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Epileptogenesis: left or right hemisphere dominance? Preliminary findings in a hospital-based population

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The aim of this study was to determine if there is cerebral cortical hemispheral asymmetry in human epileptogenesis. We studied 75 epilepsy patients using electroencephalograms, neuroimaging, ictal semiology and physical examination to determine if epilepsy originates more frequently from the left or the right hemisphere. We considered epilepsy to be definitely-lateralized if one or more of these was abnormal unilaterally and there were no contradictory findings. Twenty-seven of the patients had lateralized epilepsy: 20 from the left hemisphere and seven from the right hemisphere ($P < 0.05$). These findings from our hospital-based ambulatory patient population suggest that the left hemisphere is more epileptogenic than the right. Further study of lateralization of epileptogenesis in a community population-based sample of incident new-onset cases seems warranted.

Key words: epilepsy; lateralization.

INTRODUCTION

Scattered previous studies have shown more left-sided EEG abnormalities than right-sided EEG abnormalities in patients with seizures[1,2]. From the first phase of our research, we reported left cerebral cortical hemisphere predominance of epileptiform discharges in 1360 consecutive electroencephalograms (EEGs)[3]. In this current second phase of our research, we further explored the possibility of hemispheral asymmetry in epileptogenesis. This time, rather than comparing the hemispheral predominance of EEG abnormalities, we determined the lateralization of the seizure focus in patients from our Epilepsy Center by studying their EEG, neuroimaging and ictal semiology and by physical examination. This current hospital-based pilot study is intended to lay the groundwork for the future third phase of our research, which will involve studying lateralization of seizure sources in a community-based population of incident cases of new-onset epilepsy.

METHODS

We prospectively studied 75 consecutive outpatients seen in our Comprehensive Epilepsy Center in order to acquire data on their physical examination, EEG, neuroimaging, and ictal semiology. Seizures were classified according to the International League Against Epilepsy scheme [simple partial (SP), complex partial (CP), or generalized convulsive (GC)]. To minimize the possibility of referral bias based on a single source of patients, we obtained 25 adult patients from the office practice of one author (DL), another 25 children from the office practice of another author (GS), and the last 25 adults from our Seizure Clinic. Thirty-one men and 44 women, aged 3–71 years, were obtained on the basis of a history of two or more non-febrile seizures.

The epilepsy was considered to be definitely-lateralized if one or more of the following findings was abnormal on one side and there were no contradictory abnormal findings on the other side: (1) physical examination—unilateral weakness or numbness, aphasia, unilateral neglect syndrome or a

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homonymous visual field deficit; (2) neuroimaging—focal cortical signal abnormality on the computed tomographic (CT) scan or with magnetic resonance imaging (MRI); (3) EEG—focal spikes, sharp waves, slowing or attenuation; (4) ictal semiology—unilateral focal clonic or tonic movements or unilateral visual hallucinosis. EEG interpreters and neuroradiologists were not aware of the study paradigm at the time of EEG or MRI/CT interpretation.

Because normal distribution of the data could not be assumed, we employed non-parametric statistics. These included chi-squared and Mann–Whitney *U* tests.

RESULTS

Patients were divided into two groups: those with definitely-lateralized epilepsy and those who did not meet our criteria for lateralization. This second group consisted of patients who had no lateralizing findings or had bilateral findings in the physical examination, EEG, ictal semiology and neuroimaging.

Twenty-seven of the 75 patients were found to have definitely-lateralized epilepsy. EEG was lateralizing in 19 patients, imaging in 18, ictal semiology in 10 and neurological examination in five. Twenty lateralized to the left hemisphere and seven lateralized to the right hemisphere (chi-squared test, $P < 0.05$). The right-lateralized patients had epilepsy of significantly shorter duration (Mann–Whitney *U* test, $P = 0.03$). There were no significant differences between the left- and right-lateralized groups in terms of sex, occurrence of secondarily generalized seizures, history of febrile seizures or handedness (all chi-squared tests, all $P > 0.05$) or age of onset of epilepsy (Mann–Whitney *U* test, $P = 0.78$) (see Table 1).

Table 1: Patient characteristics.

Characteristics	Left-lateralized	Right-lateralized
Total patients	20	7
Sex		
Male	8	3
Female	12	4
Mean age of seizure onset [years] (range)	21(1–57)	17(3–33)
Mean duration of epilepsy [years] (range)	20(2–45)	10(2–22)
Handedness[a]		
Left	3	1
Right	14	6
Seizure type		
SP	1	1
SP + SGC	1	0
CP	8	4
CP + SGC	10	2
History of febrile seizures	1	1

SP = simple partial seizures; CP = complex partial seizures; SGC = secondarily generalized convulsive seizures. [a]In three left-lateralized pediatric cases, handedness could not be determined.

DISCUSSION

In our previous study[3], in which we looked at 1360 consecutive EEGs, we included EEGs of patients with and without epilepsy. We categorized EEGs with asymmetric bilateral activity as having predominantly left or right lateralization. For the current study we developed more strict criteria. All the patients had clinical seizure disorders. We considered an EEG record as lateralized if it showed unilateral abnormalities only. We only considered epilepsy as lateralized if all localizing abnormalities were on the same side of the head. We believe this increased the specificity of our lateralization criteria by: (1) doing away with the need to gauge right or left predominance in cases of asymmetrical bilateral EEG discharges; and (2) doing away with patients with epileptiform abnormalities but without clinical seizures.

The most definitive way to lateralize epileptogenesis would have been to record multiple seizures on video-EEG for every patient. However, that was not practical. Instead, we used indicators of lateralized cerebral cortical dysfunction (focal abnormalities on EEG, neuroimaging, seizure semiology or neurological examination) that were easy to obtain on every patient. We believe that most neurologists would agree that such indicators of lateralized cerebral dysfunction correlate well with an underlying lateralized epileptogenic capacity, particularly in the absence of any abnormalities whatsoever on the other side of the head. We did not wish to report only on patients admitted to our Epilepsy Monitoring Unit because they comprise a highly selected patient population composed only of those with severe epilepsy.

Hemispheric lateralization at the functional and anatomical level in humans has been established by several studies[4,5]. There are asymmetrical representations of higher cortical functions such as speech and memory in the right vs. the left hemisphere, as well as hemispheric differences in the amount of activity of certain neuroactive chemicals and neurotransmitters, namely choline acetyltransferase, gamma-aminobutyric acid and norepinephrine[5,6]. Functional lateralization has also been suggested in neuropsychiatric studies which have correlated left hemisphere structural abnormalities and thought disorders[7]. Foy *et al*[8] found that among patients undergoing craniotomies for brain tumors, postoperative seizures occurred more frequently with left-sided lesions. Furthermore, in cerebral palsy, right-sided hemiplegia has been found to occur twice as frequently as left-sided hemiplegia[9].

In our current study, 74% of the patients with localization related epilepsy lateralized to the left hemisphere. This is consistent with our previous study of EEGs[3], again suggesting that the left hemisphere is more epileptogenic than the right hemisphere. Our current study adds that this seems to be the case irrespective of gender, age of seizure onset, and seizure type. We do not believe our results are due to left-side origin epilepsy being more symptomatic than right-side origin epilepsy, and therefore being reported earlier and being over-represented in our population. Even if left-side cases do seek medical attention earlier, right-side cases do seek medical attention eventually. In our arbitrary consecutive series of 75 patients, we would be just as likely to see 'early-presenting' cases as 'late-presenting' cases, since we indiscriminately included consecutive new and follow-up patients seen at the three sites. In fact, in our series of patients, we found exactly the opposite results; the left-side patients had epilepsy for significantly longer than the right-side patients.

We believe that the same neuronal mechanisms that give rise to hemispheral functional differences endow the left hemisphere with a higher propensity for developing abnormal excess neuronal excitability. Thus, events during prenatal and early childhood neuronal development that lead to functional hemispheric differences may make the left hemisphere more susceptible to cortical damage[10].

Of the diseases encountered by neurologists, epilepsy is one of the most common. Although it has been studied extensively, many of the pathophysiologic phenomena surrounding this condition are not well understood. For example, the finding in our series of patients that epilepsy of right-side origin was of shorter duration than epilepsy of left-side origin remains unexplained. Our data point to the need for continued investigation into mechanisms of cerebral functional lateralization, epileptogenesis and the relationships between these processes.

An alternative hypothesis to explain our findings is that left hemisphere epilepsy is more medication resistant than right hemisphere epilepsy, thereby generating more office visits and becoming over-represented in our study. In other words, both hemispheres may generate an equal number of seizure disorders; however, the seizure disorders of left hemisphere origin are more severe and require more medical attention, thereby appearing more frequently in our series. This issue might be of concern when interpreting our results because our practices and Clinic are located in a tertiary care hospital. However, we believe this is a less likely hypothesis. In our previous study[3], EEG epileptiform abnormalities were more frequent on the left than on the right. In that previous study, each patient was represented by only one EEG, and medication responsiveness or resistance did not affect our results. Furthermore, in an unrelated clinical setting, patients undergoing neurosurgery for treatment of brain tumors had more seizures if they had left-side lesions than if they had right-side lesions. However, in order to minimize these case-ascertainment methodological concerns, we are implementing a prospective study of lateralization of epileptogenesis in a population-based sample of incident new-onset seizure disorders.

CONCLUSION

Our preliminary findings from our hospital-based ambulatory patient population suggest that the left hemisphere is more epileptogenic than the right. Further studies of laterality on new-onset epilepsy in a community-based patient population seem warranted.

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