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Memantine for axonal loss of optic neuritis

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Abstract
Background To determine the effect of memantine on axonal loss and visual function during the course of optic neuritis (ON).
Methods Sixty ON patients in a single-center, institutional setting were randomly assigned to the memantine or placebo groups. Patients with first attack of acute unilateral optic neuritis, with visual symptoms of 8 days' duration or less were enrolled in this trial. No patient had known multiple sclerosis, and none had taken immunomodulatory agent prior to or at the time of presentation. For all patients, the following characteristics were recorded and compared at initial presentation and 3 months afterward: visual acuity, retinal nerve fiber layer (RNFL) thickness, visual field parameters (mean deviation and pattern standard deviation), visual evoked potential, and contrast sensitivity.
Results Fifty-four patients completed the 3-month follow up. There were no significant differences between the placebo and memantine groups for any of the characteristics at initial presentation. After 3 months, the only statistically significant difference between the two groups was in RNFL thickness. Memantine group subjects had higher thickness in nasal (P=0.01), superior (P=0.006), inferior (P=0.01) quadrants and average (P=0.01). However, temporal quadrant thickness was not different between two groups (P=0.35).
Conclusion Memantine was effective in reduction of RNFL thinning, although this structural difference was not associated with improved visual function.

Keywords Optic neuritis · Optical coherence tomography · Retinal nerve fiber layer · Memantine

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Introduction

Optic neuritis (ON) is an acute inflammatory, demyelinating disease of the optic nerve which typically presents in young adult women. Despite its favorable prognosis, many patients with ON report decreased vision in the affected eye after recovery. Studies have demonstrated a 90% prevalence of disturbances in sense of light brightness, stereopsis, color vision, and visual field of recovered ON patients with at least 20/30 visual acuity [1]. During the course of ON, axonal loss occurs, leading to thinning of the nerve fiber layer and ultimately resulting in persistent disturbances in visual function [2]. Using the measurements of the optic nerve atrophy to infer axonal loss is unfortunately confounded by accompanying myelin loss. However, the axons of the retinal ganglion cells are unmyelinated in the RNFL, and reductions in its thickness are likely to relate more

directly to loss of ganglion cell axons. Axonal loss has been quantified using optical coherence tomography (OCT) in cross-sectional studies of patients with clinically isolated optic neuritis [2–6].

Some authors have suggested that measurement of RNFL thickness by OCT may be a better way than brain MRI to be used as an outcome in clinical trials for MS, because OCT is easy to obtain, and resolution of recent generation of OCT (spectral domain OCT) is far better than brain MRI when measuring axonal loss [7]. In addition, Henderson et al. [5] estimated sample sizes for clinical trials of neuroprotective agents in acute ON that use OCT-measured RNFL loss as the outcome measure.

Neuroprotection can be achieved by inhibition of apoptosis of retinal ganglion cells. Memantine, a N-methyl-D-aspartate (NMDA) receptor antagonist, has shown promising neuroprotective effects in neurodegenerative disorders such as Alzheimer's disease [8].

However, no previous study has considered the effect of memantine on visual function in ON patients. In this study, we compared the visual function in ON patients who received memantine vs placebo 3 months after the initial presentation of disease.

Subjects and methods

This is a single-center randomized, double-masked, placebo-controlled study. Patients with (1) age range of 18 to 46 years, (2) first attack of acute unilateral optic neuritis, with visual symptoms of 8 days' duration or less, and (3) a relative afferent pupillary defect, and pain with eye movement were referred (after advertising the study) to a tertiary neuro-ophthalmology center and enrolled in this trial. No patient had known multiple sclerosis, and none had taken an immunomodulatory agent prior to or at the time of presentation. No subject had other ocular pathology, or history of ocular surgery in either eye. We excluded subjects if they were pregnant or breastfeeding, or if they found to have autoimmune disease (based on clinical history of associated signs and symptoms). All patients were informed about the purpose of the study, and informed written consent was obtained. All of them were admitted, and received intravenous methylprednisolone (250 mg every 6 hours for 3 days) followed by oral prednisone (1 mg/kg) for 11 days [9]. After the admission, enrolled patients were randomly assigned to the memantine or placebo treatment groups. Randomization and blinding were coordinated through the hospital pharmacy's centralized service. This included computerized generation of the allocation sequence in random permuted blocks, and blinded disbursement of medication. The participants received drug and placebo in the form of capsules that were made in the same shape (University of Pharmacology). In the memantine group, subjects received each capsule containing memantine 5 mg for the first week and 10 mg for the next two weeks. Placebo group received oral placebo on the same schedule as the memantine group. Medication bottles were collected at the end of the study to document compliance. Best-corrected distance visual acuity (BCVA) was checked by Snellen's chart, and was recorded as the logarithm of the minimum angle of resolution (logMAR). Contrast sensitivity was determined by Mentor B-VAT II Video Acuity Tester (Mentor O&O Inc., Norwell, MA, USA). The contrast of the grating decreases from left to right in each spatial frequency (cycle per degree) tested. The patient was asked to identify the grating pattern in each column. If no grating pattern was visualized, then the patient reported both patches were blank. The contrast level of the last correct response was recorded as the contrast sensitivity in logarithmic values. Central 24-degree visual field was examined with Humphrey automated perimeter using the SITA 24–2 algorithm (Zeiss Meditech, Dublin, CA, USA). Wide-angle lenses were used to correct refractive errors when necessary. For each patient, we recorded mean deviation (MD) and pattern standard deviation (PSD). Visual fields were considered unreliable if the false-positives, false-negatives, and fixation loss indices exceeded 25%. Pattern visual evoked potential (VEP) was performed to 100 cm distance, on the optoelectronic stimulator Vision Monitor MonPack by Metrovision system (Pérenchies, France) using International Society for Clinical Electrophysiology of Vision (ISCEV) compliant protocol [10]. VEP was identified by a series of N75, P100, and N135 peaks, and then for each eye the mean value of the time-to-peak of P100 peaks (msec) from both cortical lobes was studied. Spectral domain OCT system (Cirrus; Carl Zeiss, Dublin, CA, USA) was used to obtain a circular 3.4 mm peripapillary scan centered on the optic nerve head. RNFL measurements were reported by quadrant, i.e., temporal, superior, nasal, inferior, and average. Scans with low quality and failing RNFL segmentation were excluded. Measurements were repeated until excellent quality (signal strength more than six out of ten) was achieved. RNFL values of the unaffected eye at baseline and follow-up were not provided because of funding problems. RNFL thickness and visual field were the primary measures of outcome. Visual acuity, contrast sensitivity, and VEP measures were secondary measures. Follow-up visits were scheduled on or about days 4, 15 and 30, and months 2 and 3. The data collected at the 3-month visit were the major measurement of visual outcome. At beginning and 3-month follow up, we took all the visual function measures we have already mentioned. The personnel assessing visual function were always unaware of whether the patient was assigned to the placebo or memantine group. Additional testing included fundus photograph and brain fluid-attenuated inversion recovery MRI. Each MRI scan was assessed at a reading center for changes consistent with inflammatory demyelination (brain plaques).

Table 1 Demographic and clinical characteristics of patients at study entry

Group	Patients, *n*	Mean age±SD	Female, *n*	Mean VA (Log MAR)±SD	Optic disc swollen, *n*	Presence of MRI lesions, *n*
Placebo	31	29.5±7.3	22	1.25±0.9	13	6
Memantine	29	26.4±6.5	25	1.38±0.9	9	5
P- value	_	0.1	0.1	0.5	0.3	0.3

SD: standard deviation, VA: visual acuity, MAR: minimum angle of resolution

Statistical analysis

The necessary sample size was projected to be 35 patients per group on the base of the following assumptions: loss of average RNFL in the placebo group at 3 months would be 30 μm, the expected reduction in RNFL loss by treatment would be 50%, the alpha error would be 0.05, and the power of the study would be 80 percent with a 10% dropout rate [5].

Summary statistics, including age, gender, presence of optic nerve swelling and brain MRI lesions, baseline and follow-up visual acuity, RNFL, visual field parameters, and VEP measures were compared between the two groups using the Chi-square test and *t*-test. *P*-value less than 0.05 was considered significant.

Results

Demographics and clinical characteristics

Seventy-five patients were assessed for study eligibility between December 2008 and December 2010. Eight patients were seen beyond 8 days. Two patients were found to have associated autoimmune process, two patients had multiple sclerosis [11], and two patients were pregnant. A total of sixty patients were enrolled, randomized, and allocated to placebo (*N*=31) and memantine (*N*=29) groups. Details of the patients' demographics and clinical characteristics at presentation are summarized in Table 1. There were no significant differences between the placebo and memantine groups for any of the characteristics in Table 1. Also, other baseline characteristics including visual acuity, RNFL thickness, visual field parameters, VEP latency, and contrast sensitivity between two groups were not statistically different (Tables 2, 3, 4 and 5).

Detailed patients' data and representative visual field, OCT, and VEP at baseline and after 3 months are shown in appendices A (1), A (2), and Figs. 1 and 2. Eight patients were lost to follow up. Twenty-six participants in each group completed the study, and compliance with the intervention was complete for all participants.The overall rate of missed visits among five follow-up visits was 5.5 %. During the 3-month period, no patient experienced a second clinical episode of demyelination [11].

Optical coherence tomography measurements

All patients underwent RNFL evaluations by OCT. No images were excluded from the final analysis due to poor image quality. The RNFL thickness findings are summarized in Table 2.

We found that 22 of 60 patients had anterior forms of neuritis, with an increase in RNFL thickness in the acute episode to 160.4±57 μm compared to 91.2±19.5 μm in retrobulbar optic neuritis. There were no significant differences for mean RNFL thickness of anterior ON patients between the placebo (159.5±66.5) and the memantine groups (161.7±43.4) at presentation (*t*-test, *P*=0.9).

Considering all patients, there were no significant differences in RNFL thickness measurements (nasal, temporal, superior, inferior quadrants and overall) between the two groups at initial presentation (Table 2).

As inflammation resolved, RNFL thickness decreased in both anterior and retrobulbar neuritis and mild to severe optic atrophy developed. At 3 months, mean RNFL thickness

Table 2 The mean and standard deviation (SD) of retinal nerve fiber layer (RNFL) thickness in the memantine and the placebo patients at presentation

RNFL quadrant	Nasal mean (SD) μm	Temporal mean(SD) μm	superior mean(SD) μm	Inferior mean(SD) μm	Overall mean(SD) μm
Placebo	92.4 (62.1)	76.6 (48.5)	153.1 (84.4)	144.2 (67.1)	115.7 (67.6)
Memantine	96.8 (43.7)	85.7 (42.0)	161.1 (77.1)	142.6 (50.7)	117.4 (42.0)
P-value †	0.7	0.6	0.7	0.9	0.8

†: *t*-test

Table 3 Retinal nerve fiber layer (RNFL) thickness findings in the memantine and the placebo patients after 3 months

RNFL quadrant	Nasal mean (SD) μm	Temporal mean (SD) μm	superior mean (SD) μm	Inferior mean (SD) μm	Overall mean (SD) μm
Placebo	60.9 (14.5)	53.7 (18.2)	95.2 (23.3)	93.5 (27.1)	78.9 (17.9)
Memantine	72.4 (16.7)	58.2 (14.7)	112.0 (15.5)	110.5 (16.1)	91.3 (16.3)
P-value †	0.01	0.35	0.006	0.01	0.01

†: *t*-test

decreased to 86±22.5 μm in anterior ON and to 84.3 ±15.4 μm in retrobulbar ON (*t*-test, $P=0.7$).

After 3 months, RNFL thickness (overall, nasal, and superior and inferior quadrants) in the memantine group was significantly more than that in the placebo group. No significant difference was observed in the temporal quadrant (Table 3).

Visual field

There were no statistically significant differences between MD and PSD at the initial presentation. At 3 months, the mean MD and PSD were −3.3±2.5 (mean±SD) dB and 2.6±1.8 dB in retrobulbar ON respectively. Corresponding measures were −3.0±2.0 and 2.4±0.9 in anterior ON. There were not any significant outcome differences in patients with and without disc swelling at presentation (*t*-test, $P=0.6$, $P=0.7$ respectively).

After 3 months, there were no statistical differences between two groups (Table 4).

Visual acuity

At 3 months, visual acuity was 0.23±0.37 (mean log MAR±SD) in retrobulbar ON, and 0.11±0.22 in anterior ON. There were no significant outcome differences in patients with and without disc swelling at presentation (*t*-test, $P=0.2$).

After 3 months, mean visual acuity (log MAR±SD) was 0.12±0.13 in the memantine group and 0.24 ±0.43 in the placebo group ($P=0.2$). There was no statistically significant difference in visual acuity improvement between the memantine (1.20±0.91 logMAR) and the placebo (1.1±0.82 1ogMAR) patients (*t*-test, $P=0.6$).

Contrast sensitivity

The mean and standard deviation of contrast sensitivity log values for patient eyes are shown in Table 5. There were no statistically significant differences in contrast sensitivity between these two groups after 3-month follow-up.

VEP

At baseline, mean time-to-peak of P100 of affected eyes was 138.50±16.54 msec compared to 122.77±13.32 msec of non-affected eyes (*t*-test, $P=0.000$). Mean baseline characteristics of the placebo group and the memantine group were 136.0±17.5 and 141.1±15.3 respectively ($P=0.2$). After 3 months, mean time-to-peak of P100 was not statistically different between the memantine (123.9±13.9) and the placebo patients (124.3±14.0) ($P=0.9$).

Discussion

Recent evidence supports the view that axonal degeneration may be a major determinant of neurological disability in patients with MS [12, 13]. Most studies have used time-domain OCT for quantifying retinal nerve axons, but high-resolution spectral domain OCT avoids artifacts caused by eye movement or poor fixation [14]. We found an average RNFL thickness of 78.9 μm in our placebo group with spectral domain OCT after 3 months. Mean time to 90% loss from initial values to the eventual RNFL thinning was 2.38 months in one study [5], and no further RNFL loss was observed 6 months after symptoms began [6]. Therefore, it seems 3-month follow-up with OCT in our study is reasonable for clinical trial of memantine.

Table 4 Mean "mean deviation" (MD) and "pattern standard deviation" (PSD) at initial presentation and after 3 months

Visual field parameters	Before intervention			After 3 months		
	Placebo	Memantine	*P value* †	Placebo	Memantine	*P value* †
MD (dB) mean±SD	−15.1±9	−11±9	0.2	−3.6±2.6	−2.8±2.01	0.2
PSD mean±SD	5.7±2.5	6.7±3.4	0.6	2.7±1.7	2.3±1.3	0.4

†: *t*-test

Table 5 The mean and standard deviation of contrast sensitivity at different frequency (cycle per degree: CPD) in two groups at initial presentation and after 3 months

Contrast sensitivity (log units)	Before intervention			After 3 months		
Spatial frequency (CPD)	Placebo	Memantine	*P value* †	Placebo	Memantine	*P value* †
4.8	5.5±2.8	4.8±1.7	0.3	17.3±10.5	20±11	0.5
7.5	5.0±2.7	4.5±1.6	0.5	12.1±6.4	15.5±7.4	0.1
9	3.7±1.7	3.3±1.3	0.4	9.4±5.1	10.8±4.9	0.2
12	3.0±1.7	2.7±1.3	0.3	6.8±2.6	8.1±2.7	0.1

†: *t*-test

Treatments that only aim at blocking the inflammatory component of the disease have not been successful at reducing neuronal loss [11]. For example, the early use of intravenous corticosteroids did not improve RNFL thickness [15]. Previous studies demonstrated that modalities, such as intravenous steroids, could induce short-term visual function recovery without an associated long-term benefit [9].

Memantine treatment reduced clinical deterioration in moderate-to-severe dementia [8].

However, two as-yet unpublished, randomized clinical trials of the neuroprotection of memantine in patients with open-angle glaucoma did not show significant efficacy with respect to their primary outcome measures [16]. This outcome is despite prior encouraging evidence from the studies which showed memantine treatment provided substantial protection against retinal ganglion cell death in animal models of glaucoma [17, 18]. NMDA receptors are also involved in the pathogenesis of experimental allergic encephalomyelitis

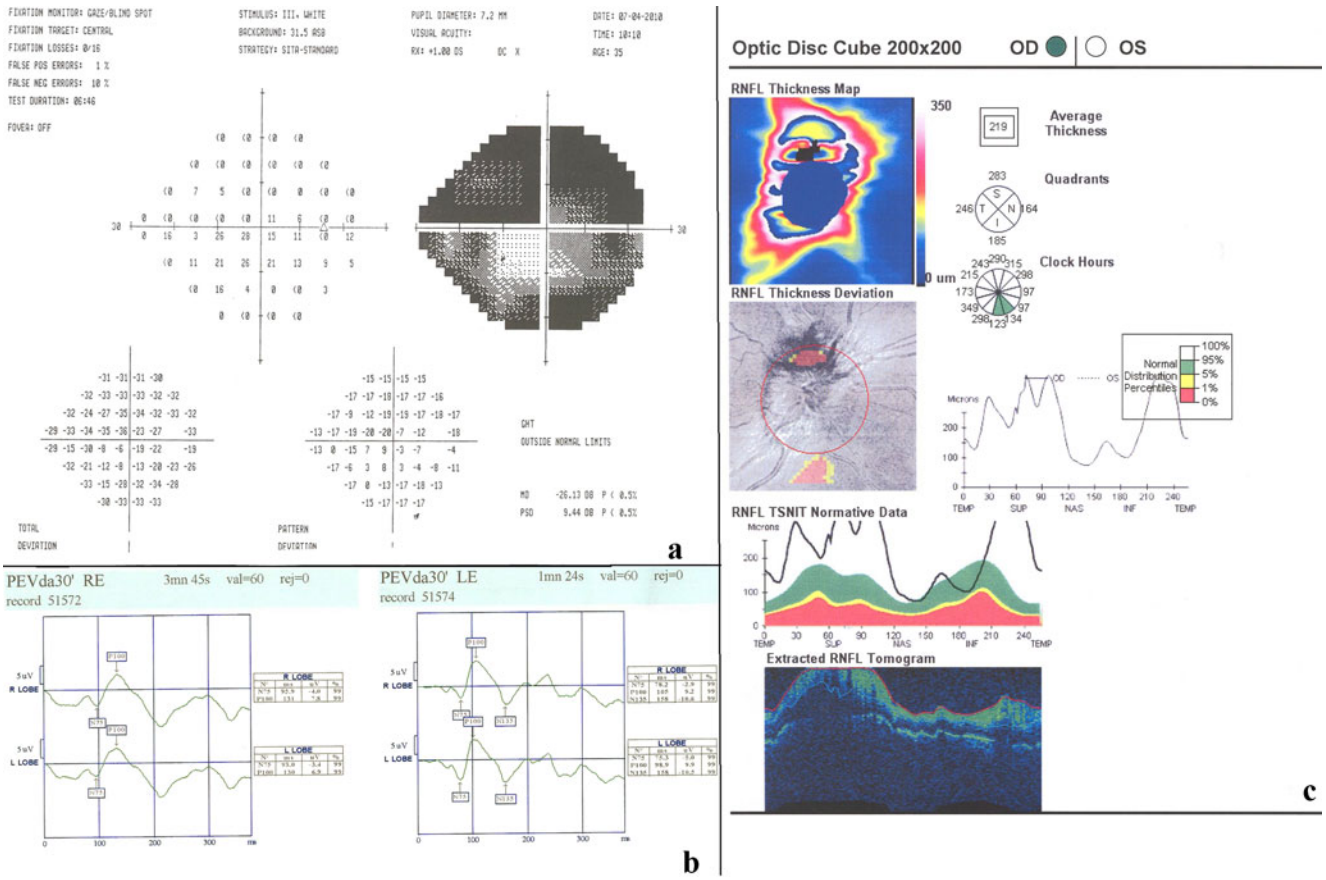

Fig. 1 A patient with right optic neuritis at presentation. **a** Humphrey perimeter showed generalized visual field defect, **b** visual evoked potential depicted abnormal delay of right eye P100 peak, and **c** OCT showed retinal nerve fiber layer thickening

(EAE) as an animal counterpart of MS, and memantine modulates certain aspects of neurological disease development in acute EAE [19]. Glutamate receptor antagonists are efficient in reducing axonal damage, death of oligodendrocytes, and in ameliorating clinical EAE [12, 20, 21]. In optic nerve, activation of the glutamate receptors acts as a negative regulator of the size of oligodendrocytes [22]. This evidence suggests the role played by glutamate and NMDA receptor in ON.

This study showed that RNFL thickness (overall, nasal, and superior and inferior quadrants) in the memantine group is significantly more than that in the placebo group. Bock et al. [23] showed the extent to which RNFL thinning varies across quadrants in ON eyes, and how the temporal peripapillary quadrant was more affected. This might explain why we did not find any benefit associated with the use of memantine in the temporal quadrant.

In addition, our study showed that memantine did not improve visual acuity, visual field, VEP parameters, and contrast sensitivity in patients with isolated ON. Prior studies have found RNFL loss to be correlated both to visual function, and interestingly, to disability scores composed of dysfunctions other than visual CNS dysfunctions [13, 24]. In addition, greater RNFL loss correlates with a less complete visual recovery, and one that is unlikely to show later improvement [2]. The reason why the anatomical changes did not result in improved visual functional outcome can be explained in several ways. First, we did not find any benefit in the temporal RNFL (corresponding to the papillomacular bundle), the area that shows robust correlation with visual acuity, visual field, and color vision deficit [25]. Maybe it is the lack of effect on temporal quadrant that explains this marked discrepancy. Second, visual acuity depends on the small area of fovea that comprises few RNFL from total RNFL we measured. Therefore, total RNFL might be protected without foveal-RNFL protection. Additionally, some parameters, such as VEP latency, are not associated with any OCT measures because the characteristics of demyelination that lead to greater VEP latency are not correlated with the degree of axonal loss [4]. Finally, our patients were only followed for up to 3 months. A longer follow-up period might demonstrate significant differences in visual functions, which may take time to materialize.

To the best of our knowledge, no previous study has considered the effect of memantine on visual function in ON patients. Further studies with longer follow-up periods are required in order to establish the efficacy of neuroprotective agents such as memantine in preventing axonal loss in ON.

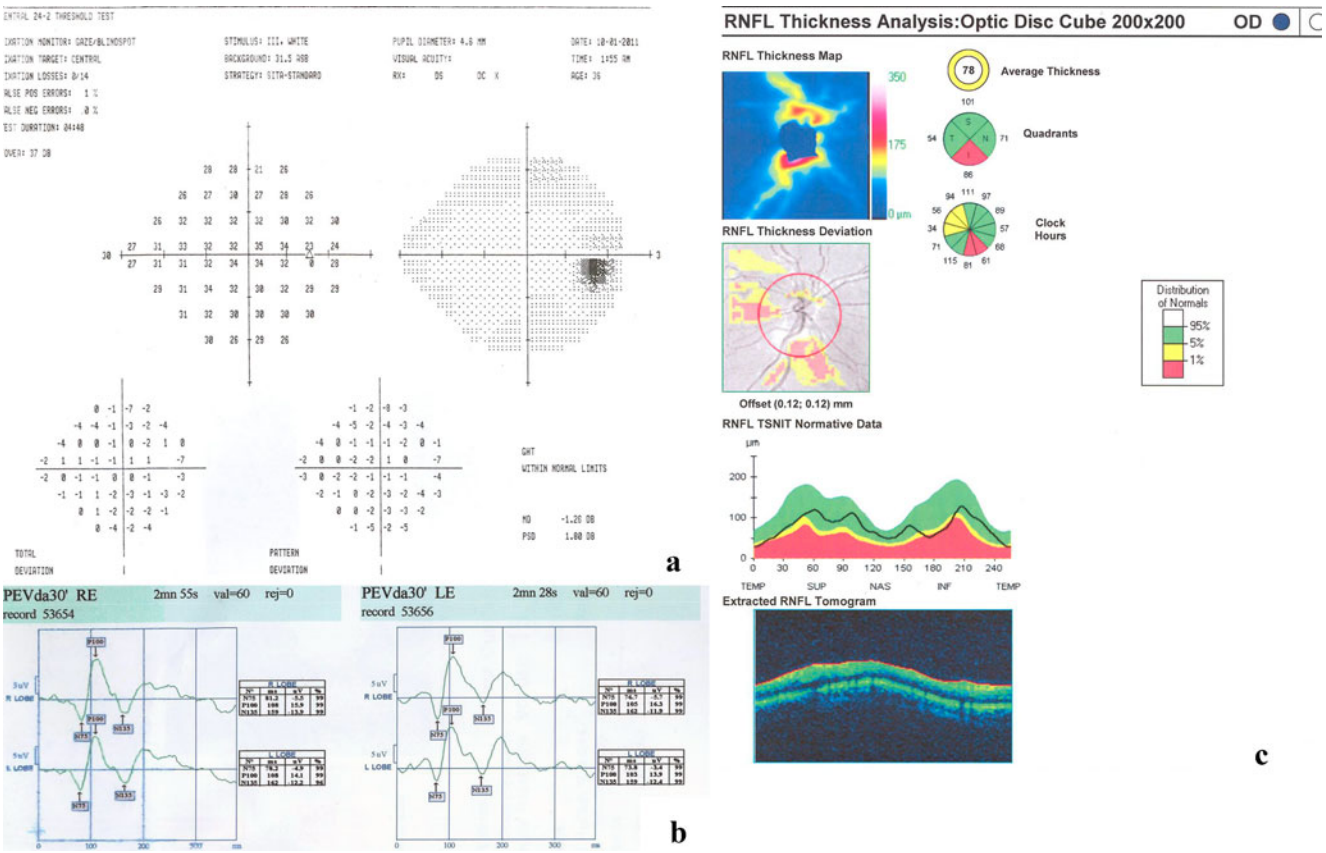

Fig. 2 Same patient after 3 months. **a** Visual field and **b** delay of P100 peak on visual evoked potential were improved. **c** OCT showed inferior retinal nerve fiber layer thinning

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