Abstract

Background:

There is a need for biomarkers that can distinguish optic neuritis (ON) episodes as belonging to either neuromyelitis optica spectrum disorder (NMOSD) with optic neuritis or relapsing remitting multiple sclerosis (RRMS) with optic neuritis. This study utilized optical coherence tomography (OCT) data to perform a preliminary contrast between ON of NMOSD and MS by analyzing peripapillary retinal nerve fiber layer (pRNFL).

Objectives

To compare peripapillary retinal nerve fiber layer thickness in patients with NMOSD and MS in eyes with or without optic neuritis.

Method

A cross sectional study includes 76 patients meeting International consensus diagnostic criteria for NMOSD and 2010 McDonald criteria for MS with or without history of ON. The patients was collected in Baghdad Teaching Hospital, MS clinic and Ghazy Al-hariri Hospital for surgical specialities from first of February 2018 to first of February 2019 and sent for OCT.

Results

Considering all eyes with ON episode (83), we found that in NMOSD group the pRNFL thickness was significantly lower than those with MS in average and all location except the nasal sector. With respect to average and all other location thickness, the temporal quadrant has higher sensitivity and accuracy and can be used to differentiate NMOSD from MS (0.873).

Conclusions

Identification of ON attacks can be done and the differentiation between those of NMOSD patients from MS could be predicted by using OCT.
Keywords: NMOSD, MS, optic neuritis

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Introduction:
Neuromyelitisoptica (NMO) is a central nervous system (CNS) disorder of inflammatory origin that predominantly affects the spinal cord and optic nerves (1). Traditionally, the term NMO was applied to those who experienced a monophasic event consisting of bilateral simultaneous optic neuritis (ON) and acute myelitis. It is now applied to typically evolve as a relapsing disorder that also includes patients with unilateral ON and those with events of ON and myelitis occurring weeks or even years apart (2).

As had been assumed for decades, NMO is not a subform of multiple sclerosis (MS), but rather an autoimmune condition with distinct immunopathogenesis from that of MS despite overlap in clinical presentation and paraclinical findings between them (3). The identification of aquaporin-4 antibodies (AQP4-Ab) has highly simplified the singularity between NMO and MS. This antibody (also termed NMO-IgG) was found almost exclusively in patients with NMO and its formes frustes but not in patients with classical MS (4).

The classical features of NMOSD are optic neuritis and transverse myelitis. The clinical manifestations may implicate sites outside optic nerve and spinal cord. These may be the presenting or the only features of the disease (5). These include area postrema, brainstem syndrome, symptomatic macroelepsy and symptomatic cerebral syndrome.

The International Panel for NMO Diagnosis (IPND) applies AQP4-Ab status in patient suspected to have NMOSD (4). Criteria are developed for NMOSD with AQP4-IgG, NMOSD without AQP4-IgG and NMOSD with unknown AQP4-IgG status.

A curative treatment for NMOSD does not exist to date (6). The goal of NMOSD therapy is to decrease neurological disability by improving acute attacks and preventing future relapse.

Multiple sclerosis (MS): It is a chronic inflammatory disease of the central nervous system of unknown etiology; however, genetic and environmental factors have important role in the MS development. MS is characterized by inflammation, demyelination, and axonal loss. It is thought to be an autoimmune disorder (7). It is typically white matter disease of brain and spinal cord along with evidence of inflammation affecting the normally appearing gray matter, white matter and cortex and deep gray matter nuclei (8).

Typically, diagnosis of MS remains clinical and supported by magnetic resonance imaging (MRI), laboratory findings (cerebrospinal fluid oligoclonal bands and raised IgG index), evoked potential studies and exclude alternatives (9).
Optical coherence tomography (OCT): Is a non-invasive technique that was generated in the 1990s and is widely used currently. It enables quantitative and qualitative changes in the optic nerve and the macula (10). It can provide information about thicknesses of peripapillary and macular retinal nerve fiber layer (RNFL) and generate macular maps with segmental thicknesses and volumes (11).

It is rapidly evolving giving cross-sectional images of tissue morphology. It utilizes the echo delay of light to generate images with higher resolution instead of sound that is used in ultrasound image. It is less expensive than MRI and safer than radiographic devices (12).

In previous studies, time domain OCT (TD-OCT) was used. Recently, the development of spectral domain optical coherence tomography (SD-OCT) allows higher resolution, faster imaging and detailed evaluation of each retinal layer, including the ganglion cell layer (GCL) with elimination of mechanical movement that was required in TD-OCT for acquisition of image (13) (14).

The peripapillary retinal nerve fiber layer thickness (pRNFL) has become a dependable OCT marker for diagnostic evaluation in translational research and care. RNFL are arising from the retina and migrating the eye through the optic nerve head forming the optic nerve. These fibers are suitable for axonal damage and neuroprotection in diseases presenting with ON, such as NMOSD and MS. The pRNFL is calculated in ring scans of known circumference (most commonly 12° or 3.5 μm) circling the optic nerve head as mean thickness (in μm). By using a ring scan around the optic nerve head, all axons going out the eye are involved in the measurement, thereby permitting representation of the full axonal content of the optic nerve (15).

**Aim of the study:** The aim of study is to Compare peripapillary retinal nerve fiber layer (RNFL) thickness in patients with neuromyelitis optica spectrum disorder (NMOSD) and relapse remitting multiple sclerosis (RRMS) with or without a history of optic neuritis using optical coherence tomography (OCT).

**Patients and method:**

**Study design and setting:**

It is a cross sectional study was undertaken at Baghdad Teaching Hospital and MS clinic. Our patients were collected from first of February 2018 to first of February 2019.

**Participants**

The number of patients included was 76 that divided into two groups. One for MS that consisted of 43 patients (86 eyes) from whom 81 eyes were studied, 5 were excluded due to ON history in last six months and number of eyes with ON were 50. The second group for NMOSD that consisted of 33 patients (66 eyes) from whom 65 eyes
were studied, 1 was excluded owing to inoculation and number of eyes with ON were 43. The history was taken from the entire patient and examination was done. All patients were reviewed by neurologist.

**Inclusions criteria:**

All patients diagnosed as NMOSD following International consensus diagnostic criteria for NMOSD and those with RR MS according to the 2010 McDonald criteria were included.

An attack of acute ON was proved by medical list review. The confirmation of an ON episode was depend on the findings of decreased visual acuity, visual field abnormality, changes in colour of vision, macus gun pupil, painful eye movements and examination of fundus.

**Exclusion criteria:**

Patients excluded from the study were
1. Those less than 18 years or greater than 50 years.
2. ON episodes within 6 months.
3. History of optic neuropathies other than ON.
4. History of glaucoma, diabetes and retinal disease.

**Data collection:**

OCT examination by the RTVue (software version #6, 8, 0, 27) was done to all patients diagnosed as NMOSD and RRMS to measure the thickness of the pRNFL. The protocol measures pRNFL at a diameter of 3.45 μm targeted around the head of optic nerve. Parameters that are taken from OCT were average, superior, temporal, inferior and nasal pRNFL. The normal values of average, superior, temporal, inferior and nasal pRNFL were 87.88, 95.90, 57.70, 105.4 and 56.45 respectively (16) (17) (18) (19). The examinations of OCT were achieved by investigators trained on OCT acquisition.

**Statistical analysis:**

Discrete variables presented using their number and percentage, chi square test used to analyze the discrete variable. Two samples t test used to analyze the differences in means between two groups (if both follow normal distribution with no significant outlier).

Receiver operator curve used to see the validity of different parameters in separating MS from NMOSD and area under the curve i.e. AUC prescribe this validity (if AUC ≥ 0.9 mean excellent test, 0.8 – 0.89 means good test, 0.7 – 0.79 fair test otherwise unacceptable). Trapezoidal method was used to calculate the curve.

In a ROC curve the true positive rate (Sensitivity) is plotted in function of the false positive rate (100-Specificity) for different cut-off points. Each point on the ROC curve represents a sensitivity/specificity pair corresponding to a particular decision threshold. A test with perfect discrimination (no overlap in the two distributions) has a ROC.
curve that passes through the upper left corner (100% sensitivity, 100% specificity). Therefore the closer the ROC curve is to the upper left corner, the higher the overall accuracy of the test (Zweig & Campbell, 1993).

SPSS 22.0.0 (Chicago, IL), MedCalc Statistical Software version 14.8.1 (MedCalc Software bvba, Ostend, Belgium; 2014), software package used to make the statistical analysis, p value considered when appropriate to be significant if less than 0.05

**Results:**

Mean age of patients with NMOSD was significantly higher compared to those with MS, female gender shows significantly higher frequency in MS compared to NMO patients.

There was no significant difference in the rate of optic neuritis between MS and NMOSD patients, additionally about half of the NMOSD patients had positive aquaporin-4.

Retinal thickness was significantly lower in NMOSD patients compared to MS patients in all location and their average except for nasal position, as illustrated in table 1 and figure 1.

Table 1: Assessment of retinal thickness (mean ± SD) in eyes with ON.

<table>
<thead>
<tr>
<th></th>
<th>MS</th>
<th>NMOSD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>50</td>
<td>43</td>
<td>-</td>
</tr>
<tr>
<td>Average</td>
<td>83.4 ± 11.5</td>
<td>70.5 ± 13.9</td>
<td>&lt;0.001 [S]</td>
</tr>
<tr>
<td>Superior</td>
<td>104.1 ± 18.8</td>
<td>90.2 ± 20.1</td>
<td>0.001 [S]</td>
</tr>
<tr>
<td>Inferior</td>
<td>109.7 ± 18.1</td>
<td>94.0 ± 19.7</td>
<td>&lt;0.001 [S]</td>
</tr>
<tr>
<td>Temporal</td>
<td>61.4 ± 13.2</td>
<td>44.2 ± 9.6</td>
<td>&lt;0.001 [S]</td>
</tr>
<tr>
<td>Nasal</td>
<td>83.4 ± 11.5</td>
<td>70.5 ± 13.9</td>
<td>0.097</td>
</tr>
</tbody>
</table>

Independent t-test
Figure 1: Comparison between MS and NMOSD in retinal thickness (average reading)

Figure 2: Comparison between MS and NMOSD in retinal thickness (superior location reading)
Figure 3: Comparison between MS and NMOSD in retinal thickness (inferior location reading)

![Graph showing comparison between MS and NMOSD in retinal thickness (inferior location reading)]

Figure 4: Comparison between MS and NMOSD in retinal thickness (temporal location reading)

![Graph showing comparison between MS and NMOSD in retinal thickness (temporal location reading)]

Figure 5: Comparison between MS and NMOSD in retinal thickness (nasal location reading)

![Graph showing comparison between MS and NMOSD in retinal thickness (nasal location reading)]
Retinal thickness show fair ability to predict MS from NMOSD in the average of OCT, superior and inferior location, while temporal location shows good ability to predict MS from NMOSD, however nasal location show poor ability to predict MS from NMOSD, as illustrated in table 2.

Table 2: ROC analysis of retinal thickness to predict MS from NMOSD patients in eyes with ON

<table>
<thead>
<tr>
<th></th>
<th>AUC</th>
<th>Cut-off</th>
<th>+LH</th>
<th>-LH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average</td>
<td>0.777</td>
<td>&gt;67.75</td>
<td>2.26</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Superior</td>
<td>0.714</td>
<td>&gt;99</td>
<td>2.84</td>
<td>0.44</td>
</tr>
<tr>
<td>Inferior</td>
<td>0.761</td>
<td>&gt;91</td>
<td>2.58</td>
<td>0.064</td>
</tr>
<tr>
<td>Temporal</td>
<td>0.873</td>
<td>&gt;47</td>
<td>3.67</td>
<td>0.081</td>
</tr>
<tr>
<td>Nasal</td>
<td>0.618</td>
<td>&gt;52</td>
<td>1.72</td>
<td>0.37</td>
</tr>
</tbody>
</table>

AUC: area under the curve, LH: likelihood ratio

Table 3: validity analysis of retinal thickness of utility to predict MS from NMOSD patients in eyes with ON

<table>
<thead>
<tr>
<th></th>
<th>SN</th>
<th>SP</th>
<th>AC</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average</td>
<td>100%</td>
<td>56%</td>
<td>79.7%</td>
<td>73%</td>
<td>100%</td>
</tr>
<tr>
<td>Superior</td>
<td>66%</td>
<td>77%</td>
<td>71.1%</td>
<td>77%</td>
<td>66%</td>
</tr>
<tr>
<td>Inferior</td>
<td>96%</td>
<td>63%</td>
<td>80.7%</td>
<td>75%</td>
<td>93%</td>
</tr>
<tr>
<td>Temporal</td>
<td>94%</td>
<td>74%</td>
<td>84.8%</td>
<td>81%</td>
<td>91%</td>
</tr>
<tr>
<td>Nasal</td>
<td>80%</td>
<td>53%</td>
<td>67.5%</td>
<td>67%</td>
<td>70%</td>
</tr>
</tbody>
</table>

SN: sensitivity, SP: specificity, AC: accuracy, PPV: positive predictive value, NPV: negative predictive value

There was no significant difference between MS and NMOSD in all location of OCT, as illustrated in table 4.

Table 4: Assessment of retinal thickness (mean ± SD) in the eyes without ON

<table>
<thead>
<tr>
<th></th>
<th>MS</th>
<th>NMOSD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>31</td>
<td>22</td>
<td>-</td>
</tr>
<tr>
<td>Average</td>
<td>102.3 ± 8.4</td>
<td>97.8 ± 14.5</td>
<td>0.192</td>
</tr>
<tr>
<td>Superior</td>
<td>123.9 ± 15.1</td>
<td>121.7 ± 18.9</td>
<td>0.643</td>
</tr>
<tr>
<td>Inferior</td>
<td>132.8 ± 15.7</td>
<td>126.3 ± 24.1</td>
<td>0.273</td>
</tr>
<tr>
<td>Temporal</td>
<td>76.1 ± 16.1</td>
<td>70.4 ± 10.8</td>
<td>0.125</td>
</tr>
<tr>
<td>Nasal</td>
<td>76.5 ± 11.9</td>
<td>72.6 ± 16.5</td>
<td>0.321</td>
</tr>
</tbody>
</table>

Independent t-test

Discussion

This study was held to compare the thickness of pRNFL in NMOSD and RRMS in eyes involved with ON and those without ON and to see whether there is different in thickness in specific side of pRNFL than other in those eyes.
In the current study, the mean age of patients was significantly higher in NMO than RRMS (36.8 ± 11.8 vs. 27.8 ± 6.2 years, p-value =<0.001) and this was in agreement with Sinnecker T et al and Eshaghi A et al studies(20)(21).

In this study, female gender in NMOSD group was significantly lower in contrast to MS groups which is in contrast to most previous studies and could be explained by our sample was small.

The numbers of eyes with history of ON in NMOSD and RRMS were not vary statistically (61.7% eyes with ON in MS group vs 66.2% eyes in NMOSD group). This difference could be explained because of sample of patient which was complain of ON which was taken for comparison was nearly equal in both groups.

Additionally, the positivity of AQP4-Ab was about half of the NMOSD patient. About one quarter of patient was negative AQP and this may be false negative result due to serum sample taken after receiving high dose of steroid that lower the AQP4-Ab titer. In our search, one quarter was unknown AQP status.

The most beneficial finding when used OCT in patients with ON is thinning of the pRNFL(10). In our search, the eyes with ON episode were investigated to estimate the degree of thinning between the NMOSD and RRMS groups.

In the current study, the mean average of pRNFL thickness in eyes with ON episode in NMOSD group was 70.5 ± 13.9 μm which is significantly lower than RRMS group83.4 ± 11.5 μm; this findings is in agreement with Mekhasingharak N et al. that found average thickness was 65±11 μm in NMOSD with ON vs 79±9 μm in RRMS with ON (p-value =<0.001) (22), and also in agreement with Merle H et al in which the average thickness of the RNFL in NMOSD vs MS (65.44 ±24.19 μm versus 83.85 ±24.12 μm,P = 0.01) (23).

Moreover, there was statistically significant difference in the thickness of pRNFL between NMOSD and RRMS in the superior and inferior sectors (90.2 ± 20.1 vs 104.1 ± 18.8 for superior, p-value = 0.001 and 94.0 ± 19.7 vs109.7 ± 18.1 for inferior, p-value <0.001); this findings is in harmony with Mateo J et al. that state the damage involves every quadrant, mainly the superior and inferior sectors in NMOSD (10). Also Mekhasingharak N et al. found pRNFL from superior and inferior sides were significantly thinner in eyes with ON in NMOSD than those with MS (22).

In contrast to Naismith RT. et al study that claimed no significant difference in temporal and nasal thickness between NMOSD and MS (24), our search found that the temporal sector thickness was significantly thinner in eyes with ON in NMOSD than MS groups (44.2 ± 9.6 vs. 61.4 ± 13.2, p-value < 0.001), this may be explained by the attack of ON tend to be more sever and less likely to improve in NMOSD patient compared with MS group. On the other hand, our study was in agreement with Naismith RT. et al study in that there was no significant difference between NMOSD and MS patients with ON in nasal quadrant thickness.
Despite the result of thinning of the entire RNFL thickness in both NMOSD and RRMS in eyes with ON, the involvement of the temporal side was preponderance and more severe in ON eyes of MS than NMOSD patients as Mateo J. et al and Bennett JL. Et al studies concluded (10) (11). This was in disparity with our study in which the temporal quadrant was affected in eyes with ON of both groups but was more severe in NMOSD than MS. This could be clarified due to the axons of the temporal quadrant of the retinal nerve fiber layer are much and small diameter; make their atrophy after ON episode in NMOSD patient more severe in comparism with MS.

The new in our study that does not done before was that we can use the retinal nerve fiber as a marker for differentiation between NMOSD and RRMS. Using ROC analysis, we found at cut point >47 μm had AUC =0.873; indicating it is an excellent predictor of severity, with 84.8% accuracy, and 94% sensitivity and 74% specificity.

Further examination of the data was the likelihood (LH) ratio. The benefit of LH ratio is to determine the use of the investigated test in either confirmatory or exclusion pathway in the diagnostic decisions, for positive LH in the average position we found 2.26 LH which is indicate between 15 – 20% increase in the probability of conformation of diagnosis, as similar conclusion for superior, inferior position but for temporal position 20 – 25% increase in the probability, while for nasal position 0 – 15% increase in the probability.

The negative LH indicate the ability of the test to exclude the diagnosis, in which the best position is the their average (~45%), similar probability also obtained by inferior and temporal position, while superior position can give 15 – 20% increase in exclusion the diagnosis, while nasal position can give 20 – 25%

Average, inferior and temporal show the highest sensitivity, while superior and temporal location show the highest specificity, inferior and temporal location show the highest accuracy, this indicate that temporal location is the best location to predict MS from NMOSD with cut-off >47

In our study, there was no significant difference between NMOSD and RRMS groups in eyes without ON in average and all quadrant of pRNFL. This was unlike Schneider E. et al study that found involvement of eyes of MS patient without ON episode (25). This may be due to small numbers of eyes without ON that were studied.

**Conclusions**

It can differentiate between eyes with ON from those without. Using pRNFL, we can identify patient with NMOSD and RRMS through measuring thickness of RNFL in eyes with ON episode and the most important quadrant is temporal side.

**Recommendations**

Number of attacks of ON need to be study to assess the correlation between number of episodes and OCT thinning.

The patients need to be following to estimate whether RNFL thickness can be changes with treatment.
References


