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Effects of lateralisation and gender on temporal lobe ictal behaviour associated with hippocampal sclerosis

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Summary *Introduction*: Information derived from animal models and neuroradiological studies in humans indicates that males and females exhibit differences in the functional and anatomical organisation of the brain. This study aimed to evaluate the effect of gender in ictal behaviour considering lateralisation in a group with homogeneous pathology. *Methods*: Patients with hippocampal seizures who underwent temporal lobectomy and who were seizure-free during one year of follow-up were selected. Surgery was performed on the right side in 27 patients and on the left side in 21. Videotape recordings of the patients were reviewed in order to investigate ictal behaviour. There were 42 seizure episodes in 20 males and 40 in 21 females. For auras, 48 patients' data were reviewed. Ictal behaviour was evaluated taking into consideration the lateralisation of seizures and gender differences. *Results*: Ictal vocalisation was significantly higher in females with right temporal lobe epilepsy (RTLE) ($P < 0.05$). Forced head deviation was significantly higher in males with left temporal lobe epilepsy (LTLE) ($P < 0.03$) and in females with RTLE ($P < 0.0001$). Unforced head deviation was significantly higher in males with RTLE ($P < 0.002$). Ipsilateral eye deviation was significantly higher in RTLE, with no differences between males and females. Postictal coughing was significantly higher in RTLE, again with no differences between males and females ($P < 0.03$). With regard to automatisms, posturing and nose wiping, there was no difference between right and left temporal lobe seizures or between genders. *Conclusions*: To the best of our knowledge, this study is the first demonstrating differences in ictal behaviour between females and males, thus showing that gender is related to different functional and anatomical organisations of the human brain.

Introduction

The evaluation of ictal behaviour both at the onset and throughout a seizure can give us further information about the functional anatomy of the brain. Mesial temporal lobe epilepsy is a well-defined syndrome with a standard surgical

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therapy, and it is possible to be seizure-free after successful epilepsy surgery; thus, analysis of this syndrome is very useful for studying ictal manifestations.

Although several studies have defined ictal behaviour, few have examined its features throughout a seizure.[1–9] Considering the importance of ictal semiology before epilepsy surgery, many groups have analysed this aspect and reported that some features can have a lateralising effect.[1–19] However, most of these studies did not describe the pathological details or the localisation of these lesions clearly. Further, other groups of patients did not have homogeneous pathological findings. Most of these studies did not consider the effect of gender. Information derived from animal models and neuroradiological studies in humans indicates that females and males have differences in the functional and anatomical organisation of the brain.[20–22] These studies suggest that sexual dimorphism can influence cerebral transmission, and inter- and intrahemispheric cerebral connections. At present, to the best of our knowledge, there are no other studies evaluating the effect of sexual dimorphism on seizure semiology. We propose that if sexual dimorphism causes differences in the functional organisation of the brain and if some regions are more or less associated with other areas depending on gender, this should be evidenced in the ictal semiology.

In this study, we evaluated the ictal semiology of patients with mesial temporal lobe epilepsy who underwent surgery with pathological findings of hippocampal sclerosis and who were seizure-free for the following year. The aim of this study was to investigate the effects of the lateralisation of TLE and of gender on ictal semiology.

Methods

The subjects were patients with mesial temporal lobe epilepsy (MTLE) who underwent temporal lobectomy with hippocampectomy at our centre between September 1996 and December 2001 with the diagnosis of hippocampal sclerosis, and who were seizure-free for at least 1 year. Before surgery, all patients were evaluated with non-invasive tests (detailed history and neurological evaluation, MRI according to the epilepsy protocol, ictal and inter-ictal EEGs with cable video EEG telemetry—Telefactor beehive system, neuropsychological tests and WADA tests). All selected patients had cranial magnetic resonance imaging showed unilateral hippocampal sclerosis. Unilateral hippocampal atrophy and hyperintensity were used as the diagnostic markers of hippocampal sclerosis which was confirmed by pathological investigation after surgery.

Patient evaluation

All patients were continuously monitored with simultaneous closed-circuit video-surface EEG during the pre-operative period. Nurses observed the patients and examined them during and after seizures. Videotapes of seizures were repeatedly reviewed by two of the authors (A.K. and F.I.T.), who were blinded to the lateralisation of the seizure onset. As authors had to examine the faces of individual patients they could not be blind to gender.

Information on aura type was obtained from patient descriptions on videotape and from medical records. The auras of 48 patients (23 males, 25 females) were included. Three males (M) and four females (F) were not included in the video-tape analysis for the following reasons: (1) inadequate video recordings, (2) rapid secondary generalisation of seizures, (3) seizures without examination by nurses. Eighty-two seizures were evaluated. As it was not possible to record all clinical features properly during every seizure, the denominators might have varied for each one.

Forty-two seizures in 20 men and 40 seizures in 21 women were analysed using a check-list of behavioural characteristics including ictal duration, vocalisation-speech (humming or understandable words), oral automatisms, automatisms in the extremities, posturing (dystonic, tonic), forced head deviation (head deviation in extension and rotation at least of 45° lasting more than 10 s), unforced head deviation, eye deviation, postictal coughing and postictal nose wiping. Ipsilateral and contralateral determinations for head and eye deviation were performed according to the side of the surgery. If the patient issued a warning and pushed the button, seizure onset time was determined from the first action; otherwise, the initial appearance of an abnormal movement or interaction with the environment was used as the indication of ictal onset. Ictal duration was determined from the onset to the cessation of movements.

For each patient, the appearance of these behavioural characteristics in the first 10 s was also recorded in order to clarify whether any differences occur before the spread of ictal discharges to other sites of the brain.

Hospital charts and a database were reviewed to obtain demographic data, clinical history and pathology.

Statistical analysis

Chi-square and Fisher's exact tests were used to compare behavioural characteristics between right and left temporal lobe seizures and between sexes.

Results

Demographic data

Mean age was 26.9 ± 6.2 years for 21 patients with left-sided seizure onset and 25.9 ± 5.3 years for 27 patients with right-sided seizure onset. Age of onset of habitual epilepsy in male group was 9.18 ± 5.15 and 10.28 ± 4.02 in female group (not significant: NS). Besides, between left- and right-sided seizures, no statistical significance of age at onset of seizures was detected. Febrile convulsions were reported by 14 male patients (8 right side, 6 left side) and 20 female patients (11 right side, 9 left side) (NS). Secondary generalisation developed in 17 seizures, and 65 seizures were complex partial seizures. There was no statistical difference between right and left temporal lobe seizures in terms of secondary generalisation (NS). Seizure duration was successfully determined in 80 seizures: it was 105 ± 65 s for right temporal lobe seizures ($n = 43$) and 96 ± 60 s for left temporal lobe seizures ($n = 37$) (NS).

Aura

Twelve patients had no aura. An aura was reported by the remaining 36 patients and there was no difference in terms of reporting an aura between the right and left temporal lobes or between sexes. Fourteen of these 36 patients (39%) reported an epigastric aura. Four of the 7 female patients with LTLE and 1 of the 11 female patients with RTLE had an aura as a vague feeling of discomfort. This was more frequent in epileptic women with left-sided temporal lobe seizures ($P < 0.05$). Other types of aura could not be evaluated statistically because they occurred in small numbers.

Ictal behavioural characteristics during right and left temporal lobe seizures and gender differences

All clinical features were evaluated according to their left or right temporal origin, and according to the gender of the patient. The results are summarised in Tables 1–3.

Table 1 Ictal behavioural characteristics of seizures[a] in 41 patients with left or right temporal lobe epilepsy.

Clinical features	Sex	LTL		RTL		*P*-value
		+	−	+	−	
Ictal vocalisation	M + F	7	28	12	32	NS
	M	6	10	5	18	NS
	F	1	18	7	14	<0.05
Oral automatisms	M + F	14	24	12	32	NS
	M	5	14	4	19	NS
	F	9	10	8	13	NS
Postural changes	M + F	29	9	30	12	NS
	M	15	4	14	8	NS
	F	14	5	16	4	NS
Automatisms in extremities	M + F	13	24	14	30	NS
	M	2	16	7	16	NS
	F	11	8	7	14	NS
Postictal coughing	M + F	0	37	6	36	<0.03
	M	0	18	2	20	NS
	F	0	19	4	16	NS
Postictal nose wiping	M + F	3	34	11	32	NS
	M	1	17	5	17	NS
	F	2	17	6	15	NS

[a]If particular ictal characteristics could not be determined, it was excluded, so total number of seizures might be different for some characteristics.

Table 2 Forced and unforced head deviation throughout 82 seizures in 41 patients.

Head deviation	Sex	LTL		RTL		*P*-value
		+	−	+	−	
Forced	M + F	11	27	19	25	NS
	M	10	9	4	19	<0.03
	F	1	18	15	6	<0.0001
Unforced	M + F	9	29	19	25	NS
	M	3	16	15	8	<0.002
	F	6	13	4	17	NS

Ictal vocalisation and speech were significantly higher in RTLE compared with LTLE in female patients ($P < 0.05$). When the total group or only the male patients were evaluated, no significant difference was detected. No significant difference in oral or extremity automatisms, or in dystonic posture was detected between females and males, or between right or left temporal origin (Table 1).

Forced head deviation throughout the seizure was significantly lower in males with RTLE compared with LTLE ($P < 0.03$). In females, it was significantly lower in LTLE ($P < 0.0001$), while in the total group there was no significant difference (Table 2).

Unforced head deviation was significantly higher in males with RTLE compared with LTLE ($P < 0.002$), while there was no difference between the two lobes in females or in the total group (Table 2). As the number of samples was not very high, classification of ipsilateral or contralateral head deviation could not be performed. Eye deviation for the entire duration of seizures was frequently ipsilateral in all groups, and this finding was more significant in RTLE ($P < 0.05$) (Table 3). There was no difference between males and females with regard to this sign.

Postictal coughing was not detected in LTLE. When the total group was evaluated without considering gender, it was significantly higher in RTLE compared with LTLE ($P < 0.03$) (Table 1). There were no gender differences.

There was no difference regarding postictal nose wiping between LTLE and RTLE or between genders (Table 1).

Ictal behavioural features during the first 10 s of right and left temporal lobe seizures

All patients had seizures lasting 10 s or longer. All their data are summarised in Tables 4 and 5. As the number of samples got smaller, the total group was not divided according to gender, and only differences between LTLE and RTLE originated seizures were considered. Unforced head deviation was detected more frequently in RTLE compared with LTLE ($P < 0.03$). In addition, in the first 10 s of seizures, eye deviation patterns differed between the RTLE and LTLE groups ($P < 0.05$), and eye deviations during the first 10 s of seizures in the RTLE group tended to occur ipsilaterally. All other ictal

Table 3 Eye deviation throughout 81 seizures in 41 patients. In only one seizure, eye deviation was not detected due to position of the patient.

Sex	LTL			RTL			*P*-value
	Ipsilateral	Contralateral	−	Ipsilateral	Contralateral	−	
M + F	13	6	19	25	8	10	<0.05
M	7	4	8	12	5	6	NS
F	6	2	11	13	3	4	NS

Table 4 Ictal behavioural characteristics of seizures during the first 10 s in 41 patients with left or right temporal lobe epilepsy.

Clinical features (M + F)	LTL		RTL		*P*-value
	+	−	+	−	
Ictal vocalisation	6	29	5	36	NS
Oral automatisms	2	34	3	40	NS
Head deviation (forced)	5	31	8	35	NS
Head deviation (unforced)	4	33	13	27	<0.03
Postural changes in extremities	13	24	15	28	NS
Automatisms in extremities	8	30	5	38	NS

Table 5 Eye deviation (M + F) in 81 seizures of 41 patients during the first 10 s of the right and left temporal lobe seizures.

LTL			RTL			*P*-value
Ipsilateral	Contralateral	–	Ipsilateral	Contralateral	–	
5	4	29	16	3	24	<0.05

behaviours showed no differences between right and left origin during the first 10 s.

Discussion

In some studies, features such as contralateral dystonic posture, ipsilateral manual automatisms, early onset non-forced ipsilateral head deviation, contralateral forced head deviation before secondary generalisation, ictal speech, ictal vomiting, postictal aphasia, partial responsiveness, postictal coughing and nose wiping have been demonstrated to be essential for lateralisation.[1–19] However, in these studies, the pathological results were not homogeneous,[1,2,4–7,9–13,15–17] and patients were diagnosed with medial or lateral temporal lobe epilepsy, thus forming a heterogeneous group.[1,2,4,6,9,10,12,13,15–17] In our study, a homogeneous group with hippocampal sclerosis was evaluated with regard to behavioural differences depending on the seizure source in the temporal lobe and on the patient's gender.

In some neurocognitive and neuroradiological studies, gender differences have been linked to the functional and anatomical organisation of the brain.[23–26] In our study, the variations in ictal behaviour in the two sexes were thought to indirectly reflect different organisations of the brain. An aura was reported in 75% of patients. In a previous study, 22% of patients reported vague feelings of discomfort for a total of 163 complex partial seizures, thus being the most frequent type of aura.[9] In our study, this type of aura was reported in females with LTLE more frequently than in other groups. In other studies, epigastric sensation is the most frequently reported aura (38%);[5,6,14,27] however, in our study, epigastric aura could not be compared between the groups because of the limited number of patients. In three studies, no lateralising value of auras was reported.[1,5,14]

Ictal vocalisation and speech were significantly more frequent in female patients with RTLE compared with all other groups, while in males and in the total group there was no significant difference between RTLE and LTLE. In previous studies, the right temporal lobe has been recognised as the area mainly responsible for ictal speech.[1,6,7]. In the same studies, gender differences were ignored; females were dominant in the second one but information on sex was not available in the others. This, together with the fact that in our study besides clear speech we also included non-verbal sounds, can partially explain why we were unable to demonstrate right lateralisation. The high frequency of ictal vocalisation and speech in females with RTLE might be due to their well-developed associations with verbal abilities.[23]

In the clinical approach, dystonic posture contralateral to the epileptic focus and ipsilateral unilateral motor automatisms are common and have a highly lateralising value (15–70%).[7,10,11] However, Dupont et al.[12] stated that these features are more characteristic for MTLE than for neocortical TLE. In our study, composed patients with hippocampal sclerosis occurrences of posturing, oral automatisms and automatisms in extremities did not differ in terms of right temporal and left temporal lobe seizures or sex. It is suggested that projections used in seizure spread originating from the amygdala and hippocampus to the medial frontal cortex,[29] and basal ganglia[29–31] do not show any differences between sexes and hemispheres. For temporal lobe seizures, Fakhoury et al.[6] demonstrated in a group with heterogeneous pathology that extremity automatisms do not exhibit any differences between the two hemispheres.

In frontal lobe originated seizures, forced head deviation has been demonstrated to be contralateral to the epileptic focus.[32,33] Ochs et al.[15] showed that forced head deviation may also be a component of temporal lobe seizures. However, for this feature, they gave neither localising nor lateralising values.[15,34,35] In animal studies, it has been shown that ictal seizures originating from the amygdala were more prone to spread contralaterally,[36] while hippocampal originated episodes usually invade the ipsilateral hemisphere.[37] It has been observed that early head deviation was ipsilateral while later head deviation was contralateral.[28] Chee et al.[18] reported unforced head deviation to be 80% ipsilateral and forced head deviation to

be 94% contralateral. Fakhoury et al.[6] observed that contralateral forced head deviation was more common in patients with left temporal seizures.

In our study, we suggest that in the first 10 s of seizure, unforced head deviation was significantly higher in RTLE. However, if we evaluate all seizure durations without considering patient gender, there was no difference between forced and unforced head deviations between the two lobes. Interestingly, in all seizure durations, forced head deviation was significantly higher in males with LTLE and in females with RTLE, while unforced head deviation was higher in males with RTLE. It has been described in a SPECT study that male patients often had a frontal lobe hypometabolism which was ipsilateral to seizure onset.[26] Most probably, projections between the frontal and temporal lobes have asymmetries between the right and left hemispheres and in both sexes. Future anatomical and functional studies can help us understand these details better.

In this study, it was also shown that ipsilateral eye deviation was significantly more frequent in RTLE but there was no difference between the genders. In the first 10 s of seizures, ipsilateral eye deviation was prominent in RTLE but it was not statistically significant due to the small sample size. This data indicates that the connections between the anterior temporal lobe and frontal eye fields can show asymmetry between the two hemispheres and there is no connection with gender.[16,35,38]

Postictal coughing had been demonstrated to occur in 9—40% of temporal lobe seizures.[5,14,27] This has been explained by increased secretions due to autonomic activity, especially in hippocampal seizures.[5] It has also been suggested that the central nucleus, insula and medial frontal lobe play a role in the autonomic system of the frontal lobe.[10] In our study, we observed that postictal coughing is seen only in right temporal lobe seizures, as previously reported,[13] and we detected no sex-dependent differences. Like postictal coughing, postictal nose wiping is seen in temporal lobe seizures and the increased activity of the autonomic system and increased oropharyngeal secretions would account for them.[10] Lateralisation and gender had no effect on the occurrence of postictal nose wiping.

In 1983, Wieser[39] suggested that epileptic processes follow some preferential paths instead of all the anatomical paths. However, it was reported that these connections were built up depending on their localisation, sensitivity, the degree of discharge, local ionic changes, their prior sensitisation and the area of focus.[39,40] The path of spread may be different in patients with the epileptic focus in the same area, while only one focus in a single patient can use different ways to spread.[41] In temporal lobe epilepsy, studies using depth electrodes or animal models showed that seizure spread can invade the contralateral temporal lobe prior to the ipsilateral or contralateral frontal lobes and, in contrast, the invasion of both ipsilateral and contralateral frontal lobes often precedes the invasion of the contralateral temporal lobe. This pattern of spread gives clear evidence of the importance of the interhemispheric connections of both the hippocampal fissure and the forebrain in seizure activity. In our study, we speculate that intra- and interhemispheric connections can exhibit differences depending on gender and lateralisation.

In summary, ictal semiology can help us to obtain more information about the brain, and studies on this topic can indirectly reflect differences between the right and left hemispheres and between sexes. We suggest that in further studies concerning ictal semiology sex should be evaluated as a separate parameter.

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