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Attenuation of retinal nerve fibre layer in people with epilepsy receiving valproate

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ABSTRACT

Objectives: Valproate (VPA) is one of the most frequently used anti-epileptic drugs (AEDs) worldwide. Its effects in decreasing the retinal nerve fibre layer (RNFL) thickness remain debatable. We aimed to evaluate the effect of VPA usage on the RNFL in comparison with other AEDs and no AED usage in people with epilepsy (PWE).

Methods: In this observational case-control study, PWE were enrolled and divided into three groups: PWE 1) receiving VPA monotherapy throughout their clinical course; 2) receiving an AED other than VPA as monotherapy; and 3) who never took any AED. RNFL thickness of the right eye was measured by optical coherence tomography (OCT). In each individual, disease-related information was recorded.

Results: A total of 86 individuals (51 males; median age, 25 years) with an average epilepsy duration of 6.88 years were enrolled. No difference in the demographics except for sex was noted between the groups. The average RNFL thickness in 26 individuals who had received VPA (group I) was 93.73 ± 9.24 μm, which was significantly lower than the corresponding values for the 31 individuals who received other single AED regimens (group II; 99.71 ± 8.50 μm; $p = 0.031$) or the 29 individuals who never used any AED (group III; 102.79 ± 8.05 μm; $p = 5.67 \times 10^{-4}$), especially in the superior and inferior quadrants. The RNFL attenuation was significantly correlated with the epilepsy duration in groups II and III ($r = 0.351$, $p = 0.006$). However, no correlation between epilepsy duration, cumulative dosage of VPA, duration of treatment with VPA and RNFL thickness was found in group I.

Conclusion: These preliminary findings suggest an association between VPA usage and reduction of retinal thickness in PWE, especially in the superior and inferior quadrants. Epilepsy itself might also be another risk factor for RNFL attenuation. Further studies need to confirm this finding and to unravel the underlying mechanism.

1. Introduction

Valproate (VPA) is a highly effective and broad-spectrum anti-epileptic drug (AED) that has been widely used to treat all types of seizures and epilepsy syndromes since first approved for the treatment of epilepsy in 1967. Other non-epilepsy indications for VPA include migraine and mood disorder, and potential indications for cancer have also been reported (Blaheta et al., 2005; Terbach and Williams, 2009). The most common adverse effects of VPA include sedation and fatigue, while the most prominent adverse effect was teratogenicity and toxicity to offspring (Tomson et al., 2016). Adverse effects of VPA on the eye have also been reported, including loss of colour vision and visual-field defects (Hilton et al., 2004; Steinhoff et al., 1997; Verrotti et al., 2007), and the mechanisms underlying these adverse effects were further investigated by assessing the thickness of the retinal nerve fibre layer (RNFL) with optical coherence tomography (OCT), which allows early disease detection by providing fast and precise measurements of the thickness to characterize the structural abnormalities that precede

Abbreviations: VPA, Valproate; AED, anti-epileptic drugs; RNFL, retinal nerve fibre layer; PWE, people with epilepsy; OCT, optical coherence tomography; VGB, vigabatrin; LEV, levetiracetam; OXC, oxcarbazepine; LTG, lamotrigine

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functional abnormalities (Lawthom et al., 2009).

However, previous studies have reported conflicting results for RNFL attenuation in people with epilepsy (PWE) receiving VPA (Akcakaya et al., 2010; Balestrini et al., 2016; Dereci et al., 2015; Lobefalo et al., 2006; Wild et al., 2006). RNFL attenuation due to VPA in PWE has not been confirmed decisively because most studies enrolled subjects treated with other concomitant AEDs and exaggerated the possible insult of VPA on RNFL by using healthy subjects as controls, and none of the studies compared the RNFL thickness in PWE treated with VPA monotherapy to that in untreated PWE. The issue was critical since VPA is widely used and is the first-line medication in some types of epilepsy, like absence epilepsy in children. Since most PWE were on long-term medication, balancing the benefits with potential long-term adverse effects is important.

Thus, the aim of this case-control cross-sectional study was two-fold: 1) to explore whether the usage of VPA had a negative effect on RNFL thickness in comparisons with PWE receiving other AED monotherapies and untreated PWE, and 2) to perform a further correlation analysis to determine the risk factors for this insult.

2. Methods

2.1. Participants

Adults attending a specialist clinic between 31 December 2016 and 1 November 2018 and diagnosed with epilepsy according to the criteria of the International League Against Epilepsy were asked to participate in the study (Fisher et al., 2014). We consecutively included patients who had never received more than one type of AED throughout their clinical course, and divided them into three groups: group I was composed of PWE receiving VPA monotherapy throughout their clinical course; group II consisted of PWE receiving an AED other than VPA as monotherapy during the clinical course; and group III contained PWE who never took any AED. For groups I and II, we only included patients receiving regular medication for more than six months. Individuals were asked to respond to a uniform questionnaire about general history and the existence of eye diseases, and they were excluded if they had previous exposure to vigabatrin (VGB); evidence of vascular dementia; a history of alcohol abuse; psychiatric disorders or a history of psychotropic drug consumption; metabolic diseases; arterial hypertension; other neurological diseases; previous history of optic media opacity, cataract or early lens opacity; retinal detachment; early age-related macular degeneration or other macular degeneration; or retinal vascular diseases.

2.2. Clinical data

The study protocol was approved by the West China Hospital Medical Ethics Committee. After obtaining informed consent, clinical data, including information for age, sex, ethnicity, epilepsy duration (from the time of diagnosis to the date of OCT assessment), yearly seizure frequency, neuroimaging data, history of surgery or brain injury, and AED history were recorded. For group I, information regarding the duration of treatment by VPA and the cumulative VPA dosage was obtained.

2.3. OCT

Peripapillary RNFL of both eyes was evaluated using Cirrus HD-OCT 5000 (Carl Zeiss Meditec Inc., Dublin, CA) by experienced operators blinded to the group assignment. The scanner allows mapping of the average RNFL thickness data in the peripapillary area in four 90° quadrants (superior, nasal, inferior, and temporal) and twelve 30° sectors (from -15° to +15° for sector one and so on). For subjects aged over 18 years, the average RNFL thickness and RNFL thickness in each 90° quadrant and each 30° sector were considered normal if they fell within the $\leq 95^{th}$ to $\geq 5^{th}$ percentiles of the normal distribution percentiles provided by the manufacturer's inbuilt database, and as abnormally thin if they were below the 5^{th} percentile (Knight et al., 2012). Comparisons for patients under 18 years of age were performed with the percentiles for an 18-year-old because the inbuilt database does not contain information for individuals aged less than 18 years.

2.4. Statistical analysis

For statistical analysis, only the right eyes were evaluated. The median (interquartile range) was obtained for age, while means (± standard deviation, SD) were obtained for other data. SPSS (version 19.0; IBM Corp., Armonk, NY) was used for analysis. Variance analysis with one-way ANOVA and Bonferroni post-hoc analysis was performed to compare the intergroup differences in the values of average, quadrantile, and 30° sector analyses of RNFL between the three groups. The chi-squared test was used to assess the differences in categorical variables between groups. Pearson's correlation test was used to identify the correlations between OCT parameters and age and epilepsy duration in the three groups. For group I, the correlation of RNFL thickness with VPA treatment duration and cumulative VPA dosage was also determined by Pearson's correlation test. For discontinuous variables like the presence of brain abnormality and the seizure type, Spearman correlation coefficients were obtained. $P < 0.05$ was considered statistically significant.

3. Results

Eight-six participants (53 males) were enrolled and scanned. The cohort consisted of 26 PWE treated with VPA monotherapy (group I), 31 PWE treated with monotherapy with another AED (group II), and 29 PWE who never received an AED during the clinical course (group III). The demographics of the 86 subjects are provided in Table 1, and detailed information for brain abnormalities is provided in a supplementary table. In group I, the duration of VPA therapy ranged from 3 to 240 months (60.18 ± 53.17 months), and the cumulative VPA dose ranged from 144 to 13000 g (5954 ± 6243 g). In group II, 18 patients were on levetiracetam (LEV), 10 were on oxcarbazepine (OXC), and three were on lamotrigine (LTG). Except for sex, none of the other patient characteristics showed statistically significant intergroup differences, with group I containing more male patients than the other two groups.

Table 1
Demographic and clinical features of the three groups.

	Group I (26)	Group II (31)	Group III (29)	p
Age (years, P50 (P25, P75))	26.5 (21.5,37.5)	25 (19.25,33.00)	23 (18,33)	0.599
Sex (M/F)	21/15	16/15	14/15	0.028
Ethnicity (Han/non-Han)	26/0	31/0	28/1	0.998
Duration (years)	8.70 ± 6.89	7.19 ± 8.59	7.50 ± 7.92	0.128
Seizure type (No.)				0.115
Focal onset	13	26	19	
Generalized onset	10	4	7	
Unclassified	2	0	3	
Unknown	1	1	0	
Seizure frequency (yearly)	3.42 ± 2.12	3.18 ± 2.43	2.98 ± 2.90	0.694
Brain abnormality	12	13	13	0.947
Surgery history	1	1	0	0.587

Group I consisted of people with epilepsy (PWE) receiving VPA monotherapy during the clinical course. Group II consisted of PWE receiving monotherapy with anti-epileptic drugs (AEDs) other than VPA. Group III consisted of PWE who had never taken any AED.

Table 2
RNFL thickness comparison in the different groups.

RNFL thickness, μm	Group I (26)	Group II (31)	Group III (29)
Average RNFL thickness across all 4 quadrants, mean ± SD	93.73 ± 9.24	99.71 ± 8.50**	102.79 ± 8.05**
C/D ratio	0.53 ± 0.15	0.46 ± 0.16	0.44 ± 0.17
Superior quadrant	113.96 ± 14.19	125.23 ± 14.86*	132.07 ± 16.77**
Nasal quadrant	61.73 ± 10.63	66.35 ± 14.68	65.31 ± 10.64
Inferior quadrant	123.04 ± 15.40	129.61 ± 16.93	135.59 ± 17.29*
Temporal quadrant	74.04 ± 19.19	78.45 ± 14.97	78.76 ± 14.33
30° 1	111.85 ± 24.91	124.19 ± 27.76	133.93 ± 31.78*
30° 2	97.12 ± 19.78	107.55 ± 23.92	116.52 ± 28.08*
30° 3	70.35 ± 15.92	80.19 ± 24.38	80.59 ± 19.18
30° 4	52.85 ± 8.68	55.65 ± 11.32	53.69 ± 9.70
30° 5	61.92 ± 13.54	61.10 ± 13.28	60.79 ± 13.14
30° 6	93.12 ± 19.27	96.16 ± 22.60	99.31 ± 18.62
30° 7	129.92 ± 25.90	136.81 ± 28.04	148.45 ± 31.14
30° 8	145.08 ± 26.83	154.32 ± 20.01	158.79 ± 25.05
30° 9	74.96 ± 24.02	82.32 ± 19.15	86.00 ± 23.85
30° 10	59.00 ± 15.57	62.39 ± 11.67	60.48 ± 10.03
30° 11	86.38 ± 23.41	93.39 ± 18.31	92.52 ± 20.01
30° 12	132.88 ± 19.26	145.87 ± 22.22	146.83 ± 22.71

RNFL: retinal nerve fibre layer; ** $P < 0.01$; * $P < 0.05$ compared to the average of right eyes in group I.
The number of RNFL clock hours go clockwise in the right eye.
Group I consisted of people with epilepsy (PWE) receiving VPA monotherapy during the clinical course. Group II consisted of PWE receiving monotherapy with anti-epileptic drugs (AEDs) other than VPA. Group III consisted of PWE who had never taken any AED.

3.1. Average RNFL thickness between the three groups

The average overall RNFL thickness was significantly lower in group I compared to the thickness values in groups II and III ($p = 0.031$ compared to group II and $p = 5.67 \times 10^{-4}$ compared to group III), as shown in Table 2. No significant difference was noted between groups II and III. No difference was noticed in the RNFL symmetry or the C/D ratio between the three groups.

3.2. Quadrant RNFL thickness in the three groups

The thickness of the superior quadrant in group I was significantly lower than those in groups II and III ($p = 0.035$ compared to group III and $p = 3.13 \times 10^{-4}$ compared to group III), as shown in Table 2. Significant difference in thickness was also noted in the inferior quadrant between group I and group III ($p = 0.019$). The 30° sector analyses also showed significant differences in the first and second sectors between groups I and III. No significant difference was noticed between groups II and III.

3.3. The frequency of abnormal RNFL thickness in the three groups

The magnitude of the percentile (1^{st}, 5^{th}, 100^{th}) compared with the measured value of the RNFL thickness averaged across all the quadrants and for each quadrant in each individual of the three groups is given in Table 3. Although group I showed significantly attenuated RNFL compared to the other groups, only one and seven patients from group I showed abnormal average and quadrant RNFL, respectively, and the number of patients exhibiting an abnormally attenuated averaged or quadrant RNFL (i.e., 1 st or 5th percentile) were few and compatible among the three groups. Some patients in group II or even III manifested an abnormal quadrant RNFL thickness. Six patients showed abnormal RNFL in quadrants other than the inferior quadrant in group II, among which four were receiving regular LEV, one was receiving LTG, and one was receiving OXC. Four PWE in group III also showed abnormal quadrant RNFL thinning.

3.4. RNFL thickness was correlated with clinical characteristics of epilepsy

As shown in Table 4, among groups II and III, a significant correlation was found between the epilepsy duration and the average nasal and inferior quadrant RNFL thickness. The age at examination was significantly correlated with the C/D ratio and nasal quadrant RNFL thickness. However, group I showed no correlations between the RNFL thickness and the age, epilepsy duration, duration of VPA treatment, or cumulative VPA dosage. No other correlation between the average or quadrant RNFL thickness and the presence of brain abnormality, seizure type, and seizure frequency was found after statistical analysis (data not shown).

4. Discussion

This study aimed to clarify whether negative effects on RNFL in PWE are caused by epilepsy itself or are a result of the long-term consequence of AEDs. Our findings suggest an association between VPA monotherapy and a reduction in RNFL thickness independent of epilepsy itself, especially in the superior and inferior quadrants.

Although none of the subjects reported chief complaints of any eye illness, the overall RNFL thickness in group I was significantly less than that in the other two groups, which suggested a possible negative effect of VPA on the RNFL. Further quadrant analysis revealed a significant attenuation in the superior quadrant in group I compared to the corresponding values in other two groups, and the inferior quadrant in comparisons between groups I and III. Except for sex, none of the other demographic factors showed significant intergroup differences; the difference in sex distribution could be attributed to the fact that VPA is prescribed with caution in women because of its potential toxic effect on offspring (Tomson et al., 2016).

Although the precise mechanism underlying the actions of VPA is not well established, VPA is largely presumed to be a mildly GABAergic drug (Loscher, 2002). VGB, another GABAergic AED, also shows definite retinal toxicity and can cause attenuation of the RNFL, presumably resulting from the elevated level of gamma-aminobutyric acid (GABA) within the retina, or a combination thereof (Lawthom et al., 2009). VPA might have the same mechanism as VGB in decreasing the RNFL thickness since it elevated GABA levels in the central nervous system as well (Loscher, 2002). Two studies that investigated the effect of VPA on the eye reported the suppressive effect of VPA on the visual evoked-potentials in rats (Myslobodsky and Morag, 1981a, b), which was subsequently also reported in patients receiving VPA (Verrotti et al., 2000). In another study, rats given VPA also exhibited degeneration of the ciliary body in electron microscopy analyses performed from the posterior segment of the eye (Goktas et al., 2015). However, in another study, rats administered VPA showed no effects of the drug in histopathological examinations of the retinal ganglion cells (Aktas et al., 2009).

The mechanism underlying the preference of insults in the superior quadrant was also unknown. The use of an average of four quadrants enabled the study to detect early defects in one particular quadrant. The quadrants may be affected separately in different conditions. For example, the abnormal thinning of RNFL was most frequently seen in the superior and inferior quadrants in PWE (Balestrini et al., 2016). Another study suggested that the VGB toxicity on the retina had a specific pattern of nasal RNFL thinning with temporal RNFL sparing, which was a more sensitive marker for retinal toxicity than visual-field loss (Lawthom et al., 2009). However, the specific insult pattern of VPA with respect to the superior and inferior RNFL thickness remains unknown and needs further investigation.

Overall, reports of abnormal visual function in PWE treated with VPA are scarce (Dereci et al., 2015). The proportion of abnormalities in RNFL reported herein was also smaller than that reported in a previous study (Balestrini et al., 2016), which was explainable since patients in our cohort had shorter disease durations, less frequent seizures, and

Table 3
Frequency of the magnitude of the percentiles (≤1st, ≤5th) of retinal nerve fibre layer thickness across the three groups.

Group (No. of Individuals)	Percentile														
	Average RNFL			Superior			Nasal			Inferior			Temporal		
	N	≤5%	≤1%	N	≤5%	≤1%	N	≤5%	≤1%	N	≤5%	≤1%	N	≤5%	≤1%
I (26)	25	1	0	23	1	2	23	3	0	25	1	0	26	0	0
II (31)	31	0	0	28	1	2	27	3	1	31	0	0	30	1	0
III (29)	29	0	0	28	0	1	27	2	0	28	0	1	29	0	0

RNFL = retinal nerve fibre layer thickness; N = a normal value (i.e. > 5th percentile).
Group I consisted of people with epilepsy (PWE) receiving VPA monotherapy during the clinical course. Group II consisted of PWE receiving monotherapy with anti-epileptic drugs (AEDs) other than VPA. Group III consisted of PWE who had never taken any AED.

Table 4
Participant characteristics and bivariate associations between RNFL in Groups II and III.

	Disease duration		Age at examination	
	r_s	p	r_s	p
Average RNFL	0.351	0.006**	0.024	0.853
C/D ratio	0.219	0.095	0.272	0.035*
Superior quadrant	0.253	0.053	−0.047	0.723
Nasal quadrant	0.311	0.016*	0.312	0.015*
Inferior quadrant	0.241	0.066	0.005	0.969
Temporal quadrant	−0.066	0.621	−0.202	0.122
30° 1	0.134	0.312	0.027	0.715
30° 2	0.363	0.005**	0.048	0.811
30° 3	0.283	0.030*	0.276	0.033*
30° 4	0.210	0.111	0.247	0.057
30° 5	0.291	0.025*	0.284	0.028*
30° 6	0.218	0.098	0.089	0.500
30° 7	0.204	0.121	−0.048	0.714
30° 8	−0.075	0.573	−0.001	0.995
30° 9	−0.091	0.495	−0.122	0.353
30° 10	−0.165	0.212	−0.277	0.032*
30° 11	−0.075	0.571	−0.194	0.137
30° 12	−0.012	0.930	−0.213	0.103

RNFL, retinal nerve fibre layer. ** P < 0.01; * P < 0.05.
Group II consisted of people with epilepsy (PWE) receiving monotherapy with anti-epileptic drugs (AEDs) other than valproate (VPA). Group III consisted of PWE who had never taken any AED.

moderate to good responsiveness to AEDs, which are all risk factors for the RNFL insult. The abnormality might appear as an early insult of epilepsy and AEDs, and the current study without follow-up data was underpowered to determine whether it was a part of the structural changes preceding functional abnormalities, since changes in the structural appearance of the RNFL have been reported to precede the development of visual-field loss in glaucoma and VGB toxicity (Greenfield et al., 2003; Sommer et al., 1991). Interestingly, PWE receiving AEDs like LEV, LTG, and OXC showed abnormal thinning in the RNFL quadrant, which was not reported previously. The attenuation of RNFL by AEDs other than VPA has been reported before; for example, one study noted that three of the 13 patients receiving non-GABAergic drugs, primarily carbamazepine, showed an abnormally thin nerve fibre layer (< 5th percentile) in the superior or inferior quadrants, which was consistent with our findings and was also attributable to no clinical reasons (Lawthom et al., 2009).

The correlation of RNFL thickness to disease duration in groups II and III indicated a disease-driven change in RNFL that was not seen in the patients taking VPA, which could be because the disease-driven effect was smaller and covered by the VPA toxicity. A recent study showed the disease duration, drug resistance, and intellectual insults were correlated with the RNFL attenuation in PWE (Balestrini et al., 2016). Our study also showed an effect of the disease on RNFL, even in patients whose seizures were well-controlled with one AED, as an RNFL attenuation correlated with the duration of epilepsy. However, if possible, a group of healthy controls should be included in a further study to compare whether the epilepsy itself has a negative effect on the RNFL thickness. Moreover, we were unable to find a correlation between the course or cumulative VPA dosage usage and the RNFL thickness. Few previous studies have tested the correlation of cumulative VPA dosage and visual function, and the results were usually negative (Sorri et al., 2005). However, with regard to the correlation of cumulative VGB dosage and impaired visual function or RNFL thickness, most studies suggested that this was a dose-dependent side effect (Hardus et al., 2001; Hardus et al., 2000; Lawthom et al., 2009; Malmgren et al., 2001; Vanhatalo et al., 2002) and some failed to establish the correlation between RNFL thickness and the cumulative dosage of VGB (Hilton et al., 2002; Nousiainen et al., 2000).

There are several limitations of our study. First, we did not perform thorough eye examinations in the subjects, and only enrolled them after uniform questionnaire assessments. Second, we did not record which VPA the subjects had used nor assess the serum concentrations of VPA, which might cause a difference, even though they have comparative bioavailability and used interchangeably(Balbi et al., 1991), and many adverse effects are serum concentration-dependent and can be minimized by dose adjustment. Third, we did not enrol healthy subjects as a control group, so our current study was underpowered to determine directly whether the epilepsy itself has a negative effect on the RNFL thickness. Lastly, group II was composed of PWE receiving four different AEDs, among which some AEDs might also insult the RNFL. In the future, a well-designed cohort study with healthy control groups and long-term follow-up data is needed to confirm this preliminary finding and identify the underlying mechanisms, and various other ocular function tests may also be needed to identify other possible ophthalmic adverse effects of VPA.

5. Conclusion

Our preliminary findings suggest an association between VPA usage and reduction in the average superior and inferior RNFL that was independent of epilepsy itself, thereby underlining possible adverse effects of VPA on vision. Furthermore, epilepsy itself might also have a negative effect on the RNFL regardless of AED therapy. Together with the findings of other recent studies, our results indicate that regular follow-up of OCT might be important for those commencing VPA for treatment of epilepsy, especially for long-term usage. Further studies are required to clarify the underlying pathophysiology of the effect of VPA on the RNFL, since this may shed some light on the association noted in our study.

Conflicts of interest

The authors report no conflicts of interest in relation to this work.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eplepsyres.2019.05.015.

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