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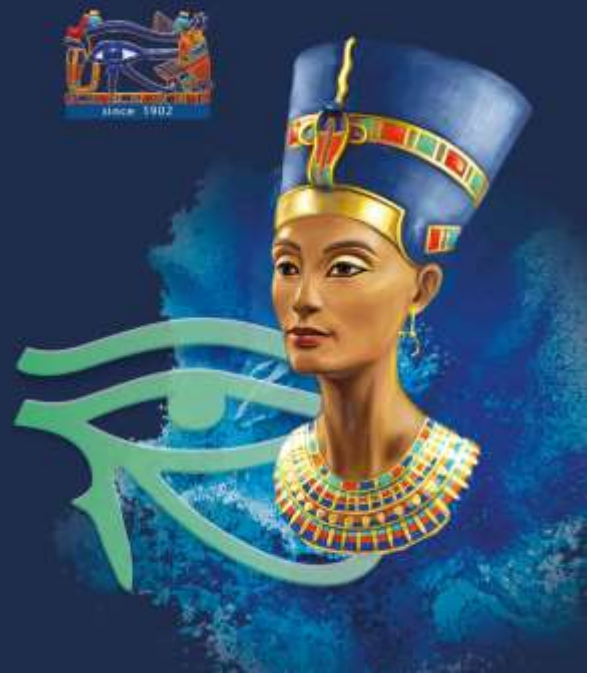

Expression of poly(ADP-ribose) polymerase-1 gene and optical coherence tomography angiographic parameters among patients with multiple sclerosis

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Expression of poly(ADP-ribose) polymerase-1 gene and optical coherence tomography angiographic parameters among patients with multiple sclerosis

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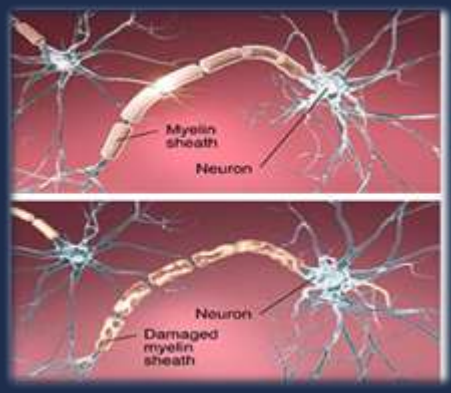
INTRODUCTION

- (MS) is a disabling disease targeting the (CNS) via an autoimmune and inflammatory route.
- Plaque formation is followed by the destruction of the myelin sheath resulting in axonal degeneration



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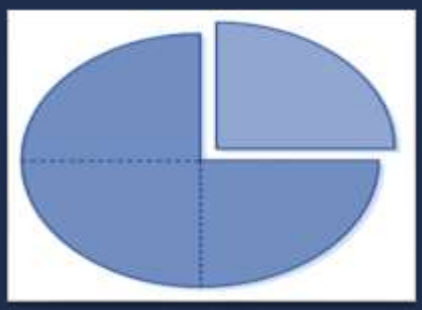
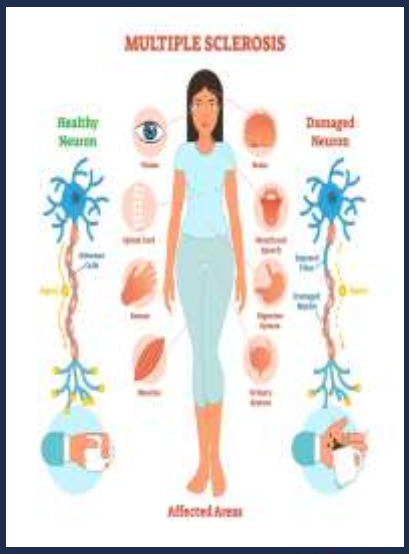
- The most common ocular presentation of MS is optic neuritis (ON), representing the 1st clinical manifestation in about 25% of cases.



- Post-mortem specimens confirmed that the visual system is affected through the (in the form of axonal loss and degeneration of the optic nerve) in about **94 to 99%** of patients with MS whether they had **previous ON or not.**

1. tiredness
2. weakness
3. pain, tingling, and numbness
4. stiffness
5. muscle spasms, stiffness and weakness
6. difficulty walking or balancing
7. vertigo and dizziness
8. problems with thinking and memory
9. changes in vision and hearing
10. vision problems
11. problems with thinking, learning and planning
12. depression and anxiety
13. sexual problems
14. bladder problems
15. bowel problems
16. speech and swallowing difficulties



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Visual pathway in patients with MS represents the only directly visible common affected partner of the CNS.

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- We can objectively quantify and assess the visual pathway, via Spectral-domain optical coherence tomography (SD-OCT) with reliable quantification of the (GCL) thickness at the level of the peripapillary (RNFL) and the macular region.
- The en-face images of OCT angiograms can be visualized in definite layers starting from the (ILM) down to the choroid, in addition to the visualization of individual vascular plexus and segmentation of the inner retina, outer retina and choriocapillaris slabs.

What is the exact mechanism of the disease?

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- Answer:
- the exact mechanism of disease remains elusive.

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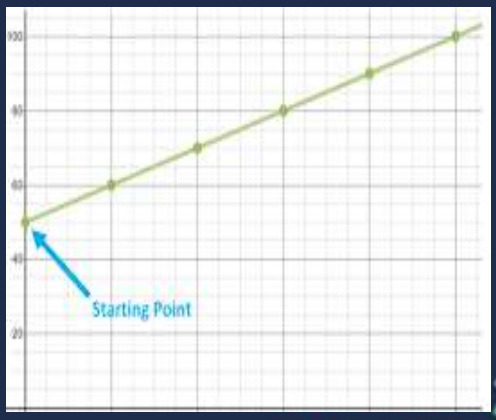
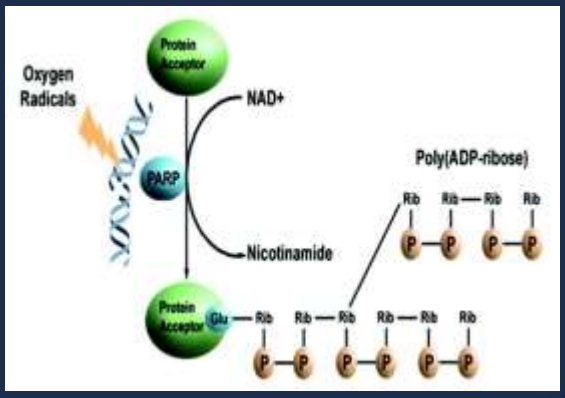
- Diagnosis and management of MS cases are based on clinical presentation, with adjunct imaging and biochemical assessment without knowing the exact cascade of the pathology



- Poly (ADP-ribose) polymerase 1 (PARP-1) is one of the well-characterised and most popular members of the **PARP nuclear enzyme superfamily**, which transfers ADP ribose units from nicotinamide adenine dinucleotide to a broad panel of acceptor proteins, such as histones and transcription factors.



PARP-1 participation was identified in various cellular processes

DNA repair & proliferation

Death signaling of the cells

Transcriptional regulation

Inflammation

- Previous studies on the experimental autoimmune encephalomyelitis model of MS pointed to the importance of PARP-1 in MS pathogenesis, suggesting that the development of PARP-1 inhibitors is a promising approach for MS treatment modulations.

Aim of the study

1. To objectively analyze different parameters of the macula and disc using OCT in addition to their vascular affection using OCT-A in patients with MS (ON +/-) vs normal control group and correlate these changes to PARP-1 gene expression in blood of patients with MS.
2. It may help predict or even prevent the development of ON and subsequent visual disabilities.

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MATERIAL AND METHODS

- The patients were recruited from neurology inpatient and outpatient clinics from May 2021 to December 2021, Sohag University Hospitals.
- ***A cross-sectional study*** included 80 eyes of the clinically diagnosed relapsing-remitting phenotype of MS, divided in 3 groups;
- ***Group (A) (MS+ON***) had 40 eyes of 20 patients with MS with a history of ON
- ***Group (B) (MS-ON)*** had 40 eyes of 20 patients with MS without a history of ON .
- ***Group (C) (control group)*** consisted of 40 eyes of 20 matched participants not suffering from any ocular or systemic disease.
- Patients aged 18 years or more diagnosed according to McDonald's criteria 2017.
- In groups (A and B), patients included at least 3months after the resolution of the attack, and all were on the same line of neurological management

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MATERIAL AND METHODS

- **Exclusion criteria:**

1. Patients with media opacity could interfere with the signal strength of images.
2. patients with any other retinal pathology (DR, retinal degeneration and retinal dystrophies).
3. Any other causes of optic neuropathy (glaucoma, ischemic and compressive optic neuropathy).
4. Patients with other demyelinating diseases (acute disseminating encephalomyelitis or neuromyelitis Optica).
5. Patients with acute attacks of ON were excluded, as (ONH) edema would prevent the accurate measurement of RNFL.
6. Eyes with high myopia (more than −6 SD).

MATERIAL AND METHODS

- The patients underwent a full ophthalmic examination ((IOP), slit-lamp examination of the anterior segment and retinal assessment by slit-lamp biomicroscopy using a+78 D lens, the OCT and OCT-A, RTVue (Optovue, Fermont, California,USA) were performed for all patients.
- Cell isolation, RNA isolation, Real-time quantitative PCR.
- Statistical analysis.

Results

- BCVA was compared between the three studied groups and showed significant reduction among MS (ON+) and MS (ON−) compared with the control group (p-value<0.007).
- It was proved that MS could be associated with poor recovery of BCVA due to neurodegenerative process that may cause dysfunctional mechanisms involving the foveal photoreceptors and bipolar cells.

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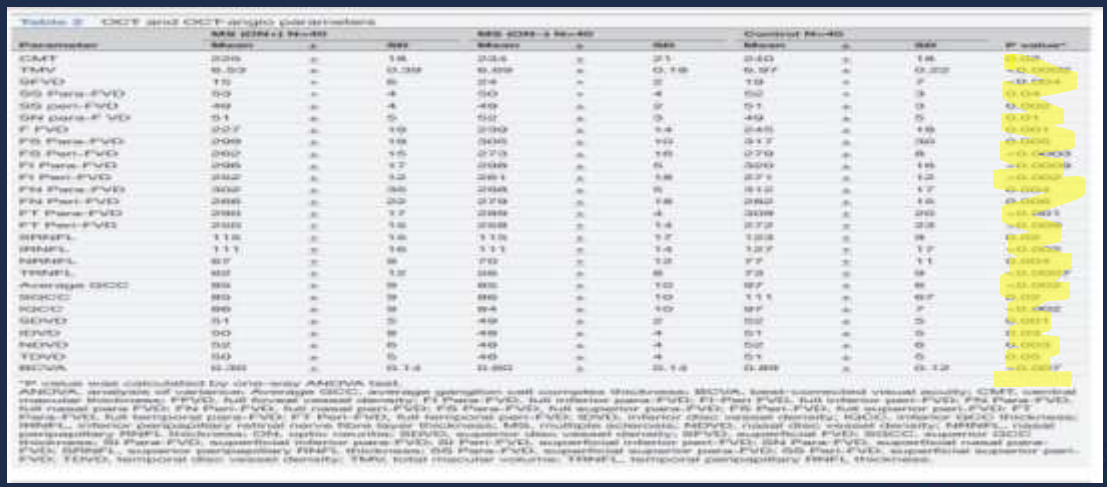
Results



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Results

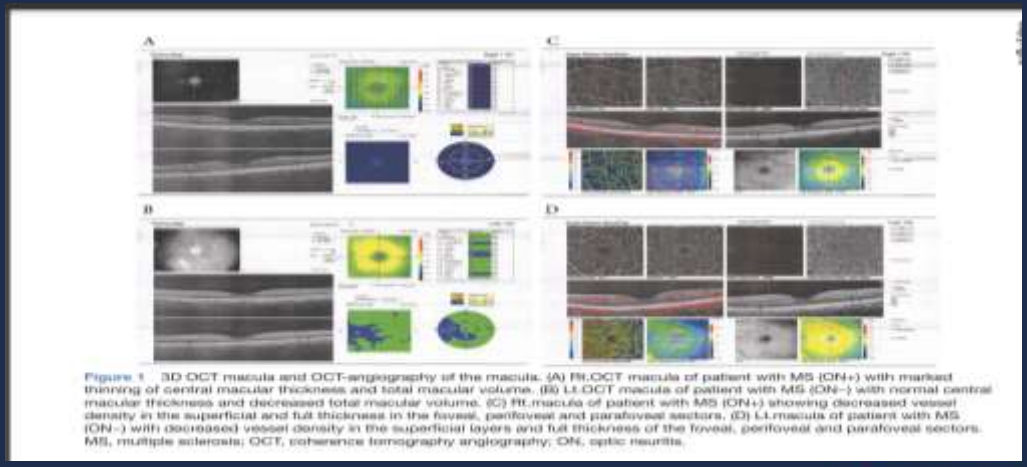


Figure 1 3D OCT macula and OCT-angiography of the macula. (A) Rt.OCT macula of patient with MS (ON+) with marked thinning of central macular thickness and total macular volume. (B) Lt.OCT macula of patient with MS (ON−) with normal central macular thickness and decreased total macular volume. (C) Rt.macula of patient with MS (ON+) showing decreased vessel density in the superficial and full thickness in the foveal, perifoveal and parafoveal sectors. (D) Lt.macula of patient with MS (ON−) with decreased vessel density in the superficial layers and full thickness of the foveal, perifoveal and parafoveal sectors. MS, multiple sclerosis; OCT, coherence tomography anglography; ON, optic neuritis.

Results

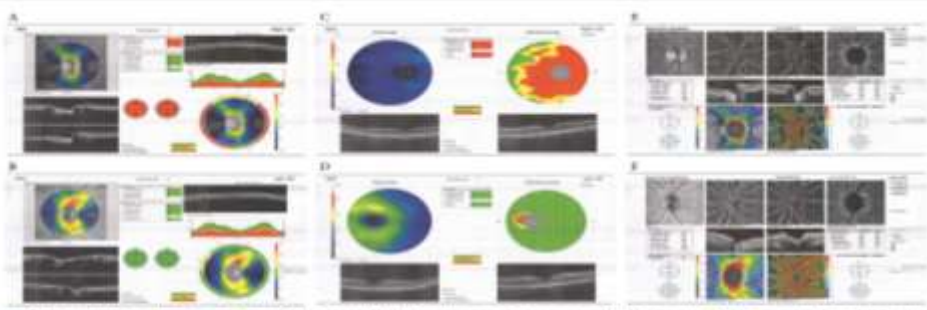
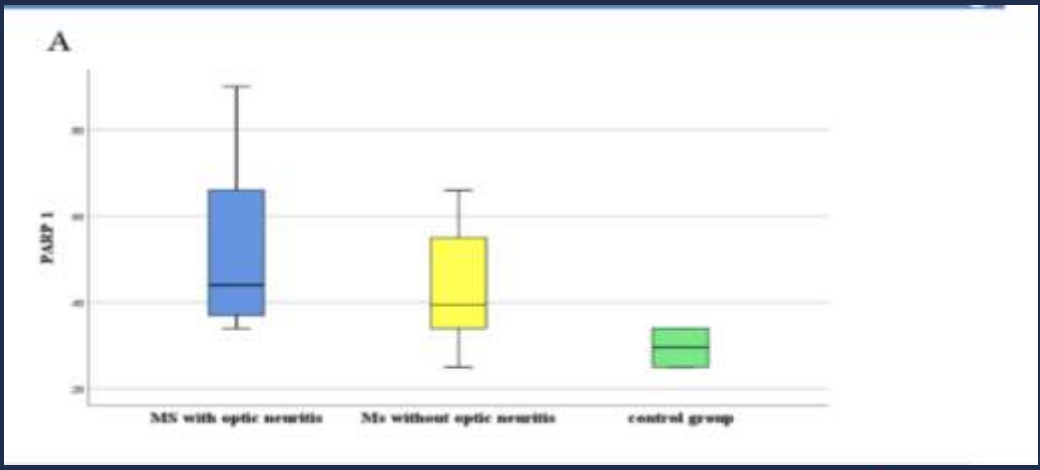


Figure 2 OCT of the optic nerve head, OCT macula-V of ganglion cell complex (GCC) and OCT-angio of the optic nerve head. (A) Rt. disc of patient with MS (ON+) showing marked thinning of the whole sectors of the peripapillary retinal nerve fibre layer. (B) Lt. disc of patient with MS (ON−) showing within the normal thickness of the peripapillary retinal nerve fibre layer. (C) Rt. GCC at the macula of patient with MS (ON+) showing marked thinning of the average, superior and inferior GCC. (D) Lt.GCC at the macula of patient with MS (ON−) showing within the normal thickness of the average, superior and inferior GCC. (E) Rt. Disc of patient with MS (ON+) showing decreased flow (highlighted in blue) with decreased vessel density. (F) Lt. Disc of patient with MS (ON−) showing decreased flow (highlighted in blue) and within normal vessel density. MS, multiple sclerosis; OCT, coherence tomography angiography; ON, optic neuritis.

Results



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Result

- We found a higher expression of PARP-1 patients with MS with ON compared with patients without ON and control groups.
- These data suggest a potentially important impact of the deregulation of the PARP-1/TGFBR axis on T-cell function in MS.(PARP-1 negatively regulates the immunosuppressive function of Treg cells at the post-translational level by way of FOXP3 poly (ADP-ribosylation).

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Results

- AUC values of the OCT variables were analyzed for correct diagnostic power to distinguish between the eyes of healthy control and MS (ON+ and ON−), **none of the parameters had the desired strong diagnostic power (all of AUC <0.5) in ROC curve analysis.** The highest AUC value was observed in the CMT, and the second one was the average GCC), while the AUC value of the TMV was determined as 0.166

Result

- In contrast, when (AUC) values of PARP-1 gene expression were analyzed for correct diagnostic power to distinguish between healthy control and MS (ON+ and ON−), the highest AUC value was 0.9.

Results

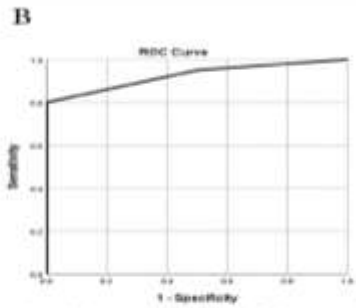
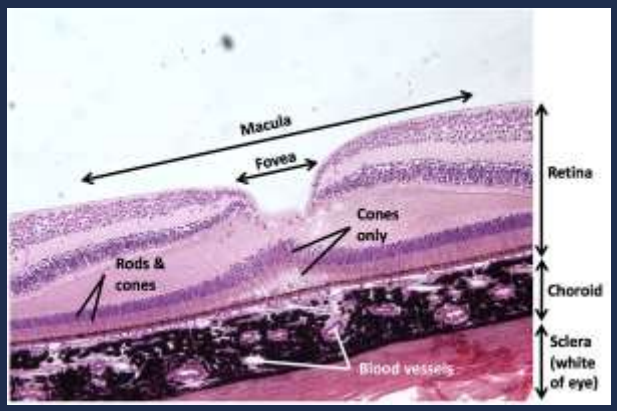


Figure 3 (A) Comparison between the three studied groups (ON+), (ON−) and control group regarding PARP 1 gene expression level. (B) ROC curve constructed by plotting the area under the receiver operating characteristic curve value is (0.9). (C) Rock curve constructed by plotting the area under the receiver operating characteristic curve value is: Blue line: Central macular thickness (0.329). Red line: total macular volume (0.166). Green line: average GCC (0.183). GCC, ganglion cell complex; ON, optic neuritis; ROC, receiver operating characteristic.

- We found that the OCT parameters are biomarkers of definite patients with MS who had previous attacks. They may be replaced by a more powerful and conclusive biomarker that may be even detected prior to ophthalmic damage, the PARP-1 gene expression level.

Results

- There was significant decrease in (CMT) in groups (A and B) compared with group C, which can be due to the preferential thinning of the central macula relative to the peripheral macular region, which could be due to the histological distribution, could be the cause of this macular thickness pattern.
- It is particularly informative of neurodegeneration in the eyes of patients with MS whether they have a history of ON or not.



Results

- We found a significant decrease in the TMV in groups (A and B) when compared with group C, which can be attributed to the analogies between the macular volume and CNS grey matter, as the macula consists of ~34% neuronal cells by average thickness in healthy eyes.
- Retrograde degeneration from lesions in the optic nerves, chiasm or tracts, could be the origin of the neuronal loss appeared as OCT-macular volume thinning in the eyes of MS measured by OCT.
- Those subclinical neurodegeneration findings may be started in eyes with MS even before ON attack and may be used in the future as a predictive biomarkers of ON attack.

Results

- However, our finding of vessel density reduction in both macula and peripapillary capillary plexus as the RNFL might suffer indirectly from vascular damage to the optic nerve, and the story might start as a vasculopathy ended by nerve fibre layer reduction.

Results

- Negative correlations were found between PARP-1 gene expression level and CMT (r=−0.3, p=0.001, TMV (r=−0.1, p=0.05) and full foveal vessel density thickness (r=−0.2, p=0.004).
- PARP-1 gene expression level was further correlated to both groups of MS (ON+ and ON−) separately, and a significant negative correlations were found between PARP-1 gene expression level and the following parameters in MS (ON+): CMT (r=−0.465, p=0.002), TMV (r=−0.420, p=0.007), temporal disc vessel density (r=−0.428, p=0.006) and BCVA (r=−0.414, p=0.008)

- To the best of our knowledge, this is the first time to correlate PARP1 gene expression level to macular OCT and OCT-angio parameters.

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PARP1 links to a cluster of stress signals arrised by inflammation

excessive inflammation predisposes the vasculature to stiffening

dysfunction and alteration of endothelial function

chronic inflammation

tissue damage (which in case of MS disease neurosis may be the sign of such tissue damage)

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Conclusion

Conclusion

1. PARP-1 may play an important role in the development of the ON cascade (excessive inflammation which lead to angiopathy and subsequent tissue damage and neurosis) in patients with MS and may be a biomarker for diagnosing and a potential molecular target of ON in MS patients' therapy.
2. OCT and OCT-angio changes that could be detected retrospectively, PARP-1 gene expression level could be considered a prospective detector to complete the full-blown picture of MS (ON+) early and prevent blindness.
3. The diagnostic and prognostic values of PARP-1 and therapeutic applications are worth further investigation.


Thank you
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