RESEARCH PAPER

Retinal nerve fibre layer thinning is associated with drug resistance in epilepsy

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ABSTRACT

Objective Retinal nerve fibre layer (RNFL) thickness is related to the axonal anterior visual pathway and is considered a marker of overall white matter ‘integrity’. We hypothesised that RNFL changes would occur in people with epilepsy, independently of vigabatrin exposure, and be related to clinical characteristics of epilepsy.

Methods Three hundred people with epilepsy attending specialist clinics and 90 healthy controls were included in this cross-sectional cohort study. RNFL imaging was performed using spectral-domain optical coherence tomography (OCT). Drug resistance was defined as failure of adequate trials of two antiepileptic drugs to achieve sustained seizure freedom.

Results The average RNFL thickness and the thickness of each of the 90° quadrants were significantly thinner in people with epilepsy than healthy controls (p<0.001, t test). In a multivariate logistic regression model, drug resistance was the only significant predictor of abnormal RNFL thinning (OR=2.09, 95% CI 1.09 to 4.01, p=0.03). Duration of epilepsy (coefficient −0.16, p=0.004) and presence of intellectual disability (coefficient −4.0, p=0.044) also showed a significant relationship with RNFL thinning in a multivariate linear regression model.

Conclusions Our results suggest that people with epilepsy with no previous exposure to vigabatrin have a significantly thinner RNFL than healthy participants. Drug resistance emerged as a significant independent predictor of RNFL borderline attenuation or abnormal thinning in a logistic regression model. As this is easily assessed by OCT, RNFL thickness might be used to better understand the mechanisms underlying drug resistance, and possibly severity. Longitudinal studies are needed to confirm our findings.

INTRODUCTION

The retinal nerve fibre layer (RNFL) contains glia and the unmyelinated axons of retinal ganglion cells. As retinal axons are devoid of myelin until they penetrate the lamina cribrosa, the evaluation of RNFL thickness has been suggested as a method of assessing axonal ‘integrity’ in the anterior visual pathway and the white matter tracts throughout the central nervous system.1 Optical coherence tomography (OCT) is a reproducible and non-invasive technique for cross-sectional imaging of retinal microstructure and has enabled high-resolution quantification of RNFL thickness. OCT has been successfully used to evaluate axonal injury and disease progression in a number of neurological conditions.2 In epilepsy, we previously reported a strong linear relationship between RNFL thickness and visual field size in people with a history of vigabatrin exposure.3 Only one other study has explored RNFL and macular thickness in epilepsy, in adolescents with newly diagnosed epilepsy before and during monotherapy with either valproic acid or carbamazepine over 1 year duration: no difference was detected.4 Widespread white matter involvement has already been shown in epileptogenesis,5 and in seizure-related degeneration associated with progressive cognitive decline in epilepsy.6 Diffusion tensor imaging and volumetric MRI have demonstrated abnormalities in white matter integrity in people with temporal lobe epilepsy.7–9 Widespread neuronal degeneration is also seen in chronic human epilepsy,10 and in most animal models of focal epileptogenesis in the immature and adult brain,11 suggesting the existence of a disordered ‘connectome’.12 We postulated that there are common biological mechanisms leading to both neuronal degeneration and RNFL changes in people with epilepsy. We therefore hypothesised that RNFL thinning would occur in epilepsy, independent of previous vigabatrin treatment, and would be associated with clinical and neuroradiological features of epilepsy.

METHODS

Participants

Four hundred and fifty-four people with epilepsy able to undertake OCT were consecutively included in this cross-sectional cohort study. People were recruited from tertiary care clinics at the National Hospital for Neurology and Neurosurgery from September 2008 to August 2013. Demographic and clinical data were obtained from medical records. Participants were excluded from the analyses if they had previous exposure to vigabatrin, diabetes, glaucoma or other known ocular disease, concurrent diagnosis of multiple sclerosis, history of trauma or surgery to the eye or orbit, a distance refractive error of >4.50 dioptres mean sphere/ >2.5 dioptres cylinder, brain MRI evidence of visual pathway involvement (defined as damage to the optic nerve, chiasm or tract, to the lateral geniculate nucleus, to the optic radiations or to the primary or association visual cortices, of traumatic, vascular or inflammatory origin as determined by
clinical neuroradiological review). Ninety healthy control participants were recruited from May 2010 to August 2013; the controls also met relevant inclusion and exclusion criteria.

Clinical data
The following variables were evaluated: age, sex, ethnicity, epilepsy diagnosis,13 duration of epilepsy (from the time of OCT assessment), handedness, intellectual disability, antiepileptic drug (AED) history, epilepsy surgery, presence of VNS (vagus nerve stimulator, active or switched off). Intellectual disability was defined as an IQ<70 from a previous psychometric assessment, with onset under 18 years of age, or systematic mention (on at least two occasions) of ‘learning/intellectual disability’ or ‘mental retardation’ in the medical notes. Drug resistance was assessed at the time of OCT assessment and defined as previous failure of adequate trials of two tolerated, appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained, appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained, appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained, appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained, appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained, appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained, appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained, appropriately chosen and used AED schedules (whether as monotherapies or in combination) to 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t test). There was no difference in the distribution of RNFL thickness according to handedness (p=0.523, ANOVA), epilepsy type (p=0.219, ANOVA) or ethnicity (p=0.436, ANOVA).

Average RNFL thickness across all quadrants and exposure to AEDs or non-medical treatments

Average RNFL thinning was associated with exposure to the following individual AEDs (correlation analysis, uncorrected p values): ethosuximide, phenytoin, primidone, sodium valproate and topiramate. The effect of different AED combinations on RNFL thickness was not tested. The presence of VNS (either active or switched off) was also associated with thinner average RNFL thickness. Previous surgical treatment for epilepsy (n=31) was not associated with a significantly thinner RNFL (see online supplementary table S3). However, operated patients had thinner average RNFL (82.5 µm±15.7 SD) than healthy controls (95.3 µm±8.8 SD; p<0.001, t test). The interval between the surgical treatment to OCT scan was not significantly correlated with the RNFL thickness in this small sample of 31 operated cases (Pearson’s correlation coefficient −0.09; p=0.647). There was no significant correlation between the average RNFL thickness and the total number of AEDs taken (Pearson’s correlation coefficient −0.09; p=0.154). People with drug-resistant epilepsy had thinner average RNFL (84.2 µm±13.9 SD) than people with non-resistant epilepsy (88.1 µm±15.3 SD; p=0.038, t test), who in turn had thinner average RNFL than healthy controls (95.3 µm±8.8 SD; p=0.001, t test). A significant association between drug resistance and VNS implant (p=0.004, Pearson χ²) was found. In the drug-resistant group, there were more females (54.8%) than males (45.2%; p=0.042, Pearson χ²).

Predictors of RNFL thickness changes in multivariate regression models

Univariate linear regression analysis showed significant association between RNFL and: female sex, epilepsy duration, intellectual disability, exposure to ethosuximide, phenytoin, primidone, valproate or topiramate, VNS implant, and drug-resistant epilepsy. Multivariate linear regression showed significant association for RNFL thinning only with epilepsy duration, intellectual disability, drug resistance (adjusted R²=0.072, p<0.001; table 3) The residuals of the model were close to a normal distribution (0.37% low severe outliers, 0.00% high severe outliers; mean variance inflation factor 1.03).

Multivariate logistic regression analysis showed an increased probability of RNFL thinning (borderline or abnormal) in people with drug-resistant epilepsy (OR=2.09, CI 95% 1.09 to 4.01, p=0.027). A global test of goodness-of-fit indicated that the model fitted the data well (Hosmer and Lemeshow’s goodness-of-fit test, Pearson χ²=175.45, p=0.497). Neither multivariate

### Table 1 RNFL thickness, considered as continuous variable, in people with epilepsy and in healthy controls

<table>
<thead>
<tr>
<th>Average RNFL thickness, µm</th>
<th>People with epilepsy</th>
<th>Healthy controls</th>
<th>Significance of difference (t test), p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average RNFL thickness across all 4 quadrants, mean±SD</td>
<td>85.4±14.3</td>
<td>95.3±8.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Superior quadrant</td>
<td>103.4±22.4</td>
<td>115.3±10.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nasal quadrant</td>
<td>68.9±14.7</td>
<td>77.7±13.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inferior quadrant</td>
<td>107.8±24.1</td>
<td>122.8±14.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Temporal quadrant</td>
<td>61.4±13.6</td>
<td>65.2±10.2</td>
<td>0.016</td>
</tr>
</tbody>
</table>

RNFL, retinal nerve fibre layer.
MRI data, brain parenchymal fraction shows a direct linear relationship with disability. In the subset of people with epilepsy and available MRI data, the presence of drug resistance and intellectual disability was associated with longer disease duration. In healthy participants, RNFL thinning is associated with longer disease duration.

**DISCUSSION**

We demonstrate that individuals with epilepsy on treatment, but not exposed to vigabatrin, have a thinner RNFL thickness than healthy participants. RNFL thinning is associated with longer duration of epilepsy, presence of drug resistance and intellectual disability. In the subset of people with epilepsy and available MRI data, brain parenchymal fraction shows a direct linear association with the average RNFL thickness. Only drug resistance emerges as a significant independent predictor of borderline attenuation or abnormal thinning of the RNFL in a logistic regression model. People with drug-resistant epilepsy have a more than twofold odds of RNFL thinning compared with people with non-resistant epilepsy.

The biological mechanisms leading to the association between RNFL changes and intellectual disability, lower brain parenchymal fraction or drug resistance are unknown. Retina and brain share common embryonic origin and patterns of gene expression. A physical association between these two structures of neuroectodermal origin is also manifest through trans-synaptic degeneration, a process occurring when damage spreads from posterior to anterior visual pathway or vice versa, described in several central nervous system diseases, with neuronal damage caused by a focal brain lesion affecting the function and morphology of remote, apparently intact, regions following interruption of brain circuits. In people with temporal lobe epilepsy, trans-synaptic degeneration of the limbic system or extratemporal areas has been demonstrated using MRI, positron emission tomography and single-photon emission CT imaging. Widespread white and grey matter involvement has already been shown to occur in epilepsy. Evidence of trans-synaptic degeneration in the human central nervous system has already been shown in previous studies using OCT. These links may underpin the observed associations between RNFL thinning and various measures, structural (eg, brain parenchymal fraction) and functional (intellectual disability, drug resistance).

Several previous studies have suggested that RNFL thickness reflects cerebral axonal integrity. Given the association between RNFL thickness and brain parenchymal fraction (brain

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### Table 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>People with epilepsy</th>
<th>Healthy controls</th>
<th>Significance of difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>B (%)</td>
<td>A (%)</td>
</tr>
<tr>
<td>Average RNFL thickness, μm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superior quadrant</td>
<td>300</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nasal quadrant</td>
<td>297</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Inferior quadrant</td>
<td>297</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Temporal quadrant</td>
<td>297</td>
<td>0</td>
<td>0</td>
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</tbody>
</table>

*Comparison of normal versus borderline or abnormal values among the two groups (2×2 table). A, abnormal (<1st centile); B, borderline (≥5th to <1st centile); RNFL, retinal nerve fibre layer; N, normal (>5th centile).

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### Table 3

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate coefficient (95% CI)</th>
<th>Multivariate coefficient</th>
<th>VIF</th>
<th>t</th>
<th>p Value</th>
<th>95% CI</th>
</tr>
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<tbody>
<tr>
<td>Epilepsy duration</td>
<td>-0.16 (-0.27 to -0.06)</td>
<td>-0.17</td>
<td>1.04</td>
<td>-3.01</td>
<td>0.003</td>
<td>-0.27 to -0.06</td>
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<td>Intellectual disability</td>
<td>-4.49 (-8.38 to -0.59)</td>
<td>-3.95</td>
<td>1.03</td>
<td>-2.02</td>
<td>0.048</td>
<td>-7.87 to -0.04</td>
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<tr>
<td>Drug resistance</td>
<td>-6.07 (-9.69 to -2.46)</td>
<td>-4.89</td>
<td>1.01</td>
<td>-2.65</td>
<td>0.009</td>
<td>-8.52 to -1.25</td>
</tr>
<tr>
<td>Female sex</td>
<td>4.19 (0.98 to 7.41)</td>
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<tr>
<td>Ethosuximide exposure</td>
<td>-7.07 (-13.23 to -0.90)</td>
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<td>Phenytoin exposure</td>
<td>-4.58 (-8.00 to -1.16)</td>
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<tr>
<td>Primidone exposure</td>
<td>-8.68 (-15.66 to -1.69)</td>
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<tr>
<td>Sodium valproate exposure</td>
<td>-4.25 (-7.97 to -0.53)</td>
<td></td>
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<tr>
<td>Topiramate exposure</td>
<td>-4.45 (-7.74 to -1.17)</td>
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<tr>
<td>VNS implant</td>
<td>-11.07 (-17.64 to -4.51)</td>
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</table>

*Comparison of normal versus borderline or abnormal values among the two groups (2×2 table). A, abnormal (<1st centile); B, borderline (≥5th to <1st centile); RNFL, retinal nerve fibre layer; N, normal (>5th centile).
epiphyseal volume normalised for baseline differences among participants,\textsuperscript{25} in multiple sclerosis,\textsuperscript{23} independent of optic neuritis.\textsuperscript{24} RNFL thickness has been proposed as a marker of early neurodegenerative processes in multiple sclerosis. Shared neurodegenerative processes have also been demonstrated in a mouse model of Alzheimer’s disease, where $\beta$-amyloid immunoreactive plaques were detected in the retina.\textsuperscript{26} RNFL thinning has been shown in a wide spectrum of neurological and ophthalmological conditions, with a highly variable interval from an acute event or disease onset to thinning, ranging from months after an acute attack of acute angle closure glaucoma\textsuperscript{27} or optic neuritis\textsuperscript{28} to years as, for instance, in multiple sclerosis.\textsuperscript{29} Shared neurodegenerative processes may also be present in the epilepsies. We report, for the first time in epilepsy, a significant association between RNFL thinning and lower brain volume as assessed by brain MRI. This association was maintained after correcting for sex and duration of epilepsy. From our cross-sectional study, we cannot determine the reasons for lower brain parenchymal fraction, but RNFL thickness does seem to reflect this cerebral measure. A cross-sectional relationship may not yield the strongest correlations since brain atrophy may lag behind RNFL changes or vice versa. If this association was confirmed in future prospective studies, RNFL thickness could be advanced as a reliable, inexpensive and easily assessed complementary surrogate marker for exploration of whole-brain cerebral processes, such as potential neurodegenerative processes,\textsuperscript{30} in human epilepsy.

Seizures have a number of adverse consequences.\textsuperscript{30} Drug resistance is the label applied when seizures continue to occur despite treatment. In our analysis, drug resistance is the only independent predictor of a borderline or abnormal RNFL thickness. One possible explanation is that ongoing seizures cause cerebral damage that may manifest in lower brain parenchymal fraction and secondary thinning of RNFL. Longitudinal studies are now needed to verify this. There are alternative interpretations, such as the concept of ‘intrinsic epilepsy severity’, which holds that there are common neurobiological factors underlying both severity and drug resistance in epilepsy.\textsuperscript{31} Developing this theory, thinner RNFL, smaller brain parenchymal fraction and presence of intellectual disability might all be part of a more severe epilepsy condition from outset. Additional effects over time may further aggravate RNFL thinning. Prospective studies will be needed to disentangle these various possibilities.

Other associations with RNFL thinning were found: epilepsy duration, intellectual disability, VNS implant. Epilepsy duration showed a significant linear inverse relationship with RNFL thickness, though it did not predict abnormal or borderline RNFL thinning in the logistic multivariable model. Age at examination was also associated with RNFL thinning in the independent association analysis, but was excluded from the regression models because of high collinearity with epilepsy duration. A thinner average RNFL was found in people with epilepsy and intellectual disability than in people with epilepsy and normal intellectual function. The underlying cause of intellectual difficulties might also influence drug responsiveness. In our analysis, intellectual disability as a variable was extracted from medical record review and in most cases was confirmed by formal neuropsychometry. Intellectual disability present in children born prematurely has been attributed to injury to the cerebral white matter and associated neuronal and axonal abnormalities.\textsuperscript{32} However, considering RNFL thickness in children, its association with the development of the anterior chamber needs to be taken in account and a number of potential confounding factors have to be considered, including age, axial eyeball length and refractive status.\textsuperscript{33} In studies of individuals with multiple sclerosis, RNFL thinning was associated with cognitive disability.\textsuperscript{34} Similarly, in healthy young individuals, RNFL thickness was associated with level of cognitive functioning.\textsuperscript{35} The association of RNFL thinning with intellectual disability or cognitive impairment may therefore also reflect compromised white matter integrity.\textsuperscript{36} VNS implant was significantly related with RNFL thinning in the univariate linear regression model, probably due to high collinearity with drug-resistant epilepsy. Thinning seems unrelated to syndromic diagnosis, but this will need to be explored in a larger study testing RNFL thinning in specific epilepsy subtypes.

There are limitations to our study. A key caveat is the cross-sectional design, which cannot ascribe causation. Prospective studies are needed to evaluate the role of RNFL thickness as a possible biomarker and to tease out the effects of other factors, such as the frequency of seizures and the use of specific AEDs, some of which have been reported to influence brain volume or resilience to injury. We recognise that, using retrospective case note data not designed for such studies, the dichotomous classification into ‘drug-resistant’ and ‘non-resistant’ is an oversimplification in absolute terms, but we note that the total number of drugs tried by the two groups is significantly different in the expected direction, so that any oversimplification is unlikely to have a material impact on our findings. The study included fewer controls than cases, though cases and controls were well matched in terms of age, sex and ethnicity, which are the only non-pathological factors known to influence RNFL thickness. All data were also compared with a larger internal data set from normal individuals. We note also that while the total number of people studied was 300, this number included people with all types of epilepsy. Some syndromes may have a greater propensity for neurodegeneration and white matter volume loss, and possibly therefore also for RNFL thinning. Though we excluded participants with known glaucoma, we recognise that glaucoma might be asymptomatic or undiagnosed. Furthermore, individuals with intraocular pressure in the normal range might still have normal-tension glaucoma and RNFL thinning. All these issues will need further exploration in a larger cohort followed prospectively.

OCT is a fast, reproducible, non-invasive, well-tolerated and cost-efficient investigation. When compared with other potential methods for investigating resistance,\textsuperscript{16} OCT is not subject to temporal sampling issues like EEG, represents about 5% of the capital outlay of typical MRI, is much cheaper to run and can be undertaken and interpreted by easily trained operators. If confirmed in a prospective study, our findings might have clinical relevance. RNFL thickness might be considered as an objective, complementary and repeatable measure of the biology of drug resistance, and possibly disease severity. Furthermore, our results provide a basis for a better understanding of mechanisms underlying neurodegeneration in epilepsy.

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Contributors SMS and LMSC were involved in study concept and design. SB, APB, LMSC, KC, JN and AC were involved in data acquisition. BW, WMS, SB, LMSC, JWS and SMS were involved in analysis and data interpretation. GSB and SB were involved in statistical analysis. SB, APB and LMSC were involved in drafting of the manuscript. SMS, JWS and JA were involved in critical revision of the manuscript for important intellectual content. SMS was involved in study supervision.
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