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

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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.

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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