Clinical Research

Intracarotid Amobarbital Procedure and Prediction of Postoperative Memory in Patients with Left Temporal Lobe Epilepsy and Hippocampal Sclerosis

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Summary: Purpose: Although temporal lobe epilepsy (TLE) patients with dominant hemisphere hippocampal sclerosis generally have good cognitive outcome after anterior temporal lobectomy (ATL), a minority of patients experience at least mild post-ATL decline on one or more standardized measures of episodic and semantic memory. The goal of this investigation was to determine whether memory outcome in this group could be predicted from preoperative intracarotid amobarbital procedure (IAP) recognition memory scores.

Methods: Data from 22 left TLE patients were studied retrospectively. All were left hemisphere language dominant and had IAP scores for each hemisphere, a significant degree of pathology-confirmed left hippocampal sclerosis (HS+), and no positive MRI findings other than atrophy. Cognitive outcome status was represented by the number of pre- to post-ATL declines across three tests, as defined by 90th percentile Reliable Change Index (RCI) criteria.

Results: Only 14% of the sample exhibited decline on more than one memory test. Low right IAP (left hemisphere injection) scores and relatively high preoperative cognitive ability and age at surgery predicted a greater risk of post-ATL memory decline.

Conclusions: A minority of left TLE HS+ patients experience at least a mild degree of RCI-defined decline in episodic or semantic memory after ATL. The right hemisphere IAP memory score, which reflects the functional reserve of the contralateral hemisphere, can help predict the risk of postoperative memory decline for TLE patients in whom HS+ is likely based on the presence of hippocampal atrophy on MRI or early age of seizure onset. Key Words: Memory—Neuropsychology—Intracarotid amobarbital procedure—Anterior temporal lobectomy—Temporal lobe epilepsy.

There are many variables that help predict vulnerability to verbal memory decline after anterior temporal lobectomy (ATL) for the treatment of intractable temporal lobe epilepsy (TLE). These include dominant hemisphere seizure onset, absence of ipsilateral hippocampal atrophy, high preoperative psychometric memory ability, and a relatively late age at the time of the initial precipitating injury (IPI), the onset of seizures, or surgery (1–8). Recently, in a small number of studies, intracarotid amobarbital procedure (IAP) recognition memory results in groups of TLE patients also have been used retrospectively in attempts to predict memory outcome after ATL (4,9–11). These IAP investigations have provided support for both the functional adequacy model of mesial temporal lobe function, in which memory outcome is inversely related to the functional adequacy of the resected tissue (1,10), and the traditional functional reserve model, in which the contralateral mesial temporal lobe must be sufficiently capable of sustaining memory functioning after surgery (4,10).

None of these studies examined the relation between IAP scores and post-ATL memory outcome in a sample consisting only of left TLE patients with significant ipsilateral hippocampal sclerosis (HS+). TLE patients without significant hippocampal sclerosis (HS−) are likely to experience very poor verbal memory outcome after left ATL. Although left TLE HS+ patients generally experience relatively little post-ATL memory decline, variability in outcome does exist within this group.

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(8,12). Therefore, the goal of the present study was to use IAP data retrospectively to explain post-ATL memory outcome differences in a series of left TLE HS+ patients. A link between IAP results and outcome, even among HS+ patients, could prove to be helpful in counseling left TLE patients with an early age of seizure onset or hippocampal atrophy evident on the preoperative MRI about their risk of any meaningful post-ATL neuropsychological decline. Both early age of onset and hippocampal atrophy are closely related to the finding of significant post-ATL pathology in the hippocampal specimen (13,14).

METHODS

Patients

The 22 left TLE patients studied underwent epilepsy surgery between 1992 and 1997 at Baptist Hospital/University of Tennessee, Memphis or Swedish Medical Center in Seattle. Table 1 lists demographic, seizure history, IAP, and surgery variables for these patients. Pre-surgery ictal scalp EEG videotelemetry monitoring was performed with all patients, and a majority also underwent intracranial monitoring with subdural electrodes. None of the patients had positive MRI findings other than atrophy. In some cases, there were MRI changes compatible with HS. Quantitative MRI was not performed for the majority of cases. For all patients, the pathologist identified significant HS, defined as >50% neuronal dropout in all sectors of the pyramidal cell layer or all sectors except CA2 (15).

Eleven of the 22 patients had a reported history of at least one febrile convulsion. The convulsion was secondary to meningitis in one case. Including the latter patient, four individuals had a history of meningitis or encephalitis. Other suspected precipitants were traumatic brain injury (n = 1) and an unspecified serious illness in infancy (n = 1). There was no clear precipitant in the remaining six patients; in these cases, the age at IPI was recorded as the age at onset of unprovoked seizures. All patients underwent neuropsychological assessments pre- and postoperatively, with the majority participating in postoperative cognitive testing about 6 months after surgery. The presurgery Full Scale Intelligence Quotient (IQ) on the Wechsler Adult Intelligence Scale-Revised (16) was ≥60 for all patients. Exclusion criteria included right or mixed hemisphere language dominance, as assessed during the IAP, and MRI abnormalities other than atrophy.

Surgery

Among the Memphis cases, 16 patients underwent a left ATL, including the resection of both lateral and mesial temporal structures, and one patient underwent a selective amygdalohippocampectomy. The current Memphis surgeon (K.D.) recently discontinued ATL in favor of selective amygdalohippocampectomy for epilepsy of mesial temporal origin, which explains why the latter patient underwent a less extensive surgery compared with others in the sample. Of the 16 Memphis patients who received an ATL, the lateral temporal lobe resection included the superior temporal gyrus as well as the inferior and middle temporal gyrus in 10 patients. The lateral resection was restricted to the middle and inferior gyrus in the remaining six patients. Resection versus sparing of the superior temporal gyrus was based on random selection for a previous study investigating language outcome after ATL (17). That study found no relation between resection versus sparing of the superior temporal gyrus and outcome in visual naming ability. All five Seattle patients underwent ATL, which included partial resection of all three temporal gyri in addition to medial temporal structures.

IAP protocol

In this report, right IAP score refers to memory performance after administration of amobarbital to the left hemisphere. Left IAP score refers to memory performance after perfusion of the right hemisphere. The internal carotid was catheterized via a transfemoral approach. The side of prospective operation was injected first, and ≥30 minutes elapsed before the other side was injected. A single bolus of 100 to 125 mg of amobarbital was injected into the internal carotid artery. For each individual patient, the dose was the same for each hemisphere. The memory stimuli and procedure were described in detail by Loring et al. (18). Approximately 30 seconds after the development of contralateral hemiplegia, eight objects were presented to the ipsilateral visual field. Each item was shown for approximately 5 seconds, and the name of the object was stated twice. Recognition

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**Table 1.** Demographic, seizure history, IAP, and surgery data for the TLE patients (N=22)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at IPI (y)</td>
<td>2.8 (5)</td>
</tr>
<tr>
<td>Age at onset (y)*</td>
<td>9 (9)</td>
</tr>
<tr>
<td>Duration of epilepsy (y)</td>
<td>25 (9)</td>
</tr>
<tr>
<td>Age at surgery (y)</td>
<td>34 (8)</td>
</tr>
<tr>
<td>Education (y)</td>
<td>11.8 (1)</td>
</tr>
<tr>
<td>IQ</td>
<td>85 (12)</td>
</tr>
<tr>
<td>Percent female</td>
<td>59</td>
</tr>
<tr>
<td>Percent right-handed</td>
<td>100</td>
</tr>
<tr>
<td>HS rating b</td>
<td>3.5 (0.5)</td>
</tr>
<tr>
<td>Right IAP score c</td>
<td>6.8 (1.2)</td>
</tr>
<tr>
<td>Left IAP score c</td>
<td>3.8 (3.2)</td>
</tr>
<tr>
<td>Extent of STG resection (cm)</td>
<td>2.6 (1.9)</td>
</tr>
<tr>
<td>Extent of MTG resection (cm)</td>
<td>3.9 (1.0)</td>
</tr>
</tbody>
</table>

SD, standard deviation; STG, superior temporal gyrus; MTG, middle temporal gyrus; ITG, inferior temporal gyrus.

* Age when unprovoked seizures began.
* Rated on a 0 to 4 scale; all patients’ HS were rated 3 or 4.
* Range, 4 to 8.
* Range, -1.5 to 8.
memory for the stimuli was assessed ≥10 minutes after the injection, when neurological deficits had resolved. At that point, the eight target objects and 16 foils were presented in random order in a yes/no recognition memory format. One point was given for each correctly recognized object and 0.5 deducted for each false-positive recognition error. For each hemisphere, a maximum score of 8 and a minimum score of −8 resulted.

The traditional measure of IAP asymmetry (right score – left score) takes into account only the difference between the left and right hemisphere scores and not the level of the individual scores. For example, an asymmetry score of one could reflect scores of seven and eight or four and five on the left and right sides, respectively. We constructed an asymmetry formula for left TLE patients that takes into account both the difference between the two scores and the sum of the two scores: \[(\text{score}_R - \text{score}_L) + 1\] \* (\text{score}_R + \text{score}_L). Adding one point to the left side of the equation greatly reduces the chance that zero could be a multiplicand because the right IAP score is almost always equal to or greater than the left score for left TLE cases. Because this new asymmetry score showed higher correlations with memory outcome compared with the traditional asymmetry score, the new score was used in this study.

**Standardized neuropsychological measures**

Initially, a total of five neuropsychological variables from four standardized neuropsychological tests of episodic and semantic memory were examined pre- and postsurgery. These consisted of immediate and delayed recall for two stories (Logical Memory subtest of the Wechsler Memory Scale) (19), the total number of words recalled across the five learning trials of a word list, and the total correct scores from two object naming tests [Visual Naming subtest of the Multilingual Aphasia Examination (20) and Boston Naming Test (BNT) (21)]. Regarding the word list, 17 patients were tested on the 16-item California Verbal Learning Test (22), and five patients were administered the 15-item Rey Auditory Verbal Learning Test (23). We included the naming (semantic memory) tests as possible outcome measures in addition to the episodic memory tests because a relationship between ipsilateral hippocampal integrity and postoperative object naming change had previously been identified (24).

Only one patient (5%) declined to a meaningful degree (see next section) on the Visual Naming test. This result is consistent with the previous report that the Visual Naming test is a less sensitive measure of object naming decline after ATL than the BNT (24). Only two patients (9%) exhibited a meaningful decline on Logical Memory-delay. This result may be partly attributable to the fact that 32% of the sample had a preoperative score of less than seven on this variable, whereas a decline of at least seven is the criterion for meaningful decline at the 90th percentile Reliable Change Index (RCI). Because patients generally did not show decline on Visual Naming and Logical Memory-delay, the relationship between IAP scores and outcome on these measures was not examined. There was a consistently higher frequency of decline on the remaining three measures: Logical Memory-immediate (LM-I; 27%), California or Rey Auditory Verbal Learning Test (VLT-total; 23%), and BNT (27%). Therefore, the relationship between IAP performance and pre- to post-ATL decline on the latter three variables was examined.

**Memory outcome cut-off**

Outcome on each measure was based on RCI criteria (25,26). This technique controls for the effects of practice, regression to the mean, and other sources of measurement error in test-retest situations so that statistically reliable performance changes can be identified in individual patients. For each patient, the number of test scores that declined at the 90th percentile RCI significance level was calculated (range, 0–3). A pre-to-post decline of at least 11 words constitutes a statistically reliable decline at the 90th percentile RCI level for the California VLT-total, and a pre-to-post decline of at least 15 words on the Rey Auditory VLT-total constitutes reliable decline at the same level. A decline of at least five words named represents decline on the 60-item BNT, whereas a decline of at least five words recalled indicates a decline on LM-I.

**RESULTS**

Only 14% of the patients exhibited a decline on more than one of the three memory measures. The magnitude of presurgery to postsurgery raw score change on LM-I was significantly correlated with right IAP performance \((r = 0.58, p < 0.01)\), but not the left IAP or IAP asymmetry scores. There were no significant correlations between pre-to-post raw score changes on the VLT-total or BNT and IAP scores.

The total number of RCI-defined test declines across the LM-I, VLT, and BNT was not associated with extent of resection of the superior temporal gyrus, extent of resection of the middle and inferior temporal gyri, seizure outcome, left hemisphere IAP score, or IAP asymmetry (Table 2). We also failed to discover any consistent relation between IPL characteristics and memory outcome. However, outcome on the three cognitive measures did correlate significantly with right hemisphere IAP score, age at surgery, age at onset, and preoperative IQ, LM-I, and BNT scores (because two different word list learning measures were administered across patients, no overall correlation with outcome could be calculated for VLT-total). Poorer memory outcome was associated with lower right IAP performance.
and higher age at surgery, age at onset, and preoperative cognitive scores.

In an initial regression analysis, right IAP score, age, age at onset, and IQ were entered as the independent variables in a backward multiple regression equation. IQ correlated significantly with preoperative performance on the standardized memory measures and was used as an index of general preoperative cognitive ability. Number of RCI-defined test declines was the dependent variable in the analysis. Right IAP score, preoperative IQ, and age at surgery, but not age at seizure onset, were significant predictors of memory outcome in the regression analysis (adjusted $R^2 = 0.57$). When preoperative LM-I and BNT were substituted for IQ in the regression, right IAP score, BNT performance, and age were significant predictors of memory outcome (adjusted $R^2 = 0.68$), whereas age at onset and LM-I were not. Figure 1 shows the mean right and left IAP score at each level of test score decline, as well as the number of patients who declined on none, one, two, or all three of the measures.

**DISCUSSION**

This study included only left language dominant, left TLE patients with pathology-confirmed ipsilateral hippocampal sclerosis. For these patients, we investigated the relation between IAP performance and the number of RCI-defined test score declines across three memory tests. On each of these three measures, approximately 25% of the group demonstrated a decline. Decline was quite rare on two other measures (Logical Memory-delay and Visual Naming), therefore the relation between IAP performance and outcome on these two measures was not considered. The vast majority of the patients (86%) experienced RCI-defined memory decline on none or only one of the three measures.

Neither the left hemisphere IAP score nor the IAP asymmetry score correlated significantly with RCI-defined memory outcome status, whereas the right hemisphere (left injection) IAP score did. A multiple regression analysis revealed that higher age at surgery, higher preoperative cognitive ability, and lower right IAP score were all significant predictors of poorer memory outcome. This relation between right hemisphere IAP performance and memory outcome defined by RCI criteria suggests that outcome depended to a significant degree on the functional reserve of the right hemisphere.

Our results are very consistent with those of Jokeit et al. (4), whose left TLE sample included cases with temporal lobe tumors. In their report, preoperative narrative memory ability and right hemisphere IAP performance were the only significant predictors of narrative memory outcome. Jokeit et al. also performed a multiple regression analysis in which the IAP score was not included as a predictor variable. In that analysis, probable age at temporal lobe damage (i.e., IPI) was one of the significant predictors of memory decline. Patients with an early IPI had a better memory prognosis compared with those with a late IPI. This finding is consistent with the results of their previous study (27), in which left TLE patients who had incurred an IPI before 6 years of age demonstrated a significantly better right IAP score compared with those with a later IPI and with our previous finding that the right hemisphere IAP score was significantly higher in left HS+ patients compared with left HS- patients (28). The absence in the current study of a significant relation between age at time of IPI and outcome can be explained by the fact that age at time of IPI was later than 3 years old for only 2 of the 22 patients. Based on their findings, Jokeit et al. concluded that trans-
fer of memory functioning to the right hemisphere occurs in some left TLE patients, and whether this transfer occurs is determined to an important extent by the timing of the injury to the left hemisphere. Our finding that variability in right IAP performance and memory outcome exists even in a sample of HS+ patients with predominantly early IPIs suggests that variability in the pathogenic mechanism of the IPI also may influence interhemispheric transfer and subsequent functional reserve (e.g., Ref. 29). Because our investigation was conducted retrospectively, detailed information about the characteristics of the IPIs was not available for our patients; therefore the relation among IPI type, interhemispheric transfer of memory, and post-ATL cognitive outcome remains to be determined. Figure 1 suggests that higher left IAP scores tended to be associated with poorer RCI-defined memory outcome, but the relationship did not approach significance in this sample. The absence of a relation between the left hemisphere IAP score and outcome probably can be explained by the relatively homogeneous level of left mesial temporal lobe integrity because all patients had significant left hippocampal sclerosis.

Consistent with previous reports, good memory outcome after ATL was associated with poor memory functioning before surgery. In the present sample, this finding suggests that, in the context of early dominant hemisphere hippocampal damage and temporal lobe epilepsy, plasticity for memory functioning is usually limited. That is, the apparent reorganization of memory to the right hemisphere after early damage to the dominant temporal lobe does not restore memory capacity to the normal level, although it does offer protection from post-ATL cognitive decline.

It should be noted that some left TLE patients may fail the IAP after a left injection of amobarbital because of an unusual degree of obtundation. Such patients may obtain a higher score with a repeat IAP using a lower but effective amobarbital dose or with a selective amobarbital procedure and then might be considered for surgery (30,31). However, a review of IAP reports revealed no evidence that any of the poor outcome patients in this study were remarkably obtunded during the IAP.

In conclusion, this study found that the right hemisphere IAP score, but neither the left hemisphere IAP nor the IAP asymmetry score, was among the variables associated with verbal episodic and semantic memory outcome in left TLE patients with left HS and ipsilateral hemisphere language dominance. The results indicate that for intractable left TLE HS+ patients, the functional reserve of the right temporal lobe is an important determinant of memory outcome. The basis for the variability in right hemisphere reserve among these patients remains to be determined. Type of IPI, in addition to timing of the IPI, may determine whether interhemispheric transfer of memory occurs. When such reorganization of memory does occur in left TLE patients, it usually is associated with poor preoperative but stable postoperative verbal episodic and semantic memory functioning. Thus, the results suggest that even left TLE patients with significant ipsilateral hippocampal atrophy may be at risk for at least a mild degree of post-ATL verbal memory decline if the right IAP score is poor, especially if they also are older at time of surgery and have relatively intact preoperative cognitive ability.

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REFERENCES


