Incidence of atypical handedness in epilepsy and its association with clinical factors

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ABSTRACT

The incidence of atypical handedness (left-handedness and ambidexterity) in patients with epilepsy, particularly its association with major clinical factors, is not well established. We evaluated a full range of clinical variables in 478 patients with epilepsy from the United States and Korea. With the Edinburgh Handedness Inventory, handedness was established as both a categorical variable (right-handed, left-handed, ambidextrous) and a continuous variable. Seizures were classified as complex or simple partial, primary generalized, or generalized tonic-clonic. The relationship between handedness and a range of clinical findings was explored. The overall incidence of atypical handedness in our patients was higher than in the general population (13.6%) and significantly higher in the U.S. patient group (17.6%) than in the Korean patients (8.8%). Handedness was not associated with sex; age; seizure type; age at onset; type, side, or site of EEG or brain imaging abnormalities; family history of seizures; refractory epilepsy; or history of epilepsy surgery.

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1. Introduction

The incidence of atypical handedness (left-handedness or ambidexterity) in the general population, along with its association with language, gender, age, heredity, culture, and certain medical conditions, has been extensively studied. Epidemiological studies report an increasing incidence of atypical handedness, with variable rates among different nations, in part because of declining forced right-handedness [1,2]. Although the underlying mechanisms of handedness are poorly understood, there is an established association between handedness and language dominance [3], as well as evidence suggesting a higher incidence of left-handedness in men [4] and in patients with migraine, depression and other affective disorders, and breast cancer [5–10].

Evidence of laterality in movement has been observed as early as 10 weeks of gestation, and some authors have suggested that motor laterality may play a role subsequently affecting neurodevelopment and behavioral laterality [11]. There is evidence suggesting that primary motor cortex is larger in the dominant hemisphere on both the gross imaging and microscopic levels along with asymmetric activity on functional MRI [12–14].

Several different hypotheses have been proposed to explain the neurodevelopment of atypical handedness, including the effect of a higher level of estrogen in the mother, which may slow the development of the left hemisphere, hence the higher rate of left-handedness in males [15]. Two prominent genetic models are the right shift model of Annett, which views hand preference as a continuous trait, and the symmetric bimodal model, led by McManus, which describes right- and left-handedness as two discrete categories [16,17]. Genetic models and sociocultural theories have been proposed based on evidence from monozygotic twins who appear to be significantly discordant, suggesting a role for other environmental factors. A recent large study examining twins and their siblings found that genetic effects accounted for approximately a quarter of the variance in handedness; the remainder was accounted for by nonshared environmental influences [18]. The role of a particular gene (LRRTM1) that might be contributing to human brain asymmetry and handedness, as well as schizophrenia, is controversial [19,20].

The "pathological left-handedness hypothesis" proposes that brain damage in early life may contribute to the development of atypical handedness [21]. This idea has been supported by several studies examining children with a history of bacterial meningitis in infancy, prematurity birth, or other causes of perinatal brain injury.
that have found higher incidences of atypical handedness in those affected [22,23]. A study of patients with epilepsy reported that left-handedness was associated with left-sided epileptiform discharges and neuropsychological deficits. These authors also found that patients who developed epilepsy prior to age 5 were more likely to be left-handed than those who developed epilepsy at a later age [24]. A similar mechanism has been proposed for pathological strong right-handedness in patients with right temporal lobe refractory epilepsy [25].

The incidence of atypical handedness and particularly its possible association with major clinical variables in patients with epilepsy has not been thoroughly studied. Therefore, we explored the incidence of atypical handedness among patients with epilepsy and its correlation with a range of clinical findings including gender, age, family history of epilepsy, age at seizure onset, seizure type, EEG and brain imaging lateralization and localization, and response to treatment (refractoriness).

2. Methods

2.1. Patients and procedures

The study was approved by the institutional review boards at both institutions in the United States and Korea. A total of 478 patients (53.1% female, 46.9% male; age 14–81 years, mean 39.85 ± 14.10) with the diagnoses of first-time seizure or epilepsy were included in this study. Age at seizure onset ranged from 0.1 to 80 years (mean 23.9 ± 16.3), and seizure frequency per month ranged from 0 to 200 (mean 3.3 ± 15.3). The patients were treated at either Georgetown University Hospital (GUH, n = 261, 54.6% of total sample, 56.4% female, 43.6% male; age 14–81, mean 41.05 ± 14.89), or Dongsan Medical Center (DMC, n = 217, 50.6% female, 49.4% male; age 16–77, mean 36.60 ± 13.02). All patients who were available to the epilepsy clinics at both centers during a 1-year period were asked to participate in the study; only three patients refused. The follow-up time ranged from 3 months to 8 years. Patients with a clinical diagnosis of static or progressive encephalopathy and mental retardation who were unable to complete, or reliably answer, the questionnaire to establish handedness were excluded.

Clinical data were obtained through chart review and included demographic information, family history of epilepsy, age at seizure onset, seizure type, EEG or video/EEG monitoring, brain imaging, seizure refractoriness, and history of epilepsy surgery including resection surgery and vagus nerve stimulator implantation.

A total of 466 patients had either outpatient EEG or video/EEG monitoring, or both. No EEG results were available for 12 patients. Brain imaging results, including MRI and CT results, were available for 452 patients. Brain MRI was used to determine abnormalities such as hippocampal sclerosis (mesial temporal sclerosis [MTS]), tumor, vascular anomalies, white matter disease, and other less specific changes. Brain MRI and CT scan findings were used for hemorrhagic or vascular abnormalities.

2.2. Handedness

Handedness was defined based on the Edinburgh Handedness Inventory (EHI) [26]. This information was obtained from the patients in the epilepsy clinic or through mail or telephone interview of the patients. The EHI scores were treated as both a categorical variable (right [R], left [L], or ambidextrous [A]) and a continuous variable (right = 1, left = -1, ambidextrous = 0).

2.3. Seizure types

Seizures were classified as complex or simple partial seizures (CPS or SPS), primary generalized epilepsy (PGE), or generalized tonic-clonic seizures (no clear partial onset or EEG evidence of PGE). Seizure frequency and responsiveness to treatment were based on patient report. Refractory epilepsy was defined as failure of two trials of monotherapy and one attempt at polytherapy.

2.4. Electroencephalography

For analysis purposes, the EEG findings were grouped either as normal; right, left, or bilateral temporal spikes; frontal spikes; non-temporal/frontal spikes; slow activity; or generalized spike/slow and slow discharges. For a separate analysis the EEG findings were also grouped as either right- or left-sided abnormality.

2.5. Brain imaging

Brain imaging findings were grouped either as normal; right, left, or bilateral hippocampal sclerosis; vascular lesions (including vascular anomalies and hemorrhages); or abnormal (tumors or nonspecific abnormalities, e.g., white matter changes, atrophy). For a separate analysis the MRI findings were also grouped as either right- or left-sided abnormality.

2.6. Statistical analysis

All analyses testing for possible associations between handedness and the selected clinical variables were run three times: once with the handedness variable at three levels (R, L, A), once with two levels (R and combined L+A), and once based on EHI score treated as a continuous variable.

2.6.1. EHI as a categorical variable

These two handedness analyses (three-level, two-level) were run for the full sample and then separately with the two cohorts broken out (GUH, DMC). Bonferroni corrections for multiple comparisons controlled the familywise error rates within each set of association tests to 0.05 (i.e., α/7 for the nominal variables [see below] with the three-level handedness variable, α/7 with the two-level handedness variable, and each of these was replicated with α/7 over all and then separately within each cohort; a similar pattern with α/3 was carried out for the continuous variables). The two cohorts were compared only on one variable (handedness distribution), so this comparison was not adjusted.

The associations between the categorical (nominal) variables were explored by computing the contingency coefficient (CC), which is based on χ² and estimates the association between nominal variables in the matrix. As in the χ² statistics, higher values suggest stronger association, but unlike the χ², the contingency coefficient ranges only between 0 and 1, with 0 indicating no association and values close to 1 indicating strong association.

The nominal variables studied were sex, seizure type, EEG findings, brain imaging findings, seizure refractoriness, history of epilepsy surgery, and family history of epilepsy.

The two-level handedness variable was used to compare the mean values of age, age at onset of epilepsy, and monthly seizure frequency using an independent sample t test. All statistics were run using SPSS Version 16.1 (SPSS Inc., Chicago, IL, USA) and all P values represent two-sided tests.

2.6.2. EHI as a continuous variable

Analyses based on continuous variables can be more powerful than analyses based on categorical definitions. We used the EHI score as a continuous variable in the following analyses.
between handedness score and other continuous variables (e.g., age, seizure frequency). A correlation was used to detect a significant association between these two (continuous) variables. For categorical variables such as family history, comparison was made between the mean handedness scores in each of those two groups to detect any significant differences.

3. Results

The overall incidence of atypical handedness (L + A) was 13.6% (7.9% L, 5.6% A) and higher in males (15.9% vs. 11.9%). This was significantly higher in U.S. patients (17.6%, 10.3%, 7.3%) than Korean patients (8.8%, 5.1%, 3.7%) (CC for group x two-level handedness = 0.128, unadjusted P < 0.01) (Table 1, Fig. 1). A total of 204 patients (42.7% of total, GUH 41.3%, DMC 44.2%) had re- cated epilepsy, which may reflect the fact that both centers receive referrals of patients with refractory epilepsy. Sixty patients (13.3%) had a family history of seizures. The mean age at seizure onset was 23.9 ± 16.39 years (GUH 24.89 ± 17.64, DMC 22.71 ± 14.71). Eight of 238 U.S. patients (3.4%) for whom the information was available reported having been forced to change handedness as a child. There was a perfect concordance between perceived handedness and EHI score for right-handers, but 2.5% of those who reported being left-handed were found to be ambidextrous by the Edinburgh measures. Seizure type, EEG, and brain imaging findings are summarized in Tables 1-4.

In the full sample of 478 individuals, no relationship was observed between any of the recorded clinical variables and the three-level handedness variable (R, L, A) (sex: CC = 0.06, P = 0.41; seizure type: CC = 0.11, P = 0.47; EEG: CC = 0.186, P = 0.91; brain imaging: CC = 0.183, P = 0.90; refractoriness: CC = 0.027, P = 0.84; epilepsy surgery: CC = 0.103, P = 0.77; family history of epilepsy: CC = 0.095, P = 0.13). Similar results, that is, no evidence of association, were observed when these associations were estimated separately within the subgroups.

When we reanalyzed the associations with handedness as a two-level variable (R, L + A), we observed no relationship (sex: CC = 0.054, P = 0.23; seizure type: CC = 0.045, P = 0.81; EEG: CC = 0.138, P = 0.77; brain imaging: CC = 0.146, P = 0.62; refractoriness: CC = 0.016, P = 0.73; history of epilepsy surgery: P only available for GUH patients): CC = 0.093, P = 0.53). The association between two-level handedness and family history had an unadjusted P value of < 0.05 (CC = 0.093, P = 0.0047); however, after correcting for the seven comparisons (requiring P < 0.0071 to achieve significance after Bonferroni correction for the seven nominal outcomes), this relationship was not significant.

Similar results were observed when these associations were estimated separately within the subgroups, although in the subgroups, the unadjusted P value for the association of handedness with family history was not significant.

When actual EHI score was used as a continuous variable, family history of epilepsy was the only variable to show a significant association in the full sample, but the result did not hold after correcting for multiple comparisons. When the same analysis was done in the GUH and DMC patients separately, there was no association between handedness score and family history; this might be caused by lower average scores in the GUH group with a larger sample size driving the test statistic toward significance.

We analyzed the associations between age, age at onset, and monthly seizure frequency with independent sample (R vs. L + A) t tests. In the full sample, no differences in age (t(173) = -1.33, P = 0.19), age at onset (t(173) = 1.82, P = 0.07), or monthly seizure frequency (t(173) = 0.34, P = 0.73) were observed.
When EHI was used as a continuous variable, for both the full sample and GUH and DMC patients analyzed separately, no correlation coefficients were significantly different from zero; that is, there was no significant association between handedness score and age, age at seizure onset, or seizure frequency.

Limiting the analysis to a specific epilepsy syndrome, we compared patients with MTS; this reduced the GUH group to 22 and the DMC group to 41. There was no significant association between handedness and any clinical variables. Similar results were observed when GUH and DMC patients were analyzed as a combined group.

When MRI and EEG results were analyzed based on mere laterality, that is, right- and left-handed abnormalities, the sample sizes were reduced to 219 for GUH and 121 for Korea. The MRI finding was not significantly associated with the continuous handedness score for either the GUH or DMC group. Handedness scores were significantly lower in those with left-sided EEG abnormalities, but after correcting for multiple comparisons this finding did not remain statistically significant. This EEG result was not significant when GUH and DMC patients were analyzed together; nor was the MRI result.

4. Discussion

We had hypothesized that patients with left hemispheric seizures, in particular those with early onset and those with refractory epilepsy, were more likely to have atypical handedness. In that regard the high ratio of patients with refractory epilepsy in our cohorts is assuring. Further, we explored any relationship between a set of major clinical variables and handedness to determine if, early in the course of seizure disorder, it was possible to formulate clinical predictions such as likelihood of responsiveness to medical therapy in different clinical settings, on the basis of handedness.

Our results show an overall higher incidence of atypical handedness in patients with epilepsy (13.6%) than in the general population in the United States (11.1%) [27] and Korea (4.2–6%) [28,29]. However, it remains unclear if this difference is in part due to differences in questionnaire and national origin and is independently associated with epilepsy. On the other hand, the significantly higher incidence of atypical handedness in the United States (17.6%) compared with Korea (8.8%) might reflect a difference in the baseline national rates in these two populations. Studies comparing handedness between different cultures and nationalities have suggested declining forced right-handedness in both the United States and Korea [26,29]. The higher incidence in males than females in both cohorts is consistent with population studies [27].

Holmes et al. found that left-handedness is associated with left-sided epileptiform discharges and left-sided neuropsychological deficits. The authors also reported that patients who develop epilepsy prior to age 5 are significantly more likely to be left-handed when they compared all left-handers as a group, they did not find any association between handedness and EEG lateralization, neuropsychological deficits, age at onset of seizures, history of febrile seizures, family history of either epilepsy or left-handedness, or other risk factors [24].

Similarly, our data also did not reveal a significant relationship between atypical handedness in patients with epilepsy and their sex; age at onset of seizures; seizure type; type, side, or site of EEG abnormality; type, side, or site of brain imaging abnormality; family history of seizures; presence of refractory epilepsy; or history of epilepsy surgery. This was the case in both patients with recent-onset epilepsy and patients with chronic refractory epilepsy. Importantly, this lack of association was observed whether we used a two- or three-level categorical definition of atypical handedness or continuous EHI score. Further, it was observed in two independent large cohorts with a high rate of refractory epilepsy.

Our patient population, however, included a variety of etiologies; further studies comparing larger groups of specific epilepsy syndromes such as patients with MTS, frontal lobe, and primary generalized epilepsy might be more relevant to handedness studies. Also, the fact that the average age at onset in our cohorts was relatively high (26.3 ± 16.7 for atypical handed group and 23.55 ± 16.3 for right-handers) might have affected the results. We do not believe that excluding patients with static or progressive encephalopathy and mental retardation, for whom it was not possible to establish handedness, had a significant impact on the results.

It has been reported that the incidence of atypical language dominance depends not only on the direction but also on the degree of handedness [30]. Using EHI as a continuous variable, we did not find significant associations with the clinical variables tested in this study. The overall results (and in each cohort separately) showed no evidence of association whether we combined left-handedness and ambidexterity or evaluated these two handedness states separately; to the extent that these levels represent “degree” of handedness, our data do not support any associations.

In a study using the Edinburgh Handedness Inventory [31], it was reported that there was a significant drop in the incidence of left-handedness from age 15 to 70 in a small town population. This drop cannot be accounted for by the effect of forced dextrality on the writing and drawing hand, which may suggest age- and/or disease-induced modification of brain functions involved in dextrality. The largest US. handedness study by Gilbert and Wysocki reported a similar drop in sinistrality after age 50 [27]. Our study was not designed to address this question, but given the higher rate of atypical handedness in our patients, a long-term follow-up study comparing EHI scores should be performed.

References

[9] Fastner OB, Askiaui HS, Hugdahl K, Oostergaard R. Non-right-handedness is associated with ——.

Table 4
Seizure types

<table>
<thead>
<tr>
<th>Seizure type</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalized tonic-clonic</td>
<td>93 (19.5%)</td>
</tr>
<tr>
<td>Complex partial</td>
<td>313 (65.5%)</td>
</tr>
<tr>
<td>Simple partial</td>
<td>24 (5%)</td>
</tr>
<tr>
<td>Primary generalized</td>
<td>48 (10%)</td>
</tr>
<tr>
<td>Total</td>
<td>478 (100%)</td>
</tr>
</tbody>
</table>
Zusammenfassung


Schlüsselwörter

Tiagabin · Status epilepticus · GABAére Inhibition


Eine von uns in eine offene Tiagabin-Studie eingeschlossene Patientin erlitt unter der Dosiserhöhung der Substanz rezidivierende nonkonvulsive Status epilepticii, eine schwere, aber möglicherweise nicht sehr leicht zu erkennende unerwünschte Wirkung, die wir im folgenden darstellen und diskutieren.

Kasuistik


Wir schlossen die Patientin in eine offene Phase-IIIb-Studie des Antikonvulsivums Tiagabin ein, das als Add-on-
A case report is given to draw attention to the risk of the occurrence of nonconvulsive status epilepticus (NCSE) under the anticonvulsant tiagabine in higher doses and dosis increases. The patient who had no previous history of status epilepticus developed several NCSE shortly after administration of tiagabine. This represents strong evidence of a causal relationship. Also, in experimental studies it has been shown that in higher doses a disequilibrium between glial and neuronal GABA uptake may aggravate the failure of GABA inhibition thus explaining this adverse side-effect.

Key words
Tiagabine - Status epilepticus - GABAergic inhibition

The treatment is documented for fokal epilepsies to be examined under tiagabine. In addition to the existing anticonvulsant medication with 100 mg lamotrigine and 1500 mg carbamazepine, we started tiagabine administration with 5 mg daily and increased this weekly by another 5 mg up to a daily dose of 15 mg. In the fifth week, we increased the dose according to protocol to 30 mg and 2 weeks later to 40 mg divided into 2 daily doses. On the subsequent study visit, the patient complained of conscious impairment, hyporeactivity, and was not fully oriented in time and place. Intermittently, oral automatisms and the gait was ataxic. The rest of the neurological status was normal. An EEG performed in this state showed generalized rhythmic slow wave activity (Abb. 1). After intravenous application of 10 mg diazepam, the patient was initially drowsy, but was fully oriented again, and the oral automatisms stopped and the rhythmical EEG discharges were interrupted (Abb. 2). The patient reported that after the increase of the tiagabine dose to 30 mg daily, similar events had occurred about an hour after morning intake for up to 5-6 h. To establish the causal relationship between the occurrence of a NCSE and the intake of the substance tiagabine further, we observed the patient under stationary conditions after administration of the morning dose. An hour after intake, an identical electroclinical picture was observed, which could be interrupted by benzodiazepines. After reducing the drug to a daily dose of 15 mg, no events of this kind occurred anymore.

Discussion
The two episodes documented by us took place after clinical, electrophysiological and pharmacological criteria without doubt as a NCSE. Even the events reported by the patient after intake of tiagabine were retrospectively assessed as NCSE. The temporal correlation with the intake of tiagabine, the cessation of these events after dosage reduction and the absence of other explanatory factors represent strong evidence that these events were caused by tiagabine. Although no increased incidence of NCSE was found in a recently presented study compared to placebo [6], some case reports have suggested that tiagabine may be a risk factor for the occurrence of NCSE under tiagabine compared with placebo in a study [6], indicating a possible risk of the occurrence of NCSE under tiagabine compared with placebo.
Ergebnisse & Kasuistik

Fp7-F8
Fp1-F7
F4-F8
F3-F7
C4-F8
C3-F7
P4-F8
P3-F7
O2-F8
O1-F7
Fz-F8
Fz-F7
Cz-F8

Fz-F7

Cz-F8

EKG

Abb. 2  ▲ EEG mit Alpha-Aktivität mit postiorem Schwerpunkt überlagert von pharmakogen induzierter Beta-Aktivität, vereinzelt Theta-Wellen

terapie mit Tiagabin nahelegen [1,4]. Die vorliegende Kasuistik läßt wenig Zweifel an einem kausalen Zusammenhang zwischen Tiagabin-Einnahme ab einer bestimmten Einzeldosis und dem Auftreten eines nonkonvulsiven Status epilepticus.


Der Fall zeigt, daß bei der Gabe von Tiagabin in höheren Dosierungen und insbesondere bei Dosissteigerung an die unerwünschte Wirkung eines nonkonvulsiven Status epilepticus gedacht werden sollte.

Literatur