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Peripapillary retinal nerve fibre layer thinning in genetic generalized epilepsy

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ABSTRACT

Purpose: The purpose of this study was to compare the peripapillary retinal nerve fibre layer (RNFL) between patients with genetic generalized epilepsy (GGE) and healthy controls.
Methods: This prospective observational study was conducted on adults aged 18–60 years. The study group comprised 26 consecutive patients who met the inclusion criteria and 26 healthy age- and sex-matched healthy adults. Peripapillary RNFL thickness was measured by spectral domain optical coherence tomography.
Results: The average peripapillary RNFL thickness was significantly thinner for GGE patients (98.61 μm) than for healthy controls (104.77 μm) ($p = 0.016$). Similar results were obtained for the left eye. The peripapillary RFNL thickness of all quadrants was lower for GGE patients than for healthy controls, but it was significant only in the superior ($p = 0.009$) and inferior ($p = 0.024$) quadrants for both eyes.
Conclusions: Our results suggest that the peripapillary RNFL is significantly thinner in GGE patients than in healthy participants. We concluded that this microstructural feature might be an intrinsic feature of GGE.

1. Introduction

Genetic generalized epilepsy (GGE) comprises common epilepsies characterized by an electroclinical phenotype, complex genetic component and presumed common pathogenetic mechanism [1,2]. GGE shows no structural lesions on conventional MRI [2]. However, studies based on more advanced imaging technologies have shown subtle differences in brain structure [3–6]. MRI volumetry and voxel-based morphometry studies have demonstrated regional changes, particularly thalamic volume loss, in GGE patients [4,7,8]. Potential pathogenic sub-mesoscopic structural and functional changes that occur during early development could explain altered seizure susceptibility into adulthood for GGE [9].

Microstructural differences in the brain cannot be adequately quantitated with available technology, such as MRI, but examination of the retina and optic nerves by optical coherence tomography (OCT) provides a window to the brain [10]. OCT is an imaging technique that uses low coherence light sources to produce high-resolution cross-sectional images, which permits the quantification of the thickness of the retinal nerve fibre layer (RNFL) to the level of microns [10,11]. Although several OCT studies have evaluated RNFL thickness for patients taking antiepileptic drugs [12–14], only one study has explored the relationship between OCT parameters and photosensitivity in patients with GGE [15]. However, that study did not use a healthy control group.

In this study, we compared the peripapillary RNFL between GGE patients and healthy people by using spectral-domain OCT (SD-OCT). As the development of the eye and brain is linked (the retina appears as

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an outpocketing of the neuroepithelium), we hypothesized that compared to healthy participants, GGE patients could show microstructural differences in peripapillary RNFL.

2. Methods

2.1. Experimental design

Twenty-six adult patients with GGE (20 females, six males, mean age 36.1 years (SD 10.9)) and 26 age- and sex-matched healthy controls (20 females, six males, mean age 36.8 years (SD 10.6)) were included in this prospective observational study. Patients with GGE were consecutively recruited from the epilepsy clinic of a tertiary hospital. One control subject was matched individually to each case by age and sex. The age range of the case match was ± 0–2 years. Healthy subjects had no history of eye or neurological diseases. All participants were Caucasian.

A diagnosis of GGE was made according to electroclinical criteria [2]. Type of seizures were absences, myoclonic jerks, or generalized tonic-clonic seizures. Juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy (JME), and epilepsy with generalized tonic-clonic seizures only (GTCS) are well-recognized sub-syndromes of adult GGE, according to age of seizure onset and predominant seizure semiology [2]. Only patients with this well-recognized and common subgroup of GGE were selected. All patients had a normal MRI and at least one abnormal EEG (generalized spike-wave discharges of 3–6 Hz on an otherwise normal background). Developmental and neurological abnormalities, focal seizures, and abnormal MRI (e.g., atrophy, brain damage, cortical dysplasia) were considered exclusion criteria. An additional criterion for selecting participants was an age between 18 and 60 years.

Each participant underwent a standard ophthalmological examination, including determination of refractive error, best corrected visual acuity, funduscopy, and noncontact tonometry. Neither electroretinogram nor visual field testing was performed. As a result of the examination, it was established that the exclusion criteria were met by those with any ocular abnormality. The cut-off for exclusion based on refraction refractive error was ± 5 dioptres.

The approval of the Ethics Committee was granted, and the research study was performed according to the Declaration of Helsinki. Following verbal and written explanation of the experimental protocol, all participants gave their written consent.

2.2. Optical coherence tomography

The nine-point advised protocol for OCT study terminology and elements (Advised Protocol for OCT Study Terminology and Elements [APOSTEL]) recommendation [16] was applied for the study design.

SD-OCT imaging was performed using a Topcon 3D OCT-1 Maestro (firmware version 1.27, Topcon Medical Systems Tokyo, Japan). The instrument captures 50,000 axial scans per second, with a fully automated “alignment, focus, and capture” procedure. The device simultaneously captures the macula and optic nerve head areas, giving both a digital fundus image and a 12 × 9 mm automated segmentation OCT scan (“wide scan” setting). The device produces a 20 µm lateral and 6 µm axial resolution (Topcon; http://www.topconmedical.com/products/3doct1 maestro-literature.htm). SD-OCT imaging was carried out by the same examiners (F.J.P., I.R.M., and P.N.C.) during the morning in a dark room and under the following settings: 3D Wide Scan (12 x 9 mm) and 3D Macula. The RFNL thickness in each of the 90° quadrants (i.e., superior, inferior, temporal, and nasal) around the optic disc (Fig. 1) of both left and right eyes was calculated automatically by the device software (Appendix 1). The analysis report also provides a description of which percentile (≤95th to > 5th, normal; ≤5th to > 1st, borderline; and < 1st, abnormal) the RNFL thickness falls into, based on the manufacturer’s database of age-corrected normal values.

The following parameters, also measured automatically by the OCT software, were obtained for each eye: central retinal thickness, central macular thickness, and macular RNFL thickness in each of the 90° quadrants. Scans were assessed for quality, and they were excluded if they were off-centre, had significant movement artefacts, or had an image quality value (IQV) below 30. The IQV is machine generated and is unrelated to decentration. Values of 30 or above reflect a good quality scan.

Both eyes were examined for each patient and control subject. The right eye was imaged first, and the scan was repeated for the left eye. We were successful in obtaining scans for both eyes without mydriasis for all participants.

2.3. Statistical testing

Statistical analysis was performed with STATA, version 14.2 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP). All variables were expressed as the mean and standard deviation. Each eye was compared independently for each group. Data were tested for normality and homogeneity of variances. The paired *t*-test was used to compare the groups.

Then, only the group of people with epilepsy was analysed. To identify the independent predictors (i.e., duration of epilepsy, number of FAEs, treatment with VPA for more than two years, and current treatment with VPA) of RNFL changes, we considered peripapillary RNFL thickness (four models, all quadrants) the dependent variable in a multivariate linear regression model.

For all tests, $p < 0.05$ was considered statistically significant.

3. Results

The clinical details of the 26 patients are summarized in Table 1. The best-corrected visual acuities, anterior and posterior segment examinations, intraocular pressure, and pupillary light reflexes were normal for both eyes of all participants. None of the eyes were excluded because of unreliable SD-OCT scans.

The average RNFL thickness was significantly thinner in GGE patients [98.61 µm (10.15)] than in healthy controls [104.77 µm (7.57), ($p = 0.016$)]. Similar results were obtained for the left eye (Table 2).

The RFNL thickness of all quadrants was lower in GGE patients than in healthy controls, but it was only significantly different in the superior and inferior quadrants (Table 3) for both eyes. Neither the patients nor the controls showed abnormal RNFL thinning (i.e., < 1st percentile) in each of the 90° quadrants (superior, nasal, inferior, and temporal) around the optic disk.

Twenty-three patients (88.5%) were seizure free (for generalized tonic-clonic seizures) during the 12 months before OCT. With respect to AED prescriptions, 11 patients (42.3%) were taking valproic acid (VPA) at the time of the study (four for monotherapy; seven for combination therapy). Seven patients (26.9%) had never taken VPA. None of the patients had taken vigabatrin. The number of AEDs being taken, treatment with VPA for more than two years, taking VPA and time since diagnosis were not associated with the peripapillary RFNL thickness of all quadrants for GGE patients.

The central retinal thickness, central macular thickness, and macular RNFL thickness in all four quadrants were similar between the groups ($p > 0.05$) for both eyes.

4. Discussion

The present study explores the pattern of peripapillary RNFL thickness in a well-defined group of GGE patients by using SD-OCT. Compared to healthy controls, GGE patients showed a reduction in peripapillary RNFL thickness in both eyes that was mainly localized to the superior and inferior quadrants. The average RFNL thickness was also significantly lower in both eyes for GGE patients. To the best of our

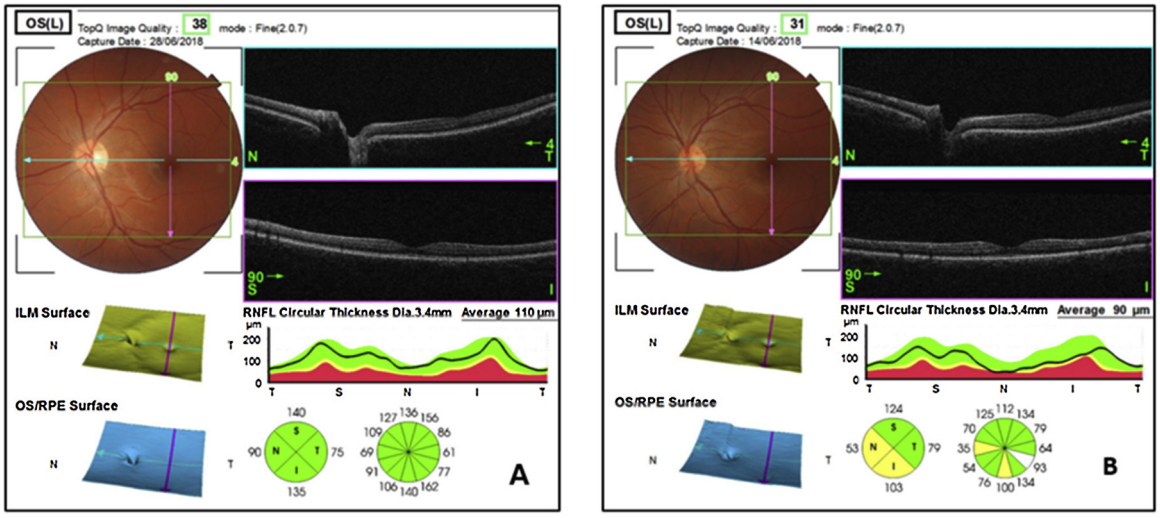

Fig. 1. Left-eye sample optical coherence tomography of peripapillary retinal nerve fibre layer (RNFL) thickness.
Left-eye sample optical coherence tomography of peripapillary RNFL thickness was taken from a healthy control (A), showing normal RNFL thickness with an average RNFL thickness of 110 µm, and GGE patient (B) with an average RNFL thickness of 90 µm. The RNFL thickness in the nasal and inferior quadrants is shown in yellow, as the measurements fall between the 5th and the 1 st percentile of the normal distribution percentiles provided by the manufacturer's internal database.
The RNFL thickness in each of the 90° quadrants is shown in green, as the measurements fall within the ≤95th to ≥5th percentile of the normal distribution percentiles provided by the manufacturer's internal database. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

knowledge, this study is the first to investigate microstructural differences in the RNFL for GGE patients.

Dereci et al. investigated peripapillary RNFL thickness with OCT in children with epilepsy receiving valproic acid monotherapy. The average peripapillary RNFL thickness (91.6 µm ± 9.7 vs. 95.5 µm ± 7.4; p = 0.047) and superior peripapillary RNFL thickness (112.0 µm ± 13.2 vs. 120.0 µm ± 14.7; p = 0.021) were thinner in patients with epilepsy who were receiving VPA than in healthy controls [12]. Although these results were found in children and were attributed to VPA, we found similar results in adult patients diagnosed with GGE. However, less than half of the adult patients diagnosed with GGE were under treatment with VPA, and one-fourth of the patients had never taken VPA. Valproic acid is one of the treatments of choice for GGE [17]. Whether all or almost all of those children taking VPA had been diagnosed with GGE could be questioned. Conversely, Lobefalo et al. showed no alterations in RNFL thickness parameters after one year of treatment with valproic acid and carbamazepine monotherapy for patients with partial and generalized cryptogenic epilepsy [13]. To our

Table 1
Age, sex, and clinical details of the 26 epilepsy patients.

Patient ID.	Age (Years)	Sex	Syndrome	Disease duration (months)	Last generalized tonic-clonic seizure (months)	AEDs (mg/d)
1	20	Male	JME	22	12	VPA 800mg
2[a]	37	Female	JME	240	181	TPM 400mg
3	24	Male	JME	120	48	VPA 300 mg + TPM 200 mg
4	46	Female	GTCS	228	23	LTG 300 mg
5	18	Female	JME	72	49	LTG 200 mg
6	41	Female	GTCS	300	243	LTG 450mg
7	45	Female	GTCS	216	6	VPA 500mg
8[a]	18	Female	JME	27	18	TPM 100 mg + LEV 2000 mg
9	36	Female	JME	279	4	LEV 3000 mg + VPA 500mg
10	44	Male	JME	276	1	LEV 3000 mg + ZNS 400mg
11	50	Female	GTCS	492	120	VPA 1000 mg
12[a]	35	Female	GTCS	228	24	LEV 1000 mg
13	56	Female	GTCS	564	120	VPA 1000 mg
14[a]	50	Female	GTCS	182	63	LEV 1000 mg
15[a]	18	Female	JAE	180	22	LEV 1500mg
16	34	Female	GTCS	321	26	LTG 200 mg + ZNS 300 mg
17	29	Female	JAE	204	48	VPA 2000 mg + ZNS 500mg
18	44	Female	JME	372	72	VPA 1000 mg + TPM 400mg
19	45	Female	JAE	336	156	LEV 1000 mg
20	23	Female	JME	122	47	ZNS 300 mg
21	37	Female	JAE	348	46	TPM 200 mg
22[a]	44	Male	GTCS	396	120	PHT 300 mg + LEV 2000 mg
23	31	Male	GTCS	180	156	VPA 1000 mg + CBZ 400mg
24	45	Female	GTCs	324	45	VPA 1000 mg + LTG 400mg
25[a]	33	Female	JME	180	168	LTG 150mg
26	36	Male	JME	216	2	VPA 2000 mg + LEV 2000 mg

Abbreviations: GTCA (Generalized Tonic-Clonic Seizures Only), JAE (Juvenile Absence Epilepsy), JME (Juvenile Myoclonic Epilepsy), AED (Antiepileptic Drug) VPA (Valproate), LEV (Levetiracetam), TPM (Topiramate), LTG (Lamotrigine), ZNS (Zonisamide), CLZ (Clonazepam), CBZ (Carbamazepine), PHT (Phenytoin).:
[a] Patient who has never taken Valproate.

Table 2
Average peripapillary RFNL thickness.

	Control subjects N = 26	GGE patients N = 26	Difference CI	*p* Value
Left **average pRFNL** (μm)	106.15 (SD 7.50)	99.73 (SD 9.75)	1.58 to 11.27	0.014*
Right **average pRFNL** (μm)	104.77 (SD 7.57)	98.61 (SD 10.15)	1.18 to 11.15	0.016*

Mean (SD) value of the average peripapillary RFNL thickness (μm) for each of the 90° quadrants of the control and patient groups. Confidence Intervals for the Difference in Means (Difference CI). Significance of difference *t*-test, p value.
* Statistically significant data.

best knowledge, except for vigabatrin-associated visual field loss [14], no other studies have demonstrated RNFL thinning for people exposed to antiepileptic drugs. In this study, for average RNFL thickness across all quadrants, 38% of patients showed abnormal RNFL thinning (i.e., < 1st percentile) [14], while GGE patients did not show abnormal RNFL thinning.

Balestrini et al. showed a significantly thinner RNFL for individuals with epilepsy (not exposed to vigabatrin) than for healthy participants. A total of 454 people with epilepsy were consecutively assessed in this cross-sectional cohort study [18]. The seizure or epilepsy type and the aetiology or associated neurological comorbidity were not taken into account. This study concluded that RNFL thinning was associated with a longer duration of epilepsy, the presence of drug resistance, and intellectual disability [18]. Since we did not include people with all types of epilepsy but rather a homogenous group of patients with GGE without intellectual disability or drug resistance, our findings did not allow us to reach the same conclusions. Although it was not the purpose of our study, we did not find an association between peripapillary RNFL thickness (in any quadrants) and the number of AEDs, the time since diagnosis, or whether patients were taking VPA or not taking VPA.

In the subset of patients studied by Balestrini et al. with an available MRI scan (38% had abnormal MRI), the authors demonstrated that the brain parenchymal fraction (brain atrophy can be described in terms of a decrease) showed a direct linear association with the average RNFL thickness [18]. In a similar study, Tak et al. also recently showed thinning RNFL in patients with epilepsy. Although the authors did not find an association between disease duration, seizure frequency, or antiepileptic treatment, they considered that these data might indicate neurodegeneration [19]. However, whether RNFL thinning in epilepsy reflects neurodegeneration could be demonstrated only in a longitudinal study with quantification of progressive RNFL thinning as a function of time [20]. As expected in GGE [2], the patients in our study showed no structural lesions or atrophy with conventional MRI. As RNFL thinning has been shown in a wide spectrum of neurological conditions and is reduced among patients with the greatest degrees of brain atrophy [10,21,22], the study of a heterogeneous group of patients with epilepsy without considering the underlying aetiology or epilepsy type could result in questions regarding the assumption of causality.

Gomceli et al. studied patients with JME and compared patients with the photoparoxysmal response (PPR) and those without the PPR with regard to EEG measurements. The authors found that the peripapillary RFNL thickness of the superior quadrants in the right and the left eyes was significantly higher in the first group. These authors concluded that microstructural differences in the optic nerve fibre layer may be a consequence or cause of photosensitivity [15]. Although there are differences in image acquisition and processing methods, their results are similar to our findings for GGE patients (e.g., average RFNL thickness: 94.65 μm ± 10.92 and 87.96 μm ± 7.60 for those with and without PPR, respectively). However, the authors did not use a control group [15].

The average peripapillary RFNL thickness in our control group was consistent with the reported normal reference measurements from the Topcon 3D OCT-1 Maestro (average RFNL: 104.72 μm ± 11.829) [23].

Based on these data, we speculate that the reduction in peripapillary RNFL thickness in our patients does not reflect a pathological process affecting the visual pathway as a consequence of treatment or long-lasting epilepsy but microstructural differences such as those found in thalamic structures in GGE patients [3–8].

Although its heredity is not well defined [1], genetic studies for large families with GGE have identified mutations in some neurotransmitter receptor genes, such as *GABRG2* and *GABRA1* [24–26]. Recently, an exome-based case-control study suggested that disruptive and rare variants in genes encoding GABA-A receptor subunits could increase the risk of GGE [27]. Apart from loss of function, there is evidence that mutations in GABA receptors might also be associated with abnormal development of neuronal networks, which could be one of the critical mechanisms leading to GGE [9]. During brain development, GABA acts as an excitatory neurotransmitter, playing a key role in various aspects of the maturation process, such as neuronal migration [28].

Morphometric MRI studies have shown subtle grey matter abnormalities in the thalamus and frontal cortex in GGE patients [5]. Although there is some variance across the studies, thalamic volume

Table 3
Peripapillary RFNL thickness (μm) in each of the 90° quadrants around the optic disk.

Quadrants	Control subjects N = 26	GGE patients N = 26	Difference CI	*p* Value
Superior (μm)				
Left	132.04 (SD 15.37)	120.08 (SD 16.99)	2.94 to 20.99	0.010*
Right	132.38 (SD 15.88)	120.42 (SD 15.88)	3.10 to 20.82	0.009*
Inferior (μm)				
Left	135.50 (SD 11.14)	127.31 (SD 16.47)	0.36 to 16.03	0.041*
Right	134.38 (SD 12.19)	125.54 (SD 15.04)	1.22 to 16.47	0.024*
Temporal (μm)				
Left	78.92 (SD 11.42)	74.96 (SD 8.92)	−1.746 to 9.669	0.170
Right	75.35 (SD 11.92)	72.73 (SD 15.27)	−5.016 to 10.247	0.494
Nasal (μm)				
Left	72.62 (SD 13.71)	72.08 (SD 14.75)	−7.393 to 8.470	0.892
Right	82.50 (SD 14.58)	80.23 (SD 19.92)	−7.456 to 11.994	0.641

Mean (SD) value of the peripapillary RFNL thickness (μm) in each of the 90° quadrants around the optic disk of control subjects and GGE patients. Confidence Intervals for the Difference in Means (Difference CI). Significance of difference *t*-test, p value.
* Statistically significant data.

loss seems to be consistently documented [4,7]. It is important to note that reduced grey matter volume in the thalamus has been documented at the initial onset of GGE in AED-naive patients, suggesting that thalamic structural abnormalities could be an intrinsic feature of GGE and not a consequence of AEDs or disease duration [8]. Moreover, high-field proton magnetic resonance spectroscopy (1H MRS) showed a decrease in NAA [29,30] and GABA in the thalamus in GGE, which suggests a reduction in GABAergic neurons [31].

Other genes associated with GGE, such as Myoclonin1/ EFHC1 microtubule-associated protein and intestinal-cell kinase, are involved in cell division and radial migration during brain development [32–34].

The patterns of activity and genetic programmes that interact to specify the composition and organization of developing neural circuits, mainly through the excitatory action of GABA, have been extensively studied in the developing retina [35,36]. Indeed, Chabrol et al. showed that disrupting GABAergic signalling in the developing retina has profound effects on retinal ganglion cell (RGC) dendritic growth [37]. The RGCs are the output neurons of the retina, and their axons travel through the RNFL. The issue of mutations previously described in GGE that could influence the organization and composition of inhibitory neural circuits during development [9,38], modifying not only the thalamocortical network connections [9,31] but also RGCs, opens new and interesting lines of inquiry.

Although the fundamental pathogenesis and the neuroanatomical correlates of GGE are not fully elucidated, taking into consideration previous observations, we believe that our findings could indicate that microstructural differences may be not limited to the neural networks involved in the pathophysiology.

Several limitations of the present study should be noted. First, the study consisted of a small sample size, which prevents further generalization of the conclusions. Second, the possible effects of VPA or other AEDs on RFNL thickness could not be entirely discounted. However, to our knowledge, there is no robust evidence that the use of AEDs (except vigabatrin) affects RFNL thickness [13,14]. Future prospective studies, including those regarding AED-naïve, newly diagnosed GGE patients, would provide a hint to disentangle whether peripapillary RFNL thinning could be an underlying structural disease feature and not the consequence of AED treatment or longstanding seizures. Finally, we did not compare GGE patients with focal onset epilepsy patients, so the conclusions from the previous much larger study [18] that included patients with longer durations of epilepsy with prolonged treatment, cortical atrophy, and cognitive impairment cannot be evaluated or excluded in this small study.

Regarding this study, we assumed that peripapillary RFNL thickness may be a shared feature between GGE sub-syndromes, but we consider that future studies could explore the potential differences between EAJ, EMJ, and GTCS.

In conclusion, we present the first OCT findings in GGE patients. We have shown that peripapillary RNFL thickness measurements in the average, superior, and inferior quadrants in both eyes of GGE patients were significantly lower than those of healthy controls. These microstructural findings might be an intrinsic feature of GGE. As OCT is a highly repeatable, easily quantifiable, and objective technique, a larger group of patients can ultimately confirm our data.

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Data availability

Anonymized data will be shared on request from any qualified investigator.

Declaration of Competing Interest

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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