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The relationship between retinal layer thickness and cognition in patients with multiple sclerosis: A systematic review of current literature

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Abdorreza Naser Moghadasi[1], Omid Mirmosayyeb[2,3], Narges Ebrahimi[4], Mohammad Ali Sahraian[1], Aida Mohammadi[5], Mahsa Ghajarzadeh[1,5]

[1] Multiple Sclerosis Research Center, Neuroscience institute, Tehran University of Medical Sciences, Tehran, Iran
[2] Department of Neurology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran
[3] Isfahan Neurosciences Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
[4] School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran
[5] Universal Council of Epidemiology, Universal Scientific Education and Research Network, Tehran University of Medical Sciences, Tehran, Iran

Keywords
Cognition; Multiple Sclerosis; Retina

Abstract

Background: This study was conducted to evaluate the relationship between retinal layer thickness (RLT) and cognition in patients with multiple sclerosis (MS).

Methods: We searched PubMed, Scopus, Embase, Web of Science, and Google Scholar. The search strategy included the MeSH and text words as [“ora serrata” OR “retina” OR (“coherence tomography” AND “optical”) OR “OCT tomography” OR (tomography AND OCT) OR “optical coherence tomography” OR “OCT” OR “retinal thickness” OR “inner plexiform layer” OR “nerve fiber layer” OR “ganglion cell layer” OR “inner nuclear layer” OR “outer plexiform layer” OR “outer nuclear layer” OR “external limiting membrane” OR “inner segment layer” OR “outer segment layer” OR “retinal pigment epithelium”] AND [“cognition”* OR “cognitive function”* OR (function* AND cognitive)] AND [(sclerosis AND multiple) OR (sclerosis AND disseminated) OR "disseminated sclerosis" OR "multiple sclerosis" OR "acute fulminating"].

Results: The literature search revealed 1090 articles; after deleting duplicates, 980 remained.

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Corresponding Author: Mahsa Ghajarzadeh
Email: m.ghajarzadeh@gmail.com

Finally, 14 studies were included. Totally, 1081 patients were evaluated. Mean age ranged from 31 to 55 years. In some studies, there was a correlation between cognition and retinal thickness, while others did not confirm this finding. Some authors found cognitive impairment (CI) in patients with MS with RLT.

Conclusion: The results of this systematic review show that there are discrepancies between the results of studies regarding the relationship between RLT and cognition status in patients with MS. Further studies with more included original studies and meta-analysis are recommended.

Introduction

Multiple sclerosis (MS), an autoimmune disease of central nervous system (CNS), has a wide range of physical and psychological consequences.[1] One of the most complaints of patients with MS is cognitive impairment (CI), affecting 40%-70% of MS population,[2,3] even in early stages of the disease.[3] Brain atrophy, which occurs earlier in MS cases, could be an indicative factor of CI and can be assessed by conventional magnetic resonance imaging (MRI) sequences.[4] To monitor neurodegeneration in the retinae of patients with MS, optical coherence tomography (OCT) was introduced to be used along with MRI.[5] Loss of optic nerve axons and retinal ganglion cells could be detected by OCT.[6,7] It is a non-invasive, cost-effective, and easy optical imaging that applies near-infrared light to construct images of the retina. It allows assessment of retinal nerve fiber layer (RNFL) and ganglion cell layer (GCL).[8]

Retinal layer thickness (RLT) is independent of optic neuritis (ON) that shows neurodegenerative process[9-11] and axonal damage in patients with MS.[3] Britze and Frederiksen suggested that peripapillary RNFL (pRNFL) thickness was a good predictor of neurodegeneration in MS.[8]

In different MS populations, researchers assessed the relationship between CI and RLT with different tests, while there is no systematic review regarding this issue.

We designed this systematic review to evaluate the relation between RLT and cognitive status in patients with MS.

Materials and Methods

Literature search: Two researchers independently and systematically searched PubMed, Scopus, Embase, Web of Science, and Google Scholar. They also searched the gray literature (references of the included studies, and conference abstracts) which were published up to June 2021.

Inclusion criteria: We included cross-sectional studies which had reported the results of Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS) or Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) tests as well as the results of retinal thickness assessment.

Exclusion criteria: Letters to the editor, case-control, case reports, and cross-sectional studies which had no clear data regarding the results of MACFIMS or BICAMS tests as well as the results of retinal thickness assessment were excluded.

The subscales of MACFIMS include: Controlled Oral Word Association Test (COWAT), Brief Visuospatial Memory Test-Revised (BVMT-R), Paced Auditory Serial Addiction Test (PASAT), Judgment of Line Orientation (JLO), California Verbal Learning Test-Second Edition (CVLT-II), Symbol Digit Modalities Test (SDMT), Delis-Kaplan Executive Function System Sorting Test (D-KEFS ST). BICAMS subscales include: SDMT, CVLT, BVMT-R.

Data search and extraction: The search strategy included the MeSH and text words as ["ora serrata" OR "retina" OR (coherence tomography AND optical) OR "OCT tomography" OR (tomography AND OCT) OR "optical coherence tomography" OR "OCT" OR "retinal thickness" OR "inner plexiform layer" OR "nerve fiber layer" OR "ganglion cell layer" OR "inner nuclear layer" OR "outer plexiform layer" OR "outer nuclear layer" OR "external limiting membrane" OR "inner segment layer" OR "outer segment layer" OR "retinal pigment epithelium"] AND ["cognition"* OR "cognitive function*" OR (function* AND cognitive)] AND [(sclerosis AND multiple) OR (sclerosis AND disseminated) OR "disseminated sclerosis" OR "multiple sclerosis" OR "acute fulminating"]. Two independent researchers independently evaluated the articles.

Data regarding total number of participants, first author, publication year, the country of origin, mean age, female/male ratio (F/M ratio), disease duration, type of cognition test, retinal thickness, Expanded Disability Status Scale (EDSS), and relationship between cognition and retinal thickness were recorded.

Risk of bias assessment: We evaluated the risk of potential bias by the Newcastle-Ottawa Quality Assessment Scale (adapted for cross-sectional studies).[12]

Results

The literature search revealed 1090 articles; after

deleting duplicates, 980 remained. Finally, 14 studies were included (Figure 1).

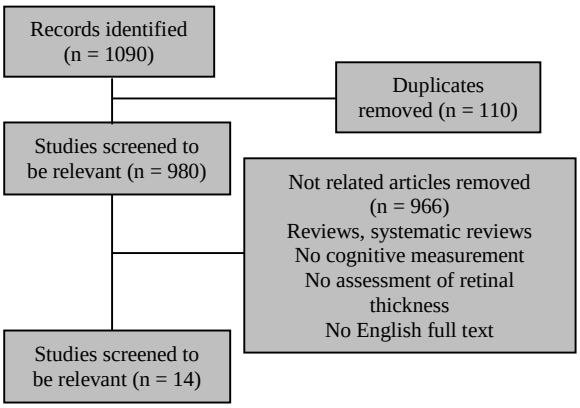

Figure 1. Flow diagram of including studies

Finally, 14 articles were assessed. Totally, 1081 patients were evaluated. Mean age ranged from 31 to 55 years (Table 1). In some studies, there was a correlation between cognition and retinal thickness, while others did not confirm this finding. Some authors found CI in patients with MS with RLT.

Discussion

To our knowledge, this is the first systematic review evaluating the relationship between retinal thickness and CI. Some studies provided only mean values of cognitive test and retinal layer, while others evaluated the correlation between the two items.

In a study which was conducted by Baetge et al., 64 patients with MS were evaluated. They applied BICAMS test for cognitive evaluation and reported CI in 36%. They found that higher retinal thickness was associated with better function on Trail Making Test-Part B (TMT-B test) (which is related with cognitive flexibility as a domain of executive functioning).[5] Cognitive flexibility is a complex ability of cognition which covers a wide range of functions such as working memory, attention, and inhibition operating.[5,13] It is suggested that it is one of the first domains which is affected after atrophic process of retinal layer and could lead to rapid neuropsychological assessment.[5] As well as other studies, they reported no association between RLT and BICAMS or TMT-A when including continuous variables and concluded that OCT could only be a supplementary evaluation not a replacement.[5,14,15] In some studies, which only used SDMT, there was a correlation between cognition and retinal thickness such as studies which were conducted by Lima et al.[16] and Gilroy et al.,[17] while others (Coric et al.[18] and May et al.[19]) reported a significant correlation between SDMT findings and RLT. The discrepancies between study results could be due to different inclusion and exclusion criteria of participants. Some included patients with CI and some included patients at baseline. In most studies, the sample size was limited and the study designs were single center in a country.

Lima et al. found that RLT was not significantly different between cases with and without CI and only inner plexiform layer (IPL) was correlated with SDMT,[16] while Baetge et al. reported no significant correlation between inner nuclear layer (INL) and cognition status,[5] which confirms the previous findings indicating that axonal and neuronal atrophy in MS is related with pRNFL, ganglion cell-IPL (GCIPL), and macular RNFL (mRNFL), while pRNFL is the most related factor with cognition.[14,20-22]

On the other hand, other studies demonstrated that thinning of mRNFL and GCIPL started at early stages of the disease regardless of pRNFL thinning indicating that retinal injury may start from the macular ganglion cells.[10,23,24] Temporal pRNFL is considered as the sensitive measurement for thinning of pRNFL and is the most affected quadrant in MS cases.[7,25]

The most common modality for MS follow-up is MRI and correlation between MRI findings and SDMT.[26,27] OCT is suggested for monitoring of patients with MS to assess disease progression.[28]

This study has some limitations. First, all included studies did not report the same method for cognition evaluation. Second, the sample sizes of each study were limited. Third, the analysis method was not similar between studies.

Therefore, larger multi-centric original studies by means of special cognition tests (MACFIMS or BICAMS) are recommended.

Conclusion

The results of this systematic review show that there are discrepancies between the results of studies regarding the relationship between RLT and cognition status in patients with MS. Further studies with more included original studies and meta-analysis are recommended.

Conflict of Interests

The authors declare no conflict of interest in this study.

Acknowledgments

None.

Table 1. Basic characteristics of the included studies (Part I)

References	Country	MS, Female, Male (Number)	Age (mean ± SD or median, range, IQR)	Disease duration (mean ± SD or median, range, IQR) (year)	EDSS (mean ± SD or median and range)	Cognition test and/or measurements
Baetge et al.[5]	Austria	50, 40, 10	Median: 47.00, range: 18-59, IQR: 13.25	Median: 7.34, range: 0.26-28.21, IQR: 12.10	2.59 ± 1.17	BICAMS
Abdel et al.[29]	Egypt	50, 32, 18	31.72 ± 7.03	7.15 ± 5.18	4.57 ± 2.16	BICAMS
Birkeldh et al.[7]	Sweden	465, 318, 147 RRMS: 336 SPMS: 112 PPMS: 17	Total (n = 336): 38.90 ± 9.70 (n = 112): 53.80 ± 10.00 (n = 17): 50.20 ± 13.20	Total (n = 336): 9.10 ± 7.20 (n = 112): 21.80 ± 9.40 (n = 17): 10.60 ± 8.30		SDMT
Frau et al.[14]	Italy	66, 48, 18	43.40 ± 12.00	Mean: 10.80, median: 8.50, range: 0-34	Median: 2.00, Range: 0-7.50	BICAMS
Coric et al.[18]	UK	217, 150, 67 MSNON: 102 MSON: 35	54.30 ± 9.96	20.34 ± 6.99	Median: 4.00, Range: 1.00-8.00	SDMT
May et al.[19]	Cleveland	286, 149, 137	55.50 ± 7.30	14.90 ± 9.05		SDMT
Lima et al.[16]	Portugal	60				SDMT, JLO
Nguyen et al.[30]	USA	131, 66, 65	45.00 ± 12.30	11.00 ± 8.80	Median: 3.00	MACFIMS
Gilroy et al.[17]	USA	30, 21, 9 All RRMS	Mean: 44.0, range: 30-63	Range: 1-25	Range: 0-5.50	SDMT
Petracca et al.[23]	USA	25, 14, 11	51.20 ± 10.41	9.04 ± 4.64		BICAMS
El Ayoubi et al.[31]	USA	Number of subjects Interferon: 32 Fingolimod: 15 Total: 47 26 21	Interferon: 32.80 ± 11.20 Fingolimod: 29.20 ± 9.40	MS duration in months Interferon: 29.40 ± 24.00 Fingolimod: 33.50 ± 24.10	Mean EDSS (SD) Interferon: 1.00 ± 1.00 Fingolimod: 1.50 ± 1.00	SDMT MoCA BVMT-R T25FWT
Giedraitiene et al.[32]	Lithuania	88	42.80 ± 10.90		3.50 ± 1.30	BICAMS
Sedighi et al.[20]	Iran	60, 51, 9				BICAMS
Gencer et al.[33]	Turkey	71, 47, 24	39.58 ± 10.06			PASAT

Table 1. Basic characteristics of the included studies (Part II)

References	Cognition scores (mean ± SD or median, range, IQR)	RNFL score (mean ± SD)	Other correlations and scores	Key finding	Score
Baetge et al.[5]	SDMT: 43.66 ± 8.62 VLMT: 55.50, 13.00-73.00, 16.00 BVMT-R: 25.00, 0-34.00, 11.25	pRNFL: 89.53 ± 12.61 mRNFL: 31.33 ± 4.82 GCIPL: 65.57 ± 7.09 INL: 34.46 ± 2.55		RLT in pRNFL, mRNFL, and GCIPL were predictors of cognitive flexibility. Patients with lower layer thickness performed worse on TMT-B than patients with higher layer thickness. Effect sizes (β) for pRNFL (β = -0.246), mRNFL (β = -0.259), and GCIPL (β = -0.199) with TMT-B can be classified as small effects. Only thickness of mRNFL remained a significant predictor of TMT-B.	5/10
Abdel et al.[13]	SDMT: 19.54 ± 9.44 CVLT-TR: 51.08 ± 9.59 BVMT-TR: 19.76 ± 7.00		RNFL with SDMT: Beta: -0.129, P: 0.686 GCC with SDMT: Beta: -0.058, P: 0.214	Positive correlation was detected between scores of all neuropsychological tests and the thickness of each RNFL and GCC.	5/10
Birkeldh et al.[7]				Lower pRNFL was associated with cognitive dysfunction.	
Frau[14]	SDMT: 45.10 ± 12.30 CVLT-II: 41.60 ± 10.30 BVMT-R: 47.60 ± 10.80	RNFL: 93.80 ± 10.70 PMB-RNFL: 49.60 ± 9.40	r (P) Average-RNFL with: SDMT: 0.01 (0.96) CVLT-II: 0.20 (0.18) BVMT-R: 0.08 (0.60) Temporal RNFL with: SDMT: 0.01 (0.95) CVLT-II: 0.09 (0.57) BVMT-R: 0.08 (0.58) PMB-RNFL with: SDMT: 0.04 (0.78) CVLT-II: 0.09 (0.55) BVMT-R: 0.13 (0.38)	The OCT measures did not correlate with the results of BICAMS tests.	5/10
Coric et al.[18]		pRNFL thickness (µm): 83.16 ± 11.18 mGCIPL thickness (µm): 82.66 ± 14.89	Partial correlation coefficients (r) between pRNFL and mGCIPL thickness and test scores of separate cognitive tests pRNFL r (P-value) with SDMT in MSNON: 0.34 (0.004) in MSON: 0.26 (0.225) mGCIPL r (P-value) with SDMT in MSNON: 0.29 (0.014) in MSON: 0.20 (0.433)	PRNFL thickness showed a significant, inverse association with cognitive impairment. Both associations remained significant after adjusting for age and sex, resulting in an OR for pRNFL of 1.11; pRNFL thickness was only significantly correlated with the SDMT.	7/10

Table 1. Basic characteristics of the included studies (Part II) (continue)

References	Cognition scores (mean ± SD or median, range, IQR)	RNFL score (mean ± SD)	Other correlations and scores	Key finding	Score
May et al.[19]			SDMT with RNFL thickness: (P = 0.0007, β = 0.309, N = 266) SDMT with GC thickness: (P = 0.0002, β = 0.418, N = 191)	RNFL correlated with SDMT. OCT measures of RNFL and GC thickness correlated with clinical measures of cognition, specifically SDMT, in progressive MS. SDMT was correlated with RNFL thickness and GC thickness.	NA
Lima et al.[16]			IPL thickness with SDMT: (r = 0.332, P = 0.012) IPL thickness with JLO: (r = 0.280, P = 0.035)	There were no significant differences in RLT between MS patients with and without cognitive impairment. IPL thickness correlated with scores for SDMT and JLO. There was no correlation between RLT and cognitive performance.	NA
Nguyen et al.[30]			Average GCIPL thickness β (P-value) MSFC (n = 93): -0.18 (0.78) SDMT (n = 69): 0.43 (0.56) BVMT-R total recall (n = 63): 0.13 (0.06) BVMT-R delayed recall (n = 63): 0.07 (0.26) JLO (n = 30): -0.09 (0.79) D-KEFS (n = 24): 0.73 (0.22) COWAT (n = 31): 0.06 (0.59) BDI (n = 26): 0.22 (0.18) MFIS (n = 69): 0.06 (0.19) Average retinal thickness MSFC (n = 93): -0.25 (0.86) SDMT (n = 69): 0.62 (0.70) BVMT-R total recall (n = 63): 0.27 (0.11) BVMT-R delayed recall (n = 63): 0.19 (0.20) JLO (n = 30): 0.52 (0.73) D-KEFS (n = 24): 1.53 (0.23) COWAT (n = 31): 0.13 (0.59) BDI (n = 26): 0.36 (0.32) MFIS (n = 69): 0.10 (0.29)	There was a significant association between GCIPL thickness and D-KEFS-Sorting in patients with RRMS. Additionally, average retinal thickness was associated with both BVMT-R DR* and D-KEFS scores, while trended towards significance with BVMT-R TR** scores in RRMS.	6/10
Gilroy et al.[17]				There was no significant relationship between GCL, IPL, INL, OPL, and SDMT.	NA
Petracca et al.[23]	SDMT: z-score: -1.98 ± 1.44 CVLT: z-score: -0.33 ± 1.17 BVMT: z-score: -1.86 ± 0.97 BICAMS: z-score: -1.39 ± 1.02	RNFL: 86.34 ± 13.49 GCIPL: 66.43 ± 9.56 TMV: 3.00 ± 0.21		Among OCT metrics, RNFL was not associated with individual cognitive z-scores; TMV was associated with CVLT z-score, and GCIPL was associated with SDMT z-score, CVLT z-score, and BICAMS mean z-score. Logistic regression identified GCIPL as a predictor of objective cognitive impairment.	5/10

Table 1. Basic characteristics of the included studies (Part II) (continue)

References	Cognition scores (mean ± SD or median, range, IQR)	RNFL score (mean ± SD)	Other correlations and scores	Key finding	Score
El Ayoubi et al.[31]	Mean ± SD of T25FWT in seconds Interferon: 4.10 ± 1.10 Fingolimod: 4.60 ± 2.20 Mean ± SD of 9HPT in seconds Interferon: 20.30 ± 3.10 Fingolimod: 22.10 ± 4.10 Mean ± SD of SDMT score Interferon: 58.70 ± 13.10 Fingolimod: 59.70 ± 17.50 Mean ± SD of MoCA score Interferon: 25.80 ± 2.70 Fingolimod: 26.60 ± 2.60	pRNFL (µm): Interferon: 92.90 ± 8.70 Fingolimmod: 87.20 ± 8.40 GCIPL (µm): Interferon: 79.90 ± 6.70 Fingolimod: 75.10 ± 6.60		Cognitive scores given by the SDMT, total BVMT recall, and delayed recall correlated negatively with T25FWT and 9HPT. PRNFL correlated negatively with the 9HPT, but not with the T25FWT. PRNFL thickness correlated positively with the SDMT, but not with any of the MoCA, BVMT total recall, or delayed recall scores. GCIPL thickness did not correlate with any of SDMT, MoCA, BVMT total recall, or delayed recall scores.	5/10
Giedraitiene et al.[32]			SDMT with the left eye temporal segment: (r = 0.32, P = 0.03) SDMT with PMB thickness: (r = 0.36, P = 0.01)	There was a significant correlation between SDMT and the left eye temporal segment and PMB thickness.	NA
Sedighi et al.[20]			Coefficient regression model of BICAMS (SDMT, CVLT-2, BVMT-R) and OCT Standard error, Standard estimate, t-Value, P-value SDMT: 0.116, 0.646, 3.228, 0.002 CVLT: 0.181, -0.003, -0.017, 0.986 BVMT-R: 0.282, 0.112, 0.649, 0.519	OCT predicts the SDMT component (processing speed) of the BICAMS test at a rate of 64.6%, but not BVMT-R and CVLT-2.	5/10
Gencer et al.[33]		RNFL (µm) (right + left eyes): 97.80 ± 16.00	RNFL with PASAT: r: 0.316 P: 0.0001	There was a significant positive correlation between RNFL thickness and the scores of PASAT.	5/10

MS: Multiple sclerosis; RLT: Retinal layer thickness; OCT: Optical coherence tomography; BICAMS: Brief International Cognitive Assessment for Multiple Sclerosis; PASAT: Paced Auditory Serial Addition Test; RNFL: Retinal nerve fiber layer; mRNFL: Macular retinal nerve fiber layer; PMB: Papillomacular bundle; pRNFL: Peripapillary retinal nerve fiber layer; MSON: Multiple sclerosis-associated optic neuritis; MACFIMS: Minimal Assessment of Cognitive Function in Multiple Sclerosis; CVLT-2: California Verbal Learning Test-Second Edition; BVMT-R: Brief Visual Memory Test-Revised; SDMT: Symbol Digit Modalities Test; EDSS: Expanded Disability Status Scale; GCIPL: Ganglion cell-inner plexiform layer; NA: Not appreciable; MoCA: Montreal Cognitive Assessment-Arabic; T25FWT: Timed 25-foot walk test; 9HPT: Nine-Hole Peg Test; MSFC: Multiple Sclerosis Functional Composite; IPL: Inner plexiform layer; TMV: Total macular volume; GC: Ganglion cell; MFIS: Modified Fatigue Impact Scale; VLMT: Verbaler Lern-und Merkfähigkeitstest; COWAT: Controlled Oral Word Association Test; TMT-B: Trail Making Test-Part B; GCC: Ganglion cell complex; D-KEFS: Delis-Kaplan Executive Function System; OPL: Outer plexiform layer; JLO: Judgment of Line Orientation; INL: Inner nuclear layer; ONL: Outer nuclear layer; RRMS: Relapsing-remitting multiple sclerosis; SPMS: Secondary-progressive multiple sclerosis; PPMS: Primary-progressive multiple sclerosis; IQR: Interquartile range; mGCIPL: Macular ganglion cell-inner plexiform layer; OR: Odds ratio; SD: Standard deviation; BDI: Beck Depression Inventory; MSNON: Multiple sclerosis without optic neuritis

* BVMT-R DR is z-Scores which were used in regression analyses. **BVMT-R TR is z-Scores which were used in regression analyses.

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