Can pursuit eye movements reflect the efficacy of antiepileptic drugs?

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Background: We evaluated whether eye movements could reflect the efficacy of antiepileptic drugs in patients with epilepsy.

Methods: Thirty patients with epilepsy of unknown cause as well as age- and sex-matched normal controls were enrolled in this study. We divided the patients into drug-controlled epilepsy (n = 22) and drug-resistant epilepsy (n = 8) groups according to their seizure controls. We analyzed the differences in the parameters of the eye movements in these two groups compared with normal controls using video-based electro-oculography. In addition, we investigated the differences in the cerebellar volumes of these two groups using whole-brain T1-weighted images.

Results: The latency and accuracy of saccade in patients with epilepsy were significantly different from normal controls, but they were not different between patients with drug-controlled epilepsy and drug-resistant epilepsy. However, the gain of pursuit was significantly decreased in patients with drug-resistant epilepsy compared with normal controls ($p = 0.0010$), whereas it was not different between patients with drug-controlled epilepsy and normal controls ($p = 0.9646$). In addition, the patients with drug-resistant epilepsy had lower cerebellar volumes than normal controls ($p = 0.0052$), whereas the cerebellar volumes in patients with drug-controlled epilepsy were not different from normal controls ($p = 0.5050$).

Conclusions: We demonstrated that pursuit eye movements could reflect the efficacy of antiepileptic drugs in patients with epilepsy, a finding that may be related to cerebellar dysfunction.

Key words: Epilepsy; Eye movements; Anticonvulsants; Cerebellum

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INTRODUCTION

Epilepsy is one of the most common chronic neurological disorders, and the median incidence of epilepsy is approximately 50.4/100,000/year.[1] Antiepileptic drugs (AEDs) are the treatment of choice for most patients with epilepsy.[2] However, approximately 25% of patients with newly diagnosed epilepsy never become seizure free, and 16% of patients have a fluctuating course in seizure control.[3]

The efficacy of AEDs is the ability of the medication to produce seizure freedom; the tolerability of AEDs involves the incidence, severity, and impact of medication-related adverse effects, and the effectiveness of AEDs encompasses both efficacy and tolerability, as reflected in the retention of the medication.[4] The International League Against Epilepsy (ILAE) published papers regarding the efficacy and effectiveness of AEDs for patients with epilepsy in 2006 and 2013, and they assessed which AEDs have the best drugs for epilepsy based on their efficacy and effectiveness.[5,6] There have been several studies concerning biomarkers for the efficacy and effectiveness of AEDs. Siddiqui et al.[7] suggested an association with the 3435 CT polymorphism in multidrug-resistance gene 1 (*MDR1, ABCB1, PGY1*) and drug-resistant epilepsy. Another study found an association between the single-nucleotide polymorphisms of SCN1A, 2A and 3A and AED responsiveness.[8] Moreover, several studies demonstrated a strong association between carbamazepine-induced Stevens–Johnson syndrome and *HLA-B*1502* in subjects from China, Thailand, Malaysia, and India, and other studies revealed an association between the carbamazepine-induced hypersensitivity reaction and *HLA-A*3101* in Caucasian, Japanese, and Korean populations.[9] Additionally, we recently demonstrated that saccadic eye movements using video-oculography (VOG) can be screened to identify patients with a high risk of adverse reactions to AEDs.[10]

However, no study has investigated whether eye movements could reflect the efficacy of AEDs in patients with epilepsy. The aim of this study was to determine whether the efficacy of AEDs could be assessed with eye movements using VOG.

MATERIALS AND METHODS

Patients

This study was conducted with the approval of the Institutional Review Board at our institution. This study was performed at a single tertiary hospital. We prospectively enrolled 30 patients with a clinical diagnosis of epilepsy with unknown cause by the current ILAE classification.[11] Of the 30 patients with epilepsy, eight patients had drug-resistant epilepsy and 22 patients had drug-controlled epilepsy. The definition of drug-resistant epilepsy in this study was the failure of adequate trials of two tolerated, appropriately chosen and used AEDs to achieve sustained seizure freedom.[12] The inclusion criteria were as follows: patients 1) with an age ≥ 16 years, 2) without structural lesions on magnetic resonance imaging (MRI), 3) taking AEDs regularly for at least one year, 4) not taking any other medications that could influence eye movements, 5) with normal results on a neurologic examination, 6) without a history of alcohol or drug abuse, or 7) without any other neurological or psychiatric disease because of the potential influence on brain atrophy. We collected demographic and clinical data, including age, sex, age of seizure onset, duration of epilepsy, seizure type, and dosage, and number of AEDs from these patients. 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, where the defined daily dose corresponded to the assumed average maintenance daily dose of a drug that is used for its primary indication.[13]

Normal controls

The control group consisted of age- and sex-matched healthy subjects (matched 20 normal controls for VOG analysis and 18 normal controls for cerebellar volume analysis). Of the 20 normal controls for VOG analysis, 10 patients (50%) were men and 10 patients (50%) were women. The mean age was 38.9 ± 14.8 years. Of the 18 normal controls for cerebellar volume analysis, 6 patients (33%) were men and 12 patients (67%) were women. The mean age was 40.1 ± 6.0 years. All subjects had a normal neurological examination and no history of cardiovascular, neurological or psychiatric disease, diabetes, hypertension, or dyslipidemia. All normal controls had a normal MRI on visual inspection.

Video-oculography

We described the process of VOG in a previous study.[10] The movements of the left eye were recorded using a high-resolution infrared scleral reflectance technique (resolution 320 × 240 pixels, sampling rate 60 Hz, SLVNG; SLMED Inc., Seoul, Korea). The visual stimulus was a white square target on a dark-blue background. The subjects were seated in a darkened room, and calibration was performed 20 seconds before the start of an eye movement recording. Spontaneous nystagmus with or without visual fixation was recorded in both the horizontal and vertical planes.

The saccades were generated by asking the subjects to follow the target that alternates between two fixed positions at fixed (1.25 s) and randomized time interval with ranges of ± 30.0° on the horizontal plane. They were told to fixate their gaze on the target and follow its movement without moving their head. 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. We analyzed the responses which were not contaminated by blinks. 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), respectively. The units for TL and TV were msec, and the unit for TA was a percentage.

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.[14] The data of peak velocity were generated by digital differentiation of position data using a central difference algorithm in Matlab (Mathworks, Natick, MA, USA). We calculated rightward and leftward gain separately at two experimental conditions of 0.2 Hz and 0.4 Hz. The parameters of the gain with both frequencies of 0.2 Hz and 0.4 Hz were summed and expressed as the total gain (TG).

MRI data acquisition, processing and analysis using FreeSurfer

All scans were performed using a 3.0T MRI scanner (AchievaTx, Phillips Healthcare, Best, The Netherlands) equipped with 8-channel head coil. All subjects underwent conventional brain MRI protocols, including axial and coronal 2D T2-weighted images, which were obtained using a turbo spin echo sequence (repetition time [TR]/echo time [TE] = 3000/80 ms, slice thickness = 5 mm, echo train length = 14, field of view [FOV] = 210 mm, matrix size = 512 × 512), and axial and coronal 2D T1-weighted images, which were obtained using an inversion recovery sequence (inversion time [TI] = 800 ms, TR/TE = 2000/10 ms, slice thickness = 5 mm, echo train length = 7, FOV = 210 mm, and matrix size = 512 × 512). All patients underwent sagittally oriented high-resolution contiguous 3D volumetric T1-weighted imaging that was suitable for cerebellar volume analysis. The 3D T1-weighted images were obtained using a turbo-field echo sequence with the following parameters: TI = 1300 ms, TR/TE = 8.6/3.96 ms, flip angle (FA) = 8°, and 1 mm3 isotropic voxel size. To accelerate the data acquisition, SENSE (SENSitivity Encoding) parallel imaging with an acceleration factor of 2 was applied. Volumetric analysis was performed using the FreeSurfer image analysis suite (version 5.1; Martinos Center, Harvard University, Boston, MA, USA) on a 64-bit Linux CentOS 5. The automated procedures for volumetric measures of the different brain structures are described by Fischl et al.[15,16] Briefly, the volumetric measure is carried out as follows. First, image preprocessing is performed, including linear registration, B1 field correction, and non-linear registration. For linear registration, each volume is rigidly registered with a specific atlas, such as the Talairach space, that is specifically designed to be insensitive to pathology and to maximize the accuracy of the final segmentation. Next, any non-homogenous signal intensity due to the B1 bias field is corrected. High dimensional non-linear morphing to the atlas is then conducted. After image preprocessing, the volume is labeled. To label both the cortical and subcortical volumes, segmentation is used for three pieces of information to disambiguate the labels: 1) the prior probability of a given tissue class occurring at a specific atlas location, 2) the likelihood of the image intensity given the tissue class, and 3) the probability of the local spatial configuration of labels given the tissue class. We obtained the absolute cerebellar vol-

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umes from these automated methods. Next, the volumetric measures were calculated using the following equation: the cerebellar volumes (%) = (absolute cerebellar volumes/total intracranial volumes) × 100.

Statistical analysis

We analyzed the differences in the demographic and clinical characteristics, parameters on VOG, and cerebellar volumes between patients with drug-resistant epilepsy and drug-controlled epilepsy compared with normal controls. Comparisons of the demographic and clinical factors were analyzed using the Chi-squared test or Fisher's exact test for categorical variables and Student's *t*-test or Mann-Whitney *U* test for numerical variables. Categorical variables are presented as the frequency and percentage. Numerical variables with normal distributions are presented as the mean ± standard deviation, and those without normal distribution are described as the median with the 95% confidence interval and range. A *p*-value less than 0.05 was considered to indicate statistical significance for all calculations. All statistical tests were performed using MedCalc® version 13 (MedCalc Software bvba, Ostend, Belgium).

RESULTS

Demographic and clinical characteristics of the patients

Of the 30 patients with epilepsy, 10 patients (33%) were men and 20 patients (67%) were women. The mean age was 40.3 ± 11.5 years. The mean age of seizure onset was 30.9 ± 13.9 years. The median duration of epilepsy was 72.0 months (95% confidence interval [CI]: 36.0-166.6 months; range: 12.0-444.0 months). Twenty-seven patients (90%) had focal seizures, and three patients (10%) had generalized seizures. Nineteen patients were on one AED (seven patients with oxcarbazepine, four patients with lamotrigine, three patients with carbamazepine, three patients with valproic acid, and two patients with levetiracetam), whereas 11 patients were on a poly-pharmacy, of whom five patients were taking two AEDs (two patients with levetiracetam and oxcarbazepine, one patient with lamotrigine and topiramate, one patient with lamotrigine and valproic acid, and one patient with lamotrigine and zonisamide) and six patients were taking three AEDs (one patient with carbamazepine, lamotrigine, and valproic acid, one patient with lamotrigine, levetiracetam, and valproic acid, one patient with lamotrigine, levetiracetam, and zonisamide, one patient with lamotrigine, oxcarbazepine, and valproic acid, one patient with lamotrigine, oxcarbazepine, and zonisamide, and one patient with levetiracetam, topiramate, and valproic acid). The median AED load was 0.90 (95% CI: 0.69-1.38; range: 0.40-4.77). The patients with drug-resistant epilepsy had a longer duration of epilepsy and a higher AED load than those with drug-controlled epilepsy (Table 1).

The differences in the parameters on VOG

There were significant differences in the VOG parameters between the patients with drug-resistant epilepsy and drug-controlled epilepsy (Table 2). In saccadic eye movements, both the TL and TA were commonly decreased in

Table 1. Differences in the demographic and clinical characteristics between patients with drug-resistant epilepsy and drug-controlled epilepsy

Variable	Patients with drug-resistant epilepsy (n = 8)	Patients with drug-controlled epilepsy (n = 22)	*p*-value
Age (years)	41.4 ± 5.3	39.9 ± 13.2	0.7569
Male	1 (12.5)	9 (40.9)	0.2103
Age of seizure onset (years)	23.8 ± 8.9	32.8 ± 14.6	0.1680
Duration of epilepsy, months (range)	184, 60-444	36, 12-252	0.0184
Partial seizure	8 (100.0)	19 (86.4)	0.5448
AED load	2.9 (2.2-4.8)	0.8 (0.4-2.8)	0.0001

Values are presented as mean ± standard deviation or n (%) unless otherwise indicated.
AED, antiepileptic drug.

Table 2. Differences in the parameters of video-based electro-oculography between patients with drug-resistant epilepsy and drug-controlled epilepsy compared with normal controls

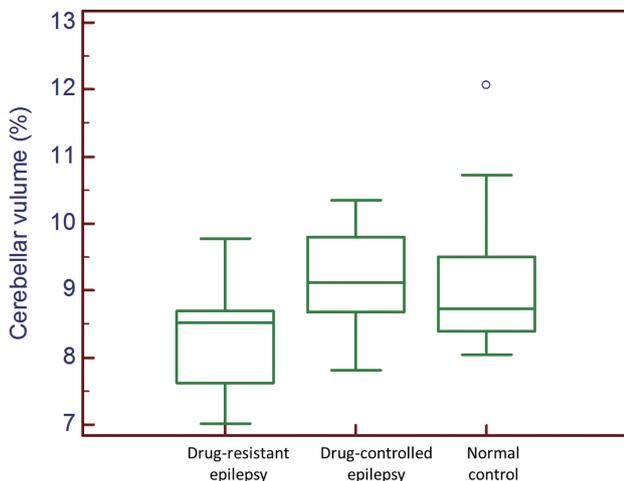|	Normal controls	Patients with drug-resistant epilepsy	*p*-value	Patients with drug-controlled epilepsy	*p*-value
Saccade					
Fixed velocity (ms)	892.3 (658.7-1235.0)	704.3 (561.3-821.7)	0.0004	827.2 (562.3-1572.7)	0.2678
Fixed accuracy (%)	193.1 ± 12.3	181.9 ± 11.7	0.0366	179.2 ± 14.5	0.0018
Fixed latency (ms)	536.6 ± 69.2	432.9 ± 114.5	0.0065	454.5 ± 80.3	0.0011
Random velocity (ms)	970.9 (643.9-1383.2)	738.2 (636.1-859.2)	0.0008	929.0 (508.6-1614.0)	0.2172
Random accuracy (%)	192.8 (160.0-206.1)	187.2 (129.0-197.4)	0.0671	188.1 (148.2-209.3)	0.0250
Random latency (ms)	620.9 (500.9-714.3)	596.6 (266.3-704.8)	0.2855	564.2 (349.1-633.0)	0.0048
Total velocity (ms)	1932.3 ± 316.9	1436.0 ± 125.3	0.0002	1829.6 ± 483.1	0.4254
Total accuracy (%)	383.6 (322.9-417.4)	371.7 (306.1-383.1)	0.0221	370.6 (308.5-408.2)	0.0038
Total latency (ms)	1171.7 (942.5-1313.2)	1043.9 (588.4-1249.8)	0.0199	1004.9 (725.6-1224.7)	0.0011
Pursuit					
0.2-Hz gain	2.0 (1.4-2.6)	1.6 (0.5-1.9)	0.0023	1.9 (1.0-3.5)	0.4729
0.4-Hz gain	1.8 (1.0-2.4)	1.3 (0.8-1.6)	0.0027	1.7 (1.0-3.2)	0.7625
Total gain	3.9 (2.6-5.1)	3.0 (1.3-3.3)	0.0027	1.7 (1.0-3.2)	0.4965

Fig. 1. Differences in the cerebellar volumes in patients with epilepsy and normal controls. The results reveal that the cerebellar volumes in patients with drug-resistant epilepsy are significantly smaller than those in normal controls (*p* = 0.0180), whereas the cerebellar volumes are not different between patients with drug-controlled epilepsy and normal controls (*p* = 0.5050).

both groups of patients with drug-resistant epilepsy and drug-controlled epilepsy compared with normal controls (TL, 1043.9 vs. 1171.7 msec, *p* = 0.0199; 1004.9 vs. 1171.7 msec, *p*

= 0.0011; drug-resistant epilepsy or drug-controlled epilepsy vs. normal controls, respectively) (TA, 371.7 vs. 383.6%, *p* = 0.0221; 370.6 vs. 383.6%, *p* = 0.0038; drug-resistant epilepsy and drug-controlled epilepsy vs. normal controls, respectively). However, during the pursuit test, the parameters of TG in patients with drug-resistant epilepsy were significantly decreased compared with normal controls (3.00 vs. 3.85, *p* = 0.0027), whereas they were not different between patients with drug-controlled epilepsy and normal controls (3.58 vs. 3.85, *p* = 0.4965).

Differences in the cerebellar volumes

The cerebellar volumes in patients with drug-resistant epilepsy were significantly smaller than those in normal controls (8.5 vs. 8.7%; *p* = 0.0180), whereas the cerebellar volumes in patients with drug-controlled epilepsy were not different from those in normal controls (9.1 vs. 8.7%; *p* = 0.5050). In addition, the cerebellar volumes in patients with drug-resistant epilepsy were significantly smaller than those in patients with drug-controlled epilepsy (8.5 vs. 9.1%; *p* = 0.0129) (Fig. 1).

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DISCUSSION

This study was the first to investigate the association between AEDs efficacy and eyeball movements in patients with epilepsy. The main finding of this study was that pursuit eye movements could reflect the AEDs efficacy in patients with epilepsy, whereas the saccadic eye movements were not associated with it. We only enrolled patients with no structural lesions and without other medications that could influence eye movements. In addition, we demonstrated that the cerebellar volumes in patients with drug-resistant epilepsy were significantly smaller than those in normal controls or drug-controlled epilepsy. We would like to suggest that the impairment of pursuit eye movements without involving saccadic eye movements in patients with drug-resistant epilepsy was associated with cerebellar dysfunction.

Saccade and pursuit are two types of voluntary eye movements.[17] Primates use a combination of saccadic and pursuit eye movements to stabilize the retinal image of selected objects within the high-acuity region near the fovea.[17] These two eye movements are controlled by similar networks of cortical and subcortical regions and, to some degree, share a similar functional architecture.[17] However, the roles and characteristics of these two eye movements are quite different. Saccadic eye movements are discrete movements that quickly change the orientation of the eyes, thereby translating the image of the object of interest from an eccentric retinal location to the fovea, whereas pursuit eye movements are continuous movements that slowly rotate the eyes to compensate for the motion of the visual object, minimizing the blur that would otherwise compromise visual acuity.[18] In humans, deficits of the pursuit eye movements have been reported with cerebral or cerebellar lesions.[19] Impaired regulation of pursuit eye movements is thought to be associated with the disruption of the cortico-ponto-cerebellar circuits.[19] For the pursuit eye movements, cortical area of the middle temporal region provides visual information to the medial superior temporal region, which projects to dorsolateral pontine nucleus or nucleus peduncle and reach at dorsal vermis or flocculus.[20] Therefore, although the cerebellum modulates the motor command for saccadic eye movements, it plays more critical roles in the generation of pursuit eye movements.[17,21] A previous study revealed that ablation of the flocculus and paraflocculus in the cerebellum caused

large and lasting deficits in pursuit eye movements in primates,[22] and a recent study using lesion-mapping imaging demonstrated that the uvula and vermal pyramid in the cerebellum were important structures for generating slow phases within pursuit eye movements in humans.[21] Thus, we could infer that the impairment of pursuit eye movements without involving saccadic eye movements in patients with drug-resistant epilepsy was associated with cerebellar dysfunction in our study. These findings were consistent with the cerebellar volumes in patients with drug-resistant epilepsy being significantly smaller than those in normal controls or patients with drug-controlled epilepsy.

However, the major limitation of this study was that we could not identify the causal relationship between the AED efficacy and cerebellar dysfunction in patients with epilepsy. We can assume that the cerebellar dysfunction in patients with epilepsy, as reflected by a cerebellar volume reduction and impaired pursuit eye movements, evokes a decreased response to AEDs. Several reports have supported this hypothesis. First of all, there is the cortico-ponto-cerebellar tract, which is a well-known anatomical connection between the cerebellum and cerebrum, including the frontal, parietal, and occipital lobes.[23] Several studies demonstrated that the cerebral-cerebellar connections were bidirectional and that the cerebellum exerted an inhibitory effect over seizure activity on the cortex using the release of the inhibitory transmitter gamma amino butyric acid from Purkinje cells.[24] Thus, cerebellar dysfunction may contribute to increased seizure activity in the cerebral cortex through this connection. This finding was consistent with that of a previous study revealing that cerebellar stimulation could improve or shorten seizure activity.[25] Moreover, total cerebellectomy increased the seizure length in a study of kindled cats, and there was an association between the cerebellar volume reduction and poorer seizure control following anterior temporal lobectomy in patients with temporal lobe epilepsy.[26]

Conversely, the decreased AEDs efficacy may have produced cerebellar dysfunction, resulting in cerebellar volume reduction and impaired pursuit eye movements. Prolonged seizures could evoke hypoxic-ischemic injury in the cerebellum. Previous studies have demonstrated a significantly negative correlation between the cerebellar volume and total number and frequency of generalized tonic-clonic seizures.[27] In addition, there was clear evidence that AEDs,

particularly phenytoin, could cause reversible cerebellar symptoms and a severe cerebellar volume reduction that were induced after even a single episode of phenytoin intoxication.[28,29] Thus, we can also assume that decreased AEDs efficacy induces cerebellar dysfunction due to hypoxic-ischemic injury during prolonged seizures or adverse effects of AEDs. This notion was also supported by the results of our study showing that the patients with drug-resistant epilepsy had a longer duration of epilepsy and a higher AED load than those with drug-controlled epilepsy. To identify the causal relationship between the AEDs efficacy and cerebellar dysfunction in patients with epilepsy, brain MRI and VOG should be conducted during the drug-naïve state in patients with newly diagnosed epilepsy, and intra-personal follow-up studies may be needed.

In conclusion, we demonstrated that pursuit eye movements could reflect the efficacy of antiepileptic drugs in patients with epilepsy, a finding that might be related to cerebellar dysfunction.

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