 22 patients aged 1–17 years, with microcephaly due to different etiologies. They observed that the most striking finding was a reduction of voltage in the waking and sleeping states and disorganized, poor patterns of sleep activity (Fois and Rosenberg, 1957).

Another report of microcephaly due to lissencephaly, in a 6 week-old infant, revealed a moderately high-voltage slow background with paroxysms of predominately frontal spikes reaching 500 uV (Stockard-Pope et al., 1992).

Modified hypsarrhythmia patterns, as described by Hrachovy (Hrachovy et al., 1984) with or without burst-suppression were identified in 11 patients. These patterns have already been related to an unfavorable outcome (Nunes et al., 2005; Menache et al., 2002).

The bursts of high amplitude slow waves, either localized in the frontal or occipital regions, were morphologically different from the frontal sharp waves or other previously described normal developmental patterns of neonatal EEG (Lombroso, 1987). They have also a good morphological correlation with the previous descriptions of Fois and Rosenberg (1957) and Stockard-Pope et al. (1992).

Sleep is the main behavioral state during the neonatal period and is an important marker of neurological development in pre-

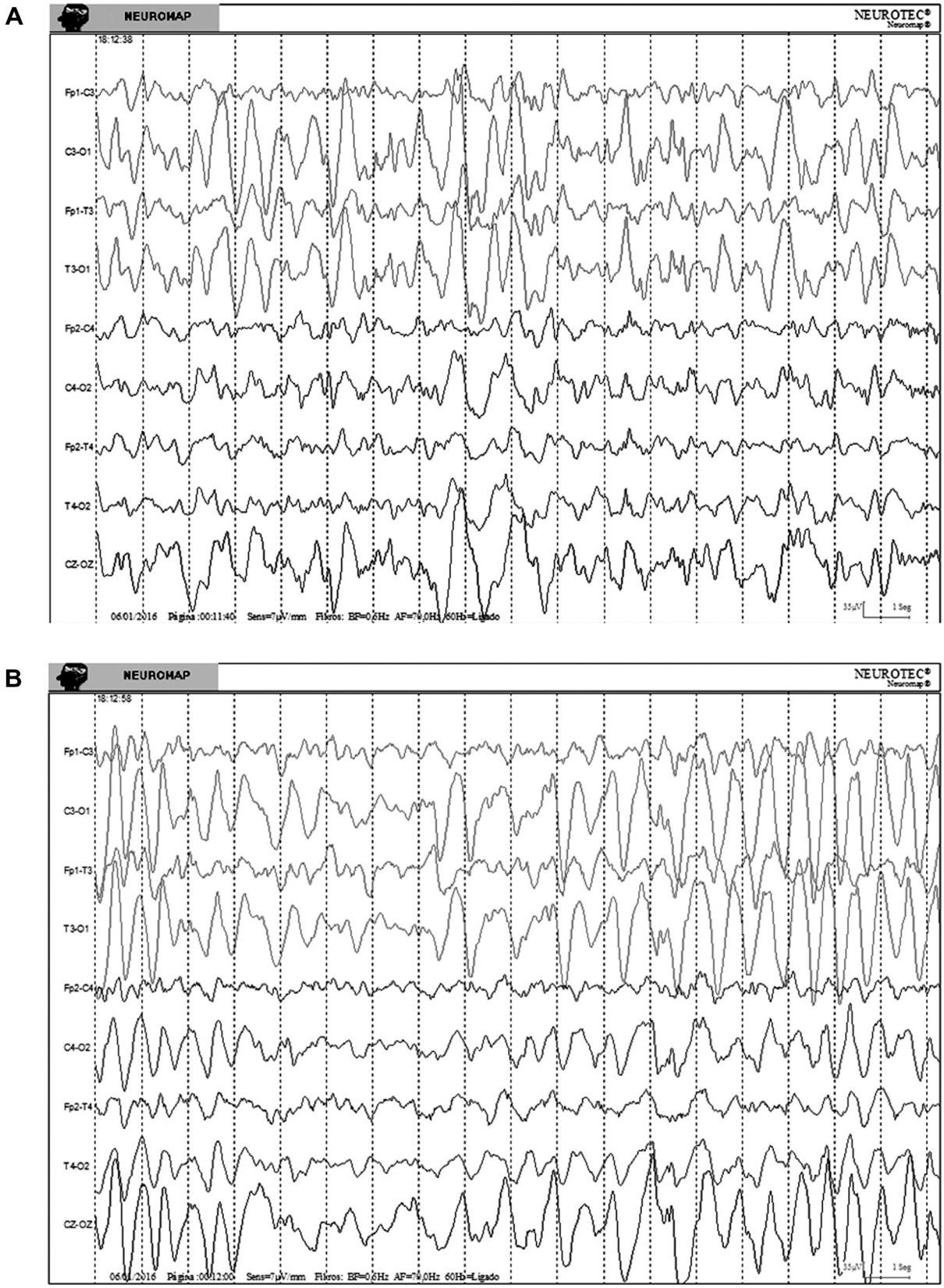


Fig. 2. (A–H) Evolution of an electrographic seizure without clinical manifestation. High voltage (200 uV) slow waves (2 Hz) were recorded in the left occipital region (A, B), as voltage increases the discharges turned more rhythmic (C, D) and latter spreading to the right hemisphere (E–G), by the end of the episode the activity is again restricted to left occipital region (H). (Patient 11).

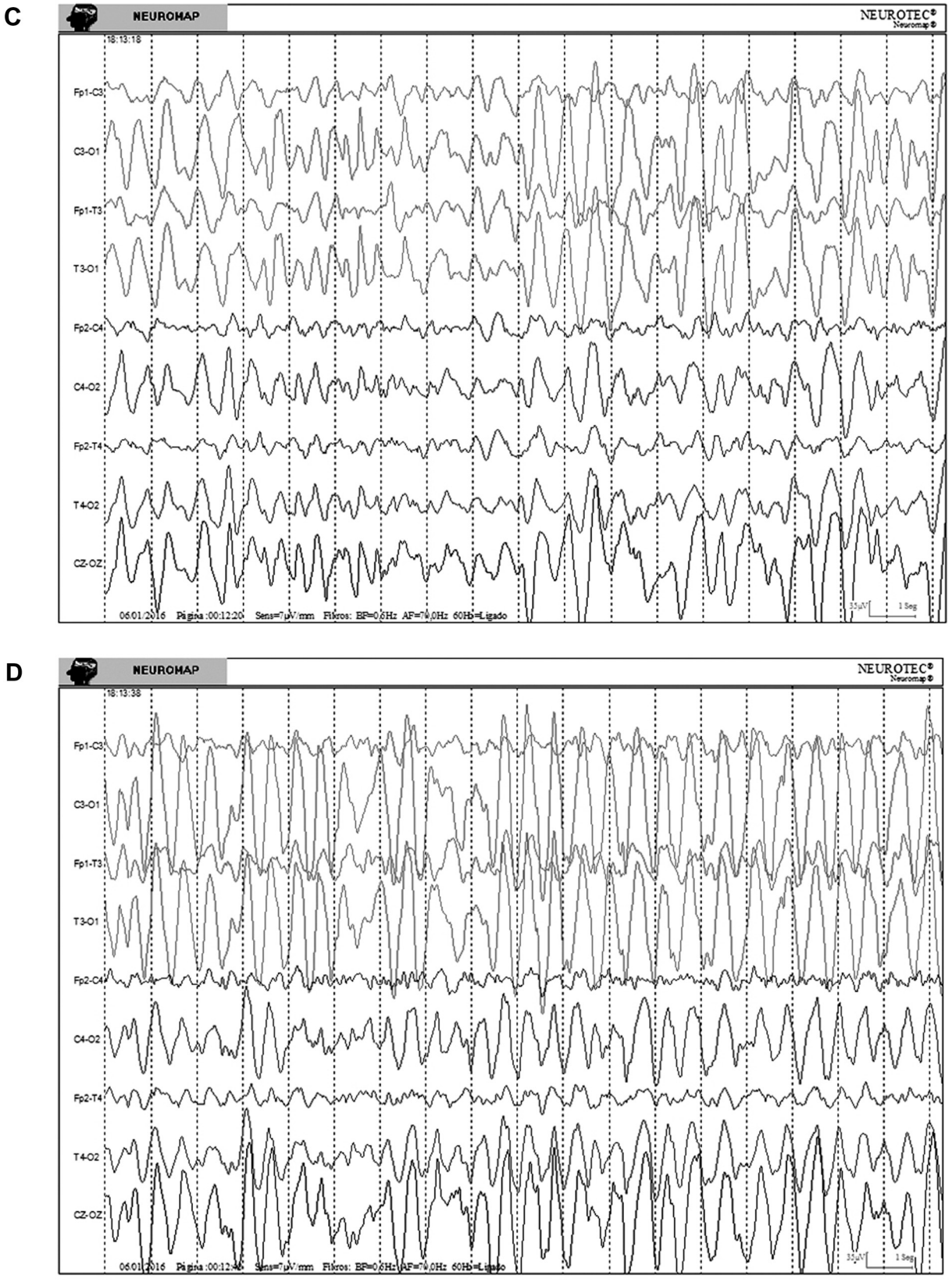
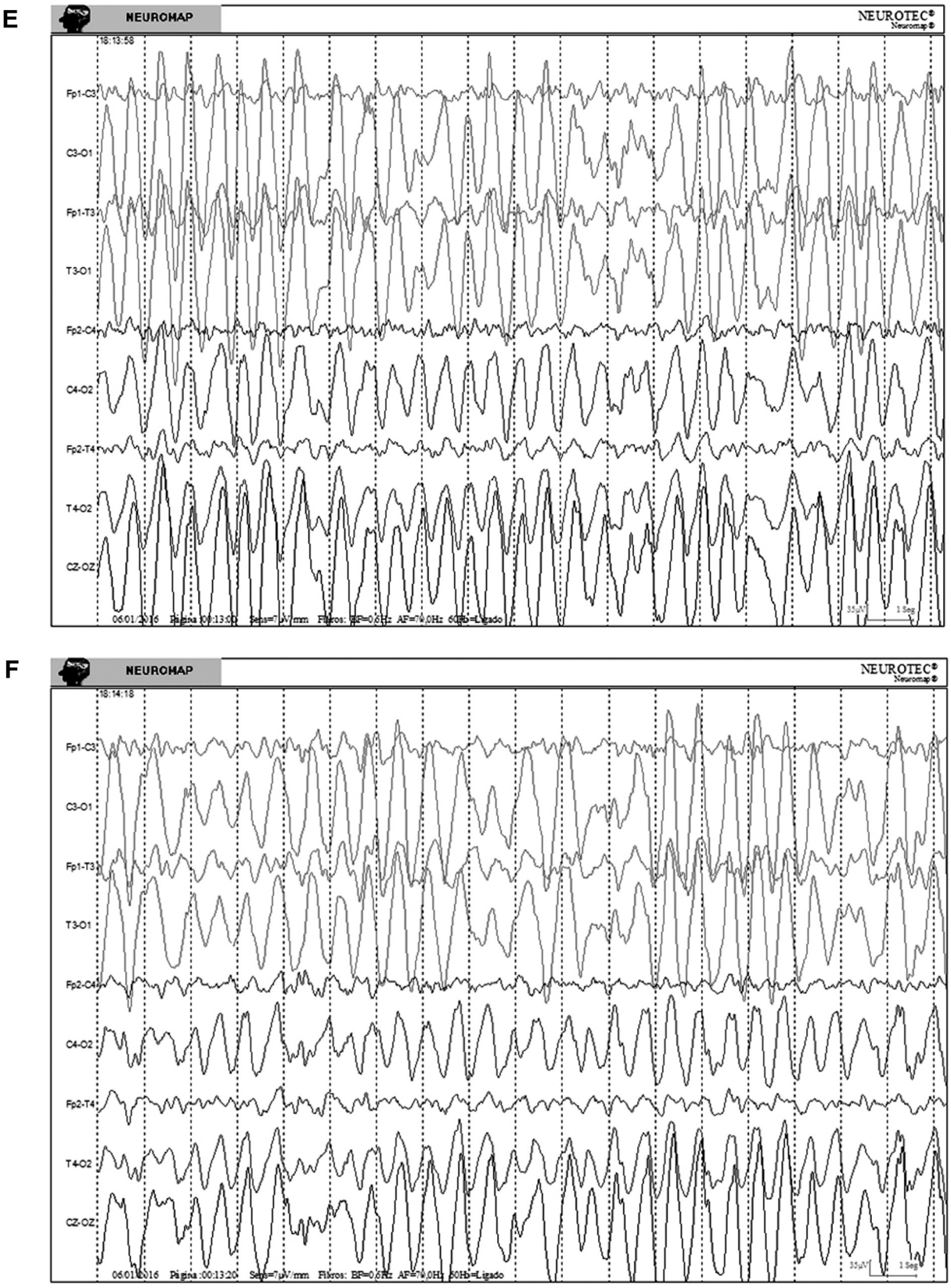


Fig. 2 (*continued*)

term and full-term neonates (Scher et al., 1992; Khan et al., 2008; Nunes et al., 1997; Nunes et al., 2014; Weisman et al., 2011). The importance of sleep stability during the neonatal period and its relationship to neurological outcome has been previously established. Excessive lability of sleep stages have often been correlated with environmental and neurological problems such as maternal



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drug abuse and developmental delay. Furthermore, endogenous or exogenous factors can alter specific behaviors during sleep (Lombroso and Matsumiya, 1985; Weisman et al., 2011). In this study, all infants were recorded under spontaneous sleep, although EEG technicians reported that most infants were extremely irritable, and that it was very difficult to obtain the registers.

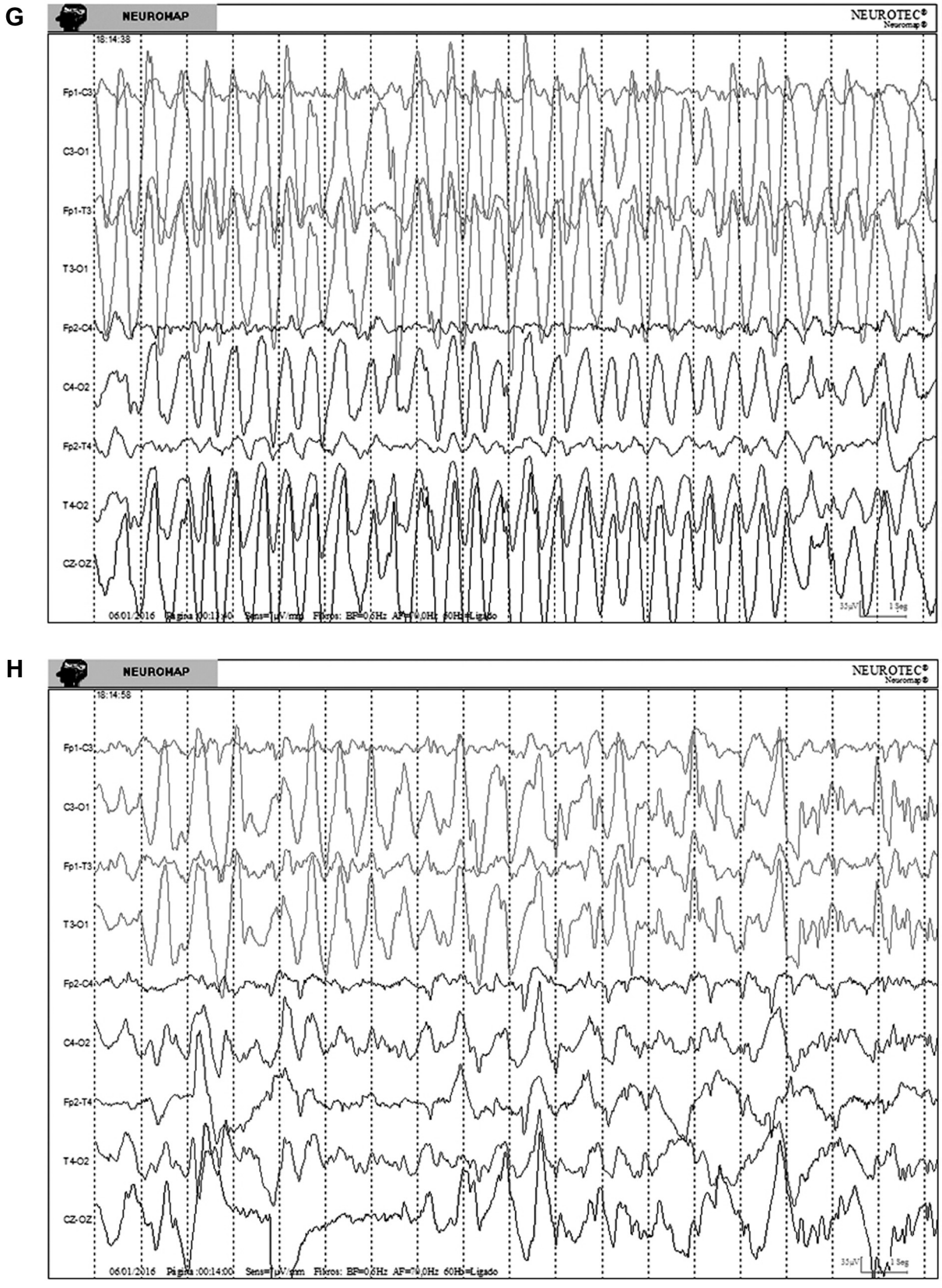

Fig. 2 (*continued*)

The Brazilian Medical Genetics Society created a task force to describe the phenotype of this new congenital infection (Schuler-Faccini et al., 2016). Algorithms to follow pregnant women with symptoms suggestive of ZikV and their neonates or stillborn are being followed in primary and secondary care units countrywide. Neuroimaging studies were included in all protocols as the findings

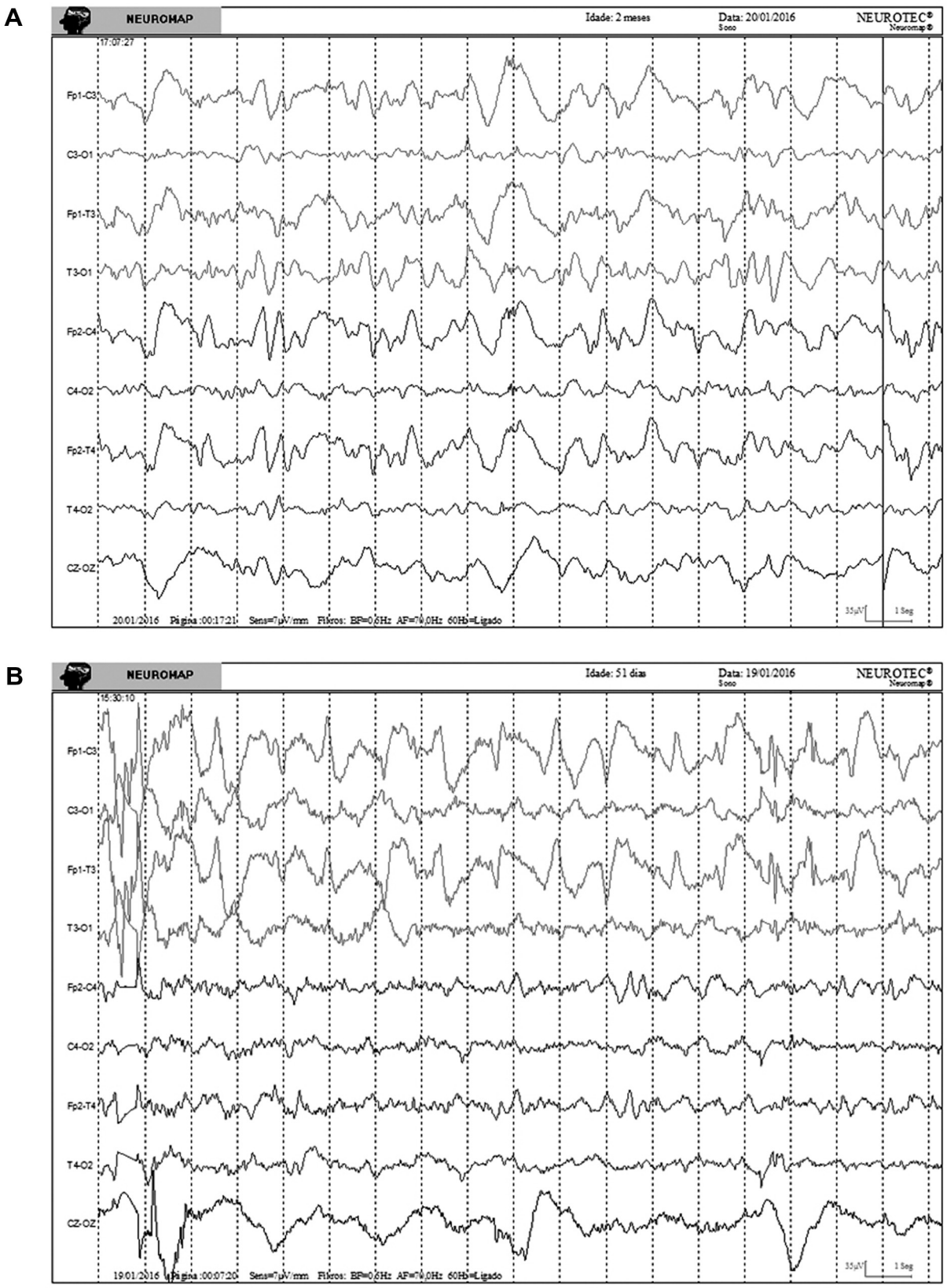

Fig. 3. (A and B) (A) Focal, bilateral frontal, slow (0.5 Hz) waves (Patient 19) and (B) Focal frontal slow waves and intermixed spikes (Patient 18).

are generally very typical and a good marker for confirming the diagnosis (de Fatima Vasco Aragao et al., 2016). The neonatal EEG has been established as a good predictor of neurological outcome because of its sensitivity to detect early central nervous system dysfunction, besides being a non-invasive method that can be used at the bedside (Holmes and Lombroso, 1993; Monod

et al., 1972; Scher and Beggarly, 1988; Mizrahi, 2001). Based on our results, we might suggest that a sleep EEG should be included in the investigation protocol of Zika virus congenital syndrome.

In conclusion, the results of this study indicated that infants with congenital Zika virus infection could show different abnormalities in their sleep EEGs. Future studies with survival analysis and long-term follow-up, could describe the association between these EEG findings and neurological outcomes in infants with congenital Zika virus infection.

Disclosures

Authors have no disclosures or conflict of interest to declare.

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