Original article

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Factors underlying scalp-EEG interictal epileptiform discharges in intractable frontal lobe epilepsy

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ABSTRACT – Aims: Scalp-EEG interictal epileptiform discharges (IEDs) may be less predictive of the outcome of frontal lobe epilepsy surgery than of temporal lobe epilepsy surgery. We identified factors associated with the location of scalp-EEG IEDs in intractable frontal lobe epilepsy.
Methods: Ten factors were assessed in a retrospective review of 53 patients with either concordant (frontal lobe seizure focus) or discordant (generalized or outside frontal seizure focus) IED or both, who had excellent surgical outcomes. The Fisher exact test and the Wilcoxon rank sum test determined statistically significant associations.
Results: Thirty-six patients (68%) had concordant IED, 24 (45%) discordant IED, and 17 (32%) both. Younger age at onset was significantly associated with discordant IED (mean, 7.5 years *versus* 17 years for patients without discordant IED; $P < 0.01$), whereas duration of epilepsy was not. Seizure foci at the frontal convexity were associated with concordant IED. About 72% of patients with a convexity seizure focus had concordant IED, compared with only 33% of patients with mesial frontal foci having concordant IED ($P = 0.06$).
Conclusions: Early seizure onset in intractable frontal lobe epilepsy is associated with IEDs discordant with seizure focus. Frontal convexity seizure foci are more likely than mesial frontal seizure foci to be associated with concordant discharges.

KEY WORDS: frontal lobe epilepsy, interictal epileptiform discharges, intractable epilepsy, risk factors

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Intractable frontal lobe epilepsy is a common and disabling neurological condition, and frontal lobe epilepsy surgery is the second most common surgical treatment for epilepsy. The evaluation for frontal lobe epilepsy surgery is more complex than that for temporal lobe epilepsy surgery [1-3]. The frontal lobes are large, and the epileptogenic lesions located within them are often extensive [4, 5]. In addition, much of the frontal lobe cortex is inaccessible to standard scalp electroencephalography (EEG), and frontal lobe seizure discharges can spread rapidly to remote regions of the brain [5, 6].

In contrast to temporal lobe epilepsy surgery, frontal lobe epilepsy surgery has few predictive factors. We recently reported that there are only three presurgical factors predictive of surgical outcome for patients with frontal lobe epilepsy; the presence of a magnetic resonance imaging (MRI) lesion [7] or a frontal beta frequency EEG discharge at seizure onset is favorable, whereas febrile seizure history is unfavorable [8]. Scalp-EEG interictal epileptiform discharges (IEDs) are predictive of outcome in temporal lobe epilepsy surgery [9], but have not been found to have prognostic significance in frontal lobe epilepsy surgery [8]. In patients with intractable frontal lobe epilepsy, scalp-EEG IEDs are often absent or poorly localized [2, 8]. The basis for this situation is not entirely understood.

The aim of this study was to determine factors associated with the location of scalp-EEG IEDs in intractable frontal lobe epilepsy.

Patients and methods

To ensure that the seizure focus was frontal in location, we included only subjects who had excellent seizure control after surgery involving one frontal lobe. Subjects in this study were initially identified from our database of patients who underwent epilepsy surgery at Mayo Clinic, Rochester, Minnesota, between July 1, 1987, and December 31, 1999. The medical records of potential study subjects were reviewed, and the subjects were included in this study if they met the following criteria:

1) frontal lobe surgery performed for intractable epilepsy but not involving regions other than the frontal lobe;
2) no prior surgical treatment for seizure control;
3) comprehensive presurgical evaluation, including both routine outpatient EEG recording and video-EEG monitoring;
4) minimum postsurgical follow-up at 12 months;
5) excellent postsurgical outcome (seizure-free, aura only, or other simple partial seizures of fewer than three per year).

The medical records of patients who met the criteria were further reviewed to collect information about demographic variables, age at seizure onset, etiology and duration of epilepsy, associated risk factors, and neuroimaging findings. IEDs were defined as focal or generalized spikes or sharp waves with or without aftergoing slow waves [10]. The presence and location of scalp IEDs recorded before surgery were determined from both outpatient routine EEGs and prolonged video-EEG recordings. Because the majority of patients were seen for the first time in our clinic, specifically for an epilepsy surgery evaluation, the only outpatient EEG performed in our laboratory and included in this study for each patient was the one obtained prior to admission for video-EEG monitoring. Both wake and sleep portions of the recordings were reviewed by the electroencephalographers in the course of the patients' presurgical evaluation. The 20-channel outpatient EEG recordings used the 10-20 system of scalp electrode placement. The 32-channel, prolonged EEG monitoring had an additional low temporal chain of electrodes on each side. In both the outpatient EEG and the prolonged EEG monitoring, electrodes were placed along the midline of the cranium. During prolonged monitoring, the EEG was sampled for 20 seconds every half-hour. Both types of recordings included subtemporal chains of electrodes. Sphenoidal electrodes and computer programs for detecting spikes were not used.

The presence and distribution of IEDs in each patient were noted. IEDs were considered to be frontal lobe in location when they occurred exclusively at or maximally involved any of the following electrodes: Fpz, Fz, Fp1/Fp2, F3/F4, F7/F8, F9/F10 (Modified Combinatorial Nomenclature) on bipolar or monopolar montages. Concordant IED was defined as IEDs occurring at the frontal region ipsilateral to the seizure focus. Concordance was accepted when any of the above frontal electrodes were maximally involved, although it might not directly overlie the surgical site. Discordant IED was defined as IEDs appearing outside the frontal region with the seizure focus.

Factors assessed for association with distribution of IEDs were 1) a family history of seizure disorder (first-degree relatives); 2) a symptomatic epilepsy etiology; 3) history of major brain trauma that resulted in a loss of consciousness, intracranial hemorrhage, or cerebral contusion; 4) history of stroke; 5) the presence of a lesion on neuroimaging; 6) history of experiencing at least 1 secondarily generalized seizure; 7) history of at least 1 status epilepticus episode; 8) a frontal convexity location of seizure focus; 9) the age at which the patient first had an unprovoked seizure; and 10) the presurgical duration of epilepsy. The Fisher exact test was used for categorical variables to determine statistically significant associations among these 10 factors and IEDs. The Wilcoxon rank sum test was used to analyze continuous variables.

The study was approved by the Mayo Clinic Institutional Review Board (Human Safety Assurance Board).

Results

Fifty-three patients met study criteria. The frontal lobe surgical procedures included stereotactic lesionectomy (n = 20), focal cortical resection (n = 10), and maximal frontal resection (n = 23) [11]. The seizure focus location within the frontal lobe was determined when the surgical treatment was a lesionectomy or a focal cortical resection.

Eighteen patients had a convexity seizure focus, whereas the seizure focus in 12 patients was mesial frontal.

Table 1 summarizes the preoperative findings in the patient cohort. The majority of the 53 patients were men (62%). Symptomatic epilepsy etiology far exceeded cryptogenic etiology (72% *versus* 28%). Major brain trauma was the most frequent risk factor for epilepsy, having preceded seizure onset in about one-fourth of the patients. Most patients in the cohort also had lesional epilepsy as determined by neuroimaging. Secondarily generalized clinical seizures were extensive, occurring in nearly four-fifths of the patients. The mean age at seizure onset was 11 years, whereas the mean age at the time of surgical treatment was 29.8 years.

Figure 1 shows the distribution of the 53 patients according to type of scalp-EEG IEDs. Ten patients (18.9%) had no IEDs of any kind. IEDs were present in the frontal regions of 38 patients (71.7%), and five patients (9.4%) had either generalized IEDs or IEDs in areas outside the frontal regions. Thirty-six patients (68%) had concordant IED, 24 (45%) had discordant IED, and 17 (32%) had both.

An analysis of the factors associated with concordant IED showed no significant associations between it and 1) symptomatic epilepsy etiology, 2) a history of brain trauma or stroke, 3) lesions on neuroimaging, 4) the presence of secondarily generalized seizures, or 5) a history of status epilepticus *(table 2)*. However, the location of the seizure focus at the frontal convexity tended to be associated with concordant IED ($P = 0.06$). About 72% of the patients with a convexity seizure focus had concordant IED, whereas concordant IED was present in only 33% of the patients when the seizure focus was mesial frontal. Age at first seizure and presurgical duration of epilepsy were not significantly associated with the presence of concordant IED *(table 3)*.

An analysis of the factors associated with the presence of discordant IED showed no significant associations *(table 4)*. However, seizure onset occurred at an earlier age in patients with discordant IED than in patients without discordant IED (mean age 7.5 years *versus* 17 years; $P = 0.01$) *(table 5)*. The presurgical duration of epilepsy was not significant.

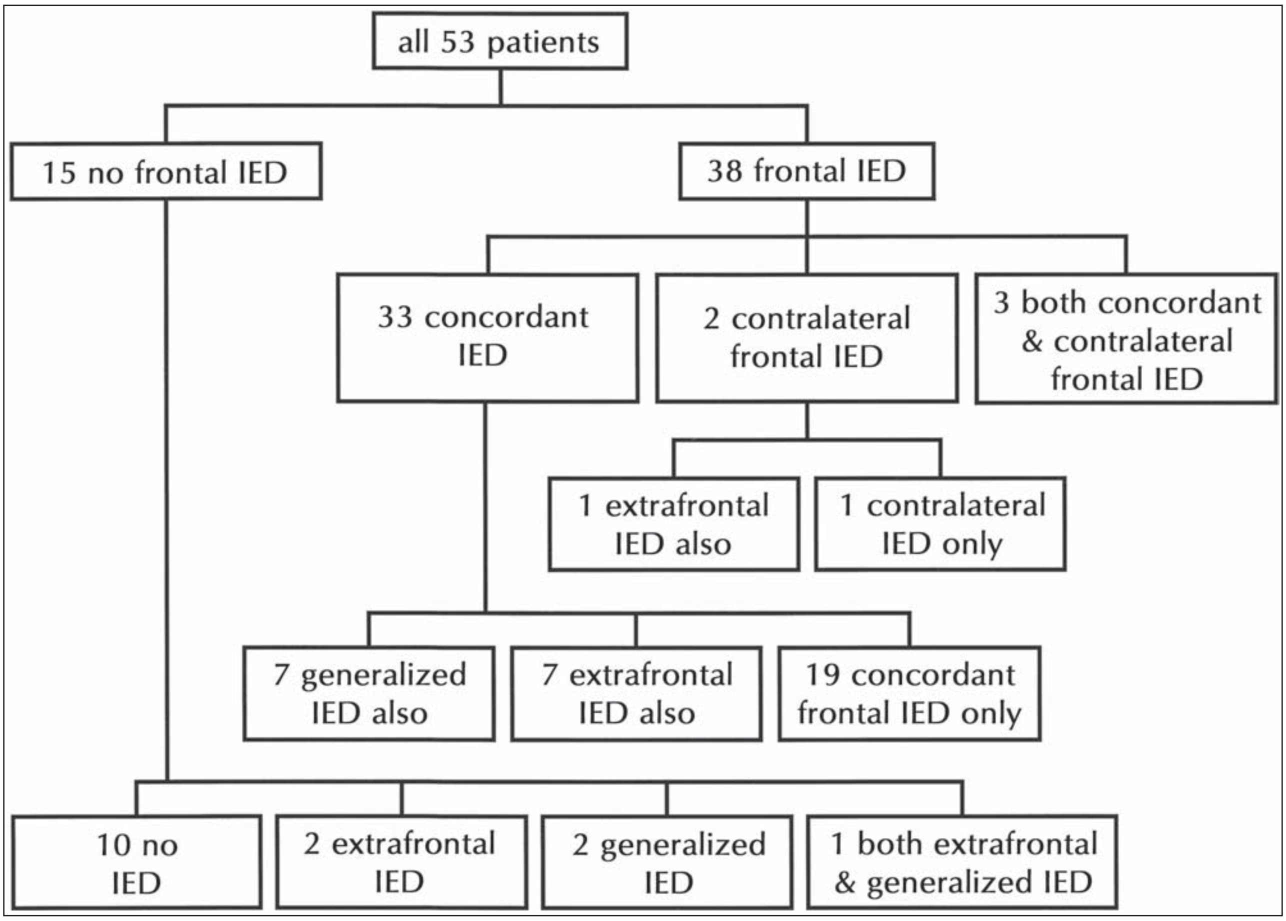

Figure 1. *Types of scalp-EEG, interictal epileptiform discharges (IEDs) in 53 patients with intractable frontal lobe epilepsy. Concordant IED consisted of discharges that occurred at the region of the frontal lobe seizure focus.*

Discussion

To accurately assess scalp-EEG IEDs in intractable frontal lobe epilepsy, we confined our study to patients whose seizures had been controlled after frontal lobe epilepsy surgery. Seizure control after frontal lobe surgery is considered to be the best evidence of localization of the seizure focus to the frontal lobe. This feature of our study should be noted when comparing our work with previous studies, many of which did not have a strict definition of frontal lobe epilepsy.

One limitation of studies involving scalp electrodes is that each electrode does not record exclusively EEG activities that arise from the area of the brain directly beneath it. Subdural electrodes may provide a closer topographic relationship between the recorded EEG and the surgical site, but subdural electrode coverage is infrequently multilobar or bilateral and therefore insufficient to detect IEDs that are multilobar or generalized. The purpose of our study was to understand better why some frontal lobe patients have scalp IEDs at the frontal lobe region, whereas other patients have IEDs outside this region. This study was not conducted to determine the accuracy of scalp IEDs in localizing the frontal epileptogenic focus.

Our findings demonstrate that nearly one-fifth of patients with intractable frontal lobe epilepsy do not have IEDs on scalp-EEG. A recent study found that patients who had no IEDs were more likely to have seizure onset in extratemporal regions, whereas patients with IEDs were more likely to have temporal lobe seizure onset [12]. However, it is not known how many patients with extratemporal epilepsy truly had frontal lobe epilepsy, because patients in that study also included those with ictal EEG onset at the frontotemporal, parietal, or occipital regions.

A high proportion (45%) of our patients had IEDs discordant with their frontal seizure foci, despite excellent outcome after resection of the foci. Rasmussen [13] reported similar findings, in that 35% of his patients had IEDs involving structures outside the frontal lobes, although prolonged EEG monitoring was not performed in most of his patients. As in our study, his study was restricted to patients who had an excellent outcome after an operation for frontal lobe epilepsy. Although a substantial proportion of the patients with a successful surgical outcome had previous discordant scalp-EEG IEDs, scalp-EEG generalized IEDs were associated, in a more recent study [14], with poor outcome in frontal lobe epilepsy surgery. This finding suggests that patients with generalized IEDs may have seizure foci that extend beyond or reside outside the frontal lobes [15]. However, the converse may not be true. Although IEDs were exclusively concordant with frontal seizure foci in 36% of our patients, we found in a previous study that exclusively concordant IED did not predict excellent postsurgical outcome [8]. This may be due to the frequent association in frontal lobe epilepsy between well-localized scalp-EEG IEDs and more extensive discharges on subdural electrode recording [16]. Yet, this observation may not apply to patients whose extratemporal seizures emanate from regions other than the frontal lobes. Holmes and colleagues [17] reported that the presence of well-localized scalp-EEG IEDs is associated with seizure-free outcome, but nearly half of their patients had surgery that concomitantly or exclusively involved regions outside the frontal lobes.

Table 1. Characteristics of a cohort of 53 patients with intractable frontal lobe epilepsy*

Characteristics	No.	%
Sex		
Male	33	62
Female	20	38
Handedness		
Right	47	89
Left	5	9
Ambidextrous	1	2
Epilepsy etiology		
Cryptogenic	15	28
Symptomatic	38	72
Potential epilepsy risk factors		
Congenital CNS abnormality	4	8
Perinatal distress	2	4
Neonatal seizures	1	2
Febrile seizures	1	2
Intracranial infection	2	4
Brain trauma	14	26
Stroke	5	9
Family history of seizures	8	15
History of status epilepticus	5	9
Lesion on neuroimaging	37	70
Secondarily generalized seizures	42	79

CNS, central nervous system.
* Age at seizure onset: mean = 11.0, range ≤ 1.0 to 35.0; age at time of operation: mean = 29.8, range = 5.9 to 49.3; and presurgical epilepsy duration: mean = 13.5, range = 0.9 to 43.6.

The inconsistent relationship between scalp-EEG IED and postsurgical outcome suggests that IEDs in patients with intractable frontal lobe epilepsy are more likely to propagate or develop in other cerebral areas [5, 6], or that risk factors for bilateral hemisphere dysfunction predominate in these patients. Yet, we could find only one factor associated with discordant IED on scalp-EEG. We found an association between younger age at seizure onset and discordant discharges, but we cannot explain its basis. We had suspected that a longer duration of epilepsy history before surgery might enhance development of discordant discharges outside the frontal seizure focus, but our analysis did not find a significant relationship between duration of epilepsy history and presence of discordant discharges. A recent study [18] reported that most children diagnosed

Table 2. Percentage of patients with concordant frontal IED* according to the presence or the absence of each factor

	Patients,% (no.), with concordant IED†		
Factor	**Present**	**Absent**	***P* value**
Family history of seizure disorder‡	37.5 (3/8)	73.3 (33/45)	0.09
Symptomatic etiology	68.4 (26/38)	66.7 (10/15)	1.00
Brain trauma§	71.4 (10/14)	66.7 (26/39)	1.00
Stroke	80.0 (4/5)	66.7 (32/48)	1.00
Neuroimaging lesion	67.6 (25/37)	68.8 (11/16)	1.00
Secondarily generalized clinical seizure¶	71.4 (30/42)	54.5 (6/11)	0.30
History of at least one status epilepticus	100.0 (5/5)	64.6 (31/48)	0.16
Frontal convexity location of seizure focus	72.2 (13/18)	33.3 (4/12)	0.06

IED, interictal epileptiform discharges.
* Occurring at the frontal region with the seizure focus.
† Values are the percentage of patients with or without each risk factor (denominator), who have concordant IED (numerator).
‡ First-degree relatives.
§ Resulting in loss of consciousness or in intracranial hemorrhage or contusion.
¶ History of experiencing at least one secondarily generalized seizure.

Table 3. Association between concordant IED* and age at first seizure and the presurgical duration of epilepsy (Wilcoxon rank sum test)

Factor	**Patients with concordant IED**	**Patients without concordant IED**	***P* value**
Age at first seizure	11.9 ± 10.0 years	14.2 ± 11.5 years	0.44
Presurgical epilepsy duration	16.2 ± 10.2	15.8 ± 10.4	0.98

IED, interictal epileptiform discharges.
* Occurring at the frontal region with the seizure focus.

Table 4. Percentage of patients with discordant IED* according to the presence or the absence of each factor

	Patients,% (no.), with discordant IED†		
Factor	**Present**	**Absent**	***P* value**
Family history of seizure disorder	62.5 (5/8)	42.2 (19/45)	0.44
Symptomatic etiology	42.1 (16/38)	53.3 (8/15)	0.55
Brain trauma‡	42.9 (6/14)	46.2 (18/39)	1.00
Stroke	20.0 (1/5)	47.9 (23/48)	0.36
Neuroimaging lesion	40.5 (15/37)	56.3 (9/16)	0.37
Secondarily generalized clinical seizures	42.9 (18/42)	54.5 (6/11)	0.52
History of status epilepticus	80.0 (4/5)	41.7 (20/48)	0.16
Convexity location of seizure focus	50.0 (9/18)	41.7 (5/12)	0.72

IED, interictal epileptiform discharges.
* Appearing outside the frontal region with the seizure focus.
† Values are the percentage of patients with or without each risk factor (denominator), who have discordant IED (numerator).
‡ Resulting in loss of consciousness or in intracranial hemorrhage or contusion.

Table 5. Association between discordant IED* and age at first seizure and presurgical duration of epilepsy (Wilcoxon rank sum test)

Factor	Patients with discordant IED	Patients without discordant IED	*P* value
Age at first seizure	7.46 ± 6.60	17.0 ± 11.3	< 0.01
Presurgical epilepsy duration	17.4 ± 10.7	14.9 ± 9.8	0.34

IED, interictal epileptiform discharges.
* Occurring at the frontal region with the seizure focus.

with frontal lobe epilepsy had multifocal, generalized, or contralateral frontal IEDs on scalp recordings. However, only eight children eventually underwent focal resections involving the frontal lobe, and seizures in five did not respond to the procedure. The diagnosis of frontal lobe epilepsy in these children was based on seizure semiology and on interictal and ictal video-EEG recordings.

Sixty-eight percent of our patients had scalp-EEG IEDs concordant with their frontal seizure foci. This finding agrees with that of a previous study that also was confined to patients who had responded to frontal lobe epilepsy surgery [5]. In our search for factors that underlie concordant IED, we found location of the seizure focus at the frontal lobe convexity to be the only potential factor. Patients with convexity seizure foci were more than twice as likely to have concordant IED than were patients with mesial frontal seizure foci. The difference between these two groups of patients nearly reached statistical significance ($P = 0.06$). A larger sample of eligible patients may enhance the statistical power of the analysis and produce a statistically significant outcome. We had to confine this analysis to a smaller subgroup of 30 patients in whom the location of the seizure foci within the frontal lobes could be ascertained. Nonetheless, our finding seems intuitively correct. Electrodes applied on the scalp are expected to be nearer to frontal convexity foci than to mesial frontal foci [19]. A previous study [20] found that four patients with seizure foci at the dorsolateral frontal convexity had well-localized scalp-EEG frontal IEDs, whereas five patients with mesial frontal seizure foci did not. Unfortunately, the small number of patients in that report precluded a determination of statistical significance.

Conclusions

We are not aware of any study that has attempted to identify systematically the factors that explain the distribution of scalp-EEG IEDs in intractable frontal lobe epilepsy. Additional studies are needed to further define the factors beyond those we have found in this study, because scalp-EEG EEG is universally a noninvasive procedure used in the initial assessment of epilepsy patients, including patients being considered for frontal lobe epilepsy surgery. □

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