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Surgical outcome in patients with epilepsy and dual pathology

L. M. Li,[1] F. Cendes,[1] F. Andermann,[1] C. Watson,[2] D. R. Fish,[3] M. J. Cook,[4] F. Dubeau,[1] J. S. Duncan,[3] S. D. Shorvon,[3] S. F. Berkovic,[5] S. Free,[3] A. Olivier,[1] W. Harkness[3] and D. L. Arnold[1]

[1]*Department of Neurology and Neurosurgery, Montreal Neurological Institute and Hospital, McGill University, Montreal, Canada,* [2]*Department of Neurology, Wayne State University, School of Medicine, Detroit, Michigan, USA,* [3]*Epilepsy Research Group, Institute of Neurology, National Hospital for Neurology and Neurosurgery, London, UK and* [4]*Royal Melbourne Hospital and* [5]*Austin and Repatriation Medical Center, Melbourne, Australia*

Correspondence to: Dr Frederick Andermann, Montreal Neurological Institute and Hospital, 3801 University Street, Montreal, Quebec, Canada H3A 2B4

Summary

High-resolution MRI can detect dual pathology (an extrahippocampal lesion plus hippocampal atrophy) in about 5–20% of patients with refractory partial epilepsy referred for surgical evaluation. We report the results of 41 surgical interventions in 38 adults (mean age 31 years, range 14–63 years) with dual pathology. Three patients had two operations. The mean postoperative follow-up was 37 months (range 12–180 months). The extrahippocampal lesions were cortical dysgenesis in 15, tumour in 10, contusion/infarct in eight and vascular malformation in five patients. The surgical approach aimed to remove what was considered to be the most epileptogenic lesion, and the 41 operations were classified into lesionectomy (removal of an extrahippocampal lesion); mesial temporal resection (removal of an atrophic hippocampus); and lesionectomy plus mesial temporal resection (removal of both the lesion and the atrophic hippocampus). Lesionectomy plus mesial temporal resection resulted in complete freedom from seizures in 11/15 (73%) patients, while only 2/10 (20%) patients who had mesial temporal resection alone and 2/16 (12.5%) who had a lesionectomy alone were seizure-free ($P < 0.001$). When classes I and II were considered together results improved to 86, 30 and 31%, respectively. Our findings indicate that in patients with dual pathology removal of both the lesion and the atrophic hippocampus is the best surgical approach and should be considered whenever possible.

Keywords: hippocampal sclerosis; dual pathology; epilepsy; surgery; outcome

Introduction

In patients with partial epilepsy and an underlying epileptogenic lesion it is likely that seizures originate from that lesion or its vicinity (Gloor, 1987). Recognition of the underlying lesion and definition of the extent of the epileptogenic area are key points in the presurgical evaluation of patients with refractory partial epilepsy (Gloor, 1987; Awad *et al*., 1991; Cascino *et al*., 1993*a*). Surgical removal of these epileptogenic areas can be curative or provide significant reduction in seizure frequency in the majority of individuals.

The most common pathological finding in surgical specimens of patients with refractory partial seizures is hippocampal sclerosis, followed by tumour, cortical dysgenesis and vascular malformation (Babb and Brown, 1987; Engel, 1993).

Hippocampal sclerosis can now be diagnosed *in vivo* by its morphometric and signal intensity changes on MRI by two-dimensional visual inspection (Jackson *et al*., 1994; Bronen *et al*., 1995), by quantitative measurements, such as volumetry (Jack *et al*., 1990; Cook *et al*., 1992; Cendes *et al*., 1993; Jack *et al*., 1995*a*; Watson *et al*., 1996*a*) or by T_2 relaxometry (Van Paesschen *et al*., 1995). Strong correlation has been found between hippocampal volume and pathological findings in different centres (Cascino *et al*., 1991; Lencz *et al*., 1992; Lee *et al*., 1995; Watson *et al*., 1996*b*; Van Paesschen *et al*., 1997). Surgical removal of a unilateral atrophic hippocampus can render >80% of patients seizure-free (Arruda *et al*., 1996) while surgical outcome is less favourable in patients with bilateral atrophy (Jack *et al*., 1995*b*; Arruda *et al*., 1996) and in those without atrophy (Berkovic *et al*., 1995; Jack *et al*., 1995*b*; Arruda *et al*., 1996).

The surgical outcome in lesional epilepsy is variable and

good results range from 39 to 83% (Cascino *et al*., 1993*a*). In our previous study (Li *et al*., 1997*a*), we found that incomplete removal of the lesion appeared to be the main reason for an unfavourable surgical result. In patients with complete removal of the macroscopic lesion, 85% became seizure-free or had an important reduction in seizure frequency (Engel's class I–II).

In some patients, however, MRI can show the association of hippocampal atrophy with an extrahippocampal lesion, defined as dual pathology. The frequency of this association ranges from 5 to 30% in patients with refractory partial epilepsy (Levesque *et al*., 1991; Cascino *et al*., 1993*b*; Raymond *et al*., 1994; Cendes *et al*., 1995; Li *et al*., 1995). This wide range in the reported frequency of dual pathology reflects the different populations being studied and the methods of analysis. In quantitative MRI-based studies, the frequency of dual pathology was more homogeneous and found to be ~15% (Cascino *et al*., 1993*b*; Raymond *et al*., 1994; Cendes *et al*., 1995). The most common types of extrahippocampal lesions found in dual pathology are developmental abnormalities, such as cortical dysgenesis, followed by gliotic lesions acquired in early childhood (Levesque *et al*., 1991; Raymond *et al*., 1994; Cendes *et al*., 1995).

There have been very few reports suggesting the optimal surgical strategy in individuals with dual pathology. Cascino *et al*. (1993) reported three patients who became seizure-free only after a second operation in which the atrophic hippocampus was removed. In our previous study of surgical outcome in patients with single and dual pathology (Li *et al*., 1997*a*) we concluded that, in patients with dual pathology, both the extrahippocampal lesion and the atrophic hippocampus were likely to be involved in seizure generation. The best result was obtained when both the extrahippocampal lesion and the atrophic hippocampus were removed. However, because of the small number of patients with dual pathology (Li *et al*., 1997*a*), we could not conclude whether the type of lesion or the degree of hippocampal atrophy is the most important factor when the surgical strategy is being decided. In the multicentre study reported here we extended our analysis to a much larger group of patients with dual pathology who underwent surgical treatment for refractory epilepsy.

Patients and methods

We used as the criterion for inclusion concomitant hippocampal sclerosis and an extrahippocampal lesion diagnosed either by pathology or by MRI when the lesion was not resected. The patients were from five centres: the Montreal Neurological Institute and Hospital, Canada; the National Hospital for Neurology and Neurosurgery, London; Wayne State University, Detroit, Michigan, USA; the Royal Melbourne Hospital, Australia; and the Austin and Repatriation Medical Center, Victoria, Australia. All had a postoperative follow-up of at least 1 year.

Thirty-eight patients (15 women) with a mean age of 31 years (range 14–63 years) were studied (Table 1). The mean age of seizure onset was 13 years (range 1–31 years). Mean postoperative follow-up was 37 months (range 12–180 months; seven patients had a follow-up of <2 years).

Hippocampal sclerosis was defined either by preoperative MRI volumetric measurement of the hippocampal formation (Cook *et al*., 1992; Cendes *et al*., 1993; Watson *et al*., 1997) or by pathology (Babb and Brown, 1987; Meencke and Veith, 1991).

MRI volumetric measurements of the hippocampal formation were performed using 1–3 mm thick coronal slices following a specific protocol (Cook *et al*., 1992; Cendes *et al*., 1993; Watson *et al*., 1997). Forty-four age-matched normal control individuals were scanned using the same protocol. Volumetric studies from the centres were validated by cross-measurement (Cendes *et al*., 1992). The volume of the hippocampal formation in the control group had a normal distribution curve. We compared the volumes of hippocampal formation of the patients with those of the control group, and analysed the amount of asymmetry between sides, expressed as the ratio of the smaller to the larger hippocampal volume. Values of <0.94 (<2 SD) from the mean of the control group were considered abnormal. Values of <0.75 were considered as indicating severe hippocampal sclerosis (Watson *et al*., 1996).

Histopathological diagnosis of hippocampal sclerosis was based on qualitative and descriptive analysis. Sommer's sectors (CA1 to CA4) showed a pattern in keeping with hippocampal sclerosis, and because no quantitative cell counting was performed a broader grading system was chosen: (i) mild to moderate hippocampal sclerosis (mild or moderate astrogliosis and neuronal loss in the hippocampal specimen); and (ii) severe hippocampal sclerosis (severe neuronal loss in the hippocampus and pronounced proliferation of astrocytes involving more than one medial temporal structure). The term hippocampal sclerosis in the present study reflects a spectrum of neuronal cell loss and astrogliosis in the mesial temporal structures. This includes not only the 'classical hippocampal sclerosis' (Mathern *et al*., 1997) but also mild degrees of hippocampal neuronal loss and astrogliosis of mesial temporal structures.

Extrahippocampal lesion classification was based on the pathology described in the surgical specimen. When the lesion was not included in the resection it was classified according to the MRI findings using spin echo (T_1- and T_2-weighted), inversion recovery and gadolinium–DTPA enhanced images. The lesions were all visible on MRI.

Prolonged scalp EEG recordings were obtained using the International 10–20 system and sphenoidal electrodes. Interictal EEGs showed epileptiform activity over the temporal regions in 34/38 patients, predominating over the side of hippocampal sclerosis. Independent interictal epileptiform activity was also seen over the underlying lesion in 30/38 patients. Ictal EEG was recorded in 36/38 patients. Six patients with coexistent periventricular nodular heterotopia had chronic intracranial recording for further

Table 1 *Summary of clinical data in 38 patients with dual pathology*

Age/age of seizure onset (years)/sex	Ictal EEG	Type of extrahippocampal lesion	Ratio S/L	Degree of hippocampal sclerosis	Type of resection	Follow-up (months)	Outcome*
38/2/F	R CT	R TPO cortical dysgenesis	–	Severe	MT + part LS	40	I
30/17/M	L T	L T cortical dysgenesis	0.88	Inconclusive	MT + part LS	50	I
19/1/M	No change	L TPO contusion	0.72	Inconclusive	MT + part LS	25	I
16/2/M	Bi F	R TO infarct	0.41	Severe	MT + part LS	12	III
59/22/F	Not recorded	R T ganglioglioma	–	Severe	MT + LS	48	I
35/26/M	R T	R T ganglioglioma	–	Severe	MT + LS	60	I
34/18/M	L T	L T ganglioglioma	–	Severe	MT + LS	84	I
31/16/M	L T	L T vascular malformation	–	Moderate	MT + LS	48	I
14/1/M	L T	L T cortical dysgenesis	–	Severe	MT + LS	36	I
29/18/F	Not recorded	L T vascular malformation	0.76	Moderate	MT + LS	14	II
63/17/M	L T	L T vascular malformation	–	Mild	MT + LS	48	I
43/13/F	Bi T L > R	L T contusion	0.75	Not available	MT + LS	19	I
28/12/F	R T	Bi periventricular nodular heterotopia	0.91	Moderate	MT	31	III
23/17/M	Bi	R periventricular nodular heterotopia	–	Severe	MT	53	III
18/2/M	L T	L T dysembryoplastic neuroepithelial tumour	–	Severe	MT	24	I
38/25/M	Bi R > L	L insula vascular malformation	–	Moderate	MT	24	IV
37/13/M	L T	Bi periventricular nodular heterotopia	–	Mild	MT	24	III
36/10/F	L CT/PO	L P cortical dysgenesis	0.73	Inconclusive	MT	18	II
33/28/F	R hemisphere	Bi periventricular nodular heterotopia	–	Moderate	MT	60	IV
27/16/M	Bi FT	R periventricular nodular heterotopia	–	Severe	MT	56	IV
27/7/M	Bi	Bi periventricular nodular heterotopia	–	Mild–moderate	MT	42	III
34/15/F	L F	L F cortical dysgenesis	0.64	Severe	MT	17	I
15/9/M	Bi	R FTP cortical dysgenesis	0.79	–	LS (part)	16	IV
39/7/F	L FCT	L F contusion	0.89	–	LS	57	III
36/26/F	No change	L F astrocytoma	0.71	–	LS	34	III
50/31/M	R T	R T dysembryoplastic neuroepithelial tumour	0.87	–	LS	12	I
30/19/M	L TF	R F orbital and L T polar epidermoid tumour	0.86	–	LS	26	II
20/15/M	L T	L T cortical dysgenesis	0.89	–	LS	24	IV
16/1/F	L hemisphere	Bi T cortical dysgenesis	0.78	–	LS	24	II
41/2/F	L T	R F meningioma	0.66	–	LS	180	IV
37/13/M	L T	L T dysembryoplastic neuroepithelial tumour	0.45	–	LS	31	III
32/1/M	L T	L T contusion	0.84	–	LS	12	IV
28/17/F	R T	R TO cortical dysgenesis	0.88	–	LS	33	II
23/8/F	Bi F	L FT contusion	0.87	–	LS	17	I
18/14/M	L T	L T ganglioglioma	0.86	–	LS	35	IV
30/10/M	L T	L T vascular malformation	–	Severe	1st LS, 2nd LS + MT	40	III
36/19/M	R FT	R F contusion	–	Severe	1st LS, 2nd LS + MT	36	I
18/1/F	R T	R P contusion	0.75	Inconclusive	1st LS, 2nd LS + MT	18	I

M = male; F = female; R = right; L= left; Bi = bilateral; F = frontal; P = parietal; C = central; T = temporal; O = occipital; S/L = small/larger hippocampus; MT = mesial temporal resection; LS = lesionectomy. *Engel's modified classification (see text for details).

seizure localization/lateralization; however, the nodules were not implanted.

The surgical decision was based on all available clinical information, prolonged video-EEG monitoring and results of other complementary tests. The most likely origin of the seizures, as defined by neurophysiological studies, was the target of the resection. Three patients had two operations: 41 surgical procedures were analysed with respect to outcome

Table 2 *Different surgical approaches and outcome in patients with dual pathology*

	Lesionectomy	Resection of atrophic hippocampus	Lesionectomy plus resection of atrophic hippocampus
Class I	2	2	12*
Class II	3	1	1
Class III–IV	11	7†	2
Seizure-free/ total	2/16 (12.5%)	2/10 (20%)	11/15 (73%)‡
Class I–II/total	5/16 (31%)	3/10 (30%)	13/15 (86%)‡

*One patient had rare auras; †six of seven patients had associated periventricular nodular heterotopia; ‡multivariate analysis of variance: $F(1,40) = 9.02$, $P = 0.0009$.

(Table 2). The 41 operations were classified into three categories: lesionectomy (removal of the extrahippocampal lesion); mesial temporal resection (removal of the atrophic hippocampus); and lesionectomy plus mesial temporal resection (removal of both the lesion and the atrophic hippocampus).

Surgical outcome was based on Engel's modified classification (Engel *et al*., 1993): class I, seizure-free or residual auras; class II, rare seizures (fewer than three complex partial seizures per year); class III, significant improvement with 90% reduction in seizure frequency; class IV, no worthwhile improvement.

We assessed the relative homogeneity in the distribution of severity of hippocampal sclerosis and of the types of lesion among different types of surgical procedures. Using either histology or MRI volumetric studies to define severe hippocampal sclerosis, 11/15 (73%) of patients who had lesionectomy plus mesial temporal resection, 5/10 (50%) of patients who had mesial temporal resection and 7/16 (44%) of patients who had lesionectomy had severe hippocampal sclerosis. There was no significant association between the severity of hippocampal sclerosis and the type of operation performed [$\chi^2(2) = 2.95$, $P = 0.29$]. Dividing the type of lesion into those with 'better' (tumours and vascular malformations) and those with 'poorer' prognosis (cortical dysgenesis, infarct and contusions) in regard to surgical outcome, 8/15 (53%) of patients who underwent lesionectomy plus mesial temporal resection, 8/10 (80%) of those who underwent mesial temporal resection and 9/16 (56%) of patients who underwent lesionectomy had a 'poorer prognosis' type of lesion. This was also not significant [$\chi^2(2) = 2.04$, $P = 0.36$].

We used multivariate ANOVA (analysis of variance) and simple main effect and *post hoc* pairwise comparison in order to assess whether the type of surgery (lesionectomy versus mesial temporal resection versus lesionectomy plus mesial temporal resection), the type of lesion (better versus worse prognosis) and the degree of hippocampal sclerosis (mild to moderate versus severe) might have an independent or an interactive effect on the surgical outcome. Fisher's exact test was used to assess the significance of the association between ictal EEG localization and surgical outcome.

Results

Freedom from seizures was achieved in 11/15 (73%) of patients who had a lesionectomy plus mesial temporal resection compared with only 2/10 (20%) of those who had a mesial temporal resection alone and 2/16 (12.5%) of those who had a lesionectomy alone. When classes I and II were considered together the percentages rose to 86, 30 and 31%, respectively.

Multivariate ANOVA showed that the surgical outcome was significantly affected by the type of surgical procedure [$F(1,40) = 9.02$, $P = 0.0009$] and that there was a significant interaction between the type of the surgical procedure and the degree of hippocampal sclerosis [$F(2,40) = 5.62$, $P = 0.008$]. Surgical outcome was not significantly affected by the type of lesion [$F(1, 40) = 0.29$, $P = 0.592$] or by the degree of hippocampal sclerosis [$F(1,40) = 0.19$, $P = 0.666$]. There was no significant interaction between the type of lesion and either the type of surgical procedure [$F(2,40) = 0.41$, $P = 0.666$] or the degree of hippocampal sclerosis [$F(1,40) = 1.07$, $P = 0.309$]. There was also no significant interaction between the type of lesion, the type of surgical procedure and the degree of hippocampal sclerosis [$F(2,40) = 0.95$, $P = 0.4$].

Simple main effect analysis, seeking the significant factor in the interaction between the type of surgery and the degree of hippocampal sclerosis on the surgical outcome, showed that the type of surgery was a significant factor both for patients with severe hippocampal sclerosis [$F(2,29) = 7.35$, $P = 0.002$] and for those with mild to moderate sclerosis [$F(2,29) = 7.11$, $P = 0.003$].

Post hoc comparison, using Tukey's honestly significant difference test, showed that there were significant differences between lesionectomy plus mesial temporal resection and both lesionectomy alone [$q(29) = 7.67$, $P < 0.01$] and mesial temporal resection alone [$q(29) = 5.02$, $P < 0.01$], but there was no significant difference between lesionectomy alone and mesial temporal resection alone [$q(29) = 1.75$, $P > 0.05$].

Simple main effect analysis of the degree of hippocampal sclerosis with respect to the outcome from different types of surgery showed that the degree of hippocampal sclerosis had a significant effect in patients who had mesial temporal resection alone [$F(1,29) = 8.20$. $P = 0.007$] but not in those who had a lesionectomy alone [$F(1,29) = 3.11$, $P = 0.088$] or in those who had lesionectomy and mesial temporal resection combined [$F(1,29) = 0.12$, $P = 0.732$. Three of five patients with severe hippocampal sclerosis treated by mesial temporal resection alone achieved a class I–II outcome compared with 0/5 of those with mild to moderate hippocampal sclerosis.

Two out of seven patients (28%) with localized ictal EEG and 3/9 (33%) with non-localized ictal EEG who underwent

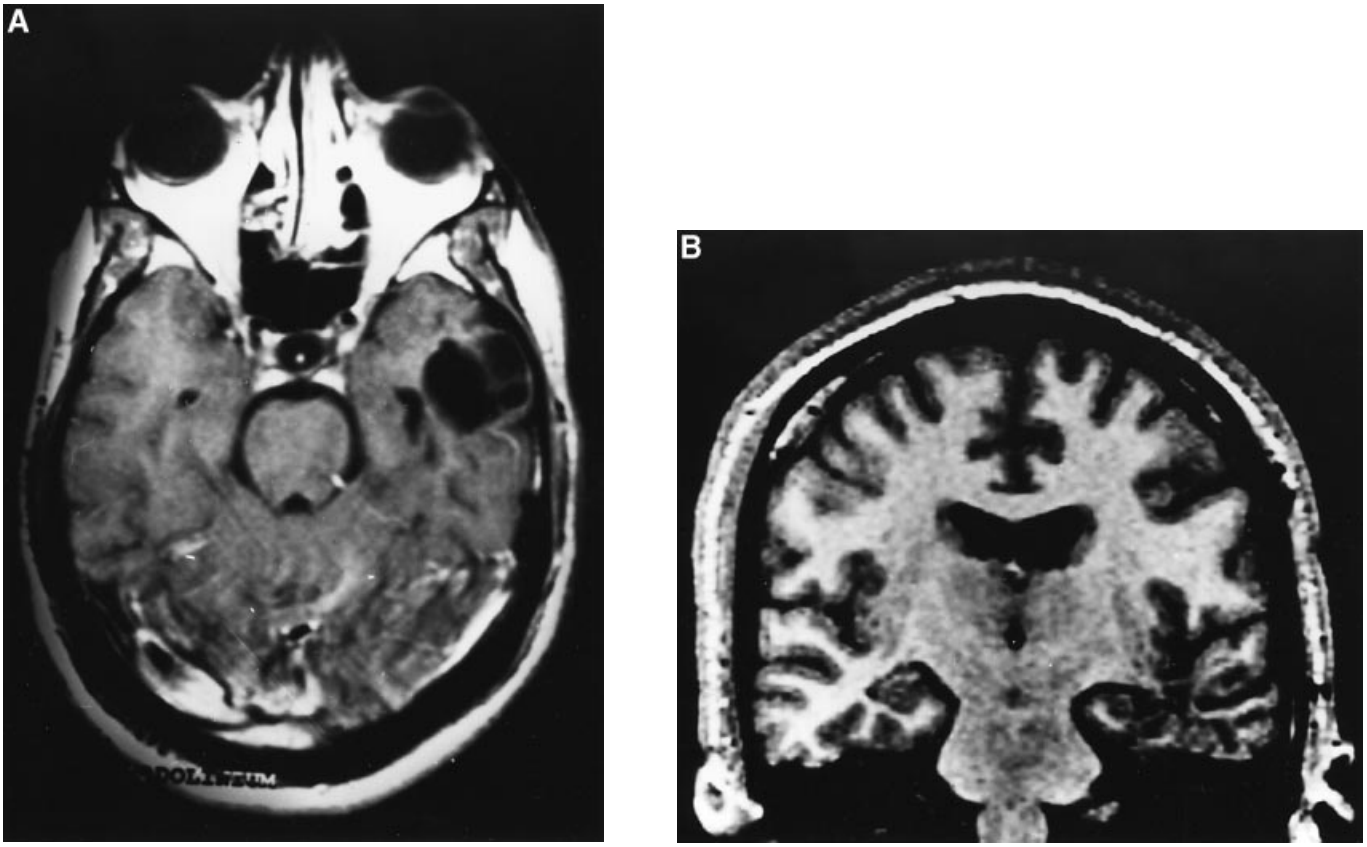

Fig. 1 37-year-old man with dual pathology and seizures since the age of 13 years. (**A**) Axial T_1-weighted MRI with gadolinium showed a left temporal lesion. He underwent lesionectomy and histopathology showed dysembryoplastic neuroepithelial tumour. (**B**) Postoperative coronal T_1-weighted MRI showed left hippocampal atrophy (ratio smaller/larger = 0.70). The hippocampus was left in place. The patients was in class III with 31 months follow-up.

lesionectomy alone were in class I–II. This was not statistically significant (Fisher's exact test, $P = 1$, two-tailed)

One of the three patients (33%) with localized ictal EEG and 2/7 (28%) with non-localized ictal EEG who underwent surgical removal of the sclerotic hippocampus alone were in class I–II. This did not achieve statistical significance (Fisher's exact test, $P = 1$, two-tailed).

Discussion

Ideally one would like to carry out a randomized prospective study of the three types of surgical procedure. Nevertheless, this study is of interest because it evaluates the result of what would be the 'optimal' individual procedure in the light of current knowledge and technology for seizure localization from five centres (in Canada, USA, UK and Australia).

Cascino *et al*. (1993*b*) reported three patients with dual pathology who had an unsuccessful outcome after lesionectomy (two vascular malformations and one ganglioglioma); they achieved freedom from seizures following a second operation in which the atrophic hippocampus was resected. In our series, the best results were seen in those patients who had both the lesion and the atrophic hippocampus removed. Seventy-three per cent became completely seizure-free compared with 20% of those who had resection of the atrophic hippocampus alone and 12.5% of those who had only a lesionectomy. The best outcome in this series was 86%, when both class I and class II were included (Table 2). This is comparable to the results obtained in mesial temporal sclerosis (90% in class I–II) (Arruda *et al*., 1996) or in lesional epilepsy syndrome (85% in class I–II) (Li *et al*., 1997*a*).

In the present series, the results of prolonged scalp EEG recording, whether localizing/lateralizing or not, showed no significant association with outcome. Our results indicate that in the presence of dual pathology both the lesion or its surround and the atrophic hippocampus are potentially epileptogenic. Invasive recording might provide further clarification about which component is the most epileptogenic. It is still unknown whether the risk : benefit ratio of such an invasive approach could significantly refine the surgical strategy and ultimately improve the outcome.

In patients who had resection of medial temporal structures alone, we found better surgical outcome in those with severe hippocampal sclerosis compared with those with mild to moderate hippocampal sclerosis (3/5 versus 0/5 in class I–II). Six of 10 patients in this group who had resection of the atrophic hippocampus alone had coexistent periventricular

nodular heterotopia, and all of them were in class III–IV. The exact role of grey matter nodules in the epileptogenicity in these cases is not entirely clear. We (Li *et al*., 1997*b*) reported a series of patients with refractory temporal lobe epilepsy and periventricular nodular heterotopia who had poor surgical results after temporal lobe removal. Possible explanations for the poor surgical results seen in these patients included: (i) periventricular nodular heterotopia as the epileptogenic source; (ii) dual pathology; (iii) periventricular nodular heterotopia being part of a more widespread epileptogenic source. Electrophysiological recording (Dubeau *et al*., 1997; Kothare *et al*., 1998) from the nodules provided support for the first two hypotheses.

In the group of patients who had removal of the lesion alone, the severity of hippocampal atrophy was not associated with either good or bad surgical outcome (Fig. 1). This suggests that the presence of hippocampal atrophy, independently of its severity, may have a negative effect on the surgical result. This is of clinical relevance because two-dimensional visual inspection may not reliably diagnose subtle hippocampal atrophy. Therefore, especially in patients with early developmental lesions referred for presurgical evaluation, a careful examination of the mesial temporal structures with quantitative measurement should be considered in view of the known association of such lesions with hippocampal sclerosis (Levesque *et al*., 1991; Raymond *et al*., 1994; Cendes *et al*., 1995).

In conclusion, assessment of possible dual pathology in patients with lesional epilepsy is important because their surgical management and outcome are distinct. For patients with dual pathology, removal of both the lesion and the atrophic hippocampus should be considered whenever possible, preferably in one step when the coexistent lesion is in the temporal lobe. For patients with a lesion outside the temporal lobe, the decision of whether the lesion or the atrophic hippocampus should be removed first should be based on the location, extent and nature of the lesion. Factors such as malignancy and the potential risk of bleeding must be considered. A two-step intervention could be planned and explained to the patient, taking into consideration the individual requirements and goals of surgical treatment.

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References

Arruda F, Cendes F, Andermann F, Dubeau F, Villemure JG, Jones-Gotman M, et al. Mesial atrophy and outcome after amygdalo-hippocampectomy or temporal lobe removal. Annal Neurol 1996; 40: 446–50.

Awad IA, Rosenfeld J, Ahl J, Hahn JF, Luders H. Intractable epilepsy and structural lesions of the brain: mapping, resection strategies, and seizure outcome. Epilepsia 1991; 32: 179–86.

Babb TL, Brown WJ. Pathological findings in epilepsy. In: Engel J Jr, editor. Surgical treatment of the epilepsies. New York: Raven Press; 1987. p. 511–40.

Berkovic SF, McIntosh AM, Kalnins RM, Jackson GD, Fabinyi GC, Brazenor GA, et al. Preoperative MRI predicts outcome of temporal lobectomy: an actuarial analysis [see comments]. Neurology 1995; 45: 1358–63. Comment in: Neurology 1995; 45: 1248–50.

Bronen RA, Fulbright RK, Kim JH, Spencer SS, Spencer DD, al-Rodhan NR. Regional distribution of MR findings in hippocampal sclerosis. AJNR Am J Neuroradiol 1995; 16: 1193–200.

Cascino GD, Jack CR Jr, Parisi JE, Sharbrough FW, Hirschorn KA, Meyer FB, et al. Magnetic resonance imaging-based volume studies in temporal lobe epilepsy: pathological correlations. Ann Neurol 1991; 30: 31–6.

Cascino GD, Boon PA, Fish DR. Surgically remediable lesional syndromes. In: Engel J Jr, editor. Surgical treatment of the epilepsies. 2nd ed. New York: Raven Press; 1993a. p. 77–86.

Cascino GD, Jack CR Jr, Parisi JE, Sharbrough FW, Schreiber CP, Kelly PJ, et al. Operative strategy in patients with MRI-identified dual pathology and temporal lobe epilepsy. Epilepsy Res 1993b; 14: 175–82.

Cendes F, Cook MJ, Watson C, Andermann F, Peters T, Free SL, et al. Hippocampal volumes in normal subjects: a multicenter study [abstract]. Epilepsia 1992; 33 Suppl 3: 49.

Cendes F, Andermann F, Gloor P, Evans A, Jones-Gotman M, Watson C, et al. MRI volumetric measurement of amygdala and hippocampus in temporal lobe epilepsy. Neurology 1993; 43: 719–25.

Cendes F, Cook MJ, Watson C, Andermann F, Fish DR, Shorvon SD, et al. Frequency and characteristics of dual pathology in patients with lesional epilepsy. Neurology 1995; 45: 2058–64.

Cook MJ, Fish DR, Shorvon SD, Straughan K, Stevens JM. Hippocampal volumetric and morphometric studies in frontal and temporal lobe epilepsy. Brain 1992a; 115: 1001–15.

Dubeau F, Li LM, Andermann F, Fish DR, Watson C, Cascino GD, et al. Periventricular nodular heterotopia and intractable temporal lobe epilepsy: contribution of heterotopic gray matter nodules to epileptogenesis [abstract]. Can J Neurol Sci 1997; 24 Suppl 1: S35.

Engel J Jr. Update on surgical treatment of the epilepsies. Summary of the Second International Palm Desert Conference on the Surgical Treatment of the Epilepsies (1992). Neurology 1993; 43: 1612–7.

Engel J Jr, Van Ness PC, Rasmussen T, Ojemann LM. Outcome with respect to epileptic seizures. In: Engel J Jr, editor. Surgical treatment of the epilepsies. 2nd ed. New York: Raven Press; 1993. p. 609–21.

Gloor P. Commentary: approaches to localization of the epileptogenic lesion. In: Engel J Jr, editor. Surgical treatment of epilepsies. New York: Raven Press; 1987. p. 97–100.

Jack CR Jr, Sharbrough FW, Twomey CK, Cascino GD, Hirschorn KA, Marsh WK, et al. Temporal lobe seizures: lateralization with MR volume measurements of the hippocampal formation [see comments]. Radiology 1990; 175: 423–9. Comment in: Radiology 1990; 175: 321.

Jack CR Jr, Theodore WH, Cook M, McCarthy G. MRI-based hippocampal volumetrics: data acquisition, normal ranges, and optimal protocol. [Review]. Magn Reson Imaging 1995a; 13: 1057–64.

Jack CR Jr, Trenerry MR, Cascino GD, Sharbrough FW, So EL, O'Brien PC. Bilaterally symmetric hippocampi and surgical outcome [see comments]. Neurology 1995b; 45: 1353–8. Comment in: Neurology 1995; 45: 1248–50.

Jackson GD, Kuzniecky RI, Cascino GD. Hippocampal sclerosis without detectable hippocampal atrophy. Neurology 1994; 44: 42–6.

Kothare SV, VanLandingham K, Armon C, Friedman A, Radtke R. Ictal EEG patterns from intracerebral depth electrodes placed within periventricular nodular heterotopias in 3 patients with gray matter heterotopias and refractory complex partial seizures [abstract]. Neurology 1998; 50 (4 Suppl 4): A25.

Lee N, Tien RD, Lewis DV, Friedman AH, Felsberg GJ, Crain B, et al. Fast spin-echo, magnetic resonance imaging-measured hippocampal volume: correlation with neuronal density in anterior temporal lobectomy patients. Epilepsia 1995; 36: 899–904.

Lencz T, McCarthy G, Bronen RA, Scott TM, Inserni JA, Sass KJ, et al. Quantitative magnetic resonance imaging in temporal lobe epilepsy: relationship to neuropathology and neuropsychological function. Ann Neurol 1992; 31: 629–37.

Levesque MF, Nakasato N, Vinters H, Babb TL. Surgical treatment of limbic epilepsy associated with extrahippocampal lesions: the problem of dual pathology. J Neurosurg 1991; 75: 364–70.

Li LM, Fish DR, Sisodiya SM, Shorvon SD, Alsanjari N, Stevens JM. High resolution magnetic resonance imaging in adults with partial or secondary generalised epilepsy attending a tertiary referral unit. J Neurol Neurosurg Psychiatry 1995; 59: 384–7.

Li LM, Cendes F, Watson C, Andermann F, Fish DR, Dubeau F, et al. Surgical treatment of patients with single and dual pathology: relevance of lesion and of hippocampal atrophy to seizure outcome. Neurology 1997a; 48: 437–44.

Li LM, Dubeau F, Andermann F, Fish DR, Watson C, Cascino GD, et al. Periventricular nodular heterotopia and intractable temporal lobe epilepsy: poor outcome after temporal lobe resection. Ann Neurol 1997b; 41: 662–8.

Mathern GW, Babb TL, Armstrong DL. Hippocampal sclerosis. In: Engel J Jr, Pedley TA, editors. Epilepsy: a comprehensive textbook. Philadelphia: Lippincott-Raven; 1998. p. 133–55.

Meencke HJ, Veith G. Hippocampal sclerosis in epilepsy. In: Luders HO, editor. Epilepsy surgery. New York: Raven Press; 1991. p. 705–15.

Raymond AA, Fish DR, Stevens JM, Cook MJ, Sisodiya SM, Shorvon SD. Association of hippocampal sclerosis with cortical dysgenesis in patients with epilepsy [see comments]. Neurology 1994; 44: 1841–5. Comment in: Neurology 1994; 44: 1947–8.

Van Paesschen W, Sisodiya S, Connelly A, Duncan JS, Free SL, Raymond AA, et al. Quantitative hippocampal MRI and intractable temporal lobe epilepsy. Neurology 1995; 45: 2233–40.

Van Paesschen W, Revesz T, Duncan JS, King MD, Connelly A. Quantitative neuropathology and quantitative magnetic resonance imaging of the hippocampus in temporal lobe epilepsy. Ann Neurol 1997; 42: 756–66.

Watson C, Cendes F, Fuerst D, Dubeau F, Williamson B, Evans A, et al. Specificity of volumetric magnetic resonance imaging in detecting hippocampal sclerosis. Arch Neurol 1997; 54: 67–73.

Watson C, Nielsen SL, Cobb C, Burgerman R, Williamson B. Pathological grading system for hippocampal sclerosis: correlation with magnetic resonance imaging-based volume measurements of the hippocampus. J Epilepsy 1996b; 9: 56–64.

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