Retinal nerve fibre layer thinning is associated with worse visual outcome following optic neuritis in children with relapsing demyelinating syndromes

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Word Count: 2396 Abstract: 193
Title: 131 characters
References: 29 Tables: 2 Figures: 2

Abstract

Background: Optic neuritis (ON) may be monophasic or occur as part of a relapsing demyelinating syndrome (RDS), such as MS, AQP4-Ab neuromyelitis optical spectrum disorder (NMOSD) or MOG-Ab-associated disease.

Methods: 42 children were retrospectively studied; 22 with MS (MS-ON) and 20 with Ab-associated demyelination (Ab-ON: MOG-Ab=16 and AQP4-Ab=4). Clinical and paraclinical features were analysed.

Results: Complete recovery of visual acuity (VA) was reported in 25/42 (60%) children; 8/38 (21%) suffered moderate or severe visual impairment (logMAR>0.5) in their worst eye, including 4/38 (11%) who were blind (logMAR>1.3) in their worst eye (2 MS, 2 AQP4-Ab NMOSD). None of the children with MOG-Ab were blind. Recurrence of ON was more common in the Ab-ON vs MS-ON group (15/20 vs 7/22, p=0.0068). RNFL thickness at baseline inversely correlated with total number of ON episodes (r=0.38, p=0.0062) and VA at final follow-up (r=-0.42, p=0.0023). There was no correlation between number of ON episodes and visual outcome.

Conclusion: In children with RDS, long-term visual impairment inversely correlated with RNFL thickness, but not with number of ON relapses. OCT may have a role in the assessment of children with ON to monitor disease activity and inform treatment decisions.

What this paper adds:

- 40% of children with relapsing demyelinating syndromes (RDS) suffer long-term visual impairment following optic neuritis (ON).
- Relapse of ON, occurring more frequently in the non-MS group, is not correlated with final visual outcome.
- Thinning of the retinal nerve fibre layer, as visualised by optical coherence tomography (OCT), is associated with worse visual outcome.
- OCT can be used alongside clinical parameters in children with RDS as an objective measure of neuroretinal loss.

Introduction

Optic neuritis (ON), defined as inflammation of one or both optic nerves in association with visual dysfunction, is one of the commonest presentations of acquired CNS demyelination in childhood, with an incidence of approximately 0.2 per 100,000[1]. Core deficits in visual acuity (VA), colour perception and visual field are commonly accompanied by ocular pain and headache[2]. 60-77% of children suffer severely decreased VA (worse than logMAR 1.0 or Snellen 20/200) in the acute phase[3-5]. ON may occur in isolation (idiopathic ON) or be associated with a relapsing demyelinating syndrome (RDS), such as multiple sclerosis (MS), aquaporin-4 antibody (AQP4-Ab) neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein (MOG) Ab-associated disease. Frequent involvement of the optic nerve in RDS may be due to the more permeable blood-brain barrier at the optic nerve compared to other CNS sites[6].

Optical coherence tomography (OCT) and electrodiagnostic tests can be useful paraclinical parameters in patients with optic neuritis[7]. OCT may detect structural retinal changes, such as retinal nerve fibre layer (RNFL) and ganglion cell layer thinning, and the development of microcystic macular oedema and retinal damage. OCT may help to differentiate between MS and NMOSD, with more severe retinal damage and hence greater RNFL thinning detected following optic neuritis in patients with AQP4-Ab NMOSD[8]. Studies carried out in adult cohorts have shown that RNFL thickness is reduced in both ON and non-ON eyes compared to healthy controls[9], and predicts visual function after ON[10], and disease activity[11] and disability[12] in MS.

Electrodiagnostic tests, particularly visual evoked potentials (VEP), may reveal loss of functional integrity in the optic pathway due to demyelination. VEP is a distinct measure of visual function from high-contrast VA (HCVA) and the two can be discrepant, especially in cases of optic atrophy. VEP correlates with other measures of visual function, such as contrast sensitivity and low contrast letter acuity. VEP can also be used to identify clinically silent ON[13]: a recent study of 24 patients with paediatric-onset MS detected prolonged VEP latency in 58% of ON eyes, but also in 55% of non-ON eyes, highlighting that subclinical involvement of the optic nerve is common in children with MS[14]. The prognostic value of both OCT and VEP in predicting future ON relapse and long-term visual outcome in children with RDS is yet to be evaluated.

Full recovery of HCVA occurs in the majority of children presenting with ON[2, 15], but subtle deficits may persist, particularly in low contrast and colour vision[2]. Furthermore, in a subset of patients with AQP4-Ab positive NMOSD and MOG-Ab-associated disease, frequent attacks are often associated with accumulating damage and functional impairment of vision, with severe impairment (functional blindness) in 18%[16] and 36%[17] of patients respectively. In adults, high-dose corticosteroid treatment hastens the recovery from acute ON[18], but does not influence final visual outcome or the risk of

subsequent MS[19]. Encouraging results from randomized-controlled trials of phenytoin[20] and erythropoietin[21] in ON suggest that neuroprotective agents, besides immunotherapy, may be of utility in acute demyelination and OCT may be used to provide outcome measures to test the efficacy of medications.

The aims of this study were to (1) test whether clinical, electrophysiological and microstructural parameters differ in MS-ON and Ab-ON; (2) identify the clinical and paraclinical characteristics of children suffering worse long-term visual outcome of RDS-ON; and (3) explore the relationship between RNFL thickness and clinical parameters in RDS-ON.

Patients and methods

Participants

Children presented to three UK & Ireland Childhood CNS Inflammatory Demyelination Working Group (UK-CID) centres: Great Ormond Street Hospital, Evelina London Children's Hospital, and Birmingham Children's Hospital. The diagnosis of RDS was defined as two or more episodes of acquired CNS demyelination lasting >24 hours, involving the optic nerve, brain or spinal cord, associated with T2 lesions on MRI. In this retrospective study, we included children with history of at least one episode of ON and the following RDS diagnoses: MS, AQP4-Ab NMOSD and MOG-Ab-associated demyelination. Patients with antibody-negative RDS were excluded. A diagnosis of ON was confirmed by an experienced neuro-ophthalmologist on the basis of history of reduced HCVA, red desaturation, pain with ocular movement, and/or visual field defect. Complete visual recovery was defined by normal HCVA, normal colour vision and normal visual fields.

All investigations were undertaken as part of the routine diagnostic protocols of participating centres. MR imaging of the brain and spinal cord was undertaken in all cases. Within 1 month of an acute demyelination event, clinically symptomatic children underwent testing for serum AQP4-Ab and MOG-Ab (not CSF), as part of routine assessments of children with demyelinating diseases, performed at the Clinical Neuroimmunology service at the Oxford Radcliffe Hospital Trust, using live cell-based assays[22, 23].

Assessments of visual function were carried out by ophthalmology departments at the three centres, including HCVA measured by the logarithm of the minimum angle of resolution (logMAR) and colour vision measured by Ishihara plates. Electrodiagnostic tests (EDT) methods for children have been described previously[24]. In brief, monocular VEPs were recorded from Oz referred to a mid-frontal electrode according to International Society for Clinical Electrophysiology of Vision (ISCEV) standards[25] and were acquired and analysed using a Espion E3 system (Diagnosys LLC, Cambridge UK). Pattern reversal and onset VEPs were produced by high contrast, black and white checks ranging in side length

from 400', 200',100', 50', 25',12.5' and 6.25', presented in a 30 degree stimulus field. Flash VEPs were produced in response to flash strength 4 from a hand held Grass strobe presented at 30cm from the patient. OCT was performed using the SPECTRALIS® system (Heidelberg Engineering Ltd. Hertfordshire, UK). The mean RNFL thickness was calculated across the inferior, superior, nasal and temporal segments.

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by Great Ormond Street Hospital Research and Development Department (reference: 16NC10).

Statistical analysis

Statistical analysis was performed using commercially available software GraphPad Prism 6 (GraphPad Software Inc) and R 3.3.2. As the AQP4-ON group comprised only four children, MOG-ON and AQP4-ON were combined together as antibody-associated ON (Ab-ON) for statistical analysis. To compare variables between MS-ON to Ab-ON, non-parametric statistical tests (Mann-Whitney tests) were used for continuous distributions, and Fisher's exact tests for nominal data. We explored the association between RNFL thickness and clinical parameters in all patients together using Spearman's rank correlation coefficient. Owing to the limited sample sizes, p-values were used sparingly, using an arbitrary level of 5% significance (two-tailed).

Results

Baseline characteristics and clinical features at presentation with ON

A total of 42 children (all under the age of 18 years) with a history of at least one episode of ON were identified. 22 patients had MS and 20 had Ab-positive ON (AQP4-Ab positive NMOSD = 4, MOG-Ab-associated disease = 16). Demographics and clinical features at onset of ON are summarised in Table 1. 20/42 (48%) children suffered severe visual impairment during the acute episode (logMAR >= 1.0, i.e. 20/200 or worse). The main differences between MS-ON and Ab-ON disease were older age at presentation in MS-ON (13 years MS-ON vs 8 years Ab-ON, $p<0.0001$), and more frequent finding of abnormal MRI brain in MS-ON than Ab-ON (21/22 (95%) MS-ON vs 2/20 (10%) Ab-ON ($p<0.0001$) (Table 1).

Clinical outcomes

Median length of follow up from first clinical presentation was 4 years (IQR 3-7). Clinical parameters at final follow up are summarised in Table 2a. Recurrence of ON was more common in the Ab-ON group compared to the MS-ON group (15/20 (75%) Ab-ON vs 7/22 (32%) MS-ON, $p=0.0068$); in particular, 13/16 (81%) MOG-Ab positive patients had recurrent ON. The total number of ON relapses was also

higher in Ab-ON children (median 1, range 0-10) compared to MS-ON (median 0, range 0-6) (p=0.029) (Figure 1a).

By the end of follow up, 71/84 (85%) eyes had been affected by clinically apparent episodes of optic neuritis; of these 63/71 (89%) had ophthalmology follow up assessments, at a median interval of 2.1 years (range 0.4-10.3). Median logMAR in eyes with a history of ON at final follow up was 0.02 (IQR 0.00-0.18) (Figure 1b). 12/42 (29%) children had persisting impairment of colour vision, defined as >1 error on Ishihara plate testing. Overall a complete functional recovery of vision occurred in 25/42 (60%) children; 8/38 (21%) had at least moderately impaired vision (logMAR>0.5) in their worst eye, including 4/38 (11%) who were blind (logMAR>1.3) in their worst eye. Children with AQP4-Ab were more likely to be blind in at least one eye than AQP4-Ab negative children (2/4 vs 2/34, p=0.043); none of the children with MOG-Ab were blind.

Electrophysiological outcomes

Electrodiagnostic tests (EDT), including VEP, were carried out in 24/42 children (57%); three were excluded as they were carried out during the acute phase of ON, leaving 21/42 children (50%) with EDT included in the study, performed at median 1.68 years interval after first presentation with ON (range 0.2-8.4). VEP was abnormal in 22/33 (67%) eyes with a clinical history of ON and 2/9 (22%) eyes without a history of ON. Electrophysiological parameters are summarised in Table 2a.

Microstructural outcomes

OCT was carried out in 31/42 (74%) children. Assessments were performed outside the acute phase of ON at a median 1.81 years interval after first presentation with ON (range 0.2-10.3). Retinal microstructural parameters are summarised in Table 2a. Abnormal RNFL thinning in >=1 segment was observed in 33/51 (64.7%) eyes with a history of ON and 1/11 (9%) eyes without a history of ON. Median RNFL thickness in ON eyes (averaged across all four segments) was 76µm (IQR 65.3-84µm) versus 100.8µm (IQR 89.3-107µm) in non-ON eyes (p=0.0002) (Table 2a). Serial OCT was performed in 9/31 (29%) cases (5 MOG-Ab, 4 MS) (Table 2b). The mean decline in RNFL (over a median interval of 1.88 years, range 0.31-3.48) was 2.06µm (±6.02 µm SD) (p=0.17, paired t test).

The Ab-ON group had a higher rate of optic nerve atrophy as determined by disc pallor compared to the MS-ON group (17/20 vs 12/22, p=0.047).

Correlation between RNFL thickness, number of relapses and final visual outcome

Among ON eyes there was an inverse correlation between mean RNFL thickness and visual impairment (logMAR) (r=-0.41, p=0.0081) (Figure 2b). There was no significant relationship between number of ON

episodes and mean RNFL (r=-0.18, p=0.3), nor any significant relationship between number of ON episdes and visual impairment (r=0.03, p=0.8).

Discussion

In this large cohort of children with RDS and ON, 48% of children had a non-MS phenotype; ON occurred more frequently in the antibody-mediated group compared to those with MS. Clinical characteristics at ON presentation such as pain, bilateral involvement and severity of acute visual loss did not differ between groups, and were similar to a historical cohort from the same three tertiary centres, comprising children with monophasic, idiopathic ON[3]. Although lacking statistical significance due to small numbers of patients with AQP4-Ab NMOSD, it is notable that 75% of AQP4-ON presented with bilateral involvement (compared to 36% of MS-ON), and 75% of AQP4-ON caused severe visual loss at nadir (compared to 45% of MS-ON). Interestingly, relapses of ON occurred more frequently in children with antibody-mediated disease, inkeeping with recent reports in adults in which patients with MOG-Ab were more likely to have multiple ON relapses[17, 26]. Nevertheless, complete visual recovery occurred in 56% of children with MOG-Ab in our cohort, and none were registered blind. HCVA at final follow up did not differ significantly between groups, although it is notable that children with AQP4-Ab NMOSD suffered worse visual recovery even after a single episode of ON, with 4 of the 7 worst eyes in the study belonging to patients with AQP4-Ab NMOSD, and 2/4 (50%) AQP4-ON patients registered blind at final follow up. We did not identify any significant decline in RNFL over time in those undergoing serial OCT, suggesting a severe first attack of ON may be the more important determinant of microstructural damage in RDS than subsequent relapses.

A key finding in this study was the absence of any correlation between number of relapses and visual outcome, alongside a significant correlation between RNFL thinning and worse visual outcome. We detected RNFL thinning on OCT in 56% of MS-ON eyes and 75% of Ab-ON eyes, similar to a recent study identifying RNFL thinning in 50% of children with MS and a history of ON[14]. OCT offers an opportunity to monitor disease activity and progression non-invasively; in adults with MS, RNFL thinning is a sensitive and specific predictor of clinical disease activity, independent of lesion accumulation on MRI brain[27]. However it is not yet part of routine clinical practice across all paediatric centers, and robust control data in healthy children remains limited, as is standardization of RNFL measurements, particularly in the acute phase of ON when swelling may complicate some automated RNFL measures. In this cohort RNFL did not differ significantly between groups, but RNFL thinning was associated with poorer visual outcome, in keeping with a previous study of paediatric RDS (Yeh et al Multiple Sclerosis 2009; 15: 802-810). In that study, which included children without any clinical episodes of ON, RNFL thinning was found to differ by number of ON episodes in the group analysis; in the present study, in which all children had >=1 clinical episode of ON, the lack of correlation observed between relapse rate and final visual outcome suggests that RNFL thinning (indicating pre-existing ganglion cell fibre loss)

may be a more sensitive parameter for monitoring disease activity and prompting treatment escalation than the relapse rate, in children with a clinical history of ON.

Our finding of clinically-silent disease by EDT – i.e. abnormal VEP in "non-ON" eyes – is consistent with previous reports[13, 14] and provides further support to the recent MAGNIMS recommendation that the inclusion of optic nerve disease identified clinically, radiologically or electrophysiologically would increase the sensitivity of dissemination-in-space criteria for MS[28]. There was a low rate of VEP normalisation in ON eyes across all groups, even in those with recovered HCVA; the time course of remyelination after ON has yet to be fully elucidated. Longitudinal analysis may be more informative in understanding the disease pathobiologies in the different groups.

A major limitation of our study is its retrospective nature, with inconsistent visual assessments, which were performed clinically and not as part of a research protocol. Low-contrast VA and symbol digit modalities were not routinely assessed at follow up and it is possible that some subtle functional impairment may have been missed[29]. The paucity of normative paediatric OCT data, especially longitudinally, should also be acknowledged. Additionally, our study design and the small numbers are not optimal for evaluation of treatment effect. Using electrodiagnostic tests we detected clinically silent disease in a proportion of children with MS, but not in antibody mediated ON, highlighting the need for further prospective studies with standardised longitudinal analysis of microstructural and electrophysiological parameters to increase our understanding of the disease pathobiologies. Nevertheless, this study shows that overall clinical relapse of ON does not adversely affect visual outcome in most children. As OCT correlates with final visual outcome, it may offer clinical utility as a tool in the assessment of children with ON; as an objective measure of neuroretinal loss in RDS; and as a surrogate endpoint to evaluate the benefit of neuroprotective agents.

Funding

This research is supported by the NIHR University College London Hospitals Biomedical Research Centre (OC) and the NIHR Great Ormond Street Hospital Biomedical Research Centre (YH, CH).

Figure legend

Figure 1: Clinical outcome of patients with optic neuritis. (A) Total number of ON relapses at final-follow up (median follow-up time 4 years) in Ab-ON and MS-ON cases. (B) High contrast visual acuity at final follow up in Ab-ON and MS-ON eyes. AQP4-Ab (square), MOG-Ab (circle), MS (triangle).

Figure 2: Correlation of retinal nerve fibre layer thickness (RNFL) with clinical parameters. (A) total number of clinical relapses (B) Correlation between mean RNFL thickness and visual impairment in ON eyes.

Table 1: Demographics and clinical features at initial presentation with ON

	AQP4-Ab positive NMOSD (n=4)	MOG-Ab associated disease (n=16)	**Ab-ON including AQP4-Ab and MOG-Ab cases) (n=20)**	**MS-ON (n=22)**	p-value*
Age at ON onset in years; median (IQR)	8.5 (5.25-12.25)	8 (6.75-9.25)	8 (6-10.25)	13 (11.75-14)	<0.0001
Sex (F:M, % female)	3:1 (75%)	9:7 (56%)	12:8 (60%)	14:8 (64%)	1.0
Ethnicity, Caucasian (%)	1/4 (25%)	10/16 (63%)	11/20 (55%)	6/22 (27%)	0.1
History of previous CNS demyelinating events (%)	2/4 (50%)	5/16 (31%)	7/20 (35%)	5/22 (23%)	0.5
Total number of previous CNS demyelinating events; median (range)	0.5 (0-1)	0 (0-2)	0 (0-2)	0 (0-4)	1.0
Painful ON	1/4 (25%)	9/16 (56%)	10/20 (50%)	10/22 (45%)	1.0
Bilateral ON	3/4 (75%)	9/16 (56%)	12/20 (60%)	8/22 (36%)	0.2
Several visual impairment at nadir (logMAR >= 1.0)	3/4 (75%)	7/16 (44%)	10/20 (50%)	10/22 (45%)	1.0
Abnormal MRI brain	1/4 (25%)	1/16 (6%)	2/20 (10%)	21/22 (95%)	<0.0001

Table 2a: Clinical, microstructural and electrophysiological outcomes

	AQP4-Ab positive NMOSD (n=4)	MOG-Ab-associated disease (n=16)	**Ab-ON (including AQP4-Ab and MOG-Ab cases) (n=20)**	**MS-ON (n=22)**	p-value*
Recurrence of ON (%)	2 (50%)	13 (81%)	15 (75%)	7 (32%)	0.0068
Total number of ON relapses; median (range)	0.5 (0-4)	1 (0-10)	1 (0-10)	0 (0-6)	0.029
Disc pallor when? Baseline?(%)	4 (100%)	13 (81%)	17 (85%)	12(55%)	0.047
Impaired colour vision in worst affected eye (Ishihara <17/17) (%)	1 (25%)	3 (19%)	4 (20%)	4 (18%)	1
High contrast visual acuity in worst affected eye, logMAR; median (IQR)	1.1 (0-2.2)	0.1 (0.02-0.11)	0.1 (0-0.21)	0 (0-0.23)	0.3
Complete functional recovery in both eyes (%)	2 (50%)	9 (56%)	11 (55%)	14 (64%)	0.8

At least moderately impaired vision (logMAR>0.5) in worst eye (%)	2 (50%)	2 (13%)	4 (20%)	4 (18%)	1
Blind (logMAR>1.3) in worst eye (%)	2 (50%)	0 (0%)	2 (10%)	2 (9%)	1
ON eyes	n=8	n=29	n=37	n=34	n/a
High contrast visual acuity, logMAR; median (IQR)	0.5 (0-1.81)	0.06 (0-0.1)	0.06 (0-0.21)	0.01 (0-0.17)	0.3
Abnormal RNFL thinning (%)	4/4 (100%)	14/20 (70%)	18/24 (75%)	15/27 (56%)	0.24
Mean RNFL thickness, μm; median (IQR)	-	73 (54.1-84.2)	73 (54.1-84.2)	78 (68.8-85.6)	0.3
Inferior RNFL thickness, μm; median (IQR)	-	99 (63-112.2)	99 (63-112.2)	99 (85.5-110.5)	0.44
Superior RNFL thickness, μm; median (IQR)	-	94.5 (73-108.3)	94.5 (73-108.3)	100 (91.5-109.5)	0.21
Nasal RNFL thickness, μm; median (IQR)	-	50 (42.3-64.3)	50 (42.3-64.3)	56 (50-63)	0.28
Temporal RNFL thickness, μm; median (IQR)	-	45.5 (39-50.8)	45.5 (39-50.8)	48 (37.5-60)	0.45
Abnormal VEP (%)	2/2 (100%)	7/13 (54%)	9/15 (60%)	13/18 (72%)	0.7
Non-ON eyes	n=0	n=3	n=3	n=10	n/a
High contrast visual acuity, logMAR; median (IQR)	-	0 (0-0.01)	0 (0-0.01)	0 (0-0)	n/a
Abnormal RNFL thinning (%)	-	0/2 (0%)	0/2 (0%)	1/9 (11%)	1
Mean RNFL thickness, μm; median (IQR)	-	110.9 (110.8-110.9)	110.9 (110.8-110.9)	95.5 (87.4-100.9)	n/a
Inferior RNFL thickness, μm; median (IQR)	-	153 (145-161)	153 (145-161)	119 (107-127.5)	n/a
Superior RNFL thickness, μm; median (IQR)	-	133.5 (125.3-141.8)	133.5 (125.3-141.8)	127 (115-132)	n/a
Nasal RNFL thickness, μm; median (IQR)	-	84.5 (83.8-85.2)	84.5 (83.8-85.2)	75 (63-77)	n/a
Temporal RNFL thickness, μm; median (IQR)	-	72.5 (71.8-73.3)	72.5 (71.8-73.3)	67 (60.5-68)	n/a
Abnormal VEP (%)	-	1/3 (33%)	1/3 (33%)	1/6 (17%)	1

Table 2b: Serial optical coherence tomography

	MOG-Ab-associated disease (n=5)	MS-ON (n=4)	p-value*
ON eyes	n=9	n=6	n/a
Abnormal RNFL thinning (%)	9/9 (100%)	4/6 (67%)	0.15
Mean RNFL thickness, μm; median (IQR)	65.3 (47.5-70.8)	76.8 (59.6-83.4)	0.14
Change in mean RNFL thickness from baseline, μm; mean (±SD)	-4.4 (±6.9)	-0.83 (±3)	
Non-ON eyes	n=1	n=2	n/a
Abnormal RNFL thinning (%)	0/1 (0%)	1/2 (50%)	n/a
Mean RNFL thickness, μm; median (IQR)	119.3	90.3 (88.5-92)	n/a
Change in mean RNFL thickness from baseline, μm; mean (±SD)	8.5	-0.3 (±2.1)	n/a

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Author disclosures

Michael Eyre, Aasim Hameed, Sukhvir Wright, Wallace Brownlee, Richard Bowman, Dorothy Thompson and Yael Hacohen have no disclosures. Olga Ciccarelli serves as a consultant for GE, Biogen Idec, and Novartis, and all the payments are made to the institution (Queen Square MS Centre, UCL Institute of Neurology, London, UK). Ming Lim receives research grants from Action Medical Research, DES society, GOSH charity, NIHR, MS Society, SPARKS charity and; receives research support grants from the London Clinical Research Network and Evelina Appeal; has received consultation fees from CSL Behring; received travel grants from Merck Serono; and awarded educational grants to organize meetings by Novartis, Biogen Idec, Merck Serono and Bayer, Evangeline Wassmer has received speaker honoraria and/or travel funding from Biogen, Teva, Genzyme, Shire, UCB, and Merck Serono. Cheryl Hemingway has received speaking honoraria from Biogen and Terumo, and an educational grant from Merck Serono, Biogen and Bayer.