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Original Article

Pseudo-Petit Mal Discharge: A Marker of Favorable Prognosis in Febrile Seizure

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Abstract

Objective To investigate whether pseudo-petit mal discharge is a useful marker of epilepsy on electroencephalogram in patients with recurrent febrile seizures.
Methods: The retrospective study included 255 out of 1255 children aged 6-66 months that were followed up in our hospital due to febrile seizures over the period 2010-2020. All the patients underwent an electroencephalogram examination and electroencephalogram abnormalities were classified into 3 groups: group I (normal), no epileptiform or background abnormalities; group II (abnormal), focal or generalized discharge or electroencephalogram slowing; group III (pseudo-petit mal discharge). Patients with pseudo-petit mal discharge were followed up for epilepsy development for a period of 7 years after the age of 72 months.
Results: The prevalence of pseudo-petit mal discharge on electroencephalogram was significantly higher in patients with complex febrile seizures compared to recurrent febrile seizures (P = .005). Ten (6.1%) recurrent febrile seizure patients with normal electroencephalogram findings were followed up for epilepsy. Pseudo-petit mal discharge was found to persist in 7 (12%) out of 58 recurrent febrile seizure patients with pseudo-petit mal discharge for a period of 7 years, after which no seizure activity was detected on electroencephalogram and thus no follow-up was performed for epilepsy. Pseudo-petit mal discharge that patients with recurrent febrile seizure seizures had 2.3 (1.107-1.988) risk of having >4 seizure times and 1.9 (1.335-2.569) times more risk of being male. Compared to complex febrile seizures, those with more recurrent febrile seizure seizures had longer pseudo-petit mal discharge periods and greater frequency.
Conclusions: The presence of pseudo-petit mal discharge on electroencephalogram could be an indication of especially recurrent febrile seizure in children with febrile seizures and pseudo-petit mal discharge could be a marker of favorable prognosis in long-term follow-up of febrile seizures patients in terms of epilepsy development since epilepsy was diagnosed in patients without pseudo-petit mal discharge and was not detected in patients with pseudo-petit mal discharge. Although pseudo-petit mal discharge is an important predisposing factor for the recurrence of febrile seizures, it has been shown that it is not a risk factor for epilepsy development.
Keywords: Electroencephalogram, febrile seizures, prognosis, pseudo-petit mal discharge

INTRODUCTION

Febrile seizure (FS) is the most common type of childhood seizure disorder and is defined by the International League Against Epilepsy as an unprovoked seizure that cannot be classified as acute symptomatic seizure and occurs in childhood after 1 month of age, associated with a febrile disease that is not caused by a neonatal seizure or an infection of the central nervous system.[1-4] Febrile seizure has a varying incidence worldwide from 2% to 5% and the incidence has been reported to vary between 6-9% in Japan, 5-10% in India, and to be as high as 14% in Guam.[2,3] Febrile seizure is divided into 2 types as simple and complex. Simple FS is defined as a short (<15 minutes) generalized seizure, not recurring within 24 hours, that occurs during a febrile illness not resulting from an acute disease of the nervous system in a child aged between 6 months and 5 years, with no neurological deficits and no previous afebrile seizures. In contrast, complex FS is defined as a seizure characterized by a focal, or generalized and prolonged seizure, lasting longer than 15 minutes, recurring more than once in 24 hours, and/or associated with postictal neurological abnormalities, more frequently a postictal palsy (Todd's paralysis), or with previous neurological deficits. In almost 16% of FS patients, the seizure recurs within the next 24 hours.[3]

The American Academy of Pediatrics does not recommend the use of electroencephalogram (EEG) in children presenting with simple FS, whereas there is no consensus on the administration of EEG in children with complex FS.[4] Nevertheless, EEG can be administered in FS patients at parents' request or in recurrent seizures at the physician's discretion.[5] On the other hand, the use of EEG for predicting the risk of recurrent seizures in children with FS remains controversial and some authors suggested that this procedure will provide no valuable information.[6,7] In the literature, a relationship among EEG attenuation, focal EEG findings, and pseudo-petit mal discharge (PPMD) has been reported in FS patients.[8] Pseudo-petit mal discharge was first defined by Gibbs and Gibbs in 1964 as a generalized or nearly generalized high voltage 3-4 Hz

wave complex with rudimentary spike, occurring paroxysmally during Non-REM stage I sleep onset. Although this pattern is accepted as a variant of the normal sleep patterns in childhood, it has a higher prevalence in FS patients.[9] The relationship between PPMD and age has been documented in studies; however, no long-term follow-up has been reported in those studies.[9-11]

The present study was designed to investigate the potential role of PPMD in children with simple/simple recurrent or complex FS and to examine whether PPMD could be a marker of favorable prognosis in long-term follow-up of FS patients in a risk factor for the development of epilepsy.

METHODS

Study Population

A total of 1255 children aged 6-66 months that were followed up in our hospital due to FS over the period 2006-2020 were reviewed. Exclusion criteria included, 1/2 simple FS, those who did not have at least 2 EEG recordings and did not attend their regular follow-ups, a history of or ongoing immunodeficiency, growth retardation febrile status epilepticus (which was defined as an FS or series of seizures lasting >30 minutes), breath-holding spell, febrile myoclonus, and no neurologic chronic systemic diseases. Of these, 255 children aged 6-66 months were evaluated retrospectively. Patients were divided into 2 groups:

-Recurrent febrile seizure (RFS): Recurrent febrile seizure was diagnosed in patients that previously experienced at least 3 simple FS (SFS) and relapsed in 6 months without focal features.

Complex febrile seizure (CFS): Complex febrile seizure was defined as a seizure of prolonged duration (>15 min) with focal features, recurring repeatedly within the first 24 hours, and/or associated with postictal neurological abnormalities (Todd's Paralysis).

An EEG examination was performed in each patient and all the patients included in the study presented to our clinic after the third and first complex FS. The presence of PPMD varies across different age groups. Therefore, patients who had at least 2 EEG recordings due to this condition were included in the study and all of them continued their long-term follow-up in our hospital. RFS patients with recurrent FSs were divided into 2 groups according to seizure frequency (3 seizures and >4 or more). The frequency and duration of the discharges in the EEG in children with PPMD were recorded. Patients that were diagnosed with RFS during the follow-up period were monitored for the persistence of PPMD and for epilepsy development. Patients with PPMD were followed up for epilepsy development for a period of 7 years after the age of 66 months.

A control group of 150 healthy children from the same age group with normal neurological development and without chronic diseases was also included in the study. Each family was informed that the EEG scans would not cause any harm to the child and would be used for research purposes only in the third, fifth, and seventh years patients who had 2 EEG recordings and were regularly followed up were evaluated for seizure status with telephone interviews. An EEG scan was performed at the end of the seventh year. Patients who had at least 2 EEG recordings due to this condition were included in the study, and this detail was added to the manuscript. Pediatric neurologists who read the EEG recordings had at least 10 years of EEG reporting experience. An EEG scan was performed at the end of the seventh year. Regular follow-up was ensured in each patient. The ethical approval was obtained from the ethics committee of our hospital with the protocol number 2018/212.

EEG Procedure

All the EEG records were acquired and reviewed within an average period of 1 month after the first seizure, using a bipolar (double banana) montage with the 10/20 system of electrode placement. Each recording lasted 40 minutes and included wake and sleep stages 1-2 and activation procedures. The incidence and duration of PPMD were noted for every 10-second tracing. A pediatric neurologist interpreted the records. Electroencephalogram abnormalities were classified into 3 groups: group I (normal), no epileptiform or background abnormalities; group II (abnormal), focal or generalized discharge or EEG slowing; group III (PPMD), a paroxysmal disorder characterized by generalized or nearly generalized high voltage (3-4 Hz) wave complex with rudimentary spike, occurring during sleep onset (non-REM stage I).

Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences Version 23.0. (IBM SPSS Corp.; Armonk, NY, USA) Categorical variables were expressed as frequencies (n) and percentages (%) and continuous variables were expressed as mean, standard deviation, minimum, and maximum. The normal distribution of continuous variables was determined using Kolmogorov–Smirnov test. Variables with non-normal distribution (age and body weight) were analyzed using Mann–Whitney U-test and categorical variables were analyzed using the chi-square test. The odds ratio (OR) was assessed with 95% CI. Logistic regression analysis with unadjusted OR was performed to examine the factors affecting the recurrence of FSs. A P value of <.05 was considered significant.

A total of 1255 children presented to our outpatient clinic due to FS over the period 2010-2020. Patients with a history of 1 SFS were excluded from the study. As a result, 255 children aged 6-66 months who continued their follow-up in our hospital and had a history of more than 2 simple and 1 complex seizure were included in the study. Table 1 presents the clinical and demographic characteristics of the patients. The results indicated that the risk of FS increased with age (r=−0.566, P = .013) and the mean age of diagnosis was significantly lower in patients with CFS (20.8 ± 11.4 months; range, 6-52 months) than in patients with RFS (23.3 ± 13.3 months; range, 6-66 months) (P = .032). RFS was diagnosed in 196 (76.8%) patients. The analysis indicated that children aged less than 2 years who had their first seizure were 3.5 (range, 1.107-4.988) times more likely to have RFS. Pseudo-petit mal discharge was detected in 58 (29.5%) out of 196 patients with RFS as opposed to 20 (68.9%) out of 59 patients with CFS. (P = .005). The mean age of RFS patients with PPMD was 21.8 ± 12.4 (range, 6-56) months and the mean age of CFS patients with PPMD was 15.6 ± 8.23 (range, 6-48) months (P = .036). The youngest and oldest children detected with PPMD on EEG were aged 8 and 66 months, respectively, with 3 children in each category. The risk of both RFS and PPMD decreased with age (r=−0.396, P = .039). Pseudo-petit mal discharge was found to persist in 7 (12%) out of 58 RFS patients and in 4 (%20) out of 20 CFS patients with PPMD for a period of 7 years, PPMD is persist during the 7 year follow-up period without any epileptic activity and epilepsy did not develop during this period (Figure 1A–B). Table 2 presents the risk, CIs, and prevalence of epilepsy in RFS patients with PPMD. Compared to CFS, those with more RFS seizures had longer PPMD periods and greater frequency. PPMD that patients with RFS seizures had 2.3 (range, 1.107-1.988) times higher risk of having >4 seizures and also male children had a 19 (range, 1.335-2.569) times higher risk compared to female children.

In the control group, PPMD was present in 7 (4.6%) out of 150 children. No PPMD was detected in any of the children at the follow-up

Table 1. Demographic and Clinical Characteristics

Variable	All Patients	EEG		
		Normal	Epileptic	PPMD
N	255	168	9	78
Age (months)	23.3 ± 13.3 (6-66)	23.7 ± 14.0 (8-66)	23.6 ± 14.6 (11-57)	23.6 ± 14.6 (11-60)
Gender (F/M)	90/165	58/110	4/5	28/50
Seizure type				
Recurrent FS	196 (76.8%)	134 (78%)	5 (55%)	58 (76%)
Complex FS	59 (23.2%)	34 (22%)	4 (45%)	20 (24%)
Family history of febrile seizure	64 (25%)	45 (25%)	3 (33%)	16 (23%)
Family history of epilepsy	47 (18%)	31 (17.4%)	4 (44%)	12 (17%)
Fever	38.1±0.5	38.1±0.5	38.1±0.5	38.1±0.5
37-38°	80	48	2	16
38.1-39°	110	89	5	40
39-40°	50	32	1	9
>40°	15	9	1	3

EEG, electroencephalogram; PPMD, pseudo-petit mal discharge; F, female; M, male; FS, febrile seizure.

after 7 years. The frequency and duration of PPMD in the FS and control groups are shown in Table 3. Although the frequency of PPMD was higher in the group with recurrent FS, its duration was significantly shorter in the control and complex FS groups (P = .008). Significant difference was found between the recurrent FS and complex FS groups with regard to the frequency and duration of PPMD (P < .001). Seven years later, 10 (6.1%) RFS patients with normal EEG findings were followed up for epilepsy.

A significant relationship was found between the presence of PPMD and the male gender (P = .025). However, no significant difference was found among the groups with regard to fever and no significant difference was found between the risk of RFS and a family history of FS and epilepsy in patients with PPMD.

DISCUSSION

Pseudo-petit mal discharge is a sleep pattern characterized by high voltage, rhythmical bursts of 4-6 Hz in the parietal region. This pattern occurs during sleep onset and is accepted as a variant of normal sleep patterns in childhood.[10] Among the studies that have investigated the relationship between FS and PPMD, Alvarez et al reported the prevalence of PPMD in children with FS as 23% and Cappellari reported it as 27.5%.[8-11] In contrast, Olofsson et al[12] reported that the prevalence of PPMD in their healthy children was 7.9% and that all of those children were aged younger than 8 years.[12] In the present study, we found a higher prevalence of PPMD both in the RFS (29.5%) and control groups (4.6%) compared to those reported in the literature. To our knowledge, our study is the most comprehensive study to investigate the prevalence of PPMD in RFS with 7-year follow-up and the factors

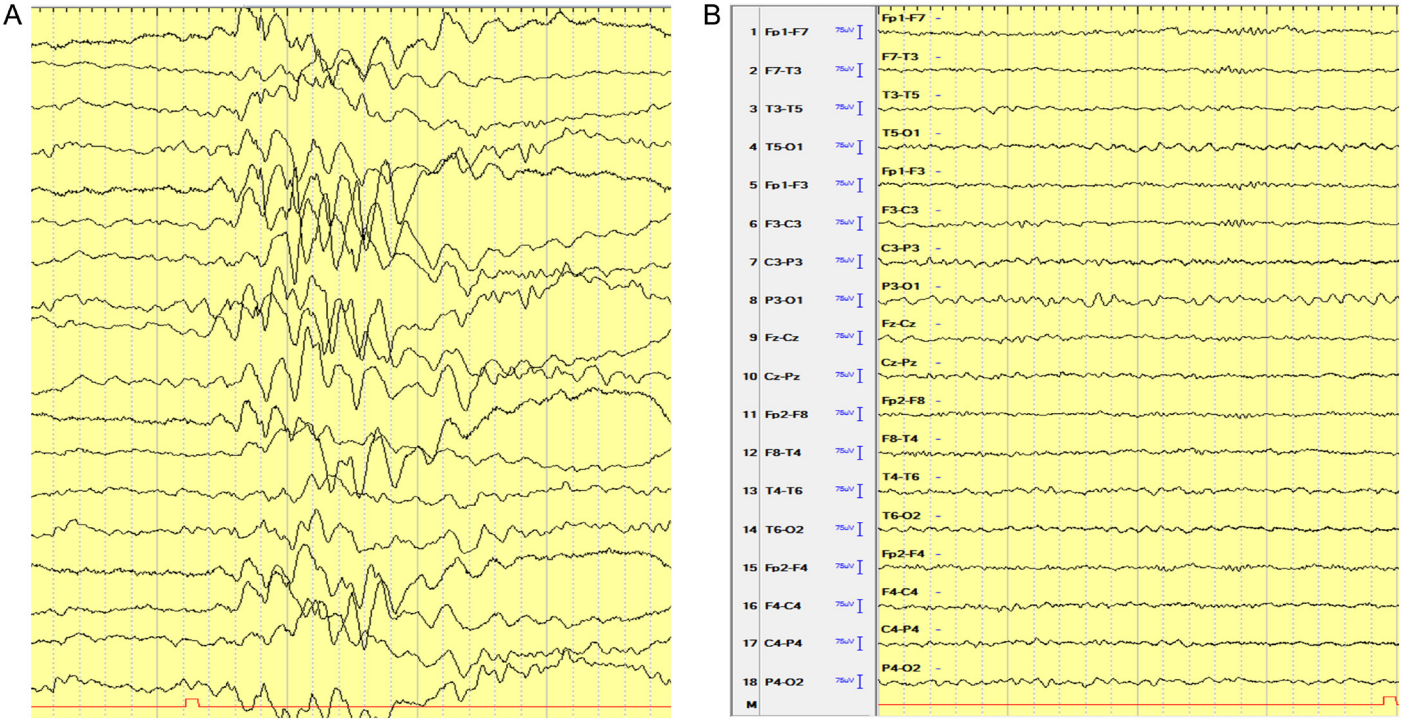

Figure 1. (A) Generalized high voltage 3-4 Hz wave complex with rudimentary spike, occurring paroxysmally during Non-REM stage I sleep onset, (B) Normal.

Table 2. Risk and CIs and Prevalence of Epilepsy in RFS Patients with PPMD

	RFS (n=196)	Relative Risk (95% CI)	RFS+PPMD (n=58)	Relative risk (95% CI)	*P*
Age (months)	21.6±12.6 (11-57)	1.2 (0.606-3.619)	20.6±14.8 (11-72)	1.1 (0.797-2.664)	.96
Gender (F/M)	65/131	1.8 (0.744-2.146)	18/29	1.7 (0.551-1.771)	.85
Female	65	1.5 (0.375-4.412)	18	1.6 (0.256-1.556)	.92
Male	131	2.1 (1.123-3.102)	29	1.9 (1.335-2.569)	**.025**
Family history	23/43	1.1 (0.891-3.064)	3/9	1.2 (0.669-1.569)	.56
Family history of epilepsy	18/19	1.4 (1.026-4.421)	2/2	1.5 (0.433-1.899)	.67
Seizure frequency					
3 times FS	72	1.5 (0.668-1.455)	31	1.6 (1.235-1.839)	.48
>4 times FS	43	2.1 (1.256-2.558)	16	2.3 (1.107-2.988)	**.034**
EEG pattern					
Normal	109	1.1 (0.998-2.256)	51		
PPMD	58	1.2 (0.775-2.535)	7		
Abnormal	6	1.8 (0.636-2.150)	0		
Epilepsy development	10	2.3 (1.107-2.988)	**0**	0	

RFS, recurrent febrile seizure; PPMD, pseudo-petit mal discharge; F, female; M, male; FS, febrile seizure.

playing a key role in the recurrence of FS in the presence of PPMD, and also to indicate that PPMD is a marker of favorable prognosis in long-term follow-up of RFS patients.

Gibbs et al[9] reported that the prevalence of PPMD decreases with age and also noted that PPMD often disappears at around the age of 8 years and commonly occurs in children with FS.[9] Alvarez et al[11] reported that no PPMD was observed in FS children aged less than 16 months.[11] In our study, the youngest child detected with PPMD was 8 months old and no PPMD was found in children older than 76 months. Although no gender-based difference has been reported in the literature in children with FS, our study found a significant relationship between male gender and the prevalence of RFS and PPMD. On the other hand, the literature indicates that a family history of FS, young age at onset, and low degree of fever in the emergency department are the predictors of RFS.[12] In our study, however, no significant relationship was found between RFS and a family history and fever, whereas the risk of RFS was found to increase with age and the number of previous seizures. Additionally, the risk of PPMD was found to decrease with age. Patients with RFS seizures had a 2.3 (range, 1.107-1.988) higher risk of having >4 seizures and also male children had a 1.9 (range, 1.335-2.569) times higher risk compared to female children.

The role of EEG in long-term follow-up of FS children remains controversial.[13,14] Although there are several studies suggesting that EEG has no role in predicting epilepsy development, Harini et al[15] evaluated the utility of EEG in predicting epilepsy development in children with CFS and reported that EEG had a poor positive predictive value for epilepsy development.[15] Although there have been studies in the literature investigating the prevalence of PPMD in FS, none of those studies have examined long-term follow-up evaluations of the patients.[9-11] Cappellari et al[8] evaluated the prevalence of PPMD in FS children and indicated that the prevalence of PPMD was lower in patients with CFS compared to other patients.[8] In our study, a significant relationship was found between the presence of PPMD and seizure types. Moreover, the presence of PPMD was found to be an independent risk factor for RFS regardless of age and gender, and children aged under 2 years who had their first seizure were 3.5 (range, 1.107-4.988) times more likely to have RFS. On the other hand, PPMD was found to persist in 7 (12%) out of 58 RFS patients and in 4 (%20) out of 20 CFS patients for a period of 7 years, PPMD is persist during the 7 year follow-up period without any epileptic activity and epilepsy did not develop during this period.

Neligan and Almojali et al reported that the probability of transition from FS to epilepsy was 5.6-6%.[16-18] However, Dreier et al[18] showed an association between recurrent FS and the risk of epilepsy and also noted that the risk was particularly higher for children who had more than 2 FSs. UK-based study in which the risk of epilepsy increased by a factor of 2.48 (95% CI, 1.68-3.65) with the number of FSs up to a limit of 4.24. In the same study, the authors observed that the risk of epilepsy continued to increase even after the first 9 years following FS, though the relative increase became less pronounced over time.[18] Moreover, in a recent cohort study from Taiwan, the 9-year cumulative incidence of epilepsy was 3.3% in children with 1 FS and 9.2% in children with 2 or more FSs as opposed to 0.5% in the cohort without FS.[19] In our study, epilepsy developed in 6.1% of patients with RFS. 63.5% of our patients had RFS and 26.5% of them had CFS, among whom PPMD was detected in 29.5% of RFS patients and in 34% of CFS patients. Additionally, PPMD that patients with RFS seizures had 2.3 (range, 1.107-1.988) times higher risk of having >4 seizures. In contrast, Cappellari et al[8] showed that patients with CFS had a lower prevalence of PPMD.[8] In our study, the prevalence of CFS was higher in patients with PPMD and no epilepsy attacks occurred in those patients, also indicated that no epilepsy occurred during long-term follow-up of RFS and CFS patients with PPMD, implicating that PPMD could be a marker of favorable prognosis in FS patients. Although the finding that

Table 3. Comparison of PPMD Duration and Frequency Between Groups in During EEG Examination (±SD)

Variable	Recurrent Febrile Seizure	Complex Febrile Seizure	Control Group	*P*
n	58	20	7	
PPMD duration (s)	3.8 ± 0.8	2.6 ± 1.4	3.8 ± 1.3	P^1=.008, P^2=.006, P^3<.001
PPMD frequency (Hz)	5.2 ± 1.8	4.8 ± 1.9	3.5 ± 2.1	P^1<.001, P^2<.001, P^3=.049

PPMD, pseudo-petit mal discharge; s, second; P^1, between recurrent and complex febrile seizure groups; P^2, between recurrent and control groups; P^3, between complex and control groups.

indicated that the prevalence of PPMD decreases with age is a confusing finding, the detection of epilepsy in RFS children with signs of PPMD on EEG is highly interesting and significant.

The limitation of our study was the number of patients and the absence of follow-up for more than 7 years. Larger studies are needed to substantiate our findings.

In conclusion, FSs and their recurrence can be highly worrisome for parents and physicians; therefore, investigating the factors contributing to the recurrence of these seizures and determining useful prognostic markers of recurrence are highly important Our results indicated that PPMD can be frequently detected on EEG in children with RFS and that PPMD could be a marker of favorable prognosis in long-term follow-up of FS patients in terms of epilepsy development, mainly because epilepsy was diagnosed in patients without PPMD and was not detected in patients with PPMD. Although PPMD is an important predisposing factor for the recurrence of FSs, it has been shown that it is not a risk factor for epilepsy development. The presence of PPMD on EEG helps us predict or increase our awareness.

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