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Evaluation of the retinal nerve fiber layer in neuromyelitis optica spectrum disorders: A systematic review and meta-analysis

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ABSTRACT

Background: An increasing number of studies have investigated the value of optical coherence tomography in patients with neuromyelitis optica (NMO) spectrum disorders; however, no systematic review has been performed to date. We aimed to systematically review and investigate the possibility of differentiating NMO and multiple sclerosis (MS) via an optical coherence tomography measurement.

Methods: Electronic databases, including MEDLINE, EMBASE and Web of Science, were systematically searched up to June 2017. A meta-analysis was performed to compare the retinal nerve fiber layer (RNFL) thickness between patients with NMO and MS (or healthy controls).

Results: Twenty-four studies were identified. The meta-analysis demonstrated that the RNFL loss was substantially more severe in NMO than in MS; however, subclinical axon damage was also found in eyes without optic neuritis in NMO. The intereye RNFL difference between eyes with or without optic neuritis was more prominent in NMO (− 30.98 μm) than in MS (− 9.87 μm).

Conclusion: The RNFL loss was more severe in NMO than in MS, and the intereye RNFL difference between eyes with or without optic neuritis may be useful in differentiating NMO from MS.

1. Introduction

Neuromyelitis optica (NMO), also referred to as Devic's disease, is a neuroinflammatory disease that is characterized by severe episodes of optic neuritis and myelitis, which often result in bilateral blindness and paralysis. NMO in combination with a disease spectrum (e.g., LETM, Long segmental transverse myelitis) in which the astrocyte water channel aquaporin-4 antibody is present has been referred to as an NMO spectrum disorder [1].

Optical coherence tomography (OCT), a noninvasive, non-contact and repeatable scanning method, uses infrared light to generate images of the retina based on the different reflectivities of different layers (Fig. 1). OCT is widely used for “optical biopsy” of the retina [2]. The retinal nerve fiber layer (RNFL) is the most widely measured layer because it is composed of unmyelinated axons that originate from ganglion cells, which makes it the ideal structure for quantifying axonal integrity in vivo [3]. Other structures that have been studied include the macular volume, inner nuclear layer (INL) and ganglion cell layer (GCL). Numerous studies have investigated the value of OCT in differentiating NMO and MS [4,5]. However, no systematic review has been performed to date.

The aim of our study was to systematically review the literature that investigated OCT use in NMO spectrum disorders. Special care was employed to evaluate whether subclinical axonal damage exists in the eyes of patients with NMO spectrum disorders without optic neuritis and to investigate the possibility of differentiating NMO and MS using an OCT measurement.

2. Methods

The protocol of our systematic review was predefined according to the guidelines recommended by PRISMA-P 2015 (Preferred Reporting Items for Systematic reviews and Meta-Analyses for Protocols 2015) [6].

2.1. Literature-search strategy

We performed a systematic search for studies from January 1991 to June 2017. Two reviewers independently searched MEDLINE, EMBASE and Web of Science using the following terms: “Neuromyelitis optica”, “NMO”, “Neuromyelitis optica spectrum disorders”, “NMOSD”, “Devic's disease”, “optic neuritis”, “longitudinally extensive transverse myelitis”, “LETM”, “optical coherence tomography” and “retinal nerve fiber layer”. “Neuromyelitis optica” was searched as combination of medical

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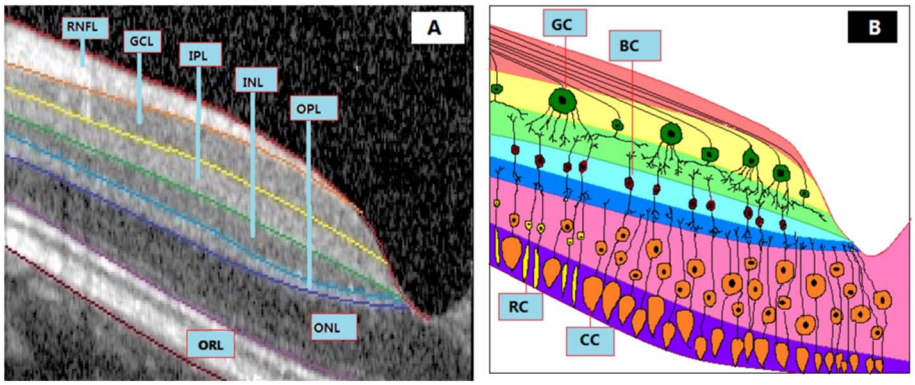

Fig. 1. A. Images of retina generated from optical coherence tomography (OCT) scan. B. Sketch map of retina. RNFL: Retinal nerve fiber layer; GCL: Ganglion cell layer; IPL: Inner plexiform layer; INL: Inner nuclear layer; OPL: Outer plexiform layer; ONL: Outer nuclear layer; ORL: Outer retinal layer; GC: Ganglion cell; BC: bipolar cell; RC: rod cell; CC: cone cell.

subject headings (MeSH) and text words. Other items were searched as text words. The references of the included studies were also identified for additional studies.

2.2. Inclusion and exclusion criteria

Patients included in the NMO spectrum disorders group met the diagnostic criteria for NMO (Wingerchuk 2006 [7], or 2015 revision [8]), and patients included in the MS group met the McDonald criteria (2001 [9], 2005 [10] or 2010 revision [11]). The diagnostic criteria for LETM included: 1) neurological dysfunction that could be attributed to the spinal cord, with symptoms progressed to nadir between 4 h and 21 days; 2) inflammation indicated by cerebrospinal fluid pleocytosis or an elevated IgG index; and 3) spinal cord MRI abnormality that involved at least 3 vertebral segments [12]. Studies were included if they were published in full text form and provided results of OCT measurement comparing NMO spectrum disorders and healthy controls (or MS). Studies were excluded if they were reviews, case reports or meeting abstracts; if they were written in other language rather than in English; if they were studies without healthy controls (or MS) as a controlled group.

2.3. Data extraction

Two reviewers (Peng and Qiu) screened the relevant studies independently. They also extracted relevant information from each eligible study with a standardized form including the following information: the first author, type of OCT, age, gender and other demographic characteristics of the studies; number of subjects and eyes in each group including NMO with or without optic neuritis (NMO + ON, NMO-ON), MS with or without optic neuritis (MS + ON, MS-ON), LETM, and healthy control; the thickness of retinal layers including peripapillary RNFL (pRNFL), macular RNFL (mRNFL), macular retinal ganglion cell plus inner plexiform layer (mGCL +, they were often measured together because the boundary between them is vague), macular inner nuclear layer (mINL), and macular volume. If any disagreement exist, it would be resolved by discussion among all authors.

2.4. Statistical analysis

Analyses were conducted using the software RevMan 5.2 (Cochrane Collaboration). OCT measurements were entered as continuous outcomes. The means, standard deviations, and sample sizes were entered for the calculation of the weighted mean difference with 95% confidence intervals (95%CI). A P value < 0.05 was considered to be statistically significant. The I^2 was used for the assessment of the heterogeneity among studies. When $I^2 \geq 50\%$, the heterogeneity was considered to be significant, and a random effects model was used. The subgroup analyses were performed according to whether the eyes were attacked by optic neuritis and the devices of the OCT used. A sensitivity analysis was performed to assess the robustness of the results by repeating the analyses with the removal of the smallest sample size study. The results were considered stable if they did not significantly change.

3. Results

3.1. Study identification and selection

Seven hundred eighty-two records were retrieved from the electronic database search. Seven hundred forty-five studies were excluded after reviewing the titles and abstracts; thus, 37 studies were eligible for full-text review. Thirteen studies were removed at this stage. One study in which the diagnostic criteria for MS were Poser criteria was also included after discussion among the authors. Finally, 24 studies were included in our meta-analysis [3–5,12–32]. No further study was identified through citation searches. The flow diagram of the literature screening is shown in Fig. 2. Among the 24 studies included, the publication year ranged from 2008 to 2016. Ten studies used Time-domain OCT (TD-OCT) [3,12–18,30–32], and the remaining 14 studies used Fourier-domain OCT (FD-OCT) [4,5,20–29,31]. The demographic characteristics of the included studies are shown in table 1.

3.2. pRNFL thickness in patients with NMO spectrum disorders versus healthy controls

For this comparison, 18 studies [3,5,12–14,18–24,26–29,31,32], which included 2086 eyes, were identified. Significant heterogeneity was identified among the studies with $I^2 = 95\%$; thus, a random effects model was used. The analysis results indicated that there was a significant loss of the mean pRNFL thickness in NMO spectrum disorders (-26.28 μm, $p < 0.001$). The sensitivity analysis verified the robustness of the results. Subgroup analyses were performed according to the

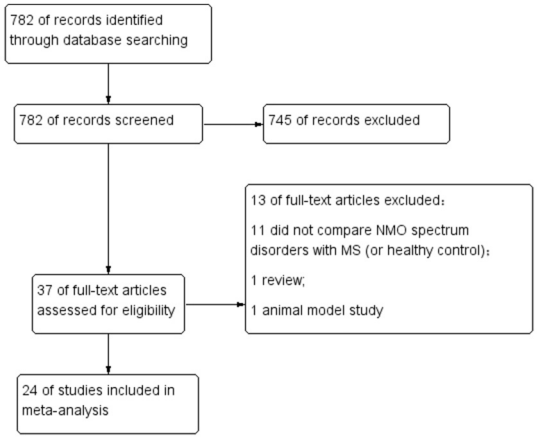

Fig. 2. The flow diagram of the screening of the literature.