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Abstract

Rationale: Our goal was to determine the frequency of repeated intracarotid amobarbital test (IAT) at our center and to estimate the retest reliability of the IAT for both language and memory lateralization.

Methods: A total of 1,249 consecutive IATs on 1,190 patients were retrospectively reviewed for repeat tests.

Results: In 4% of patients the IAT was repeated in order to deliver satisfactory information on either language or memory lateralization. Reasons for repetition included obtundation and inability to test for memory lateralization, inability to test for language lateralization, no hemiparesis during first test, no aphasia during first test, atypical vessel filling, and bleeding complications from the catheter insertion site. Language lateralization was reproduced in all but one patient. Repeated memory test results were less consistent across tests, and memory lateralization was unreliable in 63% of the patients.

Discussion: In spite of test limitations by a varying dose of amobarbital, crossover of amobarbital from one side to the other, testing of both hemispheres on the same day, practice effects, unblinded observers, fluctuating cooperation of the patients, and a biased sample of patients language lateralization was reproduced in all but one patient. In contrast, repeated memory test results were frequently contradictory. Memory results on IAT therefore seem much less robust than the results of language testing. Gain of reliable information versus the risks of complications and failed tests has to be considered when a patient is subjected to an IAT.

The intracarotid amobarbital test (IAT) is the gold standard to determine language (Wada and Rasmussen, 1960) and memory lateralization (Milner et al., 1962) in neurosurgical candidates. Considering the fact that the IAT is an invasive procedure with possible complications (Macken and Morris, 1999), it is unlikely that this risky procedure is repeated in a patient with an initially technically satisfactory IAT. However, in a survey of 62 epilepsy centers more than 25% indicated that they perform repeated IATs in all of their patients who fail their first IAT (Rausch et al., 1993). Nevertheless, almost no data on repeated tests or the Wada test reproducibility is available in the literature. A literature review reveals few abstracts with a total of 103 cases of repeated IATs (Dinner et al., 1987; Novelly, 1987; McGlone and MacDonald, 1989; Novelly and Williamson, 1989; Jones-Gotman, 1992; Benbadis and Heriaud, 2005). It was the objective of

our study to determine the frequency of repeated IATs in a large tertiary care center, to analyze reasons for repeated IATs, and to estimate the retest reproducibility of the IAT for both language and memory lateralization.

METHODS

A total of 1,249 consecutive IATs on 1,190 Cleveland Clinic patients over a 12-year period (1989–2001) were retrospectively reviewed. Of the patients who underwent repeat testing, all patients were separately catheterized for the retest procedure, and all tests were performed on separate days. The test retest interval was documented.

In all cases angiographies were performed using the standard catheter insertion technique via a guidewire. First, the side of the epileptogenic zone was injected. Side of injection and amobarbital dose were documented. Selective catheterization of the common carotid artery and subsequently the internal carotid arteries was performed using road-mapping techniques with braided 5 french or 4 french catheters with a 1-cm multipurpose curve. The catheter was placed in the cervical internal carotid artery with the tip in the center of the arterial lumen in order to prevent vasospasm.

Amobarbital was applied by intracarotid handpush injection. Amorbarbital doses ranged from 100 to 150 mg. Usual doses were determined by age and weight. Children received 100 mg, adults were tested with 125 mg, and adult patients with a body mass index over 25 kg/m^2 were injected with 150 mg. During repeated testing, amobarbital dose was frequently reduced by 12.5 to 25 mg. Average sodium amobarbital dose during the first test was 114 mg (n = 47) on the right and 114 mg (n = 47) on the left. Average sodium amobarbital dose during the second test was 102 mg (n = 26) on the right and 104 mg (n = 45) on the left.

Language testing was performed by testing separate subcategories, including spontaneous speech, word repetition, comprehension, confrontation naming, and reading during the test (Benbadis, 2002).

Language lateralization was calculated using the time in seconds until the first verbal response after injection occurred. Language was considered lateralized to one hemisphere if the speech arrest lasted at least 1 min on the side of the injection and if the interhemispheric side difference was at least 30 s in cases of speech arrest after both right- and left-sided injections.

Memory was tested by presentation of 9–20 words and objects while the patient was hemiparetic, including pictures, designs, function words, and object words or sentences (Acharya and Dinner, 1997). Memory testing was performed 15–30 min after recovery from hemiparesis using a forced selection paradigm. During retrieval, the patient was confronted with four different choices, with one of these choices being the correct picture or word, and three consisting of similar objects or words that had not been presented. Separate test object sets were used at baseline testing and during repeated IATs.

Memory function was defined as present in one hemisphere if the patient correctly identified a minimum number of items (pass/fail). The minimum number needed to prove memory was based on the probability to guess a series of results correctly in our multiple-choice paradigm ($p < 0.05$ in binomial probability tables) (Burington and May, 1970).

Correlations between the percentage of correct answers after injection of a given hemisphere at test and at retest were calculated with Pearson's correlation coefficient.

RESULTS

A total of 53 patients out of 1,190 (4.4%) underwent a second IAT, and 3 patients (0.24% of all patients, 5.6% of patients with repeated studies) had a third IAT. The charts of 3 patients were

missing. Therefore 50 patients (28 men, 46 right handed) with 31 uni- and 19 bilateral repeated IATs were included (69 hemispheres, 45 left). Average age was 29 years (range 7.7–55.3 years). Eight patients were under 18 years of age. Retest interval ranged from 1–1,119 days (median 95.5 days). Seizures started in the left hemisphere in 37, in the right hemisphere in 10, and bilaterally in 3 patients. A total of 35 patients had temporal lobe epilepsy, 8 frontal lobe epilepsy, 1 occipital lobe epilepsy, and 6 had seizures arising from multiple lobes.

Reasons for repetition included obtundation and inability to test for memory lateralization (32), inability to test for language lateralization (13), no hemiparesis during first test (2), no aphasia during first test (1), atypical vessel filling (1), and bleeding complications from the catheter insertion site (1).

Language lateralization was confirmed in 36 out of 37 patients with initial speech language results. One child had Rasmussen encephalitis of the initially dominant hemisphere.

Memory improved after left injection in 20 out of 45 patients and deteriorated in 2. After right-sided injection 10 out of 24 patients improved and 4 deteriorated. Results are illustrated in Tables 1 and 2. Pearson's correlation coefficient between the first and second memory test was low (left $r = 0.217$, right $r = -0.146$).

Bilateral repeated memory testing was available in nineteen patients. Results were consistent across the two tests for only seven patients, six of whom demonstrated bilateral memory representation during both IATs and one right-sided memory representation on both occasions. Results were inconsistent for the other twelve patients. In two patients memory dominance switched sides (each side once). Five patients went from bilateral memory representation to unilateral dominance (three right; two left), and five patients with an initially lateralized memory (three right, two left) showed bilateral memory on the second test.

DISCUSSION

In 4% of patients the IAT was repeated in order to deliver satisfactory information on either language or memory lateralization. Obtundation and inability to test for memory or language were most frequent reasons for repetition. Speech lateralization of the IAT was reproduced in all but one patient. Repeated memory test results demonstrated low test–retest correlations, and memory lateralization was not reproduced in up to 63% of the patients with repeated bilateral injections. We report the largest case series of repeated IATs. Our study is also the first study that gives percentages of repeated studies and lists detailed memory and language results of repeated IATs.

Previous studies with repeated IATs

Rausch et al. (1993) reported that 26% of 62 epilepsy centers responding to their survery repeat 100% of failed IATs, usually with a lower dose (Rausch et al., 1993). Additional 20% repeat up to a quarter of their failed IATs. However, another quarter of centers never repeats IATs (Rausch et al., 1993). Reasons for repetition in their review of the literature included contradicting results with seizure onset data, technical problems, and inattentiveness (Rausch et al., 1993). Risk factors for unsuccessful IATs in 42 children included low full-scale IQ (especially <80), young age (especially <10 years), and seizures arising from the left hemisphere, which was presumed dominant by right-handedness (Hamer et al., 2000). A literature review of previously reported repeated studies is summarized in Table 3 and demonstrates that the few cases that have been reported to date suggest that memory results are typically inconsistent across repeated tests (Dinner et al., 1987; Novelly, 1987; McGlone and MacDonald, 1989; Novelly and Williamson, 1989; Jones-Gotman, 1992; Benbadis and Heriaud, 2005).

IAT language paradigm validity

The gold standard for a valid test, resection of the dominant language areas and resulting aphasia, is ethically difficult to prove. We therefore looked to the literature for comparisons of language lateralization with the IAT and other techniques. High concordance for language lateralization between the IAT and functional magnetic resonance imaging (fMRI) (Springer et al., 1999; Vikingstad et al., 2000), positron emission tomography (PET) (Thiel et al., 1998**),** functional transcranial Doppler ultrasound (Knecht et al., 2000), magnetencephalography (MEG) (Alho et al., 1998; Ackermann et al., 1999), or by means of repetitive transcranial magnetic stimulation (Claus et al., 1993; Jennum et al., 1994; Epstein et al., 1999) has been shown. However, several cases of change in language lateralization, including our case, have been described previously in patients with Rasmussen syndrome (Boatman et al., 1999; Hertz-Pannier et al., 2002; Telfeian et al., 2002; Loddenkemper et al., 2003). We assume that the IAT was actually correct for language and valid at both tests, but that language lateralization itself changed during the test–retest interval due to the lesion in the previously dominant hemisphere (Loddenkemper et al., 2003).

IAT memory paradigm validity

Initially, the IAT was designed to test language lateralization (Wada and Rasmussen, 1960). In 1962, Milner et al. extended the IAT to include testing of memory functions in order to predict the incidence of postoperative amnesia following temporal lobectomy in epilepsy surgery candidates (Milner et al., 1962).

Prediction of amnesia

Only one well-documented case with postoperative amnesia exists that appears to be accurately predicted by IAT asymmetry on memory testing. IAT demonstrated right-sided language and right temporal memory representation. This patient underwent right temporal lobectomy in spite

of these test results and demonstrated decrease in memory function on formal testing by reports from his family (Loring et al., 1994). General memory scores and delayed recall indexes decreased 2 months after surgery, with a greater impairment of logical memory than visual reproduction (Loring et al., 1994). However, the same authors report three patients with similar asymmetries on IAT memory testing who also underwent temporal lobectomy and did not become amnestic (Loring et al., 1994). Therefore, the relationship between IAT memory test results and memory outcome after surgery is variable.

False positive results

The IAT may exclude too many patients from epilepsy surgery due its high rate of false positive tests predicting memory loss when epilepsy surgery actually does not lead to global amnesia (Simkins-Bullock, 2000). This is supported by a series of 10 patients who failed bilateral injections and subsequently underwent ipsilateral temporal lobectomy. None of these patients developed global amnesia (Kubu et al., 2000). In another series, 10 patients performed poorly on the IAT and underwent anterior temporal lobectomy resulting in improved seizure control without amnesia (Loring et al., 1990).

False negative results

On the other hand, isolated reports of six patients that passed their IAT memory testing and then became amnestic after anterior temporal lobectomy exist (Simkins-Bullock, 2000). These examples support the hypothesis that the IAT memory testing may not be valid in all cases. Recent studies suggest that the clinical relevance of the IAT may be closely linked to the memory test paradigm (Vingerhoets et al., 2006a; Vingerhoets et al., 2006b) and the type of memory assessed during the IAT (Simkins-Bullock, 2000).

Possible explanations for incongruencies in IAT memory testing

Dose effect

Previous authors suggested difficulties reproducing IAT memory testing. Data from previous repeat IAT series indicates that test parameters such as amobarbital dose may influence pass or fail rates in memory testing. Novelly and Williamson reported IAT memory test failure in 25 out of 325 cases using a pass/fail paradigm. In these cases, memory testing was repeated with a lower dose of amobarbital. Subsequently 21 out of these 25 patients passed. None of these patients was amnestic after temporal lobectomy (Novelly and Williamson, 1989).

Incomplete inactivation

An additional possible explanation for IAT memory test incongruencies may include incomplete inactivation of the suspected location for memory, the hippocampus. A study using Tc = 99m = hexamethylpropyleneamine oxime single photon emission computed tomography (HMPAO-SPECT) to trace the amobarbital distribution during IAT revealed an unpredictable distribution of amobarbital that did not correlate with angiography findings (Hart et al., 1993). Medial temporal structures were only perfused in 28% of patients (Hart et al., 1993). Depth electrode recordings suggest inactivation of the hippocampus during the IAT (Gotman et al., 1992). Temporary deafferentiation of the hippocampus by inactivation of the surrounding brain tissue has therefore been suggested as mechanism (Gotman et al., 1992).

Memory representation

Furthermore, not all memory generation may be located in the hippocampus. Frontal (Ojemann and Kelley, 2002) as well as parietal (Corkin, 2002) memory representation has been suspected for selected memory features and may play a role in IAT memory test results.

Memory testing paradigm

Finally, the time point of presentation of memory stimuli during anesthetization and paradigm may also play a role as illustrated by a single patient that became amnestic after temporal lobectomy. Based on this anecdotal report, early asymmetries during testing may be more predictive than asymmetries during the later stages of testing (Loring et al., 1994). In addition, there may be hemispheric side-differences in the encoding of stimuli, necessitating specific test material for each hemisphere (Vingerhoets et al., 2006b).

Limiting factors

Our data has to be interpreted with caution because of a biased sample of patients. Therefore, conclusions from our results may be limited to patients who failed the first IAT. Other limiting factors that may impair conclusions regarding the reliability of the IAT include retrospective data collection, a varying dose of amobarbital, crossover of amobarbital from one side to the other and individual vascular supply patterns, testing of both hemispheres on the same day, practice effects, medication effects, unblinded observers, fluctuating cooperation of the patients, slightly different presentation of objects during the memory testing, sedation, and encephalopathy in many patients. However, despite all of these uncontrolled factors, language did not change whereas memory results were much more erratic. In addition, confusion and obtundation during the early phase of the IAT does not prevent imprinting of memory (Lesser et al., 1986). Language assessment during Wada testing also included assessment of repetition, reading, naming, and paraphasias, but scoring and assessment paradigms except speech arrest changed several times during the retrospective study period making comparison impossible and completion of the domains was frequently difficult during obtundation.

Unfortunately no other data are available at this point and prospective data is hard to gather due to the need for repeated IATs in only 4% of patients. In addition, prospective repeated testing in

patients with convincing IAT data is ethically hard to justify, because prolonged and repeated catheterizations may increase the risk of complications.

CONCLUSION

Whereas repeated language testing proved to be reproducible, memory lateralization with the IAT may be varying and unreliable in patients who failed the first test. These results have already influenced our decision making in our epilepsy patient management conference at the Cleveland Clinic. Our patient management conference abandoned repeated Wada testing for memory and abandoned Wada testing for memory in uncomplicated temporal lobe epilepsy surgery candidates. Gain of reliable information versus the risks of complications of IATs, such as carotid artery dissections (Loddenkemper et al., 2002), strokes, localized hemorrhage at the catheter insertion site, allergic reaction to contrast, and infection (Loddenkemper et al., 2004) have to be considered when a patient is subjected to a (repeated) IAT. Alternative techniques of memory lateralization, such as fMRI, may gain further significance in the future (Golby et al., 2002).

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TABLE 1. *Left hemispheric memory testing*

		Memory test 2 left	
	Fail	Pass	Total
Memory test 1 left			
Fail	11	20	31
Pass	2	12	14
Total	13	32	45

$p = 0.178$; not significant.

TABLE 2. *Right hemispheric memory testing*

		Memory test 2 right	
	Fail	Pass	Total
Memory test 1 right			
Fail	3	10	13
Pass	4	7	11
Total	7	17	24

$p = 0.659$; not significant.

TABLE 3. *Previous case series of repeated IATs in the literature*

Author	Year	Patients with repeated tests (n)	Language	Memory: change in pass/fail ratio	Test–retest interval
Dinner et al.	1987	5	Not mentioned	5 (100%)	Unknown
Novelly	1987	18	Not mentioned	12 (67%)	Unknown
Novelly and Williamson	1989	25	Not mentioned	21 (84%)	Unknown
McGlone and MacDonald	1989	10	Not mentioned	8 injections (44%)	5 days to >10 years
Jones-Gotman	1992	14	Not mentioned	3 (21%)	3 days–4 years
Benbadis and Heriaud	2005	14 (9 with results)	No change	8 (89%)	Unknown