EEG Patterns in Patients with Prader-Willi Syndrome

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Abstract

Prader-Willi syndrome (PWS) is a rare disease determined by the loss of the paternal copy of the 15q11-q13 region, characterized by hypotonia, hyperphagia and obesity, short stature, hypogonadism, craniofacial dysmorphisms, cognitive and behavioral disturbances. The aims of this retrospective study were to analyze interictal EEG findings in a group of PWS patients and to correlate them with genetic, clinical and neuroimaging data. Demographic, clinical, genetic, EEG, and neuroimaging data about seventy-four patients were collected. Associations between the presence of EEG paroxysmal abnormalities, genotype, clinical and neuroimaging features were investigated. Four patients (5.4%) presented a drug-sensitive epilepsy. Interictal EEG paroxysmal abnormalities, focal or multifocal, were present in 25.7% of the cases, and normalization of EEG occurred in about 25% of the cases. In 63.2% of the cases paroxysmal abnormalities were localized over the middle-posterior regions bilaterally. Brain magnetic resonance imaging (MRI) was performed in 39 patients (abnormal in 59%). No relevant associations were found between EEG paroxysmal abnormalities and all the other variables considered. Interictal EEG paroxysmal abnormalities, in particular with a bilateral middle-posterior localization, could represent an important neurological feature of PWS not associated with genotype, cognitive or behavior endophenotypes, MRI anomalies, or prognosis.

Introduction

Prader-Willi syndrome (PWS) is a rare genetic condition, with an estimated prevalence of about 1:15,000, characterized by multisystemic features, such as severe early hypotonia, hyperphagia and childhood obesity, short stature, small hands and feet, hypogonadism, growth hormone or other endocrine deficiencies, craniofacial dysmorphisms, developmental delay, intellectual disability (ID), behavioral disturbances, and autism spectrum disorder [1].

PWS is a genomic imprinting disorder, due to the loss of a paternal copy of the 15q11-q13 region. More frequently (approximately 60% of cases) this is the result of a de novo paternal deletion of the 15q11-q13 region leading to a lack of expression of paternally derived genes; in about 35% of cases, maternal uniparental disomy (UPD), with both chromosomes 15 inherited from the mother, is present; imprinting center (IC) defects (micro-deletions, mutations) in the 15q11-q13 region or other chromosome abnormalities are found in the remaining 5% of PWS patients [2].

Until now a peculiar interictal electroencephalographic pattern has not been identified in PWS, as in other chromosome abnormalities, and heterogeneous EEG pictures have been reported, such as focal, multifocal or generalized epileptiform abnormalities [3–9].

Although epilepsy does not represent a typical neurological feature, recently a prevalence ranging from 4–26% has been estimated in several retrospective series worldwide. Seizures usually start before two years of age, and epilepsy is mostly of focal type, but also generalized epilepsy can occur, with generalized tonic-clonic seizures and more rarely atypical absences and atonic seizures [3–8, 10–12].

Febrile seizures account for 6.4–39.2% of children with PWS [7, 8, 12]. A definite association between the prevalence of epilepsy or the seizure type and the genotype in PWS has not been demonstrated; in fact, some studies reported a significantly higher frequency of seizures in the deletion subgroup than in the UPD subgroup [3, 5, 10], but others did not confirm that finding [6, 7].

The main aim of this retrospective multicenter study was to analyze the interictal EEG findings in a group of PWS patients. We investigate any association between EEG findings and some relevant clinical and neuroimaging data, such as genotype, cognitive level, behavioral disturbances, and brain MRI abnormalities.

Results

Patients features -

We studied 74 subjects with PWS, 39 males (52.7%) and 35 females (47.3%). Thirty-two patients (43.2%) had a 15q11-q13 paternal deletion, 38 (51.4%) a maternal UPD, 4 (5.4%) an imprinting center defect (ICD). ID was diagnosed in 67 subjects (90.5%), with a mild degree in 47 cases (63.5%), moderate in 15 (20.3%), severe in 5 (6.7%). Three patients (4.1%) had a borderline intellectual functioning (BIF) and 4 (5.4%) a normal cognitive level. Behavioral disturbances were present in 17 patients (9.5%). Four patients (5.4%) presented epilepsy with various types of seizures: absences (2), focal seizures with impaired awareness (1), generalized tonic-clonic seizures (1). One patient had febrile convulsions. Seizure onset ranged from 1 year and 3 months to 7 years, and in all cases seizures were controlled by antiepileptic drugs in monotherapy or polytherapy. The following drugs were given to treat seizures and/or behavioral disturbances: topiramate in 5 cases, valproate in 3, levetiracetam in 2 and oxcarbazepine in 1. Demographic and clinical findings are reported in Table 1.

Table 1
Demographic and clinical features of the patients with Prader-Willi syndrome (N = 74). Categorical variables are reported as frequency; quantitative variables are reported as mean ± SD (range). UPD = uniparental disomy; ICD = imprinting defect; BIF = borderline intellectual functioning; GTCS = generalized tonic-clonic seizures.

Variables	Results
Gender (males / female)	37 / 35 (52.7% / 47.3%)
Follow-up duration (years)	2.9 ± 3.9 (0.1–19.0)
Genotype	32 (43.2%)
15q11-q13 paternal deletion	38 (51.4%)
Maternal UPD	4 (5.4%)
ICD	
Intellectual disability	67 (90.5%)
Mild	47 (63.5%)
Moderate	15 (20.3%)
Severe	5 (6.7%)
BIF	3 (4.1%)
Behavioral disturbances	17 (9.5%)
Seizures	4 (5.4%)
Absences	2
Focal seizures, impaired awareness	1
GTCS	1
Drug therapy	59 (79.7%)

Fifty-nine subjects (79.7%) took drugs during the follow-up period, i.e. growth hormone or other hormones (49 cases), hypoglicemic medications (6), antiepileptic drugs (11), psychopharmacologic treatment (11).

EEG findings -

One hundred ninety-eight EEGs were recorded (range 1–10, mean 2.9 ± 1.9), 92 during wakefulness and 106 during sleep (Table 2). Age range at the first EEG was 0.08–33 years, mean age 7.7 ± 7.8 years; age range at the last EEG was 0.1–33 years, mean age 10.6 ± 7.8 years. Duration range of the follow-up was 0.1–19 years, mean duration 2.9 ± 3.9 years. BMI range at the first EEG was 9.3–67.4 kg/m^2, mean 24.2 ± 12.1 kg/m^2; BMI range at the last EEG was 13.5–67.4 kg/m^2, mean 25.6 ± 11.1 kg/m^2.

Table 2
EEG findings. Categorical variables are reported as frequency; quantitative variables are reported as mean ± SD (range).

Variables	Results
Number of recorded EEGs	198 (1–10)
Mean number of recorded EEGs ± SD	2.9 ± 1.9
Age at the first EEG (years)	7.7 ± 7.8 (0.1–33)
Age at the last EEG (years)	10.6 ± 8.3 (0.1–33)
EEG type	92 (46.5%)
Wakefulness	106 (53.5%)
Wakefulness and sleep	
Background activity at the last EEG	0 (0 %)
Slow	74 (100%)
Normal	
Abnormalities	19 (25.7%)
Middle-anterior spikes	5 (26.3%)
Middle-posterior spikes	12 (63.2%)
Focal slow waves	2 (10.5%)

In all cases background activity was normal for the age. EEG abnormalities were found in 19 patients (25.7%, age range 0.1–29.3 years, mean 8.4 ± 8.8), and they were classified as multifocal, middle-anterior (5 subjects) (Fig. 1), when localized over the frontal-central, frontal-temporal or central-temporal regions; multifocal, middle-posterior (12 subjects) (Fig. 2), when recorded over the temporal-parietal, temporal-occipital, or parietal-occipital regions.

In two cases focal slow waves were present. In five out 19 patients (26%) the EEG picture became normal at the end of the follow-up at 9.01 (range 4.7–16.3) years of age, 3.6 (range 1-11.3) years after the first abnormal EEG pattern. Age in the fourteen patients with persistent abnormal EEG pattern was 0.1–29.3 years, 9.8 ± 9.4 years at first recording and age range 0.1–36.6 years, 11.1 ± 10.6 years at the last one.

Brain MRI findings -

Brain MRI was performed in 39 subjects (Table 3). In 23 of them (59%) brain abnormalities were present: myelination anomalies (4), corpus callosum hypoplasia (3), pituitary hypoplasia (9), subaracnoid space enlargement (7), enlargement of the lateral ventricles (9), arachnoid cyst (5), cerebral atrophy (5) or cerebellar hypoplasia (2). Only two patients with seizures carried out a brain MRI, one with absences

presented myelination anomalies and subarachnoid space enlargement, the other with absences showed pituitary hypoplasia too.

Table 3
Brain Magnetic Resonance Imaging (MRI) findings in the patients with Prader-Willi syndrome (N = 39). *some patients presented more than one MRI abnormality

Findings	Number (rate)
Abnormal brain MRI	23 (59%)*
Myelination anomalies	4 (17.4%)
Corpus callosum hypoplasia	3 (13%)
Pituitary hypoplasia	9 (39.1%)
Subaracnoid space enlargement	7 (30.4%)
Enlargement of the lateral ventricles	9 (39.1%)
Arachnoid cyst	5 (21.7%)
Cerebral atrophy	5 (21.7%)
Cerebellar hypoplasia	2 (8.7%)

No differences were found between patients with and without EEG paroxysmal abnormalities as concerns age (p = .86), behavioral disturbances (p = .93), genotype (p = .66), and brain MRI abnormalities (p = .77).

Discussion

Chromosome abnormalities are often associated with epilepsy. In particular, Singh et al. [13] reported 400 different chromosome aberrations associated with epileptic seizures and/or EEG abnormalities. However, only a few chromosome anomalies have a characteristic electroclinical pattern, such as 1 p36, 4p16, 6q terminal, or 15q13.3 deletions, trisomy 12p, Angelman syndrome (AS), inv dup 15, ring 20, Down syndrome, Xp11.22-11.23 duplication, XYY [9].

An EEG study was carried out in 26 out of 50 patients with PWS and 10 of them (38.5%) showed abnormalities. In particular, five subjects (with or without seizures) presented high voltage 4–6 Hz EEG activities, four (with generalized tonic-clonic seizures) showed focal paroxysmal discharges, and one (with atypical absences) short generalized discharges of polyspike and wave complexes [3]. In other 4 patients with PWS and epilepsy focal or multifocal paroxysmal abnormalities were described [4].

In a following series of 10 patients with PWS and epilepsy, nine (90%) revealed EEG abnormalities, but only in two cases these were specified as focal left parietal discharges and nonspecific spikes [5].

Other three subsequent retrospective studies revealed EEG focal, multifocal or generalized paroxysmal abnormalities, respectively in 13 of 23 (56.5%), 13 of 22 (59%), and 38 of 38 (100%) patients with PWS

and epilepsy [6–8]. Furthermore, focal epileptiform abnormalities were found in 12 out of 94 subjects (12.8%) collected from an observational cohort study, and a subclinical electrographic seizure pattern was found in 5 of 12 of these cases [12].

EEG multifocal or focal abnormalities were found in 19 (25.7%) of our 74 patients, epilepsy in 4 (5.4%). This prevalence rates are almost at the lower end of the prevalence ranges reported in previous literature, 12.8–100% for EEG abnormalities, 4–26% for epilepsy; however, this apparent discrepancy in the prevalence rate could be due to the different settings, as all our patients were recruited in Centers specialized in pediatric and endocrinological management of PWS [3–8, 10–12]. Approximately in one quarter of our PWS patients the EEG picture normalized, a finding that could be not compared with literature, since at the best of our knowledge no EEG follow-up studies were conducted in PWS until now. We did not find statistically significant associations between the presence of interictal EEG paroxysmal abnormalities, and some other clinical, genetic and neuroimaging features of the PWS phenotype. Then, interictal EEG abnormalities – and in particular their middle-posterior localization – could represent an important and supportive neurological feature of PWS, but they do not contribute in providing information about genotype, cognitive or behavior endophenotypes, possible MRI structural anomalies, or prognosis.

Both epilepsy and interictal EEG abnormalities are more frequently found in PWS patients than in general population (3.54%) [14], but they are much less frequent than in AS (85%) which affects the same chromosomal 15q11-q13 region [15]. There is not yet a convincing evidence for this discordance, but it can be hypothesized that in PWS, although the missing paternal 15q11-q13 region includes the genes for the GABA receptor subunit cluster (GABRB3, GABRA5, and GABRG3) receptor, the maternalUBE3A is active, and this could explain the lower rate of epilepsy in PWS [12]. Another alternative genetic mechanism for pathogenesis of EEG abnormalities or epilepsy could be represented by the involvement of other contiguous genes in the region 15q11-q13.

Although our study seems to confirm that a peculiar interictal EEG pattern does not exist in PWS, and paroxysmal abnormalities are mostly focal or multifocal, approximately in two thirds of our patients spikes were localized over the middle-posterior regions. Then, this localization could represent a rather common EEG trait to be considered as a potential marker of PWS.

Brain MRI abnormalities were relatively frequent (59%) and heterogeneous in our cohort of patients with PWS. More frequently we found enlargement of the lateral ventricles (39.1%) and pituitary hypoplasia (39.1%). Dilation of lateral ventricles, a non-specific finding, has been previously observed in patients with PWS, up to approximately 45% of cases, and it can represent the consequence of loss or reduced growth of white or gray matter or both [6, 8, 11, 12]. Pituitary hypoplasia or morphological alterations, but even pituitary autoimmunity, are a very common MRI finding in patients with PWS, in whom hyperphagia, hypogonadism and deficit of growth hormone suggest a possible central hypothalamic/pituitary dysfunction [16–18]. However, no relationship has been reported between pituitary hypoplasia and interictal EEG abnormalities or epilepsy in PWS.

Our study has an important strength. The recruitment of rather large series of patients with PWS, all managed for a long period of time in highly specialized centers allowed us to establish with a certain accuracy the prevalence of interictal EEG abnormalities, considering the great number of EEG recordings carried out. On the other hand, some methodological limitations should be taken into account. In fact, this study was retrospective, all patients were managed in paediatric and endocrinological settings. In addition, brain MRI was available approximately 52% of the sample studied.

In conclusion, we show that about 25% of PWS patients present EEG abnormalities, irrespective of the genetic defect, gender and intellectual disabilities, and about 5% epilepsy. EEG normalized in about 25% of patients with EEG abnormalities. Our study shows that paroxysmal abnormalities are mostly focal or multifocal and localized in two-thirds of the patients over the middle-posterior regions. This localization might be considered a rather common EEG trait and a potential marker of PWS in about 25% of patients during the follow-up. A peculiar interictal EEG pattern does not exist in PWS. Further large prospective studies are needed to clarify pathogenesis of electroclinical findings in PWS, also addressing more strict correlations with molecular genetics and high-definition neuroimaging.

Methods

We retrospectively recruited subjects with PWS referred to 4 Italian Referral Centers, i.e., Oasi Research Center, Troina; Paediatric Unit, Casa Sollievo della Sofferenza, San Giovanni Rotondo; Paediatric Unit, University of Modena e Reggio, Modena; Department of Human Pathology of the Adult and of the Developmental Age "Gaetano Barresi", University of Messina, Messina. This study was approved by all the local Ethics Committees of the Centers where the study was run. Written informed consent was obtained from the patients' parents or patients as appropriate. All investigations were conducted according to the principles expressed in the Declaration of Helsinki.

The clinical diagnosis of PWS syndrome was made according to the consensus clinical diagnostic criteria [19] and was confirmed by genetics testing, by means of methylation analysis and FISH, or by means of analysis of the parental inheritance pattern of chromosome 15, when indicated, following the recommendations of the American Society of Human Genetics/American College of Medical Genetics [20].

For all subjects we evaluated gender, age (range and mean) at the first and last EEG, duration (range and mean) of the EEG follow-up, BMI (range and mean) at the first and last EEG, genotype, degree of intellectual disability, behavioral disturbances, presence of seizures, age (range and mean) at seizure onset, seizure type, EEG and MRI findings, drug therapy.

Intellectual disability and borderline intellectual functioning were classified according to the DSM 5 criteria [21].

Seizures were classified according to International League Against Epilepsy [22]. Interictal wakefulness or sleep EEG was recorded in all the subjects according to the International 10–20 system and all recordings

were visually interpreted by an expert neurologist (ME).

We investigated the possible correlations between the presence of EEG paroxysmal abnormalities and other clinical and neuroimaging features, such as degree of cognitive dysfunction (subjects with BIF or mild ID versus subjects with moderate or severe ID), behavioral disturbances (presence versus absence), genotype (deletion 15a11-q13 versus UPD), and brain MRI abnormalities (presence versus absence).

Statistical analysis was performed using SPSS, version 20.0,for Mac OS (IBM Corp., Armonk, NY). Age did not follow a normal distribution (Kolgomorov-Smirnov test) and thus non-parametrical Mann-Whitney U test was used for comparison between groups. The Yates-corrected chi-square test was used to assess any differences between categorical variables. Data are presented as range and mean ± SD or rate. P-value < 0.05 was considered statistically significant.

Declarations

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Author Contributions:

Conceptualization, M.D. and S.D.L.; methodology, M.E. and S.D.L.; software, L.V.; validation, M.D.; formal analysis, L.V. and M.D.; investigation, I.R., M.S., S.F.M., M.W., A.L.P., G.T., P.D.B. and L.I.; resources, P.D.B.; data curation, I.R. and L.V.; writing—original draft preparation, M.E. and M.D.; writing—review and editing, L.I., S.D.L. and M.D.; supervision, M.D. and S.D.L.; project administration, S.D.L. and M.D. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement:

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of the “Comitato Etico Indipendente interaziendale” of Bari (date of approval 15/July/2017, protocol number 5245, protocol code SDL2017). After this approval, all the other local Ethic Committees approved the study in keeping with the Italian regulation.

Informed Consent Statement:

Informed consent was obtained from all subjects and/or their parents or legal guardians involved in the study.

Conflicts of Interest:

The authors declare no conflict of interest.

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Figures

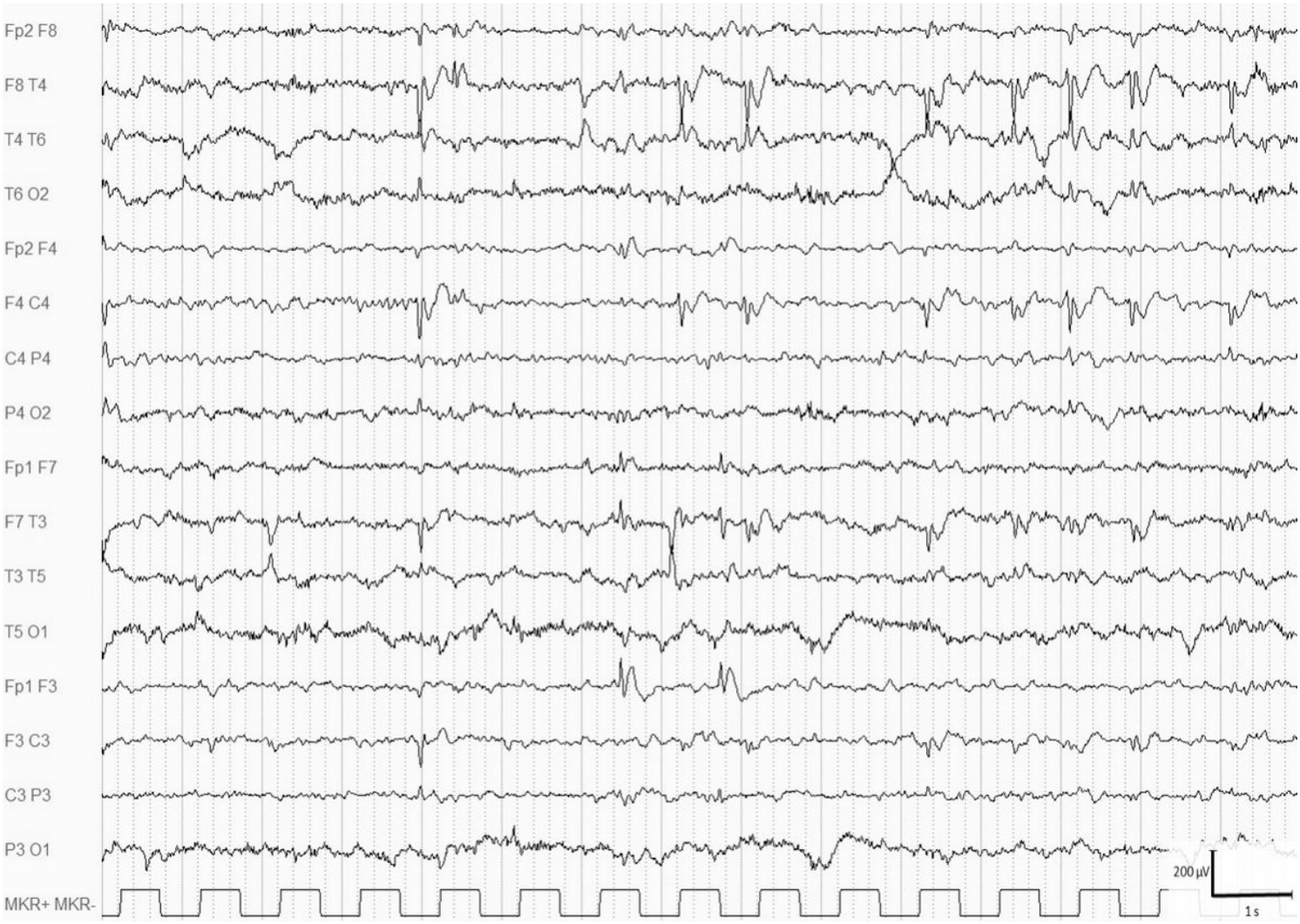

Figure 1

Wakefulness EEG of a 4-year-old boy showing numerous multifocal spikes, more prominent over the right central-temporal, and the left frontal-temporal regions.

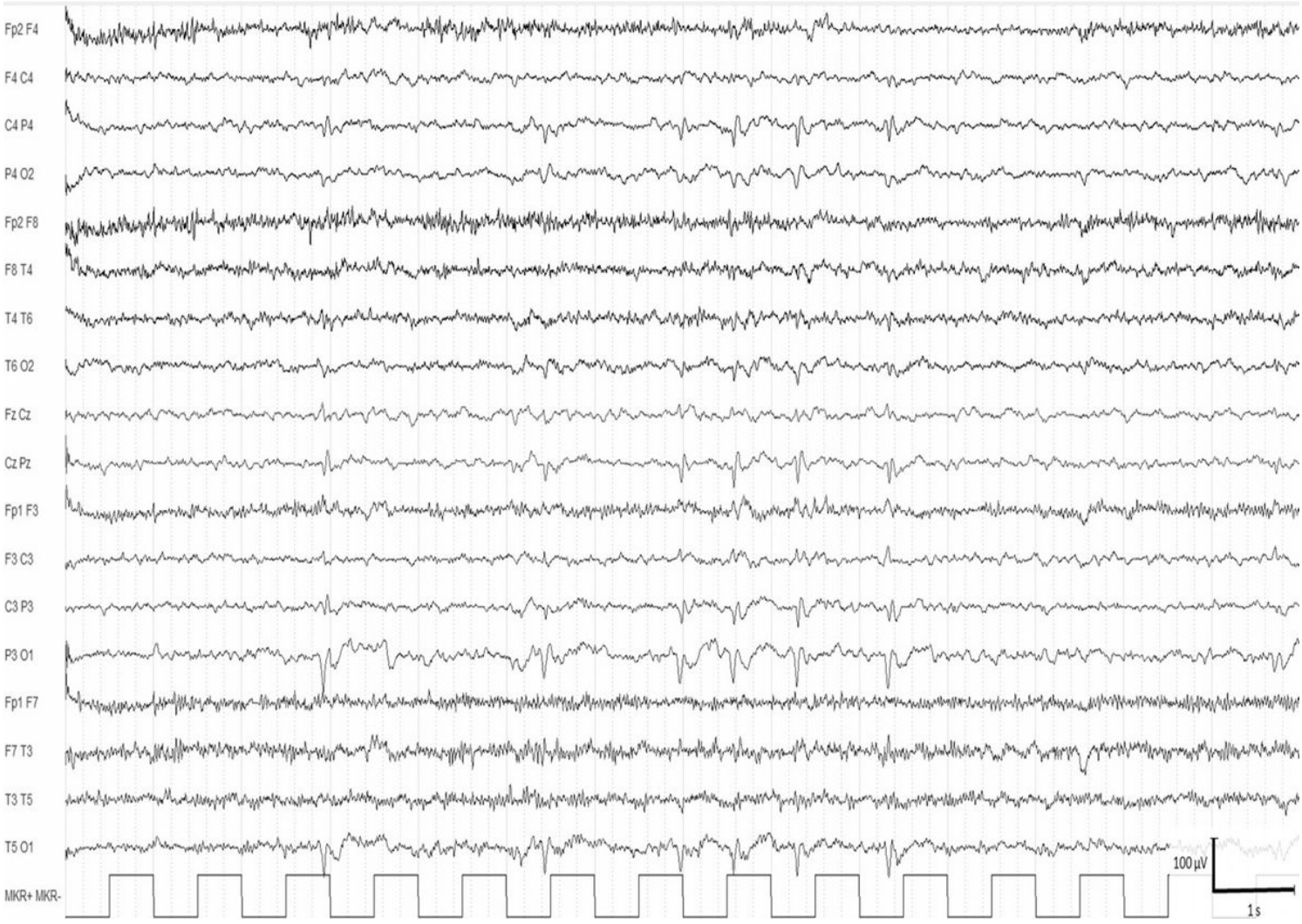

Figure 2

Wakefulness EEG of a 5 year-old boy with spikes synchronous over the parietal-temporal-occipital regions, prevalent in the left hemisphere.