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Can the adverse effects of antiepileptic drugs be detected in saccadic eye movements?

Kang Min Park, Kyong Jin Shin, Sam Yeol Ha, JinSe Park, Si Eun Kim, Hyung Chan Kim, Joon Won Lee, Sung Eun Kim *

Department of Neurology, Haeundae Paik Hospital, Inje University College of Medicine, Haeundae-ro 875, Haeundae-gu, Busan 612-896, Republic of Korea

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ABSTRACT

Purpose: The objective of this study was to determine whether the adverse effects of antiepileptic-drugs could be assessed by the eye movements of epilepsy patients.
Methods: This study was performed prospectively in a single tertiary hospital. The inclusion criteria for this study were as follows: (1) consecutive patients with epilepsy taking antiepileptic-drugs regularly for at least 1 year, (2) the absence of structural lesions on MRI, (3) an age ≥16 years old, (4) not using medications that could influence eye movement, and (5) a normal neurological examination. The latency, peak velocity and accuracy of the saccades and the gain of the pursuits were recorded by video-based electro-oculography. We analyzed the differences in the parameters of the eye movements for 75 patients with epilepsy and 20 normal controls matched for age and sex.
Results: The total latency (1017.7 ± 148.9 ms vs. 1150.7 ± 106.6 ms, $p = 0.0003$) and accuracy [370.7% (95% CI 364.1–376.4%, range 306–408.2%), 92.7% as total accuracy normalized value vs. 383.6% (95% CI 378.8–398%, range 322.9–417.4%), 95.9% as total accuracy normalized value, $p = 0.0005$] were significantly different between the patients with epilepsy and normal controls. For the detection of nystagmus with video-based electro-oculography, the clear cutoff values of total accuracy (≤388.7%, 97.2% as total accuracy normalized value) revealed 93.4% sensitivity and 28.6% specificity, and the clear cutoff values of total latency (≤1005.5 ms) showed 49.2% sensitivity and 78.6% specificity.
Conclusions: The total latency and accuracy of video-based electro-oculography may be screened to identify patients with a high risk of adverse effects with antiepileptic-drugs.

1. Introduction

The primary concern with medical treatment using antiepileptic drugs (AEDs) is that the response rate to AEDs has remained unchanged. Although new AEDs have been introduced during the last decade, at least one in three patients with epilepsy remains resistant to AEDs [1–3]. Another obstacle to medical treatment with AEDs is their adverse effects (AEs). At least 30% of patients with epilepsy taking AEDs may suffer from AEs [3–5].

Because the majority of clinicians focus on achieving a seizure-free state and tend to increase the dosage of AEDs, particularly in patients with AED-resistant epilepsy, evaluating AEs in daily clinical practice may be somewhat overlooked. AEs can be related to both a poor quality of life and a poor response to treatment [5,6]. Furthermore, patients with epilepsy who are taking AEDs tend to not voluntarily report their AEs, particularly in Asian cultures; therefore, reliance an self-report of AEs may lead to a serious underestimation of the true frequency of AEs in patients with epilepsy.

The reporting of AEs can be increased by using standardized questionnaires, such as an adverse event profile (AEP) [6]. The AEP consists of 19 items that include neurobiologically relevant taxonomy [7]. In addition, a randomized control study showed that the AEP has been a useful clinical tool, not only for detecting AEs but also for improving the control of seizures and quality of life [6]. However, both a patient's depression and non-neurological states, such as problems with the skin or mouth, can influence the AEP scores [7–9].

The objectives of this study were as follows: (1) to determine whether the AEs of AEDs could be assessed with eye movements using video-based electro-oculography (VEOG) and (2) to compare the sensitivity between the AEP and the parameters on the VEOG to identify patients at a high risk of AEs.

* Corresponding author. Tel.: +82 51 797 1195; fax: +82 51 797 1196.
E-mail address: epidoc@inje.ac.kr (S.E. Kim).

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2. Methods

This study was performed prospectively in a single tertiary hospital. The institutional review board approved this study. The inclusion criteria for this study were as follows: (1) consecutive patients with epilepsy who were taking AEDs regularly for at least 1 year, regardless of the use of mono-pharmacy or poly-pharmacy; (2) the absence of structural lesions on MRI; (3) an age ≥16 years old; (4) not taking any medications that could influence eye movement, such as benzodiazepines; and (5) normal results on a neurological examination, particularly the absence of nystagmus or ataxia.

The movements of the left eye were recorded using a high-resolution infrared scleral reflectance technique (SLVNG, SLMED Inc.). The visual stimulus was a white square target on a dark–blue background. The subjects were seated in a darkened room, and the calibration was performed 20 s before the start of eye movement recording. Spontaneous nystagmus with or without optic fixation was recorded in both the horizontal and vertical planes. The saccades were generated by asking the subjects to follow a fixed and randomized target with ranges of ±30.0° on the horizontal plane. The latency, peak velocity, and accuracy were recorded for each saccade. The latency was the time delay from the target moving to the saccade onset, the peak velocity was the maximum velocity during an eye movement, and the accuracy was computed using the following equation: saccadic accuracy (%) = (amplitude of the initial saccade/target amplitude) × 100. The stimulus for smooth pursuit was a moving target in a sinusoidal pattern with frequencies of 0.2 Hz and 0.4 Hz on the horizontal plane. The gain was computed for each pursuit, which was calculated using the following equation: pursuit gain = peak velocity of eye movement/peak velocity of target.

Each instance of latency, velocity and accuracy, with both the fixed and random objects, were summed and expressed as the total latency (TL), total velocity (TV) and total accuracy (TA). The units for TL and TV were millisecond, and the unit for TA was a percentage. In addition, TA was also expressed as $TA_{\text{normalized value}}$ (dividing by 4, i.e., random and fixed accuracy in right and left side) for 100% as the base value. The references of TL, TV and TA were obtained from 20 normal controls matched for age and sex.

The clinical variables recorded at the time of the VEOG included age, duration of exposure to AEDs, AEP score, Beck depression inventory (BDI) score, dosage and number of AEDs, AED-resistance, types of seizures and presence of nystagmus on the VEOG. AED-resistance was defined as the failure of the adequate trials of two tolerated, appropriately selected and used AEDs, to achieve sustained freedom from seizures [10]. The dosage of AEDs was standardized for the AED load. The AED load was defined as the sum of the prescribed daily dose/defined daily dose for each patient, in which the defined daily dose corresponded to the assumed average maintenance daily dose of a drug used for its primary indication [11].

The primary endpoint for this study was the differences in the parameters on the VEOG between the 75 consecutive patients with epilepsy and the 20 normal controls matched for age and sex. In addition, we analyzed the possible correlations between the clinical variables and the parameters on the VEOG.

We analyzed the parameters on the VEOG and the clinical variables using Fisher's exact test or the chi-squared test for categorical variables and Student's *t*-test or the Mann–Whitney *U* test for numerical variables according to their distribution. Of the 75 consecutive patients, we found 14 patients with nystagmus on VEOG only. These 14 patients were normal on their neurological examinations and did not complain of any AEs, including dizziness. To evaluate the sensitivity and specificity for detecting nystagmus on the VEOG, we analyzed the clear cutoff values with the receiver operating characteristic curve (ROC). We compared the sensitivity and specificity of the clear cutoff values between the AEP and VEOG for detecting nystagmus. All statistical tests were performed using MedCalc® (MedCalc Software version 13, Ostend, Belgium). The categorical variables were presented as the frequency and the percentage. The numerical variables with normal distributions were presented as the mean ± standard deviation, and those without normal distributions were described as the median with the 95% confidence interval and range. A p value <0.05 was considered statistically significant. We set a p value <0.017 (0.05/3) as significant when comparing the parameters, TL, TV and TA, on the VEOG between the patients and controls with multiple corrections.

3. Results

3.1. Demographics of the patients and controls

Seventy-five epilepsy patients met the inclusion criteria, and 20 healthy volunteers were used as the normal controls who were matched for age and sex. The mean age of the patients was 38.4 ± 11.9 years old, and that of the controls was 38.9 ± 14.9 years old (case vs. control, $p = 0.8$). Twenty-nine of the 75 patients were male, whereas 10 patients were male in the controls (case vs. control, $p = 0.5$). The median age of the onset of epilepsy was 23.5 years old (95% CI 19–28.5 years old, range 6–67 years old), and the duration of exposure to AEDs was 124 ± 112 months. AED-resistance was found in 21% (16/75), whereas 79% (59/75) had well-controlled epilepsy. Partial seizures were noted in 88% (66/75), and 12% (9/75) had generalized seizures. Forty-six patients were on 1 AED, whereas 29 patients were on poly-pharmacy, of whom 19 patients were taking two AEDs and 10 patients were taking three AEDs. Fifty-seven patients were taking at least one AED with a sodium channel blocker, such as carbamazepine, lamotrigine, phenytoin, or oxcarbazepine, two patients were taking two different AEDs with a sodium channel blocker and 16 patients were taking no AEDs with a sodium channel blocker. The median AED load was 0.9 (95% CI 0.8–1.07, range 0.33–6.33).

3.2. Difference in the parameters on the VEOG between patients with epilepsy and controls

There were significant differences in the VEOG parameters between the 75 patients with epilepsy and the 20 controls (Table 1). The parameters in the pursuits were not different between the groups; however, both the TL and TA were significantly different between the groups after multiple corrections. Both the TL (1017.7 ± 148.9 ms vs. 1150.7 ± 10 6.6 ms, corrected $p = 0.0003$) and TA [370.7% (95% CI 364.1–376.4%, range 306–408.2%), 92.7% as $TA_{\text{normalized value}}$ vs. 383.6% (95% CI 378.8–398%, range 322.9–417.4%), 95.9% as $TA_{\text{normalized value}}$, corrected $p = 0.0005$] were significantly decreased in the patients with epilepsy, but not in the controls. These significant differences in the latency and accuracy remained after stratification of the fixed and random saccadic movements. However, the presence of nystagmus on the VEOG did not influence either the TL (1055.6 ± 104.4 ms with nystagmus on the VEOG vs. 1009 ± 156.7 ms without nystagmus on the VEOG, corrected $p = 0.29$) or the TA [371.3% (95% CI 352.9–389.7%, range 333.4–399.9%), 92.8% as $TA_{\text{normalized value}}$ with nystagmus on the VEOG vs. 370.7% (95% CI 364–377.3%, range 306.1–408.2%), 92.7% as $TA_{\text{normalized value}}$ without nystagmus on the VEOG, corrected $p = 0.86$].

In addition, there were positive correlations between the TL and age ($r = 0.22$, $p = 0.03$) and the duration of exposure to AEDs ($r = 0.25$, $p = 0.08$). However, the AEP scores, the AED load, and the number of AEDs were not correlated with the TL (Table 2). We were also unable to identify any relationship between the clinical variables and the TA.