ABSTRACT

Preoperative estimates of cognitive and seizure outcome must be as accurate as possible if the candidate is to make an informed decision about epilepsy surgery. Significant declines in memory function are reported in approximately 30% of temporal lobe surgery patients. The percentage varies according to the ways in which a postoperative deterioration is defined but since the majority of outcome studies do not take into account the patient's capacity to deteriorate if they are functioning at or close to the floor of a memory test prior to surgery, the published percentages may be an underrepresentation of the true extent of memory decline following epilepsy surgery. We examined the cognitive 'cost' of epilepsy surgery in a consecutive series of 474 patients who underwent elective surgery for medically intractable epilepsy. All patients underwent a presurgical assessment prior to and 1 year after the surgery. Re- liable change indices were used to identify significant postoperative memory decline. Postoperative outcome was dichotomized using the ILAE 2008 classification. All patients in class one were classified as seizure-free (67.5% of the sample). Excluding patients already functioning at or below the 2nd percentile on standardized memory tests, 37.8% experienced a significant postoperative decline in memory function. Twelve percent experienced the 'double hit' of significant postoperative memory decline and ongoing seizures following surgery. Patients with pathologies other than hippocampal sclerosis and with signs of limited cognitive reserve, both in terms of memory function and overall intellectual ability were most likely to suffer a double hit. Our results indicate that caution should be exercised when operating on these patients and preoperative counseling should be tailored to reflect the likely risk/benefit ratio of a temporal lobe resection for medically intractable epilepsy in this group.

1. Introduction

Despite the remarkable advances in imaging and other presurgical evaluations over the past decade [1], only 60–70% of patients who undergo epilepsy surgery are seizure-free 1 year following surgery [2]. This percentage has not changed in line with the technological advances [3]. This proportion drops to below 50% in series who have been follow- ed up over longer periods [2,4]. One explanation often put forward for the static nature of outcome statistics is that centers are now operating on more 'difficult' patients. Having got used to the 30%–40% margin of failure, this continues to be the convention, even as the characteristics of the patient group change. While this may be an acceptable approach in terms of the physical risk/benefit ratios of undergoing a surgical procedure; in epilepsy surgery, the patient has often paid a considerable cognitive 'price' for their postoperative outcome whether it is successful or not. The decision to proceed to epilepsy surgery is a complex one. Prospective candidates need to weigh up the chances of being seizure- free or of having a significant reduction in their seizures against the inherent risks of the procedure [5]. The risks of stroke, infection, a permanent neurological deficit, or a worsening of seizure control following epilepsy surgery are small [6]. However, the risk of a significant decline in memory function following surgery falls into a different class of risk that prospective candidates must consider. Unlike a stroke or other untoward complication, a decline in memory function does not necessarily mean that something has 'gone wrong' with the procedure, rather it can be viewed as part of the expected outcome. The risks are different for each candidate, dependent upon their clinical characteristics but for some candidates, the chances of experiencing a significant decline in memory function are high, greater than 50% [7]. In these circumstances, a postoperative decline in cognitive function could be considered as the likely 'cost' the candidate will pay for surgery, rather than a possible risk [5]. Thus, in the surgical decision making process, the chances of a post- operative decline in cognitive function can be thought of as the likely price the candidate will pay for the chance of being seizure-free. This price is attached to the surgery, not the outcome. It is imperative that the clinicians' estimates of both the likely cognitive 'cost' and the chance of being seizure-free are as accurate as possible if the candidate is to make an informed decision about an elective surgical procedure. These estimates are typically made on base rates of decline reported in the literature.

There is a large existing literature on the predictors of poor seizure outcome following surgery and a separate literature on the factors associated with postoperative memory decline in epilepsy surgery candidates [8]. We have previously published extensive data from our own series on these outcomes [4,9,10]. This study focuses on the identification of patients who pay a high cognitive price for an unsuccessful surgical outcome. These are a distinct group of patients who deserve special attention. Surgery may be an acceptable treatment option for some patients if there is a low risk of cognitive morbidity, even if it fails to completely control seizures. For other patients, cognitive morbidity may be a price they are prepared to pay for a good chance of seizure freedom. The clinical issues associated with these suboptimal outcomes are very different to the patients who pay a high cognitive price for an unsuccessful surgical outcome.

The aims of this study were the following:

1. To determine the proportion of patients who are not seizure-free and who experience a significant postoperative decline in memory function following surgery (double loss).

2. To identify the preoperative factors associated with double loss following surgery.

2. Methods

2.1. *Participants*

The participants in this study were a consecutive series of patients who had undergone elective temporal lobe surgery for medically intractable epilepsy at the National Hospital, Queen Square from 1992 to 2015 who had completed the standard clinical neuropsychological assessment prior to surgery and 1 year after their operation. Patients were excluded if English was not their first language, and they were assessed via an interpreter. All patients are routinely followed-up at 1 year.

Complete pre- and postoperative neuropsychological data were available for 474 patients (n = 217 RTL: n = 257 LTL). The mean age of the patients at the time of the preoperative assessment was 33.4 years (range: 16–66 years, s.d. 9.9) with a mean age of onset of 12.0 years (range: 0–54 years, s.d. 9.6). The clinical and demographic characteristics of the sample are presented in Table 1.

2.2. *Neuropsychological tests*

Scores from the List Learning and Design Learning tasks from the Adult Memory and Information processing Battery (AMIPB) and the British Memory and Information Processing Battery (BMIPB) were used as measures of memory function [11,12]. The structure of the AMIPB and BMIPB memory tests is identical. However, the BMIPB is a restandardization of the original AMIPB test norms. These tests have been shown previously to be sensitive to mesial temporal dysfunction and temporal lobe surgery [13,14]. In the list learning task, the patient is presented with a list of 15 unrelated words to learn, over 5 trials (max 75). A second list is then presented as a distractor before the patient is required to return to the first list and recall as many as they can, without further exposure. The structure of the design learning test parallels that of the list learning test. The patient is presented with an abstract design with nine components and asked to reproduce it over 5 trials (max 45). A second design is then presented as a distractor, before the patient is required to reproduce the first design again without further exposure.

2.3. *Outcome measures*

The raw scores from the verbal learning and visual learning tasks were concerted to z scores for the purposes of the statistical analyses.

2.4. *Memory decline*

Previous studies of postoperative memory decline in patients with epilepsy surgery may have underestimated the true prevalence of significant deterioration by including patients who already function at or close to the floor of traditional neuropsychological tests prior to surgery. While these patients may demonstrate decline in function on behavioural measures, this will not be detected on formal psychometric tests as the patients are already functioning at the floor of the test, and further decline will not be evident using robust measure change for example, reliable change indices, [8,9]. The inclusion of patients who already function at or close to the floor of a clinical test and cannot deterioration further, will distort the true rate of postoperative deterioration, returning a lower percentage than is likely to be the true rate. Capacity for postoperative decline was, therefore, determined by a preoperative score at or above the 2nd percentile according to published norms of the test.

A significant memory decline was defined using previously deter- mined reliable change indices for each task [7]. A postoperative score lower than the preoperative score by the RCI 80% or greater was classified as a significant postoperative decline in memory function.

Postoperative outcome was determined using the ILAE 2001 classification [15]. Seizure outcome was dichotomized for the statistical analyses. Patients in the ILAE classification class one were classified as seizure-free, other outcomes were classified as not seizure-free. *Statistical analyses*

2.4.1. *Predictors of 'double loss' following surgery*

Logistic regression analyses were used to identify predictors of a postoperative 'double loss'. A double loss was defined as a significant deterioration in memory function (in either verbal, nonverbal learning tasks, or both) and ongoing seizures following surgery. Predictors were selected on the basis of the previous factors identified in the literature associated with poor seizure outcome and postoperative memory decline. The variables included in the equation were the following:

1. Side of surgery (RTL vs LTL),
2. Normal imaging (yes/no),
3. Hippocampal sclerosis (yes/no),
4. Other pathology (yes/no),
5. Age at time of surgery (years),
6. Ipsilateral functional integrity (preoperative ipsilateral memory test z score),
7. Contralateral reserve (preoperative contralateral memory test z score), and
8. Level of intellectual function (IQ).
3. Results

Capacity for postoperative decline

Fifteen point four percent of the sample (n = 73) scored below the second percentile on the test of verbal learning prior to surgery (n = 23 RTL; n = 50 LTL).

Patients scoring below the second percentile on the list learning task prior to surgery did not differ from those with higher scores in their age at seizure onset, but were older (p b 0.01), and had a lower level intellectual function (verbal IQ p b 0.01; performance IQ p b 0.01).

Fourteen point five percent of the sample (n = 68) scored below the second percentile on the test of visual learning prior to surgery (n = 34 RTL; n = 34 LTL).

In a similar pattern to that seen on the verbal learning task, patients scoring below the second percentile on the visual learning task prior to surgery did not differ from those with higher scores in their age at seizure onset but were older (p b 0.05), and had a lower level intellectual function (verbal IQ p b 0.01; performance IQ p b 0.01).

In the group as a whole, 116 patients (24.5%) demonstrated a significant decline in verbal learning following surgery (n = 37 RTL; n = 79 LTL). Excluding the patients who performed below the 2nd percentile prior to surgery, 28.4% of the participants who had the capacity for post- operative decline on the tests demonstrated a significant decline in verbal learning following surgery.

In the group as a whole, 87 patients (18.4%) demonstrated a significant decline in visual learning following surgery (n = 39 RTL; n = 48 LTL). Excluding the patients who performed below the 2nd percentile on this test prior to surgery, 21.8% of the participants who had the capacity for postoperative decline on the test demonstrated a significant decline in visual learning following surgery.

3.1. *Outcomes*

Sixty-seven point five percent of the participants were seizure-free at 1 year. Laterality of surgery was not related to outcome (RTL 66.4% seizure-free; LTL 68.5% seizure-free).

Sixty-three percent of patients who performed below the 2nd per- centile on the verbal learning test prior to surgery were seizure-free following surgery. The difference in surgical outcomes between patients performing above and below 2nd percentile prior to surgery was not statistically significant (Pearson chi square = 0.79, p N 0.05).

Seventy-three percent of patients performing below the 2nd percentile on the visual learning test prior to surgery were seizure-free following surgery. Again, there was no significant difference in surgical outcome between patients performing above and below 2nd percentile on the visual learning task (Pearson chi square = 1.2, p N 0.05).

The relationship between seizure outcome at 1 year and significant memory decline is illustrated in Fig. 1.

Fig. 1. Class one seizure outcome and memory decline in patients with a capacity to decline.

Twelve point three percent of the patients who had a capacity to de- cline preoperatively were not seizure-free and demonstrated a significant postoperative decline in memory function. Three point seven percent of the sample demonstrated a significant postoperative decline in both verbal and nonverbal learning and were not seizure-free following surgery.

3.2. *Predictors of 'double loss' (memory loss and ongoing seizures) following surgery*

Four clinical variables were significant predictors of membership of the double loss outcome in the logistic regression model (model summary chi square 22.9, df 4, p b 0.001, Cox and Snell R square = 0.05). Patients who experienced significant memory decline and were not seizure-free following surgery were less likely to have hippocampal sclerosis as their pathology (p b 0.05), had higher scores associated with the ipsilateral side of surgery (left verbal learning/right visual learning), lower scores associated with the contralateral side of surgery, and a lower verbal IQ than people in the other outcome groups (see Table 2).

3. Discussion

Our results indicate that approximately 15% of epilepsy surgery patients perform at or close to the floor of standardized tests of memory function prior to surgery. These patients tend to be older and have a lower level of overall intellectual function than those with better memory function. While a postoperative deterioration of memory function may be evident on behavioral measures of function in this group, standardized clinical tests are not sensitive to further postoperative decline in these patients. Inclusion of these patients in population-based

[a] Variable(s) entered on step 1: hippocampal sclerosis, ipsilateral memory function score, contralateral memory function score, and verbal IQ.

estimates of the proportion of patients who experience significant memory decline following epilepsy surgery will lead to a systematic error in these estimates, returning lower percentages. Excluding this group, our data indicate that close to 40% (37.8%) of patients with TLE experience a significant postoperative decline in memory function (see Fig. 1). These percentages are higher than the one in three statistics that are typically quoted in the literature [16]. Approximately one in three patients experiences a significant decline in verbal memory, and one in five experiences a significant decline in visual learning following surgery. Losses in both verbal and visual memory are seen in both RTL and LTL patients and are not exclusively dependent on laterality.

Our data indicate that 12% of patients with TLE surgery may experience a 'double loss' following surgery. That is, they experience a significant decline in memory function, evident on verbal or visual memory tests (or both), and are not seizure-free following surgery. These patients tend to have a pathology other than hippocampal sclerosis and lower intellectual reserves than those with other postoperative out- comes. We also found that they tended to have lower scores associated with contralateral structures (visual learning scores in the LTL group; verbal learning scores in the RTL group) and higher scores associated with the structures ipsilateral to surgery (verbal learning scores in the LTL group and visual learning scores in the RTL group). These findings are consistent with Chelune's model of hippocampal adequacy and hippocampal reserve in the shaping of postoperative outcome [17]. Our results indicate that limited cognitive reserves both in terms of contralateral memory capacity and overall intellectual function may also be red flags in terms of full seizure control following surgery.

In this study, we used a simple dichotomy to classify seizure out- come following surgery. We focused on patients who were seizure- free because this is the primary aim of most surgical candidates. While a significant reduction in seizure frequency is an acceptable outcome for some, the majority of patients approach epilepsy surgery in the hope of becoming completely seizure-free as this allows access to driving and freedom from many of the difficult aspects of living with an un- predictable condition that still retains a considerable social stigma.

4. Conclusions

In temporal lobe epilepsy surgery, a cognitive 'price' is paid by up to 40% of patients regardless of outcome in terms of seizure control. For some, this may be a price worth paying for seizure freedom. However, over 1 in 10 patients experience a double loss following surgery; they have a significant decline in memory function and are not seizure- free. It is important to identify the patients prior to surgery who are most at risk of this postoperative 'double hit'. Patients with pathologies other than hippocampal sclerosis and with signs of limited cognitive re- serve both in terms of memory function and overall intellectual ability are most likely to suffer this double hit. Our results indicate that caution should be exercised when operating on these patients and preoperative counseling should be adjusted to reflect the likely risk/benefit ratio of a temporal lobe resection for these patients.

Conflict of interest

None.

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Table 1

Clinical and demographic characteristics of the participants.

	RTL (n = 217) n = 474	LTL (n = 257)	Whole group
Age	34.5 (9.9)	32.5 (9.8)	
Gender	102 male 115 female	118 male 139 female	220 male 254 female
Age at seizure onset	12.8 (9.7)	11.4 (9.7)	
Preoperative verbal IQ	94.3 (14.5)	91.5 (12.2)	92.8 (13.3)
Preoperative performance IQ	97.2 (15.2)	96.2 (16.2)	98.1 (14.4)
MRI characteristics	N = 8 NAD N = 149 HS N = 60 Other Other	N = 10 NAD N = 192 HS N = 55 Other	n = 18 NAD n = 341 HS n = 115
Seizure outcome free (67.5%)	144 seizure-free (66%)	176 seizure-free (68%)	320 seizure-

HS — hippocampal sclerosis.
NAD — no abnormalities detected.
Other — other pathology including cortical dysplasia, DNET, cavernoma, glioma, and other structural lesions.

Table 2
Logistic regression analysis — significant variables in the equation.

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	HS(1)	0.661	0.312	4.475	1	0.034	1.936
	Ipsi	−0.317	0.166	3.646	1	0.056	0.728
	Contra	−0.490	0.174	7.985	1	0.005	0.612
	Verbal IQ	−0.033	0.013	6.207	1	0.013	0.967
	Constant	1.204	1.264	0.908	1	0.341	3.335