

Title: Novel and reappraised wide-band EEG findings in migraineurs: its correlation
with several clinical variables

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Highlights

- Of 144 patients with migraine, Focal subdelta slow and Focal delta slow were observed in EEG of 38 and 58 patients, respectively.
- Focal subdelta slow showed a positive correlation with several clinical variables, particularly with the phase of migraine.
- Focal subdelta slow or focal delta slow may help us delineate core or subgroup patient populations of migraineurs.

Abstract

Objective: Cortical spreading depolarization is one possible pathogenesis of migraine, of which slow neurophysiological change is barely recorded in conventional EEG settings. Using wide-band EEG conditions, we reappraised the features of EEG in migraineurs, including subdelta-band EEG changes.

Methods: This retrospective study included 144 patients with migraine. We delineated EEG of focal delta slow (FDS) (1-4 Hz) by time constant (TC) 0.3 s and focal subdelta slow (FSDS) (< 1 Hz) by TC 2 s. Relationships between clinical variables and EEG findings were evaluated.

Results: Of 144 patients, 39 had aura and 105 did not. FSDS and FDS were observed in 38 and 58 patients, respectively. No EEG was recorded during the aura. In multivariate analysis with the phase of migraine, family history, age, and percentage of sleep during EEG recording, the phase of migraine was related to the occurrence of FSDS (postdrome vs interictal, prodrome, and headache respectively (OR = 49.00 [95% CI = 3.89-616.66], 46.28 [2.99-715.78], 32.79 [2.23-481.96], $p = 0.0026, 0.0061, 0.011$).

FDS was clinically unremarkable for differential evaluation.

Conclusions: Wide-band EEG abnormality in migraineurs, i.e., FSDS, can be affected by migraine phase.

Significance: Wide-band EEG finding could be a biomarker related to clinical variables in migraines.

Key words: migraine, CSD, wide-band EEG

Abbreviations

SD, cortical spreading depression; CSD, cortical spreading depolarization; ECoG, electrocorticogram; EEG, electroencephalography; MA, migraine with aura; MO migraine without aura; DC, direct current; TC, time constant; FDS, focal delta slow; FSDS, focal subdelta slow; EEGers, electroencephalographers; CT, computed tomography; MRI, magnetic resonance imaging; ACNS, American Clinical Neurophysiology Society; OR, odds ratio; CI, confidence interval;

1. Introduction

Migraine is a common disorder characterized by headache attacks accompanied by various neurological symptoms (Headache Classification Committee of the International Headache, 2013). The 2019 Global Burden of Disease Survey ranked it as the second most common cause of global disability (expressed as years lived with disability) and the worst cause of disability-adjusted life year reduction in young women (Steiner et al., 2020). The prevalence of migraine is age-dependent. Migraine attacks begin in puberty, peak at approximately 40 years of age, and then decline. Patients with migraines often have a family history of migraine (Silberstein, 2004). Migraine attacks comprise not only the main headache phase but also the preceding prodrome, aura, and postdrome phases. Patients often develop various symptoms as a complex attack, which suggests a complex pathophysiology, but the underlying mechanisms remain unclear (Blau, 1992). Cortical spreading depression (SD) is a well-known phenomenon thought to underlie the pathogenesis of migraines. SD is preceded by a depolarization, described as cortical spreading depolarization (CSD) (Charles et al., 2013). CSD is defined as a large slow potential change measured in the low-frequency range of an electrocorticogram (ECoG) in patients with acute traumatic brain injury or cerebral ischemic attack (Drenckhahn et al., 2012). Multiple human neuroimaging studies have indirectly suggested that SD underlies migraine (Hadjikhani et al., 2001, Tfelt-Hansen, 2010). However, SD/CSD has never been observed in human patients with migraine using electroencephalography (EEG), except in a previous magnetoencephalography study (Bowyer et al., 2001).

EEG findings of migraineurs have been reported since the 1940s. In general

migraines (with the exception of hemiplegic migraines), the occurrence rate of EEG abnormalities varies (approximately 15-65%) (Facchetti et al., 1990, Selby et al., 1960, Smyth et al., 1964), as do EEG findings, such as focal slow, and diffuse slowing (Sand, 2003, Slatter, 1968). The difference in EEG between patients with migraine with aura (MA) and migraine without aura (MO) is controversial (Coppola et al., 2019, Genco et al., 1994). Therefore, until now, the clinical application of EEG in headache disorders has been almost limited to differentiating from focal epilepsy (Report of the Quality Standards Subcommittee of the American Academy of Neurology, 1995). Currently, clinical EEG are mainly focused on brain activity in the frequency band around 0.5 - 100 Hz. However, clinicians have started to use digital wide-band EEG activities, such as very slow and fast frequency (Ikeda et al., 2020, Zijlmans et al., 2017). In low-frequency band activity, activity < 1 Hz is focused on sleep, consciousness, and epilepsy. For example, a direct current (DC) shift is a low-frequency band activity thought to be related to epileptic seizures (Ikeda et al., 1999). Recent reports have shown that CSD and its partial activity can be recorded by scalp EEG, even with a time constant (TC) 2 s (high-pass filter 0.08 Hz) in patients with acute traumatic brain injury (Tsukamoto et al., 2020) and in others (Murai et al., 2020). Based on these reports, we considered that it may be possible to search for CSD or CSD-related activities on scalp EEG of patients with migraine. DC shift and CSD are thought to be generated by astrocytes because of their slow evolution, according to recent reports on the underlying mechanism (Capendeguy et al., 2004, Charles et al., 2013, Ikeda et al., 1999, Sugaya et al., 1975).

The analysis of wide-band EEG in migraineurs may provide new insights into its pathogenesis and further clinical application. In this study, we reappraised the new

scope of EEG in migraineurs diagnosed by board-certified headache specialists, that is, focal delta slow (FDS) and focal subdelta slow (FSDS) (< 1 Hz) by board-certified electroencephalographers (EEGers) using wide-band EEG. We sought to clarify whether wide-band EEG could be a potential biomarker for headache disorders by assessing the relationship between the new scope of EEG and clinical variables.

2. Methods

2.1. Patients

This retrospective case study included 145 patients with migraines who were treated at the Tatsuoka Neurology Clinic and Tominaga Hospital between December 2019 and April 2021. The research protocol was approved by the Ethical Committee of Kyoto University Graduate School of Medicine (approval R2167). Written informed consent was obtained from all patients before enrollment. They were diagnosed with migraine according to ICHD-3 by board-certified headache specialists (Japanese Headache Society) and EEG was performed based on R2167. Clinical variables were collected for each patient including age, gender, aura, age at onset of migraine, family history, frequency of headache attacks, frequency of drug use for headache attacks, disease duration, use of drugs for prophylaxis, worsening by menstruation, history of abdominal migraine, and use of psychiatric drugs and/or antiseizure drugs (ASM) (**Table1**). Immediately after EEG recording, each patient was questioned about the phase of migraine (interictal or symptomatic, symptomatic phase including prodrome, aura, headache, and postdrome) while undergoing EEG and the time interval from the last headache attack. Clinical variables were collected from the clinical records (mainly of

the first visit). Patients who had a brain lesion involving the cortex, such as old major cerebrovascular disease (not a lacunar state), or a tumor on brain computed tomography (CT) or magnetic resonance imaging (MRI), were excluded from the data analysis.

2.2. Electroencephalography (EEG)

Scalp-recorded EEG was obtained in a conventional manner using a multichannel EEG machine (Nihon Kohden, Tokyo, Japan) with Ag-AgCl electrodes the International 10-20 system and T1/T2 electrodes. Contact impedance of each electrode was kept at least below 10 k Ω . The EEGs were recorded for 30 min. The following activation procedures were done during EEG recording: eye opening and closing, and photic stimulation of 1, 3, 6, 9, 12, 14 and 20 Hz. Hyperventilation was not done to prevent SARS-CoV2 from spread in the EEG recording room just in case following the recommended protocol in the hospital. The recording TC was set to 2 s (high-pass filter, 0.08 Hz) at a sampling rate of 500 Hz. This TC setting has already been reported to allow us to evaluate low-frequency band activity, including DC shift and CSD (Kajikawa et al., 2022, Murai et al., 2020, Tsukamoto et al., 2020).

Each EEG was visually analyzed in a conventional manner. The display EEG utilized reference electrode of A1 or A2 for referential montage and also common average reference montage was applied. We evaluated focal delta-band (1-4 Hz) activity (focal delta slow: FDS) with a TC 0.3 s (high-pass filter 0.53 Hz) and low-pass filter 120 Hz. We also evaluated subdelta band (< 1 Hz) activity as a FSDS with a TC 2 s and a low-pass filter 15 Hz. Sensitivity for display was set to 10 μ V/mm. We judged both FDS and FSDS as present once the amplitude was > 50 μ V with referential montage or average montage, and once we confirmed that they were reproducible by observing

157 them twice or more during whole 30-min recording. EEG interpretation was conducted
158 by standard methods according to the guideline of American Clinical Neurophysiology
159 Society (ACNS) (Tatum et al., 2016). EEG mimics, such as eye movements, movement
160 artifacts, and waveform changes seen only at one electrode, were excluded as artifacts.
161 The EEG waveforms of the FDS or FSDS were confirmed by two board-certified
162 EEGers (certified by Japanese Society of Clinical Neurophysiology, or also by ACNS).
163 EEGers were blinded to patient's clinical information other than age, gender, and as a
164 patient with migraine.

165 In this study, we carefully accepted FDS or FSDS that were considered
166 abnormal by excluding normal variants of EEG findings as follows: 1) posterior slow
167 wave of youth: we judged it as normal when it was seen under 25 years old because it is
168 rarely seen above 21 years old (Mizrahi, 1996). 2) benign temporal transients of the
169 elderly (Schomer et al., 2011).

170 We also examined the relationship between the FDS and FSDS and the
171 patients' clinical variables. Finally, we evaluated the laterality of symptoms and EEG
172 abnormalities in the following situations:

173 1. The dominant side of habitual migraine headache and the side of abnormal EEG
174 finding.

175 2. The dominant side of headache and the side of abnormal EEG findings when
176 headache phase occurred during EEG recording.

177 3. In patients with MA the dominant side of habitual aura and the side of EEG
178 abnormality.

179 4. The dominant side of habitual aura and the side of EEG abnormality when patients
180 with MA were in headache phase during EEG recording.

We determined that the laterality was concordant if headache and EEG abnormalities occurred on the same side because ipsilateral dural innervation via the trigeminal nerve is thought to underlie migraine headache pain (Iyengar et al., 2019). If aura and EEG abnormalities occurred on the opposite side, we judged that the laterality was concordant because the symptoms of migraine aura are thought to be of cerebral cortical origin (Tfelt-Hansen, 2010).

2.3. Statistical analysis

We analyzed the occurrence rates of FDS and FSDS. The relationship between these EEG findings and clinical variables were analyzed using the chi-squared test. Fisher's exact test was used if a chi-square test was not available because 20% or more of the cells have an expected value < 5 . Odds ratios (ORs) and 95% confidence interval (CI) were also calculated. Statistical comparisons were performed for clinical variables of patients with MA and MO using the Welch's *t*-test or chi-square test. If the chi-square test was not available, the Fisher's exact test was used. Multivariate analysis was used for further assessment of the relationships between the occurrence of FSDS and each clinical variable. We performed logistic regression analysis and calculated the OR for each factor. However, the number of patients was insufficient to include all clinical variables as explanatory variables in logistic regression analysis. Therefore, explanatory variables were selected according to results of univariate analysis. All statistical analysis were performed with JMP pro 17.0.0. A *p*-value of < 0.05 was considered to be statistically significant.

3. Results

The clinical demographics of the patients are presented in **Table 1**. We excluded one of 145 patients because the patient had an old cerebral infarction lesion on brain MRI. The mean age $\pm$ standard deviation (SD) of the enrolled 144 patients was 41.7 ± 15.3 years. Of the enrolled 144 patients, 39 had MA, and 105 had MO. The male: female ratio was 20/124. Of the 39 patients with MA, 38 had a visual aura and one patient had both sensory and brainstem auras. Patients with hemiplegic migraines were excluded from the enrollment. A summary of the analysis is shown in **Table 2** and **3**. Some patients had other headache related disorders and/or psychiatric disorders as comorbidities. We also performed analysis after excluding those comorbidities (medication-overuse headache, tension-type headache, depression, panic disorder, anxiety disorder and personality disorder) (**Table S1, S2 and S3**). Psychiatric drugs and/or ASM were used for migraine prophylaxis, psychiatric disorders or unknown reason (**Table S4**).

3.1. EEG findings: FSDS was always in the posterior area whereas FDS was located differently by patients' age

The representative waveforms are shown in **Figure 1**. We were not able to evaluate FSDS in 3 patients because their baseline EEG drifts prevented us from evaluation with a TC 2 s. FSDS was observed in 38 of the 144 patients. All FSDS were observed in the posterior area during sleep. This was more seen in under 40 years (OR = 5.21 [95% CI = 2.28-11.93]; $p < 0.0001$) (**Figure 2A**). FSDS was seen 37/122 in female and 1/19 in male, and FSDS occurrence rate was significantly higher in female than in male (OR = 7.84 [95% CI = 1.01-60.89]; $p = 0.022$). The occurrence of FSDS did not differ between patients with MA and those with MO.

FDS was observed in 58 of the 144 patients. The location of FDS tended to

differ by age (**Figure 2B**). Thus, we divided the patients into the following two groups: under 40 years old vs. at or over 40 years old, and performed a statistical analysis. FDS was seen in the posterior area in < 40 years old patients (OR = 4.90 [95% CI = 1.70-14.14]; $p = 0.0017$), while in the temporal area in patients at and over age 40 (OR = 9.92 [95% CI = 2.21-44.56]; $p = 0.0004$). FDS occurrence did not differ between MA and MO patients and was also commonly observed in the posterior area in both groups. Additionally, as a minor finding, we found generalized slow in 6, sharp waves in 1, and sharp transients (morphologically resembling normal or non-specific sharply contoured waveforms (Sultana et al., 2021)) in 8 out of 144 patients with conventional EEG review conditions.

3.2. Phase of the migraine and EEG findings: FSDS was significantly seen in a symptomatic phase

We further classified the EEG according to the phase of the migraine (interictal, prodrome, headache, and postdrome) during EEG recording. No EEGs were recorded during aura. The occurrence rates of the FSDS and FDS in each phase are shown in **Figure 3**. FSDS was observed more frequently in the symptomatic phase (including the phase of prodrome, headache and postdrome) than in the interictal phase (OR = 2.29 [95% CI = 1.05-4.97]; $p = 0.035$) (**Table 2**). In contrast, FDS occurred almost similarly in each phase. The occurrence rates of FDS and FSDS did not differ between patients with MA and those with MO in each phase.

3.3. Family history was positively related to the occurrence of FSDS

FSDS occurred more frequently in the group with a family history of migraine than in

those without (OR = 2.58 [95% CI = 1.11-6.01]; $p = 0.026$). However, a family history of migraine was not associated with the occurrence of FDS (**Figure 4, Table 2 and 3**).

3.4. The other clinical variables and EEG findings

The occurrence rate of either FDS or FSDS was not affected by any of the following parameters: frequency of use of drugs for headache attacks, time interval from the last attack, use of drugs for prophylaxis, use of psychiatric drugs and/or ASM, worsening by menstruation, and presence of a history of abdominal migraine (**Table 2 and 3**).

We found that FSDS occurred in a group with frequency of headache attack ≥ 15 /month than in a group with 9-14/month (OR = 6.75 [95% CI = 1.31-34.85]; $p = 0.014$). With regards to disease duration and age at onset of migraine, FSDS was frequently observed in a group with < 20 years of disease duration than ≥ 20 years (OR = 2.37 [95% CI = 1.10-5.11]; $p = 0.026$), and in a group with onset age < 20 years than ≥ 20 years old (OR = 3.48 [95% CI = 1.40-8.65]; $p = 0.0054$). We also analyzed age and sleep status of the recorded EEG for confounding factors. The group with the frequency of headache attack ≥ 15 /month, the group with < 20 years of disease duration, and the group with onset age < 20 years old were younger than other groups ($p = 0.0091$, $p < 0.001$, $p < 0.001$), the above three groups reached stage N2 more frequently ($p = 0.033$, $p = 0.072$, $p = 0.01$).

3.5. Multivariate analysis showed that the phase of migraine was associated with the occurrence of FSDS

Considering the sample size, the stability of model for logistic regression analysis, and

the results of the above univariate analysis, we performed logistic regression analysis for the occurrence of FSDS using four factors: the phase of migraine, family history, age (< 40 years old, or $\geq$ 40 years old), and percentage of sleep during EEG recording. The phase of migraine (postdrome vs interictal OR = 49.00 [95% CI = 3.89-616.66]; p = 0.0026, postdrome vs prodrome OR = 46.28 [95% CI = 2.99-715.78]; p = 0.0061, postdrome vs headache OR = 32.79 [95% CI = 2.23-481.96]; p = 0.011), age (OR = 5.67 [95% CI = 2.07-15.50]; p = 0.0007), and percentage of sleep (OR = 1.04 [95% CI = 1.02-1.07]; p = 0.0009) was significantly related to the occurrence of FSDS. Family history showed a tendency related to FSDS occurrence but did not show a significance in multivariate analysis (OR = 2.49 [95% CI 0.93-6.71]; p = 0.070) (**Table 4**).

3.6. Results in populations without comorbidities

Once comorbidities excluded, we still found similar tendency between EEG findings and clinical variables (**Table S2 and S3**). FSDS was tended to occur more frequently in female than male patients (OR = 6.28 [95% CI = 0.78-50.41]; p = 0.061). For migraine symptom phases, FSDS occurred more frequently in the symptomatic phase than in the interictal phase (OR = 1.93 [95% CI = 0.77-4.84]; p = 0.16). FSDS occurred more frequently in the group of positive family history of migraine than in the negative one (OR = 2.26 [95% CI = 0.85-6.01]; p = 0.099). With comorbidity factors excluded, FSDS more frequently occurred in the group of no abdominal migraine than in the group of positive abdominal migraine (OR = 0.17 [0.036-0.77]; p = 0.012). Multivariate analysis was not performed for the populations without comorbidities because the number of patients was limited.

3.7. The laterality of symptoms and EEG abnormality did not show correlation

The laterality of the FDS or FSDS did not match any of the following variables: the dominant side of habitual headache, dominant side of headache while recording EEG in the headache phase, dominant side of habitual aura in patients with MA, and dominant side of habitual aura in the headache phase. Statistical analysis was not performed because of the limited number of patients included (**Table S5**).

4. Discussion

We tried to clarify the correlation between so-called wide-band EEG abnormalities and clinical variables in 144 patients with migraine. FDS occurred in 58 patients and FSDS in 38. With regard to location of them, the FDS was observed in the posterior head area in patients aged < 40 years and in the temporal area in patients aged ≥ 40 years. FSDS was always observed in the posterior parts.

The occurrence of FSDS was positively correlated with several clinical variables as follows. 1) FSDS occurred in female than male, and 2) it was significantly more common during the symptomatic phase than during the interictal phase. 3) Moreover, FSDS occurred significantly higher in positive family history of migraine than negative family history. 4) The frequency of headache attacks, disease duration, and age at migraine onset were positively correlated with FSDS occurrence. In multivariate analysis using four explanatory variables (the phase of migraine, family history, age, and percentage of sleep during EEG recording), the phase of migraine, age, and percentage of sleep were related to the occurrence of FSDS significantly. However, we did not find a difference in either the FDS or FSDS between MA and MO patients in

this study. No clear concordance in laterality was observed between the EEG abnormalities and clinical symptoms. Once comorbidities excluded, we found similar tendency between EEG findings and clinical variables. Some results showed no statistical significance possibly because the number of patients were not enough.

In this study, we selected visual inspection rather than time-frequency analysis as a method of EEG evaluation because visual analysis is still considered to be the gold standard in clinical EEG (Kural et al., 2020, Tatum et al., 2018). Furthermore, the present study included patients who have slow activity rather infrequently, and thus in those patients time-frequency analysis may have less sensitivity. Further case accumulation may allow time-frequency analysis.

4.1. Differences between MA and MO patients

MA is characterized by auras, transient focal neurological symptoms that precede or sometimes accompany the headache at the same time (Headache Classification Committee of the International Headache, 2013). Therefore, it was expected that patients with MA would have EEG abnormalities during aura. In this study, we mainly analyzed the interictal phase of EEG; EEG during aura was not included in our analysis because no cases of EEG were recorded during aura (**Figure 3**). This partially explains why we did not observe a difference in EEG abnormalities between the patients with MA and those with MO, although a recent study in a small cohort reported that high-dense scalp EEG with DC amplifier failed to record CSD during visual aura (Riederer et al., 2024). The differences between MA and MO remain controversial. Some reports compared EEG between MA and MO; for example, delta power increased the whole scalp in patients with MA compared to those with MO. However, these results did not

reach a consensus (Coppola et al., 2019, Genco et al., 1994). CSD is thought to be related to aura (Hadjikhani et al., 2001, Tfelt-Hansen, 2010), which demarcates the two subtypes of migraine. However, some researchers have described that CSD might occur even in MO and that CSD may not necessarily generate neurological symptoms clinically (Imamura et al., 2008). Therefore, our results imply that the electrophysiological pathology of the two is common, at least at the level of the scalp-recorded, wide-band EEG. In addition, patients with MA involved at times may manifest not only MA but also MO in general, which is another reason as to why it is difficult to distinguish between the two.

4.2. Feature of FSDS

In this study, we evaluated subdelta band (< 1 Hz) activity as an FSDS using wide-band EEG. Evaluating subdelta band activity of EEG in patients with migraine is a new approach.

Difference between female and male

Patients with migraine are more female than male (Silberstein, 2004). It was reported that hormone in women can trigger acute migraine attack (Kelman, 2007). Several studies using model mice showed female or ovarian hormone reduced threshold to induce CSD or increase susceptibility of CSD (Brennan et al., 2007, Eikermann-Haerter et al., 2009). FSDS which we found in this study may reflect the difference of migraine pathology between female and male. However, because there was a large difference in the number of female and male of the whole subjects in this study, we need careful interpretation.

Phase of migraine attack and FSDS

We found that the occurrence of FSDS was associated with the phase of migraine attack. The FSDS was significantly more common in the symptomatic phase than in the interictal phase. This result suggests that it reflects changes in brain abnormalities during migraine attacks. FSDS would at least partly share the common features of CSD or fragmented CSD recorded by scalp EEG because FSDS was mainly seen during the symptomatic phase. However, this argument needs to be evaluated carefully because we did not have any patients whose EEG were examined during aura in this study.

Family history and FSDS

Genetic factors may be associated with migraine, and in the present study, FSDS was significantly observed in the group with a positive family history of migraine in univariate analysis. In addition, a previous animal study showed that gene mutations underlying familial hemiplegic migraine (FHM) increase susceptibility to CSD (Charles et al., 2013, Leo et al., 2011, van den Maagdenberg et al., 2004). In multivariate analysis, the family history of migraine did not show a significant relationship with FSDS occurrence but there was a tendency that it to be related with FSDS occurrence. The limited number of patients may be one of the reasons why no significant difference was found in this study. Wide-band EEG studies of the FHM cohort will further reveal how genetic factors affect electrophysiological phenotypes in migraineurs.

Physiology and interpretation of FSDS

The physiological basis of the FSDS has not yet been fully established. There are several possibilities as follows: 1) focal hypofunctional abnormality of the distributed area, which is the same as focal slow activity in the classical EEG interpretation. 2) Activities related to CSD, or at least partly or fragmentedly reflect CSD (Tsukamoto et al., 2020), and it has been suggested that low-frequency activities such as ictal DC shifts

and CSD are related to the activities of astrocytes (Capendeguy et al., 2004, Ikeda et al., 1999, Sugaya et al., 1975). It remains controversial how well the activity of astrocytes can be recorded on scalp EEG. 3) Physiological sleep-related EEG changes because we observed activity during sleep and the factor of sleep was significantly related to the occurrence of FSDS in multivariate analysis. Physiological sleep-related subdelta band activity is usually distributed in the frontal area (Evans, 2003), although this distribution differs from our present findings.

As documented in our results, EEG changes in general migraines were moderate. It has been hypothesized that EEG changes are modulated by various factors, including gender, the phase of the migraine and genetic factors that may be related to CSD. In addition, clinical symptoms, such as the aura of the MA, could occur owing to these factors influencing neurons. Future studies should consider not only neurons or non-neuronal structures, including astrocytes, but also their combined effects on clinical symptoms and EEG findings.

The other clinical variables and FSDS

We found that FSDS was dependent on disease duration, headache frequency, and migraine onset age. However, these results may have been influenced by patient age and sleep stage during EEG recording as confounding factors. Patients' ages and/or the presence of stage N2 were significantly different. The young age of the patients and the presence of stage N2 may explain these results.

4.3. Feature of FDS different from FSDS: its location dependent on age

Previous reports on the occurrence rate of FDS varied (approximately 12-50%) (Hockaday et al., 1969, Slatter, 1968). Our FDS occurrence rate is concordant with these

results. Limited reports refer to the location of the FDS. In our study, we found that FDS was observed in the posterior area in younger patients aged < 40 years and in the temporal area in patients aged ≥ 40 years. Healthy middle to old persons > 45 years have “benign temporal transients of the elderly” as normal variant (Schomer et al., 2011). It has been reported to reflect a mild degree of vulnerability in the temporal area functionally in electrophysiology, and this area tends to have a theta range of slow activity with aging. Thus, FDS may represent hypofunction due to migraine attacks during the long course of the disease, and therefore it was thought to occur in the temporal area in patients aged ≥ 40 years. In addition, it is well known that the clinical conditions of migraines change with life stage, especially in women (Makita et al., 2017, Silberstein, 2004). Thus, the finding that the location of the FDS differs by age may reflect age-related changes in the pathology of migraine or ontogenetic features of the cortical lobes, although this needs further validation, including comparison with normal group data.

Some reports described that the occurrence of delta activity is related to disease duration or family history, and a higher EEG abnormality at juvenile onset. However, no general consensus has been reached (Hockaday et al., 1969, Smyth et al., 1964). We also did not find any relationship between the occurrence of FDS and clinical variables, except for age. Therefore, we believe that the FDS may reflect a common pathology of migraines. According to the present study, there were no common results to the relationships between FSDS/FDS and clinical variables, suggesting that the generator of each EEG change is different. After comorbidities were excluded, we found FDS more frequently in the group without history of abdominal migraine, but its significance was unknown. Further study is needed for this result.

4.4. Limitations

This study had several limitations. First, this study did not include a control group because of the difficulty in enrolling participants without a history of headache attacks that were caused by migraines. Due to the high prevalence of headache symptoms and disorders, it could not be ensured that the patients with migraine or other headache disorders were excluded from the control group undergoing EEG. However, we found the EEG abnormalities by the board-certified EEGers and showed that no difference was observed between MA/MO patients in migraineurs correctly diagnosed by the board-certified headache specialists. Second, the number of patients was insufficient especially for multivariate analysis. Therefore, it was not possible to evaluate all clinical variables in multivariate analysis. Third, in this study, clinical variables were collected from the medical records. Therefore, the frequency of headache attacks was self-reported by patients, which we thought is considered as the best approach in clinical settings. We analyzed the frequency of “headache attacks” as clinical variables, although we thought these headache attacks were almost migraine attacks.

5. Conclusions

We found that FDS and FSDS at a certain rate in the EEG of migraineurs and that FSDS had relationships with clinical variables. Although further studies are needed to evaluate the clinical utility of the FSDS and FDS, they could be a biomarker related to the clinical variables and migraine pathology. Therefore, in future studies, it will be useful to focus on the FSDS and record EEG during the aura phase. In addition, it is clinically

467 useful for migraineurs to show FSDS as well as FDS at a certain rate on EEG. Diseases
468 other than general migraine should be considered if patients have severe EEG
469 abnormalities beyond our report. Further EEG studies in patients with hemiplegic
470 migraine with severe symptoms and clear genetic factors could elucidate the usefulness
471 of wide-band digital EEG in migraineurs.

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Conflict of Interest Statement

The authors declared the following potential conflict of interest with respect to the research, authorship, and/or publication of this article: KU belongs to the Department of Epilepsy, Movement Disorders and Physiology, Kyoto University Graduate School of Medicine, which is an Industry-Academia Collaboration supported by a grant from Eisai Co., Ltd, NIHON KOHDEN CORPORATION, Otsuka Pharmaceutical Co., and UCB Japan Co., Ltd.,

AI belongs to the Department of Epilepsy, Movement Disorders and Physiology, Kyoto University Graduate School of Medicine, which is an Industry-Academia Collaboration supported by a grant from Eisai Co., Ltd, NIHON KOHDEN CORPORATION, Otsuka Pharmaceutical Co., and UCB Japan Co., Ltd., and received research supports from Japanese Society for the Promotion of Science KAKENHI (20K21573).

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Author Contributions

KH and KU contributed to the conception and design of the study, acquisition and analysis of data, drafting a significant portion of the manuscript or figures

Yuu Tatsuoka: acquisition and analysis of data

DD, TT, and Yoshihisa Tatsuoka contributed to the acquisition of data, conception and design of the study

RT contributed to the conception and design of the study

AI contributed to the conception and design of the study, analysis or interpretation of data

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Data Availability

The data and data codes used in this study are available upon reasonable request from the corresponding author.

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Figure Legends

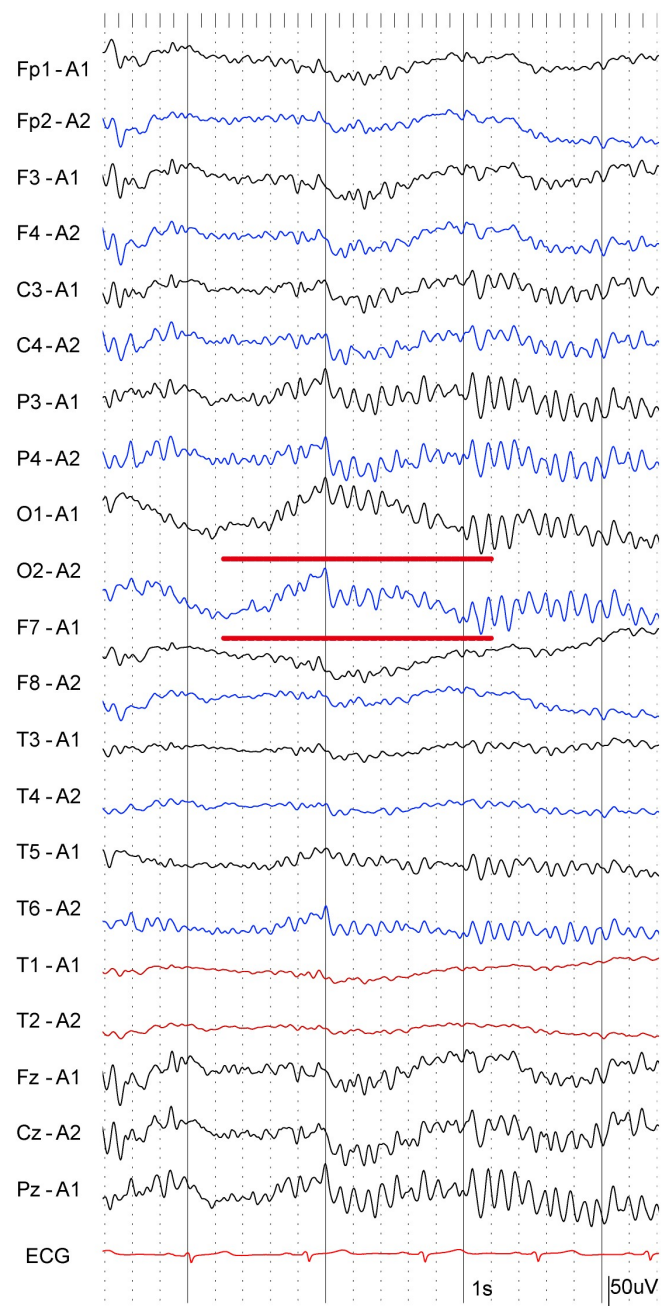
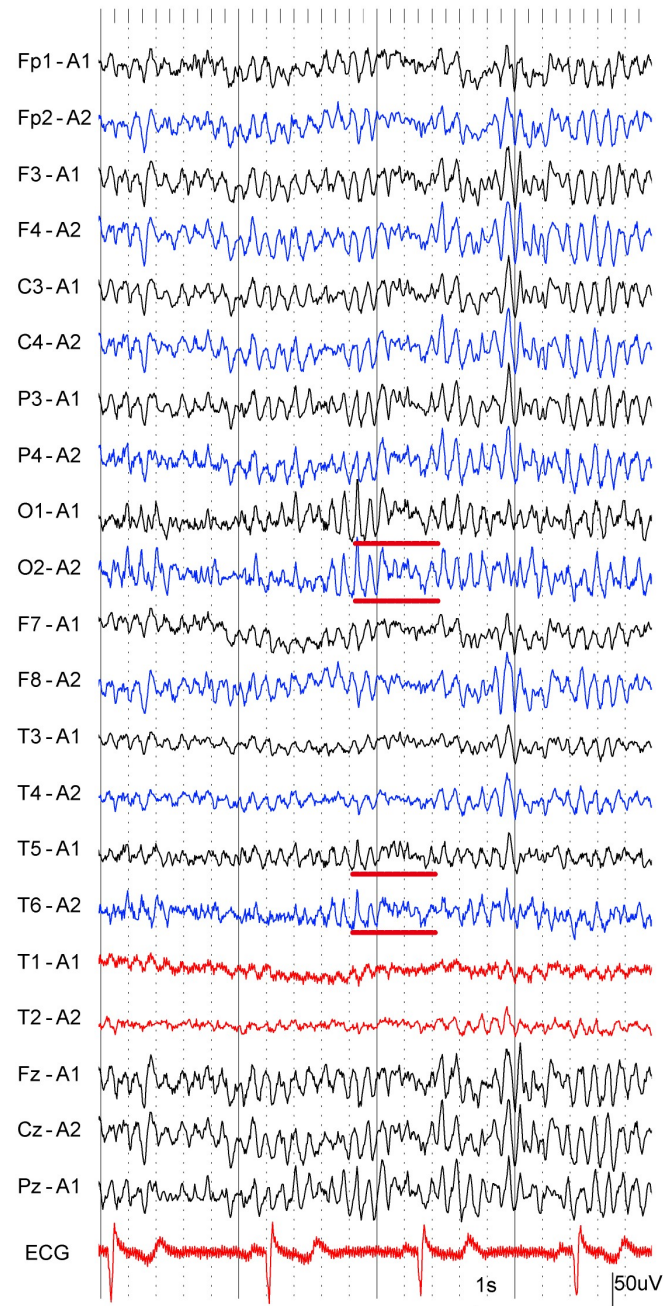
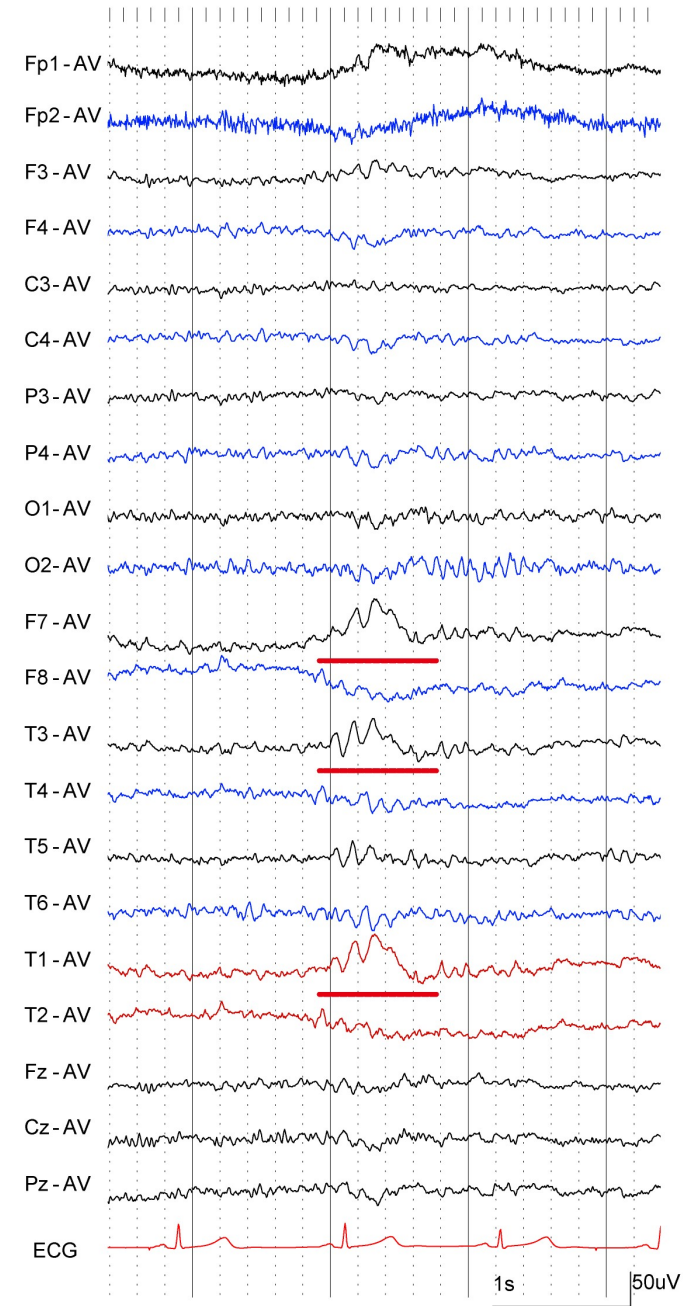
Figure 1. Representative EEG waveforms in migraineurs. (A) Focal subdelta slow (FSDS) on the bilateral occipital observed in a 31-year-old female patient with migraine with aura (MA). (B) Focal delta slow (FDS) on the bilateral occipital area observed in a 53-year-old female patient with MA. (C) FDS on the left frontotemporal observed in a 53-year-old female patient with migraine without aura (MO). Time constant (TC) 2 s (high-pass filter 0.08 Hz) in (A), TC 0.3 s (high-pass filter 0.53 Hz) in (B) and (C). Low-pass filter is 15 Hz in (A), 120 Hz in (B) and (C).

Figure 2. The number and the location of FSDS and FDS. (A) Effect of age and MA/MO status of patients on FSDS occurrence. Note that FSDS tended to be observed in patients younger than 40 years and was equally found in both MA patients and MO patients. (B) Age and MA/MO status of patients linked to FDS. Patients younger than 40 years tended to have FDS in the posterior area while patients at age 40 years and older tended to have temporal FDS. FDS was equally seen in both MA patients and MO patients. O: occipital, PO: parietooccipital, PQ: posterior quadrant, T: temporal, F: frontal, multi: multiple, none: no FSDS or no FDS. All other conventions are the same as in Figure 1.

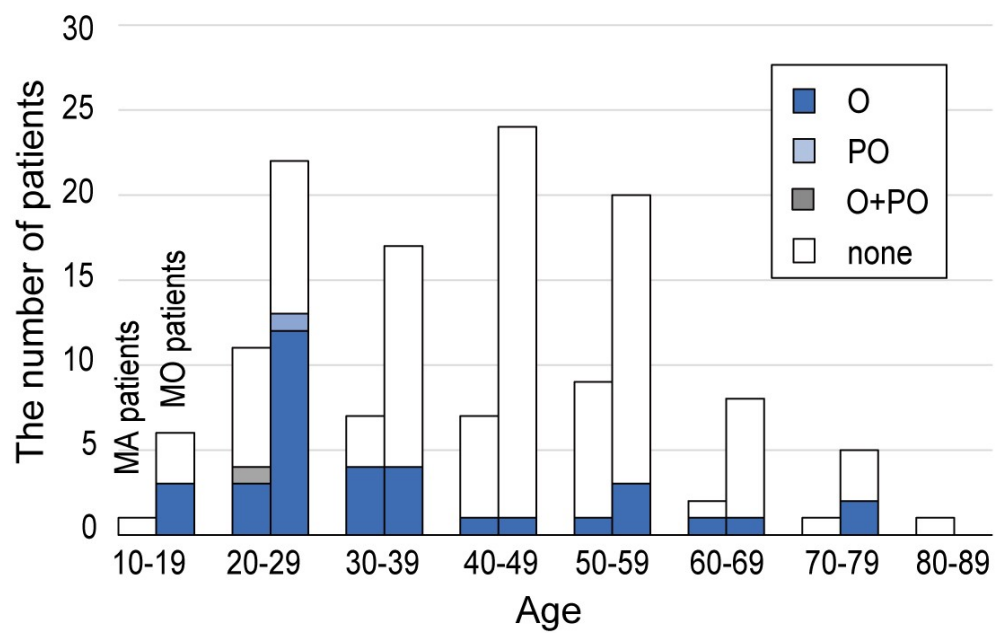
Figure 3. Symptomatic phase dependence on EEG findings in migraineurs. (A) The occurrence rate and location of FSDS in variable phases of migraine. (B) The occurrence rate and location of FDS in variable phases of migraine. Note that the occurrence rate of FDS was not significantly different in each phase. * $p < 0.05$. The

other conventions are the same as in Figure 2. †Symptomatic phase includes prodrome, headache, and postdrome. The phase of aura was not included in the symptomatic phase because no cases of EEG recorded during aura were obtained.

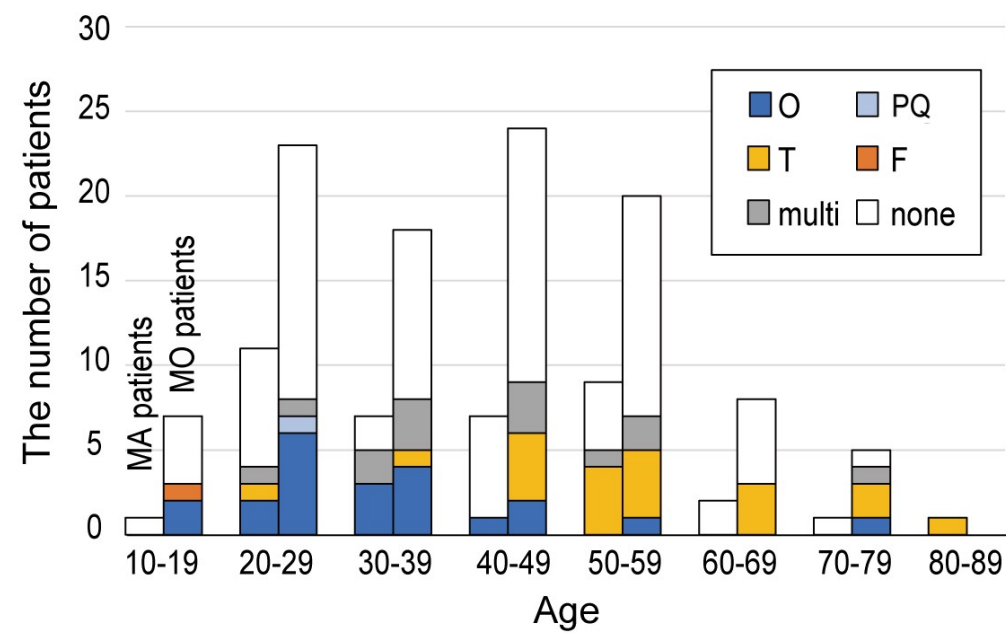
Figure 4. Effect of family history on EEG findings. (A) The occurrence rate and location of FSDS in migraineurs with family history (FH+) and in those without (FH-). (B) The occurrence rate and location of FDS in migraineurs with FH+ and FH-. The other conventions are the same as in Figure 2.

A**B****C**

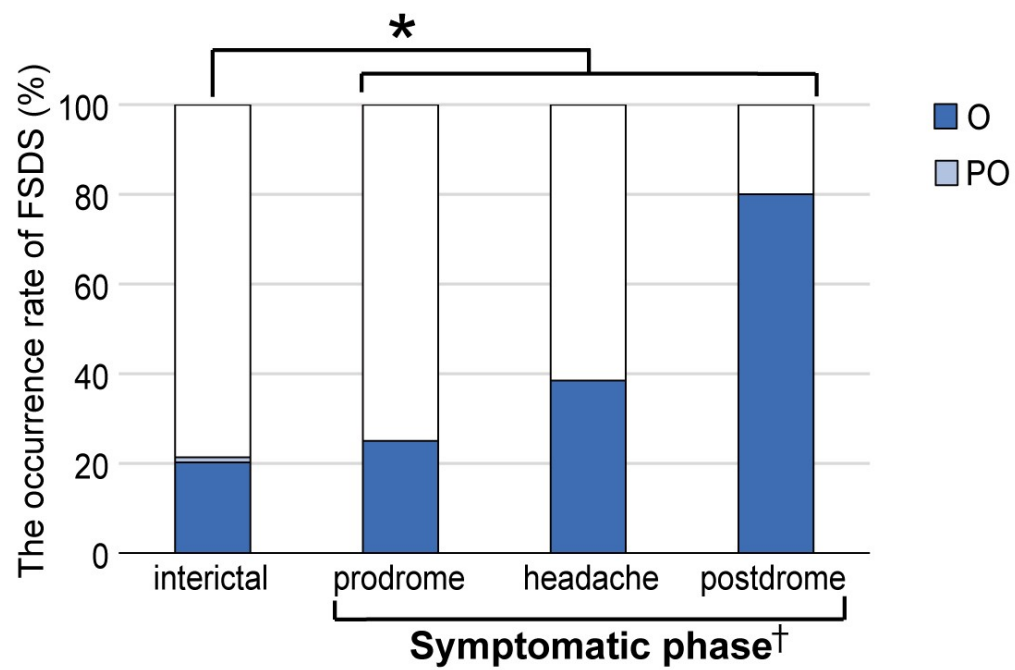
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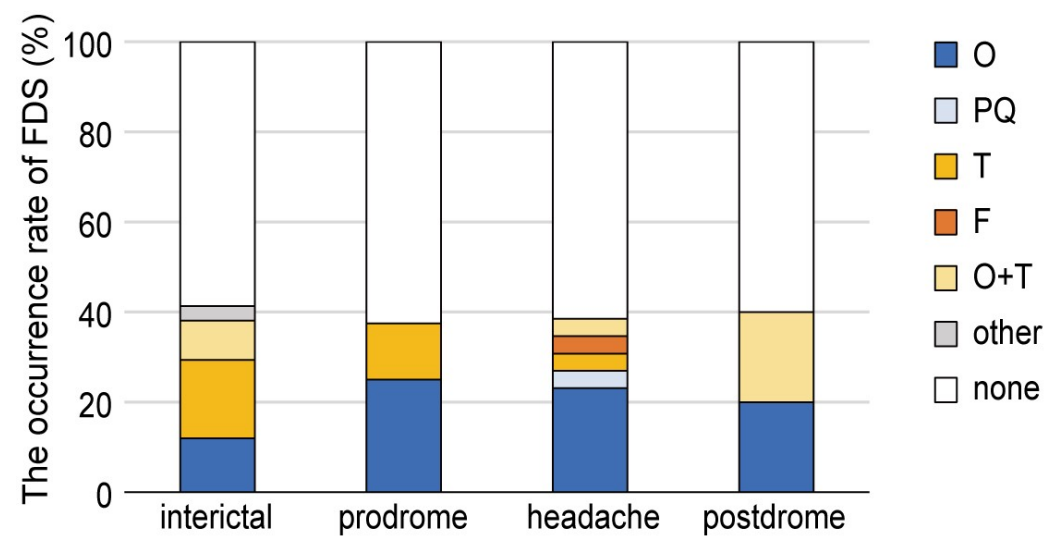
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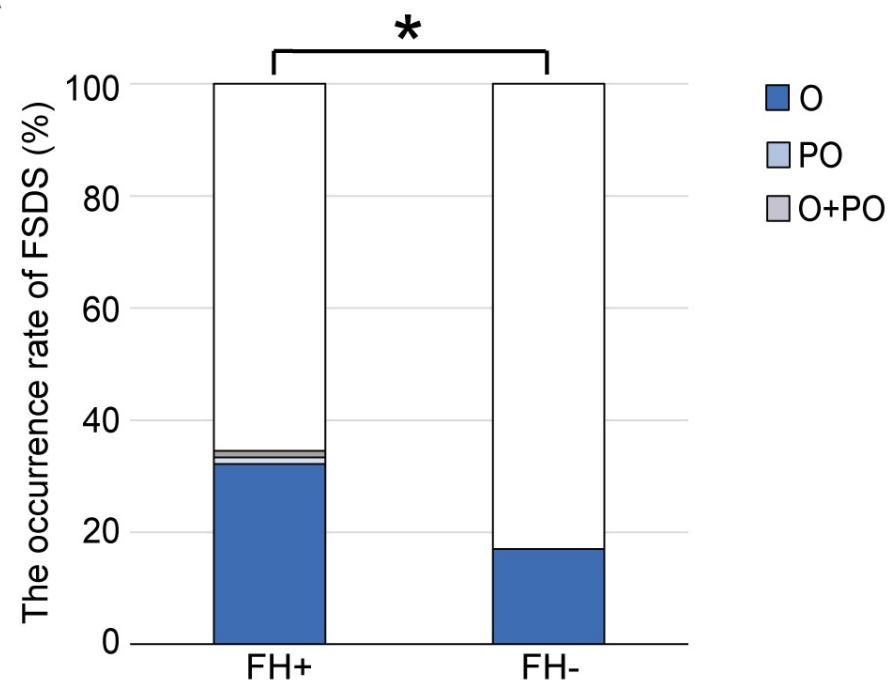
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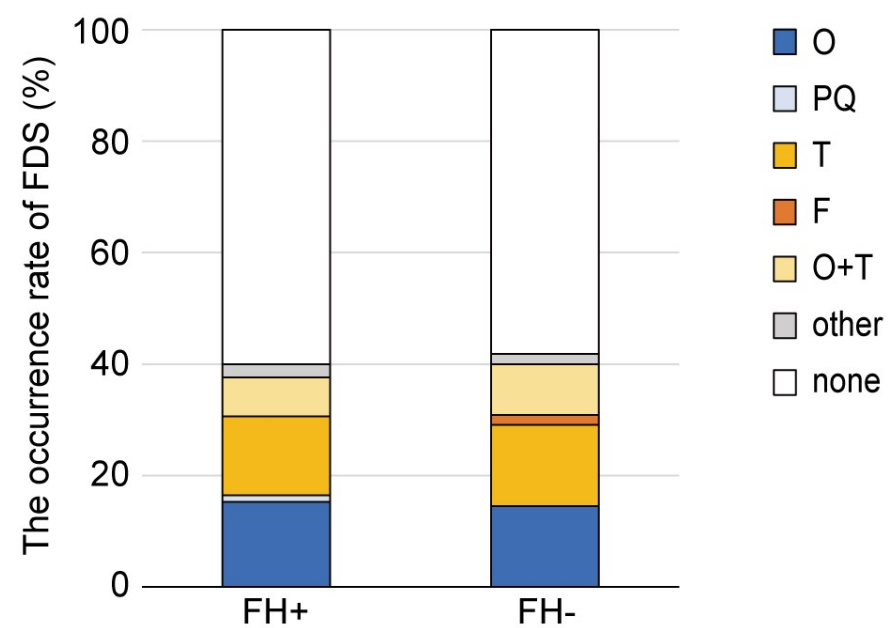


Table 1. Patient demographics

Clinical variables	MA patients n = 39	MO patients n = 105	Total n = 144	<i>p</i> -value MA patients vs. MO patients
Age, y (mean $\pm$ SD)	41.8 $\pm$ 16.5	41.6 $\pm$ 14.9	41.7 $\pm$ 15.3	0.95 ^a
Female, n	31	93	124	0.16 ^b
Phase of migraine while recording EEG, n (%)				
Interictal	22 (59.5)	70 (68.6)	92 (66.2)	0.31 ^b
Prodrome	4 (10.8)	12 (11.8)	16 (11.5)	1 ^c
Aura	0 (0)	0 (0)	0 (0)	
Headache	10 (27.0)	16 (15.7)	26 (18.7)	0.13 ^b
Postdrome	1 (2.7)	4 (3.9)	5 (3.6)	1 ^c
Positive Family History	22	63	85	0.86 ^b
Frequency of headache attacks (/month) mean (range)	6.5 (0-30)	9.9 (0-30)	9.0 (0-30)	0.015 ^{a*}
Days since last attack, days mean (range)	12.7 (1-45)	8.0 (0-60)	9.0 (0-60)	0.22 ^a
Disease duration, y mean (range)	24.6 (1-73.5)	21.9 (0-60)	22.6 (0-73.5)	0.39 ^a
Age at onset of migraine, y mean (range)	16.8 (3-36)	19.5 (3-58)	18.8 (3-58)	0.12 ^a
Worsening by menstruation	13/29	54/85	66/114	0.08 ^b
Positive history of abdominal migraine	8	14	22	0.26 ^b
Frequency of drug use for headache attack (/month) mean (range)	7.7 (0-75)	8.1 (0-60)	8.0 (0-75)	0.88 ^a
Use of drugs for prophylaxis	12	48	60	0.13 ^b
Use of psychiatric drugs and/or antiseizure drugs	6	33	39	0.06 ^b
Sleep period during EEG recording (%) mean (range)	37.8 (0-70)	41.9 (0-90)	40.8 (0-90)	0.31 ^a

Abbreviations MA, migraine with aura; MO, migraine without aura

p-values were calculated using Welch's *t* test (a), chi-square test (b), and Fisher's exact test (c).

Patients with unavailable data were excluded before *p*-value calculation for each clinical variable.

Table 2. The occurrence rate of FSDS in each clinical variable.

Clinical variables	FSDS (%)	Odds ratio [95% CI]	<i>p</i> -value
Phase of migraine			
Symptomatic phase	18/47 (38.3%)		
Prodrome	4/16 (25.0%)	1.23 [0.36-4.24] ^d	
Headache	10/26 (38.5%)	2.30 [0.90-5.89] ^d	
Postdrome	4/5 (80.0%)	14.7 [1.55-139.71] ^d	
Interictal phase	19/89 (21.3%)	2.29 [1.05-4.97]	0.035*
Family History			
+	29/84 (34.5%)		
-	9/53 (17.0%)	2.58 [1.11-6.01]	0.026*
Age			
< 40 years old	28/64 (43.8%)		
≥ 40 years old	10/77 (13.0%)	5.21 [2.28-11.93]	<0.0001*
Sex			
Female	37/122 (30.3%)		
Male	1/19 (5.3%)	7.84 [1.01-60.89]	0.022*
Frequency of headache attacks			
≥ 15/month	12/28 (42.9%)		
9-14/month	2/20 (10.0%)	6.75 [1.31-34.85]^b	0.014*^b
0-8/month	24/93 (25.8%)	2.16 [0.89-5.2] ^c	0.084 ^c
Frequency of drug use for headache attacks			
< 10/month	28/107 (26.2%)		
≥ 10/month	9/30 (30.0%)	0.83 [0.34-2.02]	0.68
Disease duration			
< 20 years	24/66 (36.4%)		
≥ 20 years	14/72 (19.4%)	2.37 [1.10-5.11]	0.026*
Age at onset of migraine			
< 20 years old	31/87 (35.6%)		
≥ 20 years old	7/51 (13.7%)	3.48 [1.40-8.65]	0.0054*
Latest attack			
The day and the day before	5/17 (29.4%)		
≥ 2 days ago	11/62 (17.7%)	1.93 [0.56-6.61]	0.32 ^a
Use of drugs for prophylaxis			
+	15/59 (25.4%)		
-	23/81 (28.4%)	0.86 [0.40-1.84]	0.70
Use of psychiatric drugs and/or antiseizure drugs			
+	10/38 (26.3%)		
-	28/102 (27.5%)	0.94 [0.41-2.19]	0.89
Worsening by menstruation			
+	19/66 (28.8%)		
-	15/46 (32.6%)	0.84 [0.37-1.89]	0.67
History of abdominal migraine			
+	3/22 (13.6%)		
-	33/114 (28.9%)	0.39 [0.11-1.4]	0.14
Sleep period during EEG recordings			
+	38/134 (28.4%)		
-	0/10 (0.0%)	3.96 [0.49-31.99]	0.063 ^a

Abbreviations: FSDS, focal subdelta slow; CI, confidence interval

p-values were calculated using the chi-square test. ^a Calculated using Fisher's exact test. ^b Comparison between ≥ 15/month and 9-14/month. ^c Comparison between ≥ 15/month and 0-8/month. ^d Comparison with interictal phase. FSDS was not evaluated in 3 patients because their baseline drifts prevented us from EEG evaluation with a time constant 2 s. These 3

patients were excluded from this analysis. Patients with unavailable data were excluded before the p -value calculation for each clinical variable. Whether migraines worsened during menstruation was assessed in female patients.

Table 3. The occurrence rate of FDS in each clinical variable.

Clinical variables	FDS+ (%)	Odds ratio [95% CI]	<i>p</i> -value
Phase of migraine			
Symptomatic phase	18/47 (38.3%)		
Prodrome	6/16 (37.5%)	0.85 [0.29-2.55] ^d	
Headache	10/26 (38.5%)	0.89 [0.36-2.17] ^d	
Postdrome	2/5 (40.0%)	0.95 [0.15-5.95] ^d	
Interictal phase	38/92 (41.3%)	0.88 [0.43-1.81]	0.73
Family History			
+	34/85 (40.0%)		
-	23/55 (41.8%)	0.93 [0.47-1.85]	0.83
Age			
< 40 years old	28/67 (41.8%)		
≥ 40 years old	30/77 (39.0%)	1.12 [0.58-2.19]	0.73
Sex			
Female	53/124 (42.7%)		
Male	5/20 (25.0%)	2.24 [0.77-6.55]	0.13
Frequency of headache attacks			
≥ 15/month	12/28 (42.9%)		
9-14/month	7/20 (35.0%)	1.39 [0.46-4.56] ^b	0.58 ^b
0-8/month	39/96 (40.6%)	1.1 [0.47-2.57] ^c	0.83 ^c
Frequency of drug use for headache attacks			
< 10/month	45/110 (40.9%)		
≥ 10/month	11/30 (36.7%)	1.2 [0.52-2.75]	0.67
Disease duration			
< 20 years	30/69 (43.5%)		
≥ 20 years	28/72 (38.9%)	1.21 [0.62-2.37]	0.58
Age at onset of migraine			
< 20 years old	36/90 (40.0%)		
≥ 20 years old	22/51 (43.1%)	0.88 [0.44-1.76]	0.72
Latest attack			
The day and the day before	9/17 (52.9%)		
≥ 2 days ago	22/63 (34.9%)	2.1 [0.71-6.2]	0.18
Use of drugs for prophylaxis			
+	24/60 (40.0%)		
-	34/83 (41.0%)	0.96 [0.49-1.89]	0.91
Use of psychiatric drugs and/or antiseizure drugs			
+	18/39 (46.2%)		
-	40/104 (38.5%)	1.37 [0.65-2.88]	0.40
Worsening by menstruation			
+	30/67 (44.8%)		
-	18/47 (38.3%)	1.31 [0.61-2.79]	0.49
History of abdominal migraine			
+	5/22 (22.7%)		
-	51/117 (43.6%)	0.38 [0.13-1.1]	0.067
Sleep period during EEG recording			
+	53/134 (37.3%)		
-	5/10 (50.0%)	0.65 [0.18-2.37]	0.52 ^a

Abbreviations: FDS, focal delta slow; CI, confidence interval

p-values were calculated using the chi-square test. ^a Calculated using Fisher's exact test. ^b Comparison between ≥ 15/month and 9-14/month. ^c Comparison between ≥ 15/month and 0-8/month. ^d Comparison with interictal phase. Patients with unavailable data were excluded before the *p*-value calculation for each clinical variable. Whether migraines worsened during menstruation was assessed in female patients.

Table 4. Results between FSDS and 4 clinical variables by multivariate analysis.

Clinical variables	Odds ratio [95% CI]	<i>p</i>-value
Phase of migraine		
Postdrome vs Interictal	49.00 [3.89-616.66]	0.0026*
Postdrome vs Prodrome	46.28 [2.99-715.78]	0.0061*
Postdrome vs Headache	32.79 [2.23-481.96]	0.011*
Headache vs Interictal	1.49 [0.48-4.66]	0.49
Headache vs Prodrome	1.41 [0.30-6.73]	0.67
Prodrome vs Interictal	1.06 [0.27-4.14]	0.93
Family History		
+ vs -	2.49 [0.93-6.71]	0.070
Age		
< 40 years old vs $\geq$ 40 years old	5.67 [2.07-15.50]	0.0007*
Sleep		
% during EEG recordings	1.04 [1.02-1.07]^a	0.0009*

Abbreviations: FSDS, focal subdelta slow; CI, confidence interval

^a: unit odds ratio

Table S1. Patient demographics (exclusion of comorbidities)

Clinical variables	MA patients n = 33	MO patients n = 69	Total n = 102	<i>p</i> -value MA patients vs. MO patients
Age, y (mean $\pm$ SD)	39.8 $\pm$ 14.6	41.0 $\pm$ 15.1	40.6 $\pm$ 14.9	0.72 ^a
Female, n	25	62	87	0.08 ^c
Phase of migraine while recording EEG, n (%)				
Interictal	18 (56.3)	49 (74.2)	67 (68.4)	0.07 ^b
Prodrome	3 (9.3)	8 (12.1)	11 (11.2)	1 ^c
Aura	0 (0)	0 (0)	0 (0)	
Headache	10 (31.3)	8 (12.1)	18 (18.4)	0.02 ^{b*}
Postdrome	1 (3.1)	1 (1.5)	2 (2.0)	0.55 ^c
Positive Family History	18	44	62	0.47 ^b
Frequency of headache attacks (/month) mean (range)	5.9 (0.5-20)	8.0 (0-30)	7.3 (0-30)	0.12 ^a
Days since last attack, days mean (range)	13.8 (1-45)	8.8 (0-60)	10.0 (0-60)	0.29 ^a
Disease duration, y mean (range)	23.8 (6-55)	21.1 (0-46)	22.0 (0-55)	0.37 ^a
Age at onset of migraine, y mean (range)	16.5 (3-36)	19.6 (3-58)	18.6 (3-58)	0.15 ^a
Worsening by menstruation	12/25	33/57	45/82	0.41 ^b
Positive history of abdominal migraine	8	9	17	0.12 ^b
Frequency of drug use for headache attack (/month) mean (range)	6.0 (0-60)	5.9 (0-30)	6.0 (0-60)	0.96 ^a
Use of drugs for prophylaxis	10	26	36	0.53 ^b
Use of psychiatric drugs and/or antiseizure drugs	2	14	16	0.07 ^b
Sleep period during EEG recording (%) mean (range)	38.3 (0-70)	42.9 (0-90)	41.4 (0-90)	0.31

Abbreviations MA, migraine with aura; MO, migraine without aura

p-values were calculated using Welch's *t* test (a), chi-square test (b), and Fisher's exact test (c).

Patients with unavailable data were excluded before *p*-value calculation for each clinical variable.

Table S2. The occurrence rate of FSDS in each clinical variable (exclusion of comorbidities).

Clinical variables	FSDS (%)	Odds ratio [95% CI]	<i>p</i> -value
Phase of migraine			
Symptomatic phase	12/31 (38.7%)		
Prodrome	2/11 (18.2%)	0.68 [0.13-3.48] ^d	
Headache	8/18 (44.4%)	2.45 [0.83-7.27] ^d	
Postdrome	2/2 (100.0%)	6.13 [0.52-72.1] ^d	
Interictal phase	16/65 (24.6%)	1.93 [0.77-4.84]	0.16
Family History			
+	22/61 (36.1%)		
-	7/35 (20.0%)	2.26 [0.85-6.01]	0.099
Age			
< 40 years old	23/47 (48.9%)		
≥ 40 years old	6/53 (11.3%)	7.51 [2.70-20.91]	<0.0001*
Sex			
Female	28/86 (32.6%)		
Male	1/14 (7.1%)	6.28 [0.78-50.41]	0.061 ^a
Frequency of headache attacks			
≥ 15/month	9/15 (60.0%)		
9-14/month	0/8 (0.0%)	12.0 [1.18-122.28]^b	0.0072^{a*}
0-8/month	20/77 (26.0%)	4.28 [1.35-13.53]^c	0.015^{a*}
Frequency of drug use for headache attacks			
< 10/month	22/82 (26.8%)		
≥ 10/month	6/14 (42.9%)	0.49 [0.15-1.57]	0.34 ^a
Disease duration			
< 20 years	21/51 (41.2%)		
≥ 20 years	8/47 (17.0%)	3.41 [1.33-8.76]	0.0089*
Age at onset of migraine			
< 20 years old	23/65 (35.4%)		
≥ 20 years old	6/33 (18.2%)	2.46 [0.89-6.84]	0.078
Latest attack			
The day and the day before	4/9 (44.4%)		
≥ 2 days ago	9/47 (19.1%)	3.38 [0.75-15.17]	0.19 ^a
Use of drugs for prophylaxis			
+	9/36 (25.0%)		
-	20/63 (31.7%)	0.72 [0.28-1.80]	0.48
Use of psychiatric drugs and/or antiseizure drugs			
+	4/16 (25.0%)		
-	25/83 (30.1%)	0.77 [0.23-2.63]	0.77 ^a
Worsening by menstruation			
+	13/44 (29.5%)		
-	13/37 (35.1%)	0.77 [0.30-1.97]	0.59
History of abdominal migraine			
+	2/17 (11.8%)		
-	26/81 (32.1%)	0.28 [0.06-1.33]	0.14 ^a
Sleep period during EEG recordings			
+	29/94 (30.9%)		
-	0/6 (0.0%)	2.68 [0.31-23.25]	0.18 ^a

Abbreviations: FSDS, focal subdelta slow; CI, confidence interval

p-values were calculated using the chi-square test. ^a Calculated using Fisher's exact test. ^b Comparison between ≥ 15/month and 9-14/month. ^c Comparison between ≥ 15/month and 0-8/month. ^d Comparison with interictal phase. FSDS was not evaluated in 3 patients because their baseline EEG drifts prevented us from evaluation with a time constant 2s. These 3 patients

were excluded from this analysis. Patients with unavailable data were excluded before the p -value calculation for each clinical variable. Whether migraines worsened during menstruation was assessed in female patients.

Table S3. The occurrence rate of FDS in each clinical variable (exclusion of comorbidities).

Clinical variables	FDS+ (%)	Odds ratio [95% CI]	<i>p</i> -value
Phase of migraine			
Symptomatic phase	13/31 (41.9%)		
Prodrome	4/11 (36.4%)	0.96 [0.26-3.61] ^d	
Headache	8/18 (44.4%)	1.34 [0.47-3.85] ^d	
Postdrome	1/2 (50.0%)	1.68 [0.10-28.07] ^d	
Interictal phase	25/67 (37.3%)	1.21 [0.51-2.89]	0.66
Family History			
+	25/62 (40.3%)		
-	14/36 (38.9%)	1.06 [0.46-2.46]	0.89
Age			
< 40 years old	23/49 (46.9%)		
≥ 40 years old	17/53 (32.1%)	1.87 [0.84-4.19]	0.12
Sex			
Female	37/87 (43.7%)		
Male	3/15 (20.0%)	2.96 [0.78-11.24]	0.099
Frequency of headache attacks			
≥ 15/month	6/15 (40.0%)		
9-14/month	1/8 (12.5%)	5.33 [0.52-54.35] ^b	0.058 ^a
0-8/month	33/79 (41.8%)	0.93 [0.30-2.86] ^c	0.90
Frequency of drug use for headache attacks			
< 10/month	34/84 (40.5%)		
≥ 10/month	4/14 (28.6%)	1.70 [0.49-5.87]	0.40
Disease duration			
< 20 years	23/53 (43.4%)		
≥ 20 years	17/47 (36.2%)	1.35 [0.60-3.03]	0.46
Age at onset of migraine			
< 20 years old	25/67 (37.3%)		
≥ 20 years old	15/33 (45.5%)	0.71 [0.31-1.66]	0.43
Latest attack			
The day and the day before	4/9 (44.4%)		
≥ 2 days ago	15/47 (31.9%)	1.71 [0.40-7.28]	0.47 ^a
Use of drugs for prophylaxis			
+	13/36 (36.1%)		
-	27/65 (41.5%)	0.80 [0.34-1.84]	0.59
Use of psychiatric drugs and/or antiseizure drugs			
+	8/16 (50.0%)		
-	32/85 (37.6%)	1.66 [0.57-4.85]	0.35
Worsening by menstruation			
+	20/45 (44.4%)		
-	13/37 (35.1%)	1.48 [0.60-3.62]	0.39
History of abdominal migraine			
+	2/17 (11.8%)		
-	37/83 (44.6%)	0.17 [0.036-0.77]	0.012*
Sleep period during EEG recordings			
+	37/96 (38.5%)		
-	3/6 (50.0%)	0.63 [0.12-3.27]	0.68 ^a

Abbreviations: FDS, focal delta slow; CI, Confidence interval

p-values were calculated using the chi-square test. ^a Calculated using Fisher's exact test. ^b Comparison between ≥ 15/month and 9-14/month. ^c Comparison between ≥ 15/month and 0-8/month. ^d Comparison with interictal phase. Patients with unavailable data were excluded before the *p*-value calculation for each clinical variable. Whether migraines worsened during menstruation was assessed in female patients.

		psychiatric drugs and/or antiseizure drugs	reason for use
Ta1	45f	amitriptyline hydrochloride	migraine prophylaxis
Ta2	50f	topiramate	migraine prophylaxis
Ta6	57m	amitriptyline hydrochloride	migraine prophylaxis
Ta8	60f	sodium valproate, amitriptyline hydrochloride	migraine prophylaxis
Ta14	69f	ethyl loflazepate	unknown
Ta15	64f	sodium valproate	migraine prophylaxis
Ta22	37f	amitriptyline hydrochloride	migraine prophylaxis
Ta24	51m	duloxetine hydrochloride	migraine prophylaxis
Ta28	34f	sodium valproate, medazepam	depression
Ta29	57f	sodium valproate, amitriptyline hydrochloride	migraine prophylaxis
Ta30	53f	sodium valproate, ethyl loflazepate	migraine prophylaxis
Ta33	42f	amitriptyline hydrochloride	migraine prophylaxis
Ta36	78f	ethyl loflazepate	anxiety disorder
Ta37	27f	lorazepam, sertraline hydrochloride, mirtazapine	depression
Ta43	70f	amitriptyline hydrochloride	migraine prophylaxis
Ta45	52f	topiramate, duloxetine hydrochloride	migraine prophylaxis
Ta46	43f	sodium valproate, duloxetine hydrochloride, ethyl loflazepate	migraine prophylaxis
Ta52	42f	sodium valproate, amitriptyline hydrochloride	migraine prophylaxis
Ta57	76f	amitriptyline hydrochloride, topiramate	migraine prophylaxis
Ta58	48f	mirtazapine	migraine prophylaxis
Ta59	54f	clonazepam, amitriptyline hydrochloride, sodium valproate	unknown
Ta63	40f	amitriptyline hydrochloride	migraine prophylaxis
Ta64	51f	clonazepam, quetiapine fumarate, lithium carbonate, brotizolam	depression, personality disorder
Ta65	67m	sodium valproate, clonazepam	migraine prophylaxis, unknown
Ta68	61f	amitriptyline hydrochloride, topiramate, sodium valproate	migraine prophylaxis
Ta69	74f	sodium valproate	migraine prophylaxis
Ta74	58f	amitriptyline hydrochloride, sodium valproate	migraine prophylaxis
To4	39f	etizolam	unknown
To8	24m	sodium valproate	migraine prophylaxis
To11	28f	brotizolam	unknown
To21	36f	ethyl loflazepate, pregabalin	migraine prophylaxis
To23	30f	lamotrigine, clonazepam, aripiprazole, duloxetine hydrochloride	depression
To25	17m	alprazolam, sertraline hydrochloride, brotizolam	depression
To27	25f	amitriptyline hydrochloride	migraine prophylaxis
To28	35f	clotiazepam	panic disorder
To41	23f	pregabalin	migraine prophylaxis
To46	61f	triazolam, etizolam	unknown
To60	35m	escitalopram oxalate, ethyl loflazepate	migraine prophylaxis
To91	39f	zolpidem tartrate	unknown

1-1. The relationship between the dominant side of habitual headache and the side of FSDS

The side of FSDS	The side of headache					
		Right	Left	Right & Left independently	Bilateral	Total
	Right	0	0	0	1	1
	Left	0	0	0	0	0
	Bilateral	4	1	4	10	19
	No FSDS	10	6	5	19	40
	N/A	0	1	0	2	3
	total	14	8	9	32	63

1-2. The relationship between the dominant side of habitual headache and the side of FDS

The side of FDS	The side of headache					
		Right	Left	Right & Left independently	Bilateral	Total
	Right	0	0	1	0	1
	Left	3	0	0	1	4
	Bilateral	5	3	3	11	22
	No FDS	6	5	5	20	36
	total	14	8	9	32	63

Abbreviations FDS, focal delta slow; FSDS, focal subdelta slow.

Sixty-three patients were included in this analysis; 81 patients out of 144 patients were excluded because it was difficult to determine the dominant side of symptoms due to a lack of accurate information regarding the laterality of symptoms.

2-1. The dominant side of headache and the side of FSDS in patients in headache phase patients

The side of headache during EEG recording					
The side of FSDS		Right	Left	Bilateral	Total
	Right	0	0	0	0
	Left	0	0	0	0
	Bilateral	2	0	1	3
	No FSDS	2	3	2	7
	total	4	3	3	10

2-2. The dominant side of headache and the side of FDS in headache phase patients

The side of headache during EEG recording					
The side of FDS		Right	Left	Bilateral	Total
	Right	0	0	0	0
	Left	0	1	1	2
	Bilateral	1	1	0	2
	No FDS	3	1	2	6
	total	4	3	3	10

Abbreviations FDS, focal delta slow; FSDS, focal subdelta slow.

Ten patients were included in this analysis. Sixteen of the 26 patients in the headache phase were excluded because it was difficult to determine the dominant side of the symptoms due to a lack of accurate information on symptom laterality.

3-1. The dominant side of habitual aura and the side of FSDS in patients with MA

		The side of habitual aura			
The side of FSDS		Right	Left	No laterality	Total
	Right	0	0	0	0
	Left	0	0	0	0
	Bilateral	0	2	3	5
	No FSDS	1	1	6	8
	total	1	3	9	13

3-2. The dominant side of habitual aura and the side of FDS in patients with MA

		The side of habitual aura			
The side of FDS		Right	Left	No laterality	Total
	Right	0	0	0	0
	Left	1	0	2	3
	Bilateral	0	2	2	4
	No FDS	0	1	5	6
	total	1	3	9	13

Abbreviations FDS, focal delta slow; FSDS, focal subdelta slow; MA, migraine with aura

Thirteen patients with MA were included in this analysis. Of the 39 patients with MA, 26 were excluded because it was difficult to determine the dominant side of the symptoms due to a lack of accurate information on symptom laterality.

4-1. The dominant side of habitual aura and the side of FSDS in headache phase MA patients

		The side of habitual aura			
The side of FSDS		Right	Left	No laterality	Total
	Right	0	0	0	0
	Left	0	0	0	0
	Bilateral	0	1	1	2
	No FSDS	0	0	2	2
	total	0	1	3	4

4-2. The dominant side of habitual aura and the side of FDS in headache phase MA patients

		The side of habitual aura			
The side of FDS		Right	Left	No laterality	Total
	Right	0	0	0	0
	Left	0	0	1	1
	Bilateral	0	1	0	1
	No FDS	0	0	2	2
	total	0	1	3	4

Abbreviations FDS, focal delta slow; FSDS, focal subdelta slow; MA, migraine with aura

Four patients with MA were included in this analysis. Six of the 10 MA patients in the headache phase were excluded because it was difficult to determine the dominant side of the symptoms owing to a lack of accurate information on symptom laterality.