



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



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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 ($\leq 388.7\%$, 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.

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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 on a 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.

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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 $\pm 30.0^\circ$ 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) $\times$ 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 $\pm$ 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 ± 106.6 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.

Table 1

Parameters on video-based electro-oculography between patients and controls.

	Normal controls	Patients using AEDs	<i>p</i>
Saccade			
Fixed velocity (ms)	892.2 (95% CI 841.4–1059.1, range 658.6–1235)	879.2 (95% CI 795–959, range 323–2075.1)	0.2
Fixed accuracy (%)	193.1 ± 12.3	182 ± 14.3	0.002
Fixed latency (ms)	536 ± 69.2	468 ± 93.6	0.0029
Random velocity (ms)	970.9 (95% CI 877.7–1075.5, range 643.9–1383.2)	877.9 (95% CI 822.7–953.2, range 736.7–1017.9)	0.08
Random accuracy (%)	192.8 (95% CI 189.1–199.2, range 160–206)	185.6 (95% CI 182.9–189.3, range 129–209)	0.003
Random latency (ms)	620.9 (95% CI 572.2–666.6, range 500.9–714.3)	558.7 (95% CI 537.8–583.4, range 513.4–606.7)	0.001
Total velocity (ms)	1894.6 (95% CI 1698.4–2156.8, range 1302.6–2505.6)	1751.3 (95% CI 1587.3–1918.6, range 958.7–3600.8)	0.13
Total accuracy (%)	383.6 (95% CI 378.8–398, range 322.9–417.4), 95.9% as TA _{normalized value}	370.7 (95% CI 364.1–376.4, range 306–408.2), 92.7% as TA _{normalized value}	0.0005
Total latency (ms)	1150.7 ± 106.6	1017.7 ± 148.9	0.0003
Pursuit			
0.2 Hz gain	2.0 (95% CI 1.8–2.2, range 1.4–2.6)	1.8 (95% CI 1.8–1.9, range 0.5–3.5)	0.12
0.4 Hz gain	1.8 (95% CI 1.6–1.9, range 1.0–2.4)	1.7 (95% CI 1.6–1.8, range 0.8–3.2)	0.25
Total gain	3.8 (95% CI 3.5–4.0, range 2.6–5.1)	3.4 (95% CI 3.3–3.7, range 1.3–6.7)	0.17

AEDs: antiepileptic drugs; TA: total accuracy.

Furthermore, we analyzed the differences of the parameters according to the epilepsy status because the significant differences found in this study might be influenced by the epilepsy itself rather than by the effects of the AEDs. We found that a status of severe epilepsy (AED-resistant epilepsy) did not affect the parameters. The TL in severe epilepsy was 1033.2 ± 207.1 ms and the TL in non-severe epilepsy was 1013.5 ± 130.8 ms (corrected $p = 0.64$). The TA in severe epilepsy was 365.5% [(95% CI 355.0–380.5%, range 306.1–396.6%), 91.4% as TA_{normalized value}] and the TA in non-severe epilepsy was 371.2% [(95% CI 365.9–377.2%, range 308.5–408.2%), 92.8% as TA_{normalized value}, corrected $p = 0.42$]. Additionally, the types of seizures did not impinge on the parameters. The TL for the partial seizures was 1014 ± 151.2 ms and the TL for the generalized seizures was 1045 ± 135.3 ms (corrected $p = 0.55$). The TA in the partial seizures was 370.7% (95% CI 363.6–376.7%, range 306.1–402.4%), 92.7% as TA_{normalized value} and the TA in the generalized seizures was 370.7% [(95% CI 342.2–384.7%, range 335.5–408.2%), 92.5% as TA_{normalized value}, corrected $p = 0.87$]. Additionally, we failed to find a difference of parameters between the number of AEDs. The TL in the mono-pharmacy was 1007.7 ± 141.7 ms and the TL in the poly-pharmacy was 1033.6 ± 160.9 ms (corrected $p = 0.46$). The TA in the mono-pharmacy was 370.9% (95% CI 363.6–377.9, range 308.5–408.2), 92.7% as TA_{normalized value} and the TA in the poly-pharmacy was 369.8% [(95% CI 360–378.2, range 306.1–396.6%), 92.5% as TA_{normalized value}, corrected $p = 0.76$]. There was a trend of increasing TL and TA as sodium channel blockers were added, but this was not statistically significance ($p = 0.072$ for TL, $p = 0.35$ for TA).

3.3. Comparison of the AEP with the VEOG parameters

Of the 75 patients with epilepsy, 14 patients showed nystagmus only on the VEOG. None of the 14 patients complained of any AEs, including dizziness, and were normal on their neurological examinations, whereas none of the 20 normal controls showed

nystagmus on the VEOG. We also analyzed the sensitivity and specificity between the AEP and the VEOG for detecting nystagmus. The ROC curve analysis showed that the clear cutoff values of the TA ($\leq 388.7\%$, 97.2% as TA_{normalized value}) and the TL (≤ 1005.5 ms) revealed 93.4% sensitivity and 28.6% specificity, respectively, and 49.2% sensitivity and 78.6% specificity for detecting nystagmus on VEOG, respectively. When using the clear cutoff value of the AEP score (AEP > 40) for detecting nystagmus, the sensitivity was only 39.3% and the specificity was 78.6%. The sensitivity of both the TA and the TL was significantly higher in the VEOG than the AEP for detecting nystagmus (Table 3).

4. Discussion

The primary finding of this study is that AEDs can affect saccades. Previous studies also support our findings, but those studies were performed in healthy volunteers and compared the effects between AEDs [12–18]. This study is the first systematic approach to determine whether the AEs of AEDs can be assessed using the eye movements obtained with VEOG. We used very strict criteria for this study, and included only patients with no structural lesions and no medications that might influence saccades. Additionally, the patients for this study were normal upon neurological examinations and did not report any clinical AEs, such as dizziness.

We compared the VEOG parameters of the patients with epilepsy with the controls and found that the TL and the TA were significantly different between the groups, even after multiple corrections. A possible explanation of this significant difference may be the effects of epilepsy itself rather than the AEDs. Epilepsy is a pathological condition in the brain, and this pathology may alter the structures in the brain involving saccades. If epilepsy impinges on saccades, the parameters of saccades would be

Table 2

Correlations between the parameters on video-based electro-oculography and clinical variables.

Variables	Correlation between total latency and variables (<i>r</i>)	<i>p</i>	Correlation between total accuracy and variables (<i>rho</i>)	<i>p</i>
Exposure	0.25	0.08	0.16	0.28
Age	0.22	0.03	0.12	0.26
Onset	−0.03	0.85	−0.17	0.24
AEP	−0.1	0.3	−0.02	0.8
AED load	−0.02	0.8	0.02	0.8
AED number	0.09	0.8	−0.02	0.8

AEP: adverse event profile; AEDs: antiepileptic drugs.

Table 3

Sensitivity and specificity of video-based electro-oculography and adverse event profile for detecting nystagmus.

Cutoff value	Sensitivity (%)	Specificity (%)
Exposure to AEDs		
Latency ≤ 1137.4 ms	81.30	60
Accuracy $\leq 378.6\%$, 94.7% as TA _{normalized value}	69.30	75
High risk with nystagmus		
Latency ≤ 1005.5 ms	49.20	78.60
Accuracy $\leq 388.7\%$, 97.2% as TA _{normalized value}	93.40	28.60
AEP > 40	39.30	78.60

AEDs: antiepileptic drugs; TA: total accuracy; AEP: adverse event profile.

different according to the epilepsy status. In addition, we would expect a dose-response in saccades, such that the more severe the epilepsy, the more disturbed the parameters of saccades. In addition, we found that the parameters did not differ according to the epilepsy status, such as intractability or type of seizures. Furthermore, we included only patients who had negative MRIs and who were not on medications that might influence saccades. Based on our findings, a reasonable explanation for the differences in the parameters of the VEOG may be because of the effects of the AEDs rather than the epilepsy itself.

Although a decreased TA is a reasonable consequence of AED use, a decreased TL was not expected. Many studies revealed that latency was prolonged with AEDs [12–14,17,18], whereas other studies did not obtain this result [16]. It is difficult to explain why both the TL and the TA were significant parameters and why the TL was decreased in patients with AEDs, whereas the TV did not differ from the controls. The complicated networks within the brain, including various parts of the cerebral cortex, the superior colliculus and brainstem, with modifications by the cerebellum and the basal ganglia, are required to generate saccades [19]. Recent studies provided indirect evidence that suggests the important roles of ion channels, particularly calcium channels, sodium channels and GABA receptors, in the generation of saccades [20–23]. The mechanisms by which the majority of AEDs act is on ion channels or GABA receptors [24]. These mechanisms may contribute to the development and effects of AEs caused by AEDs. The neurons involved in the control of saccades in the brain also exert their physiological roles through ion channels or GABA receptors. AEDs may block the inhibitory interneurons in addition to the excitatory neurons, and the neurons involved in the control of saccades may be disinhibited, resulting in decreased TL in patients taking AEDs.

Another important finding of this study is that specific clear cutoff values on the VEOG may identify patients who are at a high risk of AEs from AEDs, even though they do not complain of AEs. In this study, we found that the 14 patients who showed nystagmus on VEOG only did not complain of any AEs, including dizziness, and had normal neurological examinations. The presence of nystagmus is a very reliable neurological sign indicating the presence of AEs from AEDs. These 14 patients may be high-risk patients for developing AEs at any time. This clinical situation requires the identification of patients who are at a high risk for AEs, whether using a standardized questionnaire or biomarker. Because AEP is a good instrument for identifying patients with AEs, we compared the sensitivity and specificity between the AEP score with the parameters on VEOG to identify high risk-patients. The sensitivity of the parameters on VEOG was higher than the AEP score. When setting the clear cutoff values of TA ($\leq 388.7\%$), the sensitivity was 93.4% for detecting nystagmus on the VEOG. AEP scores are influenced by depression and a non-neurological status, such as problems with the skin or mouth, whereas the parameters on VEOG may more directly reflect the status of the brain under the influence of AEDs.

This study has limitations. First, the population for this study was limited to subjects with epilepsy without structural lesions. We are unable to use the significant parameters of the VEOG in cases of patients who have structural lesions or are taking medications that affect saccades. The neurons controlling saccades may be influenced by structural lesions that are responsible for epilepsy, which may decrease the clinical utility VEOG for monitoring AEs. Second, although the neurons involved in the control of saccades may be disinhibited, resulting in a decreased TL in the patients using AEDs, we must confirm our results, particularly the decrease in TL in the patients with AEDs. Third, we did not analyze the serum concentrations of the AEDs. It is possible that the serum concentration of the AEDs may be related to the parameters on VEOG. A future study that focuses on the serum concentration of AEDs and the parameters of saccades is necessary.

5. Conclusions

The total latency and accuracy on video-based electro-oculography may be used to screen and identify patients with a high risk of adverse effects to antiepileptic drugs.

Conflict of interest statement

None of the authors has any conflicts of interest to disclose.

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