

THE ROLE OF MIRROR FOCUS IN THE SURGICAL OUTCOME OF PATIENTS WITH INDOLENT TEMPORAL LOBE TUMORS

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ABSTRACT - Purpose: To review the clinical and neurophysiological data of 21 patients with epilepsy due to temporal lobe tumors and who had undergone evaluation and surgery at the Hospital das Clínicas da Universidade de São Paulo. The aim of this study was to investigate whether the occurrence of a mirror focus was influenced either by certain clinical factors or if the surgical outcome was influenced by the presence of a mirror focus. **Method:** We included these 21 patients who had undergone at least one interictal electroencephalogram in the pre- and post-surgical periods. They had had a minimum follow-up of one year. **Results:** Eight patients had mirror focus (Group 1) and 13 did not (Group 2). The mean age at seizure onset, duration of epilepsy disorder and total number of seizures did not vary statistically between the two groups of patients. Generalized tonic-clonic seizures occurred more frequently in the mirror focus group. All, but one patient, with a mirror focus were seizure free at follow-up. The mirror focus disappeared in all eight patients in the post-surgical electroencephalogram. In this group, the patient who was not seizure-free had a seizure recorded in his post-surgical electroencephalogram with seizure onset ipsilateral to the resected tumor. The patients who were not seizure-free had either been submitted to an incomplete resection of the tumor or showed evidence of associated cortical dysplasia. **Conclusion:** The occurrence of mirror focus is not a contraindication to surgery even when interictal epileptiform activity predominates contralaterally to the tumor and neither when seizures appear to arise from the mirror focus on scalp EEG. Good surgical outcome is expected despite EEG findings that may conflict with tumor location.

KEY WORDS: epilepsy, secondary epileptogenesis, electroencephalography, complex partial seizures, temporal lobe tumors.

Epilepsia do lobo temporal por processos expansivos e epileptogênese secundária

RESUMO - Introdução: A epileptogênese secundária é descrita como fenômeno em que, uma área epileptogênica primária, geradora de descargas, através de conexões neuronais com outra área não acometida, pode gradualmente induzir alterações epileptiformes nessa última, que, na maioria das vezes se localiza em região homóloga no hemisfério oposto ao foco primário. **Objetivos:** Analisar em um grupo de 21 pacientes com processos expansivos do lobo temporal e epilepsia a ocorrência do foco em espelho e os fatores clínicos potencialmente responsáveis pelo seu desenvolvimento e sua influência no prognóstico cirúrgico. **Método:** Foram incluídos 21 pacientes que realizaram eletroencefalograma no período interictal, antes e após o tratamento cirúrgico. Dentre os fatores clínicos estudados destaca-se a idade de início e duração da epilepsia bem como a frequência de crises epiléticas, por serem considerados relevantes no processo da epileptogênese secundária. **Resultados:** Os pacientes foram divididos em dois grupos de acordo com a presença (8 pacientes) ou não do foco em espelho (13 pacientes). Dentre os fatores clínicos analisados, a presença de crises tônico-clônicas generalizadas foi estatisticamente significante, ocorrendo de forma mais freqüente nos pacientes com o foco em espelho. Os outros fatores clínicos não apresentaram diferença estatisticamente significante entre os dois grupos. Após a cirurgia de retirada do processo expansivo, o foco em espelho não foi mais observado e ficaram livres de crises sete dos oito pacientes do grupo com foco em espelho e 10 dos 13, que não o apresentavam. Nos pacientes que não se tornaram livres de crises, a ressonância magnética mostrou em todos a persistência de tecido tumoral e em dois, presença de displasia cortical associada. **Conclusão:** Nossos resultados sugerem que a presença do foco em espelho não deve ser uma contra-indicação à excisão da lesão primária, mesmo quando no eletroencefalograma de escalpo a atividade interictal é mais freqüente do lado contralateral à lesão ou mesmo quando as crises epiléticas são também registradas contralateralmente.

PALAVRAS-CHAVE: epilepsia, epileptogênese secundária, eletroencefalograma, crises parciais complexas, tumores do lobo temporal.

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The statement that epilepsy is a progressive disorder is a controversy that began in the 19th century and continues so to this day. The concept of secondary epileptogenesis was first described by Frank Morrell¹ in experimental animal models and later moved to the clinical area. It implies that a primary epileptic focus, an abnormal cortical area capable of generating epileptogenic potentials and epileptic seizures, induces epileptiform discharges in a secondary epileptogenic area. The latter has neuronal connections with the primary area and can develop epileptogenic potentials and epileptic seizures although its cortex is histologically normal. The "mirror focus" is a special form of secondary epileptogenesis in which the secondary epileptogenic zone is located in the contralateral homotopic area, with respect to the primary epileptogenic lesion. Morrell¹, studying chronic models of epilepsy, described progressive stages of secondary epileptogenesis. In the initial stage, epileptic discharges were observed in the primary focus, which can be induced by various methods, but were not observed in synaptically related regions of the contralateral hemisphere. After some time, epileptic discharges began to occur in a homotopic or synaptically related region of the contralateral hemisphere, called the secondary focus, always time-locked to the discharges in the primary focus. This stage is called the dependent phase. During this primary stage, excision, disconnection, or pharmacological suppression of epileptiform activity in the primary focus results in an immediate cessation of the contralateral discharges. In the intermediate phase, the secondary epileptogenic zone generates independent discharges and also independent seizures. When the latter is disconnected from the primary epileptogenic zone, all the epileptogenic manifestations disappear after a variable period. In the later phase, called independent, the independent epileptogenic potentials are permanent and cannot be abolished by disconnection from the primary epileptogenic region. At this stage, the secondary focus demonstrates independence from the primary site and secondary epileptogenesis has been established. Tumors frequently induce epileptogenic discharges in the vicinity of the neoplasm, and in some cases, can cause secondary epileptogenic areas in synaptically related sites²⁻⁴. In tumor cases, the likelihood that a similar lesion may have arisen at a contralateral homotopic site is remote^{2,5,6}. In non-tumoral conditions the occurrence of secondary epileptogene-

sis is difficult to be unequivocally documented because the most common etiologies such as head trauma, birth trauma, encephalitis and vascular diseases are all potentially capable of producing multiple, independent epileptogenic lesions^{1,7,8}. The occurrence of secondary epileptogenesis in humans has been a matter of controversy and a few series related to this have been published^{9,10,11}.

We retrospectively investigated the existence of secondary epileptogenesis in a series of 21 patients with epilepsy related to temporal lobe tumors treated surgically by excision of the tumor.

METHOD

We reviewed 21 patients with single temporal lobe tumors and seizures that underwent surgery at Hospital das Clínicas de São Paulo from February 1993 to December 1999. We included all patients, irrespective of age or sex, on whom at least one interictal scalp/sphenoidal EEG had been performed before and after surgery and who had had an average follow-up of four years after surgery.

The medical records were reviewed for: sex, age, age at seizure onset, duration of seizure disorder, type and frequency of seizures, lateralization of lesion, site of lesion in temporal lobe (medial and/or neocortical), resection of the lesion (total or subtotal on MRI), histology, presence of associated cortical dysplasia and seizure outcome. The same neuropathologist analyzed all the tissue specimens. Video-EEG data in 14 and all the routine EEG data in the 21 patients were reviewed for localization of interictal and ictal epileptogenic zone, clinical semiology of seizures and also the existence of a mirror focus. The diagnosis of mirror focus was considered only when there was a clear and unequivocal evidence of recurrent, bilateral, independent interictal epileptiform spikes or sharp waves and/or ictal recording. Contralateral background slowing was not considered a sign of epileptogenesis. Our study were approved by the Ethical Committee of our Hospital.

RESULTS

Twenty-one patients were analyzed (Table 1). Fourteen patients underwent video-EEG monitoring for localization of ictal onset. The recording was performed with scalp electrodes following the 10-20 system with insertion of sphenoidal electrodes in some of them. Eight (38%) out of the 21 patients met the criteria for a mirror focus and were considered as Group 1 while 13 patients without mirror focus were considered as Group 2.

Interictal EEG

Group 1: In 5 of 8 patients who had a mirror

focus the most frequent interictal activity was present on the same side of the tumor. In 3 patients (cases 3, 5, and 8), the most frequent interictal activity was apparent on the contralateral side. Five out of 8 patients with mirror focus (cases 3, 4, 5, 7 and 8) demonstrated contralateral temporal discharges both in wakefulness and non-REM sleep. In 3 patients (cases 1, 2 and 6) the epileptiform activity was found only during non-REM sleep recording.

Group 2: In 10 of 13 patients the interictal activity was present only on the same side of the tumor. In 3 patients (cases 13, 14 and 18) the interictal EEGs were normal.

Ictal EEGs

Group 1: In 3 out of 7 patients with mirror focus who had been submitted to video EEG monitoring (cases 1, 4 and 5) the ictal epileptiform activity was recorded independently both ipsi and contralaterally to the tumor (Figs 1, 2 and 3): in case 1 - 5 seizures ipsi and 1 seizure contralaterally to the tumor; case 4 - 1 seizure ipsi and 1 seizure contralaterally to the tumor and in case 5, 11 seizures contralaterally. In this last case, this finding was considered as false lateralization. The semiology of the seizures didn't show clear lateralized signs that could suggest ictal onset. In 4 patients the ictal epileptiform activity was restricted to the side of the tumor.

Group 2: In 7 of 13 patients (cases 9, 10, 12, 15, 19, 20, 21), all the ictal epileptiform activity was recorded on the same side of the tumor.

Pathology

All the tumors were of slow growing type. Among the patients with mirror focus in Group 1, two had pilocytic astrocytoma, three ganglioneuroma, 2 ganglioglioma and one, pleomorphic xanthoastrocytoma. In this group, cortical dysplasia was found associated to the tumor in 3 patients (cases 3, 5 and 7). In Group 2, 7 had ganglioglioma, 3 pilocytic astrocytoma, one ganglioneuroma, one pleomorphic xanthoastrocytoma and one dysembryoplastic neuroepithelial tumor. Cortical dysplasia was found associated to the tumor in 5 of these patients (cases 12, 15, 16, 17, 20).

Treatment and outcome

Group 1: All but one patient underwent total resection of the tumor. These 7 patients were in Engel class I, after 3 to 7 years post-operatively (mean follow-up of 4.3 years). One patient who had

a subtotal resection of the tumor (patient 7) was in Engel class IV. In his post-surgical electroencephalogram, one seizure was recorded with ictal onset on the same side of the primary lesion. The clinical semiology was the same as those recorded in the pre-surgical period.

Group 2: 9 out of 13 patients underwent total resection of the tumor. At one to eight years post-operatively (mean follow-up 3.9 years), 7 out of 9 patients with total resection were classified in Engel class I; one, class II and the last, III. Four patients in Group 2 underwent subtotal resections of the tumor. Among them, 2 were in class I (patients 12 and 18) while the other 2 patients, whose tumors involved the neocortex as well as the medial portion of temporal lobe, which was not completely removed, were in class IV (patients 19 and 21).

Wilcoxon's rank-sum test showed no statistically significant differences between the mirror focus and the non-mirror focus groups in relation to age of onset, duration of seizure disorder and frequency of seizures. Fisher's test showed statistically significant difference for history of tonic-clonic seizures ($p=0.047$) in Group 1 (Table 2).

DISCUSSION

The existence of secondary epileptogenesis in lower animals has already been defined^{1,12}. Cases of human secondary epileptogenic lesions have been described but are few and not well documented^{9,10,11}. The electroencephalographic "mirror focus" has been regarded as evidence, at least in some individuals, that epilepsy may be a progressive disorder⁹. Goddard¹³ described the "kindling" phenomenon demonstrating that through repeated brief application of stimuli that initially do not evoke epileptic discharges, a permanent and progressive epileptic condition can be induced in normal animals. We do not know if "kindling" can even occur in human beings and if it does, what the trigger parameters might be that correspond to the "kindling" stimulus in experimental animals. As with the mirror focus, we know that evolutionary advancement is associated with progressively greater difficulty in producing kindling. The possible occurrence of kindling and secondary epileptogenesis in humans also has important therapeutic implications. It would stress the importance of early and aggressive antiepileptic medication and also call for surgical treatment as early as possible in cases in which medication was unsuccessful in control-

Table 1. Summary of 21 patients with temporal lobe tumors.

Patient	Age at onset (year)	Duration (year)	CPS (per month)	Seizures		Tumor side	Tumor type	Follow-up duration (year)	Resection	Engel's class
				GTCs						
MF-Group 1										
1	2	14,5	3	+		R	PA	4	total	IC
2	19	8	8	+		L	PX	4,5	total	IB
3	9	4	2	+		R	Gn	3,5	total	IA
4	9	30	8	-		L	Gg	4	total	IC
5	7	7	8	-		R	Gn	4,5	total	IA
6	6	9	1	-		L	Gn	3	total	IA
7	6	23	40	+		L	PA	7	subtotal	IVB
8	0,6	10,4	20	-		R	Gg	4,5	total	IA
Non-MF-Group 2										
9	0,25	10	4	-		L	Gg	3,4	total	IA
10	15	3	4	+		R	PA	8	total	IB
11	14	11	4	-		R	PA	6,3	total	IIB
12	3	19	10	-		L	DNET	8	subtotal	IA
13	2,1	0,7	1	-		L	Gn	3	total	IA
14	1,2	3,5	1	-		L	Gg	3	total	IA
15	10	1	45	-		R	Gg	3,5	total	IA
16	9	3	12	-		R	Gg	4	total	IA
17	1,5	4,5	3	-		R	Gg	3,5	total	IA
18	9	12	5	-		R	Gg	4	subtotal	IA
19	8	13	15	-		L	PA	1,6	subtotal	IVB
20	16	10	90	-		L	Gg	1,3	total	IIIB
21	13	2	15	-		L	PX	1,5	subtotal	IVA

MF, mirror focus; CPS, complex partial seizure; GTCs, generalized tonic-clonic seizure; PA, pilocytic astrocytoma; PX, pleomorphic xanthoastrocytoma; Gn, ganglioglioma; Gg, ganglioglioma; DNET, dysembryoplastic neuroepithelial tumor.

ling the seizures completely. Like other authors^{6,10,11}, we focused our attention on patients with benign tumors expecting that, without kindling or secondary epileptogenesis, epileptiform discharges would occur only in the cortex invaded by or in the immediate neighborhood of the benign tumor and certainly not at a distance from the tumor.

The results of the series published in literature show that 21 to 38% of patients with epilepsy caused by tumors were reported to develop a mir-

ror focus⁹⁻¹¹. In this series 38% had mirror focus confirming these numbers. The occurrence of bilateral independent foci may also be influenced by the state in which the EEG is obtained¹⁴. If we considered only patients who developed the mirror focus during wakefulness, excluding the effect of propagation of epileptiform discharges during non-REM sleep, this number would decrease to 23.8%. In our cases, as well as in those published in literature, the interictal epileptiform discharges in the se-

Table 2. Summary of statistical analysis.

	MF patients Group 1 (n=8)	Non MF patients Group 2 (n=13)	p - value
Sex (M:F)	6:2	7:6	0.4*
Mean age at onset (years)	7.3	7.8	0.689
Mean of duration of epilepsy (years)	13.2	7.1	0.119
Mediana of frequency of CPS (mean by month)	8	5	0.827
Ocurrence of GTCS	4	1	0.827
Mean follow up (years)	4.375	3.93	0.2

MF, mirror focus; M, masculine; F, feminine; Data evaluated by Wicoxon's rank sum test and *Fischer's test

condary epileptogenic zone were not time-locked to the spikes in the vicinity of the tumor (primary epileptogenic zone). This would suggest that the secondary epileptogenic focus had achieved relative independence, which means the phase of independent secondary epileptogenesis¹. However, even if there is no direct proof of dependence in these cases we cannot exclude the possibility that spikes in the primary epileptogenic region were actually triggering the discharges in the secondary epileptogenic region¹⁵. In these cases we should consider the possibility that the primary epileptogenic spikes might be undetectable with the recording techniques used in these cases. The EEG recorded only through scalp electrodes may not detect deep-seated foci. We recorded independent scalp-recorded EEG seizure patterns arising from the contralateral side of the tumor in 37% of the patients. This result is comparable to those of Gilmore et al.¹¹. Some factors may be important in the mechanisms of secondary epileptogenesis. The age at seizure onset was not important in our series, a finding also similar to others studies^{11,16}. Morrell et al.², reported a series of 123 patients with temporal lobe tumors and observed that patients under 30 years of age at seizure onset had more chances of developing mirror foci, especially the patients with larger duration of their disorders.

In animal models, duration of the epilepsy is also an important factor in the mechanism of secondary epileptogenesis^{1,12}. We did not find a significant relationship between the duration of seizure disorder and the mirror foci. Once more, our finding is similar to that of Gilmore et al.¹¹ who could not demonstrate this relation in a sample of 22 patients. Gupta et al.¹⁷ reported that temporal lobe seizure patients with bilateral, independent interictal abnormalities had a longer duration of

illness. In their non-tumoral patients the possibility that multiple primary lesions might have confounded conclusions about secondary epileptogenesis.

The frequency of seizures as a factor implied in the development of mirror foci and their persistence after surgery is attractive and stressed by Morrell⁷. There was no statistically significant difference between our two groups of patients. Falconer et al.¹⁰ and Gilmore et al.¹¹ also observed this tendency. In their series, however, there was no statistical significance and prognostic correlation. The occurrence of tonic-clonic seizures was a factor that showed statistical significance in our patients in contrast with others^{4,16}. Also, there are other factors that might be important in the mechanism of secondary epileptogenesis and which may interact with one another. Seeking simplistic correlations among these factors may underestimate the complexity of epileptogenesis.

Our patients were considered at a reversible stage of secondary epileptogenesis, characterized by independent secondary ictal and interictal foci; excision of the primary focus resulted in disappearance of the secondary foci and epileptic seizures originated from them. One patient with pylocytic astrocytoma associated with cortical dysplasia persisted with seizures. After 7 years of follow-up he still presented seizures and an ictal EEG recording showed seizures originating in the region of the primary foci. We believe that these seizures could be related to two factors: the eventual presence of cortical dysplasia and/or primary foci reminiscences. Gilmore et al.¹¹, in their series similar to our results, also observed only this reversible stage of intermediate secondary epileptogenesis.

The occurrence of dependent and intermediate

secondary epileptogenesis is a factor that has to be considered in the electroencephalographic diagnosis of epilepsy. The electroencephalogram can give "misleading" information regarding the location and extent of the epileptic zone. In patients with a focal tumor demonstrated by MRI, despite bilateral EEG abnormalities that could represent dependent or intermediate secondary epileptogenesis, the focal resection of brain tumor may lead to complete disappearance of epileptic seizures.

Morrell⁶ reported eight cases, which he interpreted as clear examples of independent secondary epileptogenesis. The main evidence for persistence of seizures arising from the contralateral side of the tumor was actually clinical semiology. After resection of the tumor, seizure semiology suggested that the remaining seizures were coming from the contralateral side. We agree with Lüders¹⁵ who stated that in most cases even careful analysis of video recordings do not permit reliable differentiation of seizures coming from the opposite temporal lobe in any given patient. Morrell⁶ presented evidence of a recorded seizure arising from the contralateral side of the tumor in only one case.

Careful analysis of the recording revealed that the tracing is unusual for an EEG seizure pattern with almost identical EEG patterns at left and right side of temporal chain electrodes¹⁵. If we accept that occasional cases of independent secondary epileptogenesis occur, the difficulty in finding well-documented cases clearly indicates that such cases must be extremely rare. Once more, we can not find any case of secondary epileptogenesis in the irreversible phase. If the intermediate secondary epileptogenesis was the highest stage of secondary epileptogenesis possible in humans, the necessity for early aggressive seizure control would depend

primarily on the impact of seizures on the quality of life. The occurrence of mirror focus is not a contraindication to surgery even when interictal epileptiform activity predominates contralaterally to the tumor and neither when seizures appear to arise from the mirror focus on scalp EEG. Good surgical outcome is expected despite scalp/sphenoidal EEG findings that may conflict with tumor location.

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