Epilepsy & Behavior 23 (2012) 247–253

Contents lists available at SciVerse ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Behavioral measures and EEG monitoring using the Brain Symmetry Index during the Wada test in children

Jurriaan M. Peters [a,b,*], Meritxell Tomas-Fernandez [c], Michel J.A.M. van Putten [d,e], Tobias Loddenkemper [a,b]

[a] Department of Neurology, Division of Epilepsy and Clinical Neurophysiology, Children's Hospital Boston, Boston, MA, USA
[b] Harvard Medical School, Boston, MA, USA
[c] Facultat de Medicina, Universitat de Lleida, Lleida, Spain
[d] Department of Neurology and Clinical Neurophysiology, Medisch Spectrum Twente, Enschede, The Netherlands
[e] CNPH group at MIRA-Institute for Biomedical Technology and Technical Medicine University of Twente, Enschede, The Netherlands

ARTICLE INFO

Article history:
Received 10 October 2011
Revised 5 December 2011
Accepted 12 December 2011
Available online 16 February 2012

Keywords:
Intracarotid amobarbital procedure
Wada test
Quantitative electroencephalography
Brain symmetry index
Neuromonitoring
Epilepsy surgery

ABSTRACT

EEG monitoring is used routinely during the Wada test in children. We quantified EEG asymmetry using the Brain Symmetry Index (BSI) to reduce subjectivity of EEG interpretation. Clinical and procedural variables were obtained and EEG data were retrieved from 46 patients with a total of 89 injections. The BSI, the absolute value of the relative difference of the average spectral density of the right and left hemisphere, was calculated over time for all EEGs. Lateralized slowing was correctly identified in all procedures. Asymmetry was minimal at baseline (BSI 0.16) and increased with injection of amobarbital (BSI 0.49). Various patterns of the BSI were seen in distinct clinical and procedural scenarios. In this retrospective analysis, the BSI could not predict an unsuccessful Wada procedure. Our results suggest application of the BSI during the Wada test in children is feasible. Real-time calculation of the BSI during EEG monitoring in the angiography suite is warranted for further validation.

1. Introduction

The Wada test is widely used in the evaluation process of candidates for epilepsy surgery, predominantly for the lateralization of language and memory function [1]. The reliability of rapidly applied memory and language tasks is in part dependent on the duration and depth of medication-induced anesthesia of implicated cerebral structures. However, there are no absolute criteria that allow full determination of degree and extent of hemispheric inactivation [2]. A combination of monitoring techniques is commonly used as surrogate markers of hemispheric suppression, including serial strength testing of the contralateral arm, review of the fluoroscopic angiography during the amobarbital injection, and online interpretation of EEG during Wada testing [2,3].

All of the measures are subjective, subject to intra- and interobserver variability, observer bias, and information bias. These weaknesses potentially compromise the reliable identification of eloquent structures at a critical stage of epilepsy surgery evaluation. Specific numbers on intra- and interobserver variability in the visual assessment of the duration of EEG slowing during the Wada test are not available in the literature. One study reported a smaller standard deviation of visual interpretation compared to a computed measure of slowing (2.8 vs 2.2 min, respectively) suggesting computation is less erratic [4]. In a study of intra- and interobserver reliability of EEG interpretation in critically ill children, agreement on the presence or absence of EEG slowing was only slight (kappa 0.10), the lowest of all eleven EEG features examined [5]. Hand strength, another key monitoring measure, is dependent on subject cooperation and does not provide continuous data. Moreover, suppression of gross motor function may not even be representative of anesthesia of language and memory areas [4].

During the Wada test, continuous EEG is typically visually assessed for the presence, frequency, amplitude and distribution of slowing to monitor hemispheric anesthesia [1 – 3]. Digital EEG provides an opportunity for formal quantification of asymmetry with signal processing techniques [4]. We investigated the use of a previously established measure of symmetry in the EEG, the Brain Symmetry Index (BSI) [6,7] to objectively monitor hemispheric suppression during the Wada test in addition to conventional visual assessment of the EEG. Aims were to investigate applicability of the BSI in this setting. We assessed the relation between the BSI and conventional electrographic and behavioral measures, as well as technical aspects of the procedure.

* Corresponding author at: Division of Epilepsy and Clinical Neurophysiology, Children's Hospital Boston, 300 Longwood Ave, Fe11, Boston, MA 02115, USA. Fax: +1 617 730 0282.
E-mail address: jurriaan.peters@childrens.harvard.edu (J.M. Peters).

1525-5050/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
doi:10.1016/j.yebeh.2011.12.017

2. Methods

2.1. Procedural and clinical variables

At Children's Hospital Boston, all Wada test procedures are monitored with continuous video-EEG. One examiner assists with the assessment of motor strength, while a clinical neuropsychologist applies a rapid battery of memory and language tasks. The EEG is monitored and interpreted online by an experienced clinical neurophysiologist present in the angiography suite. All team members communicate frequently and at set times during the procedure. A detailed description of the pediatric Wada test protocol at Children's Hospital Boston has been published elsewhere [3].

Retrospective data acquisition was conducted using a protocol approved by the IRB of Children's Hospital Boston. For our study, all consecutive subjects undergoing the Wada test from 2000 to 2010 at Children's Hospital Boston were reviewed and all patients with available EEG data were included. EEG and, if available, video and audio were reviewed for each subject to record behavioral parameters such as timing of injection and reported hand strength by the examiner. Duration of EEG slowing was assessed by a clinical neurophysiologist at the time of the original study. Medical records, EEG, magnetic resonance imaging and angiography findings were reviewed to obtain demographics, handedness, seizure type, epilepsy etiology and epilepsy syndrome, imaging results, antiepileptic drug regimen, and further procedural details. Strength testing results were categorized as absence of any strength (Medical Research Council (MRC) 0–1), partial strength (MRC 2–4) and return to full strength (MRC 5) [8]. Time to return to behavioral baseline was defined as absence of sleepiness, confusion and agitation and a return to pre-test language ability, level of cooperation and the ability to follow instructions. Criteria were assessed by the staff neuropsychologist towards the end of each procedure.

2.2. EEG monitoring and calculation of the Brain Symmetry Index

EEGs were recorded using the International 10–20 electrode placement system and impedances were kept below 5 kΩ at all times. Visual assessment was done in the “double banana” bipolar montage. EEGs were exported to European Data Format [9] and processing was done with in-house developed software on a MatLab platform [10], according to previously described methods [6,7,11]. The BSI is the absolute value of the relative difference in the average spectral density of the right and left hemispheres in the frequency range from 1 to 25 Hz. In brief, we calculated the mean of the absolute difference at each frequency (more precisely, at each Fourier coefficient) of all leftsided and corresponding rightsided hemisphere electrode pairs over 10 s (five 2-second bins sampled at 256 Hz). Next, this left minus right difference at each frequency was divided by their sum, and averaged to obtain an index (BSI), ranging from 0 (perfect symmetry) to 1 (maximum asymmetry). Additional details have been published previously [6,7,11] and are summarized in the appendix.

For this study, a moving average of five pages was used for signal smoothing, optimizing between temporal resolution and readability for the reader. Rather than 1–25 Hz, a bandwidth of 1–15 Hz was empirically chosen after the first 10 studies were analyzed, reducing global fast activity from barbiturates. BSI tracings were compared with the original EEG signal to document outliers, peaks, and muscle, electrode, and movement artifact to facilitate interpretation of BSI. If needed, up to two electrodes were excluded from calculations, comparable to the way a bad channel is ignored during visual interpretation. No other pre-processing or selection of artifact-free data was performed. Peak values were defined as the maximum BSI value following injection. Baseline BSI was assessed by a maximum of 10 pages of EEG prior to injection. Return to baseline was described as the first page of the averaged BSI over 10 pages with a value within 25% of the pre-injection baseline, based on a similar previously defined cut-off value from Bouwer et al., who used 30% [4]. See Fig. 1 for an example.

Statistical analysis was performed using SPSS version 19 (IBM SPSS Statistics, Chicago, IL). Comparisons were done using the Student's *t*-test and associations were explored using the Spearman's rank correlation coefficient. Contingency tables were analyzed with Fisher's exact test. P-values <0.05 were considered significant.

3. Results

3.1. Clinical variables

Forty-six subjects (24 boys, 52%) were selected, mean age 15.2 years (range 7.6–22.4). Thirty-six (78%) were right-handed, eight (17%) were left-handed, and two (4%) were ambidextrous. Together they had 89 intracarotid amobarbital injections, as three injections (two right-sided, one left-sided) were not performed or completed secondary to subject agitation with the first injection. Almost all subjects had partial seizures with impairment of consciousness or awareness (41, 89%), 25 (54%) as the only seizure type. In 16 (35%) however, these evolved into generalized, tonic–clonic seizures ($n=13$) or hemiclonic seizures ($n=3$). More than half of the patients (28 out of 46) had a left-sided lesion or seizure focus based on workup done prior to the Wada test. All non-lesional cases had a suspected focus in the temporal lobe with the exception of 2 patients with a frontal focus (one left, one right). Despite successful injection on angiography, four children had rapid recovery, incomplete hemiparesis or EEG slowing that was less than expected; referred to by some authors as anesthetic failure [12,13]. None of these patients had medications with carbonic anhydrase properties in their regimen. There was also no correlation between the presence of these medications ($n=8$) and a poor quality study ($n=10$), or the need for extra amobarbital boluses ($n=16$) (Fisher's exact test, $p=0.36$ and 0.13, respectively).

The first injection was performed on the ipsilateral side of the lesion or seizure focus in all left-sided cases and in all but 4 right-sided cases. Thus, the right side was injected second in 32 out of 46 cases (70%). There were no significant differences between left- and right-sided injections regarding amobarbital dosing ($p=0.39$), sleepiness or agitation impacting study quality ($p=0.72$), angiographic cross flow reported as more than minimal ($p=1.00$), incomplete hemiplegia ($p=0.64$), or a poor quality study due to presence of any of these factors ($p=0.72$). Compared to left-sided injections, injections on the right tended to require additional injections to achieve complete hemiparesis or sufficient EEG slowing as judged during the procedure ($p=0.06$, not significant). Subgroup analysis of those injections performed on the ipsilateral side only did not yield any significant findings. More clinical details regarding the study population and procedural aspects are found in Table 1.

3.2. Monitoring of pharmacological effects

Baseline EEG prior to Wada testing revealed intermittent or continuous focal slowing in 30 patients. In 25 of these 30 patients, slowing was located ipsilateral to the side of lesion or suspected focus. However, baseline asymmetry as expressed by the BSI in all subjects (0.16) was not significantly different from those with focal slowing (0.17). The average maximum BSI and the average delta BSI (the maximum BSI after injection compared to the BSI at baseline) were similar in right-sided (0.51, 0.34) and left-sided injections (0.48, 0.35; $p=0.34$ and 0.49, respectively). Only the maximum BSI of right-sided ipsilateral injections was significantly higher than the left-sided ipsilateral injections (0.56 versus 0.46, $p=0.005$). There was no difference in delta BSI in the 21 subjects with moderate or significant cross flow on angiography (0.33), or in the 11 subjects whose

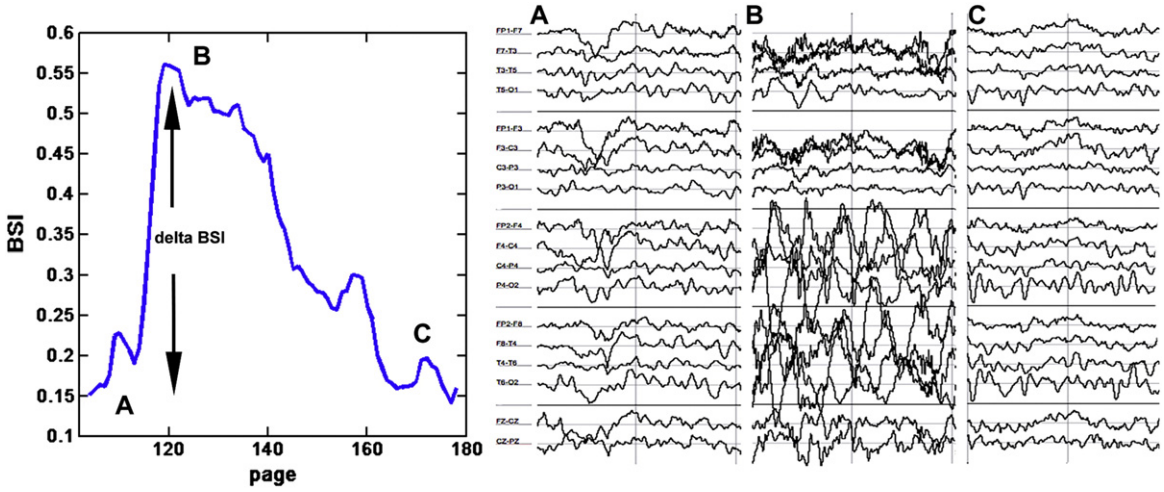

Fig. 1. Lateralized EEG slowing and the Brain Symmetry Index (BSI).BSI plot over time (left, one page = 10 s) and corresponding EEG segments (right, double banana montage with left temporal and parasagittal chains on top) of amobarbital injection in 12 year-old girl with non-lesional right temporal lobe epilepsy and complex partial seizures. (A) At baseline, the EEG is symmetric, BSI = 0.18. (B) Immediately following injection, lateralized EEG slowing is seen, BSI = 0.56. (C) At end of procedure the EEG has returned to baseline, BSI = 0.16. Delta BSI is the difference between maximum (B) and baseline (A) BSI values.

study was deemed of poor quality for various reasons (0.34). Average time to reach a maximum asymmetry (maximum BSI) from baseline was prolonged in patients who required extra barbiturate injections compared to all other patients (1 min and 42 s versus 2 min and 6 s, $p = 0.01$). Average duration of EEG slowing on visual assessment (6 min) was approximately 4 min shorter than determined through the return of the BSI to 125% of its baseline value (9 min 48 s). There was no significant difference in duration of slowing between left- and right-sided injections on both visual assessment and as determined by the BSI. Right-sided injections had a shorter recovery time for return to full strength (4.5 versus 5.3 min, $p = 0.046$) as compared to left-sided injections, with sooner return to behavioral baseline (7.1 versus 8.5 min, $p = 0.007$). An overview is provided in Table 2.

3.3. BSI and conventional measures

As single factors, neither the BSI nor any conventional monitoring measure or clinical characteristic (seizure type, etiology, medications, side of injection (left, right, ipsilateral), order of injection (ipsilateral first or second), additional injections, total amobarbital dose, or cross flow) were related to agitation, sleepiness, incomplete or rapid recovery of hemiparesis or a poor quality study. Specifically, a low delta BSI was not associated with a poor quality study.

Table 1
Clinical data, procedural variables.

Demographics			
Gender	Male 24 (52%)	Female 46 (48%)	
Handedness	Right 36 (78%)	Left 18 (17%)	Ambidextrous 2 (4%)
Epilepsy characteristics[1]	Single seizure type	Multiple seizure types	Total
Focal, impairment of consciousness	25	16	41
Generalized, tonic–clonic	0	13	13
Focal, no impairment of consciousness	2	5	7
Focal, hemiclonic	0	4	4
Generalized, tonic	1	1	2
Etiology, localization	Left	Right	Total
Dysplasia, dysgenesis, low-grade lesion[2]	8	6	14
Stroke, ischemic injury, vascular malformation	4	2	6
Mesial temporal sclerosis[3]	4	3	7
High grade neoplasm, s/p resection	2	0	2
Non-lesional[4]	10	7	17
Procedural aspects	Left (ipsi[5])	Right (ipsi)	Total (ipsi)
Side of first injection	28 (28)	18 (14)	46 (42)
Average total amobarbital injection in mg	125.0 (125.0)	130.9 (133.2)	127.9 (128.3)
Additional amobarbital injections needed	15 (11)	15 (7)	30 (18)
Sleepiness or agitation impacting study quality	5 (2)	4 (1)	10[6] (3)
Angiographic cross flow more than minimal	13 (8)	8 (4)	21 (12)
Incomplete hemiplegia	2 (1)	2 (1)	4 (2)
Overall poor quality study	6 (2)	5 (1)	11 (3)[7]

[1] Ordered by frequency. Totals exceed n = 46 as many had multiple seizure types. A single patient with an arteriovenous malformation did not have any seizures.
[2] One patient had bilateral occipitotemporal polymicrogyria, with a left-sided epileptic focus.
[3] If mesial temporal sclerosis was not a consensus diagnosis, etiology would be considered non-lesional. Two patients had meningitis prior to mesial temporal sclerosis (one on left, one on right).
[4] All subjects with non-lesional etiology had a suspected focus in the temporal lobe, with the exception of two patients with a frontal focus (one on left, one on right).
[5] *ipsi* indicates ipsilateral to focus or lesion.
[6] One patient had lowered arousal impacting study quality after each injection.
[7] Three patients had sleepiness, excessive cross flow, incomplete hemiparesis or combination thereof on both left- and right-sided injection.

Table 2
Monitoring of pharmacological effects.

	Left (ipsi)	Right (ipsi)	Total
EEG measures			
EEG focal slowing at baseline	22 (20)	6 (5)	30[1] (25)
BSI baseline			
All subjects	0.16 (0.17)	0.16 (0.15)	0.16 (0.16)
EEG focal slowing at baseline	0.17 (0.18)	0.16 (0.15)	0.17 (0.17)
Maximum BSI after injection	0.48 (0.46)	0.51 (0.56*)	0.49 (0.50)
Time to BSI maximum in min			
All subjects	1.7 (1.6)	1.7 (1.8)	1.7 (1.7)
Additional amobarbital injections needed	2.0 (1.7)	2.2 (2.6)	2.1 (2.0)
Delta (maximum–baseline) BSI			
All subjects	0.34 (0.32)	0.35 (0.41)	0.34 (0.36)
EEG focal slowing at baseline	0.32 (0.31)	0.34 (0.40)	0.33 (0.34)
Crossover more than minimal	0.32 (0.28)	0.34 (0.43)	0.33 (0.33)
Overall poor quality study	0.31 (0.30)	0.37 (0.41)	0.34 (0.35)
Duration of slowing in min			
Visual assessment	6.2 (5.6)	5.7 (5.9)	6.0 (5.8)
BSI ≤125% baseline	9.9 (9.8)	9.6 (10.3)	9.8 (10.0)
Behavioral measures			
Recovery time in min			
To level of hemiparesis	2.9 (2.8)	2.8 (2.6)	2.9 (2.7)
To full strength	5.3 (5.1)	4.5** (4.3)	4.9 (4.8)
To behavioral baseline	8.5 (7.7)	7.1*** (6.7)	7.8 (7.4)

[1] Two patients with intermittent slowing on either side with shifting predominance.
*p = 0.005, ** p = 0.046, *** p = 0.007 for left- compared to right-sided injections.

Duration of slowing on BSI did not correlate with the duration by visual assessment (Spearman Rank Order correlation 0.1, p = 0.46), while both had a comparable standard deviation of 3 and 2.5 min, respectively. Duration of EEG slowing on visual assessment correlated only modestly with return to behavioral baseline (0.36, p = 0.016) and with return of full strength (0.38, p = 0.0076). Duration of slowing assessed by the BSI correlated only with return of full strength (0.33, p = 0.032).

3.4. Patterns of BSI changes in different clinical scenarios

Various patterns of the BSI tracing during the procedure were observed in several distinct clinical scenarios. Examples include a patient with an uncomplicated procedure and two early peaks with a slow return to baseline (Fig. 2A), a patient with mild ipsilateral intermittent slowing at baseline in whom contralateral injection resulted in additional contralateral slowing, leading to a smaller change in the BSI from baseline (Fig. 2B). Another patient with a similar scenario but more prominent and continuous focal slowing at baseline (high baseline BSI) demonstrated a *decrease* in asymmetry (delta BSI is negative) when the contralateral injection induced slowing too (Fig. 2C). Finally, a patient is shown with a compromised quality study due to anterior cerebral artery cross flow with resultant slowing contralateral to the injection, and a subsequent smaller change in BSI (Fig. 2D).

4. Discussion

In this paper, we explore the use of the BSI as a measure to quantify EEG asymmetry during the Wada test. The BSI can provide additional information on the duration and strength of the barbiturate effect, and may serve as an additional biomarker towards the development of a more standardized method of monitoring hemispheric anesthesia during the Wada test. The BSI correctly identified lateralized slowing and asymmetry in all patients. In addition, this is the first large retrospective series of clinical and procedural aspects of the Wada test and their relation to EEG monitoring in children.

4.1. Clinical variables

The vast majority of our patients had temporal lobe epilepsy. Many centers prefer to test the hemisphere ipsilateral to the seizure focus first in case the procedure is interrupted or incomplete due to

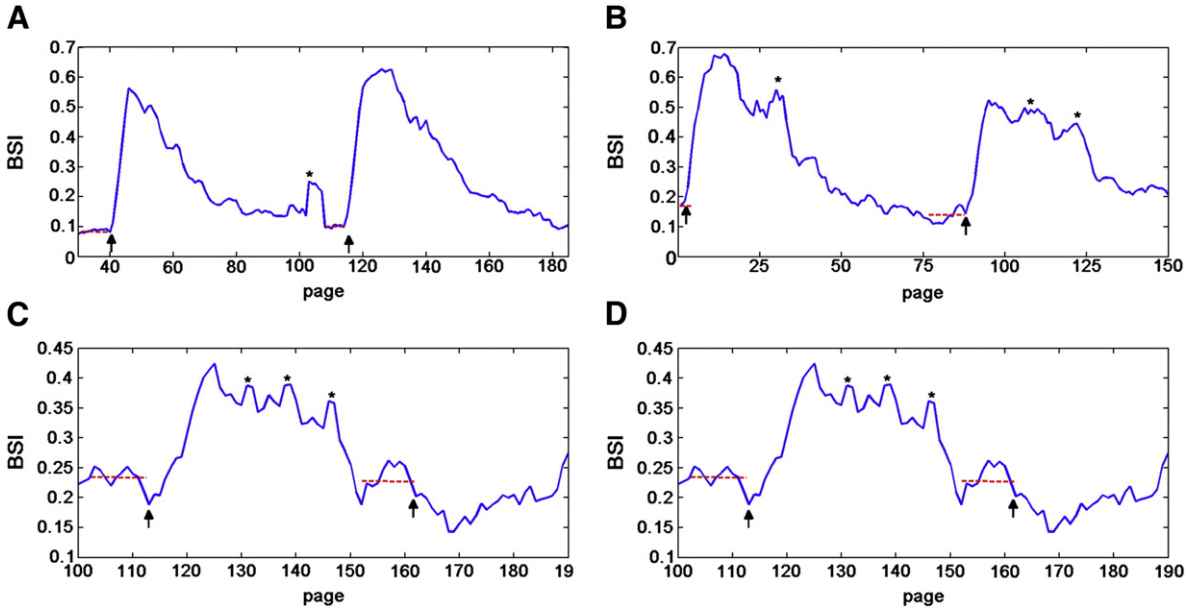

Fig. 2. BSI tracings during several scenarios. BSI is plotted for four patients over time (one page is 10 s). Dotted horizontal lines indicate baseline, arrows indicate time of injection, asterisks indicate epochs with artifact. (A) 20-year-old female with mesial temporal sclerosis and complex partial seizures. The second injection starts from a slightly higher baseline (0.11) than the first (0.09). Uncomplicated procedure. (B) 16-year-old male with non-lesional left frontal lobe epilepsy with simple partial, complex partial and secondary generalized seizures. Mild intermittent slowing is present, first injection baseline BSI 0.19, delta BSI 0.49. With the second injection (baseline BSI 0.15) slowing is also induced in the contralateral hemisphere, resulting in a smaller change of the BSI (delta BSI 0.37). Uncomplicated study. (C) 18-year-old male with mesial temporal sclerosis and more prominent continuous slowing at baseline (BSI 0.23). With the second injection slowing is also induced on the non-lesional side and both hemispheres are now prominently slow, resulting in a *decrease* of BSI, i.e. more symmetric EEG (delta BSI = −0.10). Uncomplicated study. (D) 18 year-old female with left frontal stroke and complex partial and secondary generalized seizures. With the ipsilateral, first injection there is angiographic evidence of cross flow to the anterior portions of the contralateral hemisphere, resulting in less lateralized slowing as now both hemispheres show some slowing (delta BSI 0.23), whereas with the second injection there is no cross flow (delta BSI 0.42). Poor quality study due to cross flow.

seizures, sleepiness, agitation or lack of cooperation or technical difficulties [14].

In both adults and children, 'unusually mild drug effects' or 'absence of drug effects' with the use of carbonic anhydrase inhibitors like topiramate and zonisamide [12,13] have been reported. However, in our population the use of these medications was not associated with anesthesia failure (incomplete hemiparesis or insufficient EEG slowing) or the need for extra amobarbital injections. Also, patients with polypharmacy or on sedative antiepileptic drugs like benzodiazepines or barbiturates did not have more problems sustaining attention [14]. Our average dose of amobarbital (125 mg on the left, 131 mg on the right) is consistent with the modal dose of 125 mg found in a large multicenter survey, and the repeat dosing has also been reported by other centers [2]. Duration of hemiparesis (4.9 min for all injections) was shorter than in a study of 48 adults (6.4 min) [15], despite use of a similar average dose of amobarbital. In adults, some centers adjust dosing for patient weight but there is a poor relation between body weight and brain weight. Since the injection is directly into the cerebral circulation, adjustment for body weight is unnecessary [14]. Due to the retrospective approach, a precise dose-correction based on estimated brain weight on imaging studies was outside of the scope of this study. Despite larger doses of amobarbital per gram of brain, motor effects may have been shorter due to differences in assessment, diminished local efficacy or faster metabolism. There were no significant procedural differences between left- and right-sided injections.

Sleepiness and agitation were more common with injection of the contralateral hemisphere (n = 7) compared to the ipsilateral hemisphere (n = 3), possibly related to suppression of the dominant, healthy hemisphere. However, since all but four patients underwent ipsilateral injection first, a cumulative drug-effect on sleepiness and agitation may play a role as well [14]. Incomplete hemiparesis was often associated with a need for extra injections, sleepiness or combativeness.

4.2. Monitoring of pharmacological effects

4.2.1. Pathophysiology of slowing

Several authors have investigated the physiological origin of EEG slowing during Wada testing. Temporary anesthesia of cortico-subcortical connections, as well as anesthesia of selected cortical and subcortical areas has been suspected [14]. With the use of depth electrodes in the mesial temporal lobe, slowing in hippocampal structures has been found to last significantly shorter than that measured by surface EEG [4,16]. While the BSI does not provide additional localizing information, it may prove to be a more objective marker of effect duration.

4.2.2. Alternative measures of barbiturate effect during the Wada test

The validity of surface EEG slowing as a measure of hemispheric suppression during the Wada test has been questioned (for a review, see [14]), and other markers have been investigated. Transcranial Doppler ultrasound (TCD) provides a continuous physiologic signal of cerebral blood flow and has been applied during the Wada test as a form of neuromonitoring [17]. In a study of 10 patients, delta slowing correlated with decreased mean middle cerebral artery velocities. Evidence of hemispheric suppression on TCD in two patients was found where the EEG failed to show slowing. However, this monitoring method has not been widely adapted [18]. Like TCD, EEG is also a non-invasive method but typically needs no readjustment after patient movement. It can additionally serve to exclude ictal activity during the study [15], and seizures complicate more than 1% of studies [19].

4.2.3. Influence of side, language dominance and epilepsy focus

On average, the right-sided injections demonstrated a similar delta BSI but had shorter recovery times to motor and behavioral baseline. This difference was more pronounced for ipsilateral injections. 72% of the cases with right-sided lesions were right-handed, so in the majority the non-epileptic left hemisphere was also the dominant hemisphere. Two studies from different centers involving 48 and 17 patients, respectively, have found prolonged behavioral recovery in the non-epileptic, functionally intact hemisphere. This raises the possibility that the injected hemisphere could have incorporated some of the functional capabilities of the non-injected, epileptic hemisphere [15,20]. In these studies, concomitant prolonged slowing was seen on the EEG of the non-epileptic hemisphere, indicating possible prolonged physiological disruption. Prolonged slowing was not observed in the current study, however. Possible explanations include differential sensitivity to amobarbital of the healthy compared to the epileptic hemisphere (various proposed pharmacological mechanisms are discussed in [15]), or a negative functional effect of the non-injected epileptic hemisphere on recovery of the injected intact hemisphere [20]. Biersack et al. reported a SPECT study of three patients showing that the dominant hemisphere had a more suppressed regional cerebral blood flow [21], but this difference is not noted in the studies using transcranial Doppler ultrasound [17,18].

4.2.4. Effects of preexisting EEG asymmetry

In our population, asymmetric EEG baselines as expressed by a high BSI at baseline were seen with [1] *structural* lateralized anomalies as evident on MRI (e.g. Sturge Weber, prior resective epilepsy surgery, stroke) and with [2] *functional* abnormalities such as lateralized epileptic discharges. Focal slowing may have limited impact on the *average* of BSI baseline (Table 2) due to the intermittent nature of focal slowing in most subjects. Large differences between left- and right-sided injection-induced BSI changes (delta BSI) in the same patient were seen in cases with baseline asymmetry, i.e. when lateralized slowing was already present. With ipsilateral injections, slowing would become more asymmetric, and with the next injection slowing would be induced in the contralateral hemisphere too (smaller delta BSI), and in some cases even leading to a decrease in BSI (negative delta BSI, Figs. 2B and C). Significant anterior cross flow and sleepiness lead to bilateral slowing and a smaller delta BSI in some cases (Fig. 2D).

4.2.5. Duration of slowing

Duration of slowing by visual assessment (left 6.2 and right 5.7 min) and by BSI (left 9.9 and right 9.6 min) is comparable to the literature. Bouwer et al. assessed delta-range activity visually (7.6 min) and by EEG quantification (1.17–4.69 Hz, 9.8 min) [4], whereas our algorithm included frequencies from 1 to 15 Hz. The same group reports brief, 4- to 5-minute-long anterior predominant contralateral slowing that resolves prior to the ipsilateral slowing [4,16]. Our BSI measure typically peaked early after injection, suggesting slowing is still overall predominant on the ipsilateral side. Others have documented an average duration of EEG slowing on visual assessment of 7 min [22] and 7.8 min in adults [15].

4.3. Comparison of the BSI with visual EEG analysis and behavioral measures

Computerized quantification of EEG slowing does not depend on the subjective assessment of the electroencephalographer. Other authors have found a correlation between the calculated duration of delta slowing and return of contralateral hand strength [4]. This calculation was dependent on offline manual selection of brief 20-second artifact-free EEG segments, however, and the hand strength measure was defined as the midpoint between the return of full-strength and the immediate prior assessment and was thus only available retrospectively [4]. In our study feasibility of online BSI application was assessed without selecting any artifact-free segments

prior to processing. The retrospective design of our study and choice not to pre-process the data in order to simulate the real-time environment likely compromised the finding of relations between EEG and behavioral measures. BSI measures of duration may have been further weakened by the use of a sliding average, which would have compromised the temporal resolution.

However, in cases where EEG data were of sufficient quality, the BSI measure provided the only objective measure that is comparable across all performed studies and scenarios. All other markers are subject to interpretation by different neurophysiologists (visual EEG assessment), radiologists (angiographic assessment) and neurologists (motor strength testing). For example, visual assessment of maximum slowing or return to baseline is a rough estimate at best: With the Wada test, patients are actively responding and moving, battling sleepiness and agitation, and are subject to manual fixation of the head because of the invasive and sterile nature of angiography. It is for this abundance of artifact that EEG-monitoring during Wada test has been referred to as "not worth the additional trouble…" [2] and the Wada test a "hostile environment" for EEG [23].

No other EEG-derived measure nor bilateral BIS-monitoring [23] has been shown reliable or superior to visual assessment. Using an algorithm based on non-linear dynamics, a transient decrease in functional connectivity has been shown [24], but this method was not designed for neuromonitoring during the Wada test. It is striking that reliable extrapolation of clinical experience of standard EEG interpretation to a quantitative measure [23] has not proven feasible to date in this setting.

The BSI has been previously used for real-time quantification of lateralized slowing during thrombolytic therapy in acute ischemic stroke [25]. It has also been used for online quantification of EEG slowing during carotid endarterectomy in 20 patients [26] after an objective BSI criterion for selective shunting was established in a retrospective series of 57 patients [7]. It has recently been implemented as one of eight features in the real-time computer-assisted analysis of EEG in the adult ICU [27]. For intraoperative monitoring, signal smoothing was done with a 30-second moving average for increased clarity of the trend plots on the monitor [7,26]. The temporal resolution was reduced but remained sufficient for clinical purposes. In future prospective, online implementation of the BSI during the Wada test, less signal smoothing should be needed as artifacts can be readily addressed (e.g. by omission of artifact-ridden data points).

4.4. Clinical scenarios

With a moderate or good quality EEG signal, multiple individual cases demonstrated a well-formed, smooth plot of the BSI over time. These plots correlated well with distinct clinical scenarios and facilitated estimation of ipsi- and contralateral hemispheric drug effects on the EEG which were otherwise not readily available to the observer (Figs. 2B–D). Visual assessment of the return of EEG to baseline is particularly challenging in case of preexisting asymmetry, and the BSI could provide objective assistance. The BSI, therefore, deserves further and better validation in a real-time environment, where patient and staff could be asked to briefly limit interference with the data collection to obtain good quality EEG segments and clinical and procedural variables can be collected prospectively.

4.5. Challenges

Results need to be interpreted in the setting of data acquisition. The retrospective design of our study did not allow for consistent collection of clinical, behavioral or electroencephalographic data. Referral bias and selection bias based on data acquisition at a tertiary epilepsy center may have impacted clinical variables. Selection bias explains the predominance of left-sided lesions and left-hemispheric dominance. From a technical point of view, EEG data were processed and reviewed retrospectively with inherent risks of information bias. The BSI measures of duration (e.g. time to maximum slowing) were weakened by the use of a sliding average, with resultant compromise of the temporal resolution. Online calculation of BSI values in real time would obviate the need for signal smoothing, as segments with artifact could be ignored.

5. Conclusion

We report a large retrospective series of clinical and procedural aspects of the Wada test and their relation to EEG monitoring in children, and found comparable duration of physiologic and behavioral effects as in adults. Our study confirms a prior finding of prolonged anesthetization effects on injection of the dominant or functionally intact hemisphere.

EEG during the Wada test is the only continuous physiological measure of hemispheric suppression that has been widely adopted. Retrospective quantification of the EEG using artifact-free segments has proven feasible and shown to correlate with motor measures [4]. We studied the feasibility of the use of the Brain Symmetry Index (BSI) for quantification of lateralized effects on the raw, unprocessed EEG tracing, aiming for a more standardized method of monitoring hemispheric anesthesia. The BSI was not intended to replace EEG as ictal activity and artifacts needed to be visually assessed concomitantly.

The BSI correctly identified lateralized slowing and asymmetry in all patients and correlated with motor findings. It may serve as an adjunct marker for duration of slowing and surrogate monitoring marker during Wada testing. Further exploration using the BSI online next to the EEG monitor in the angiography suite will provide further validation and experience.

Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.yebeh.2011.12.017.

References

[1] Dinner DS, Loddenkemper T. Wada test and epileptogenic zone. In: Luders HO, editor. Textbook of epilepsy surgery. 1st ed. Boston: Informa Healthcare; 2008.
[2] Rausch R, Silfvenius H, Wieser H. Intraarterial amobarbital procedures. In: Engel Jr J, editor. Surgical treatment of the epilepsies. New York: Raven Press; 1993. p. 341–57.
[3] Das R, Loddenkemper T. Intracarotid amobarbital procedure. In: Wyllie E, editor. Wyllie's treatment of epilepsy. 5th ed. Boston: Lippincott Williams & Wilkins; 2010. p. 906–913.
[4] Bouwer MS, Jones-Gotman M, Gotman J. Duration of sodium amytal effect: behavioral and EEG measures. Epilepsia 1993;34:61–8.
[5] Abend NS, Gutierrez-Colina A, Zhao H, et al. Interobserver reproducibility of electroencephalogram interpretation in critically ill children. J Clin Neurophysiol 2011;28:15–9.
[6] van Putten MJ. The revised brain symmetry index. Clin Neurophysiol 2007;118:2362–7.
[7] van Putten MJ, Peters JM, Mulder SM, de Haas JA, Bruijninckx CM, Tavy DL. A brain symmetry index (BSI) for online EEG monitoring in carotid endarterectomy. Clin Neurophysiol 2004;115:1189–94.
[8] Medical_Research_Council. Aids to the examination of the peripheral nervous system. Memorandum no. 45. London: Her Majesty's Stationery Office; 1981.
[9] Kemp B, Varri A, Rosa AC, Nielsen KD, Gade J. A simple format for exchange of digitized polygraphic recordings. Electroencephalogr Clin Neurophysiol 1992;82:391–3.
[10] MATLAB [program]. Version 7.8.0.347 (R2009a). Natick, MA: The MathWorks, Inc.; 2009.
[11] van Putten MJ, Tavy DL. Continuous quantitative EEG monitoring in hemispheric stroke patients using the brain symmetry index. Stroke 2004;35:2489–92.
[12] Burns TG, Lee GP, McCormick ML, Pettoni AN, Flamini JR, Cohen M. Carbonic anhydrase-inhibiting medications and the intracarotid amobarbital procedure in children. Epilepsy Behav 2009;15:240–4.
[13] Bookheimer S, Schrader LM, Rausch R, Sankar R, Engel Jr J. Reduced anesthetization during the intracarotid amobarbital (Wada) test in patients taking carbonic anhydrase-inhibiting medications. Epilepsia 2005;46:236–43.
[14] Simkins-Bullock J. Beyond speech lateralization: a review of the variability, reliability, and validity of the intracarotid amobarbital procedure and its nonlanguage uses in epilepsy surgery candidates. Neuropsychol Rev 2000;10:41–74.
[15] Selwa LM, Buchtel HA, Henry TR. Electrocerebral recovery during the intracarotid amobarbital procedure: influence of interval between injections. Epilepsia 1997;38:1294–9.

[16] Gotman J, Bouwer MS, Jones-Gotman M. Intracranial EEG study of brain structures affected by internal carotid injection of amobarbital. Neurology 1992;42:2136–43.
[17] Pfefferkorn T, Hundt C, Arnold S, Missler U, Noachtar S, Hamann GF. Contralateral cerebral blood flow velocity changes after intracarotid amobarbital injection. J Neuroimaging 2004;14:357–60.
[18] Acharya VJ, Acharya JN, Tegeler CH, Morris P, Meads D, O'Donovan CA. Transcranial Doppler ultrasound: a new method of monitoring hemispheric anesthetization during the intracarotid amobarbital procedure. J Neuroimaging 2002;12:153–7.
[19] Loddenkemper T, Morris HH, Moddel G. Complications during the Wada test. Epilepsy Behav 2008;13:551–3.
[20] Rausch R, Fedio P, Ary CM, Engel Jr J, Crandall PH. Resumption of behavior following intracarotid sodium amobarbital injection. Ann Neurol 1984;15:31–5.
[21] Biersack HJ, Linke D, Brassel F, et al. Technetium-99m HM-PAO brain SPECT in epileptic patients before and during unilateral hemispheric anesthesia (Wada test): report of three cases. J Nucl Med 1987;28:1763–7.
[22] Klove H, Grabow JD, Trites RL. Evaluation of memory functions with intracarotid sodium amytal. Trans Am Neurol Assoc 1969;94:76–80.
[23] Heller H, Hatami R, Mullin P, et al. Bilateral bispectral index monitoring during suppression of unilateral hemispheric function. Anesth Analg 2005;101:235–41.
[24] Douw L, Baayen JC, Klein M, et al. Functional connectivity in the brain before and during intra-arterial amobarbital injection (Wada test). Neuroimage 2009;46:584–8.
[25] de Vos CC, van Maarseveen SM, Brouwers PJ, van Putten MJ. Continuous EEG monitoring during thrombolysis in acute hemispheric stroke patients using the brain symmetry index. J Clin Neurophysiol 2008;25:77–82.
[26] Peters JM, Padberg M, Nederveen PJ, Tavy DL, van Putten MJAM. Neuromonitoring met on-line qEEG tijdens carotisendarteriectomie: ervaringen met de Brain Symmetry Index. Tijdschr Neurol Neurochir 2005;106:143–50.
[27] Cloostermans MC, de Vos CC, van Putten MJ. A novel approach for computer assisted EEG monitoring in the adult ICU. Clin Neurophysiol 2011;122:2100–9.