Multiple Sclerosis and Related Disorders 11 (2017) 45–50

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

# Severe structural and functional visual system damage leads to profound loss of vision-related quality of life in patients with neuromyelitis optica spectrum disorders

Felix Schmidt[a,c,1], Hanna Zimmermann[a,1], Janine Mikolajczak[a], Frederike C. Oertel[a], Florence Pache[c], Maria Weinhold[a], Johann Schinzel[a], Judith Bellmann-Strobl[a,b], Klemens Ruprecht[c], Friedemann Paul[a,b], Alexander U. Brandt[a,*]

[a] NeuroCure Clinical Research Center, Charité – Universitätsmedizin Berlin, Berlin, Germany
[b] Experimental and Clinical Research Center, Max Delbrueck Center for Molecular Medicine and Charité – Universitätsmedizin Berlin, Berlin, Germany
[c] Clinical and Experimental Multiple Sclerosis Research Center, Department of Neurology, Charité – Universitätsmedizin Berlin, Berlin, Germany

ARTICLE INFO

*Keywords:*
Neuromyelitis optica spectrum disorder
Vision related quality of life
Optic neuritis
Retinal nerve fibre layer
Visual function
Optical coherence tomography

ABSTRACT

*Background:* Neuromyelitis optica spectrum disorders (NMOSD) are characterized by devastating optic neuritis attacks causing more structural damage and visual impairment than in multiple sclerosis (MS). The objective of this study was to compare vision-related quality of life in NMOSD and MS patients and correlate it to structural retinal damage and visual function.

*Methods:* Thirty-one NMOSD and 31 matched MS patients were included. Vision-related quality of life was assessed with the 39-item National Eye Institute Visual Function Questionnaire (NEI-VFQ). All patients underwent retinal optical coherence tomography and visual acuity and contrast sensitivity measurements.

*Results:* Vision-related quality of life was reduced in NMOSD compared to MS patients. This difference was driven by a higher incidence of bilateral and more severe optic neuritis in the NMOSD group. Retinal thinning and visual impairment were significantly greater in the NMOSD cohort. Lower vision-related quality of life was associated with more retinal damage and reduced visual function as assessed by visual acuity and contrast sensitivity.

*Conclusion:* NMOSD-related bilateral ON-attacks cause severe structural damage and visual impairment that lead to severe loss of vision-related quality of life. The NEI-VFQ is a helpful tool to monitor vision-related quality of life in NMOSD patients.

## 1. Introduction

Neuromyelitis optica spectrum disorders (NMOSD) are autoimmune CNS conditions primarily presenting with longitudinally extensive transverse myelitis (LETM) and optic neuritis (ON), and to a lesser extent with area postrema, acute brainstem, diencephalic and cerebral syndromes (Wingerchuk et al., 2015). Initially thought to be a variant of multiple sclerosis (MS), the detection of serum autoantibodies targeting the water channel aquaporin-4 (AQP4-IgG) in up to 80% of cases established NMOSD as an own disease entity distinct from MS (Jarius et al., 2014; Zekeridou and Lennon, 2015). Recently, serum antibodies directed against myelin oligodendrocyte glycoprotein (MOG-IgG) were found in a subset of AQP4-IgG negative NMOSD patients and in patients with recurrent optic neuritis, further extending the range of NMOSD (Jarius et al., 2016a, 2016b, 2016c; Pache et al., 2016).

Although pathogenically distinct, NMOSD and MS show a considerable overlap in clinical and paraclinical presentation, including involvement of the afferent visual system by acute ON (Wingerchuk et al., 2015). ON occurs in approximately 80% of NMOSD patients, in approximately 20% of the cases bilaterally, often involving the optic chiasm (Kleiter et al., 2016; Ramanathan et al., 2016). In contrast, ON in MS occurs in up to 70% of patients, is mainly unilateral and chiasm involving optic nerve lesions are rare (Costello, 2016; Toosy et al., 2014). In most cases, ON-associated damage is more severe in NMOSD patients than in MS patients, leading to more severe residual visual loss and structural damage (Bennett et al., 2015).

Visual function has great relevance for quality of life, affecting

* Corresponding author.
*E-mail address:* alexander.brandt@charite.de (A.U. Brandt).
[1] Equally contributing first authors in alphabetical order.

http://dx.doi.org/10.1016/j.msard.2016.11.008
Received 12 October 2016; Accepted 18 November 2016

everyday tasks and vision-dependent activities like driving or social and role functioning. Consequently, in a previous study, MS patients rated vision as the second most important bodily function following lower limb function (Heesen et al., 2008). Further impact of vision-related quality of life has been previously investigated in MS patients and its association with retinal axonal and neuronal damage and reduced visual function shown (Mowry et al., 2009; Schinzel et al., 2014; Walter et al., 2012).

However, although NMOSD patients suffer from greater visual function loss than MS patients, vision-related quality of life has hitherto not been investigated in this condition. Thus, the goals of our study were to investigate vision-related quality of life in NMOSD compared to MS patients and to relate vision-related quality of life to structural damage and dysfunction of the visual system in patients with NMOSD.

## 2. Patients and methods

### 2.1. Study participants and controls

Data for this cross-sectional study was derived from two on-going longitudinal observational studies following patients with NMOSD and MS. Thirty-six patients from the outpatient clinics of NeuroCure Clinical Research Center and from the Department of Neurology, Charité – Universitätsmedizin Berlin were screened for eligibility. Inclusion criteria were NMOSD according to the current diagnostic criteria (Wingerchuk et al., 2015) or MOG-IgG associated recurrent ON and age ≥18 and ≤70 years. Exclusion criteria were any eye or retina diseases other than ON, acute ON or disease relapse within three months prior to examination or refractive errors greater than ± 6dpt. Five screened patients were not included in the study: two due to cataract, one due to diabetic retinopathy, one due to retinal detachment and one due to age over 70 years. From the 31 included patients, 20 had an AQP4-IgG positive NMOSD diagnosis according to the revised diagnostic criteria (Wingerchuk et al., 2015). Seven patients fulfilled the criteria for AQP4-IgG negative NMOSD, among them three patients with positive MOG-IgG serology and 4 patients both negative for AQP4-IgG and MOG-IgG. Another four patients tested positive for serum MOG-IgG and had at least one ON episode, but did not formally fulfil the 2015 NMOSD criteria (Wingerchuk et al., 2015). Clinically, 16 out of 31 patients showed a typical NMOSD phenotype (ON + LETM). Twenty-three patients had at least one event of ON and 13 patients had ON in both eyes (either consecutive or simultaneously bilateral). Eight patients had LETM only. One patient presented with LETM and area postrema syndrome. Twenty-nine patients were Caucasian, one patient Asian and one African.

Thirty-one age-matched (p=0.97) and sex-matched (p=0.51) MS patients from the NeuroCure Clinical Research Center's database were compared with the data of the NMOSD patients (Schinzel et al., 2014). Twenty-four MS patients with relapsing remitting (RR), 3 patients with secondary progressive (SP) MS and 3 patients with clinically isolated syndrome (CIS) according to standard clinical and neuroimaging criteria were randomly selected (Polman et al., 2011). The patients matched for an event of ON (23 events of ON, eight times no event of ON). Disease duration was longer in MS patients, however the difference was not significant.

Demographic and clinical features are summarized in Table 1.

### 2.2. Ethics statement

The study was approved by the Charité ethics committee and was conducted in accordance to the Declaration of Helsinki in its currently applicable version and applicable German laws. All participants gave written informed consent to participate in the study.

### 2.3. Vision related quality of life assessment

The validated German translation of the 39-item version of the National Eye Institute Visual Function Questionnaire (NEI-VFQ) was answered by all participants (Franke et al., 1998). The NEI-VFQ is an established scoring method that is widely used in ophthalmologic research and clinical trials (Mangione et al., 2001). The NEI-VFQ consists of 12 individual subscales measuring general health, general vision, ocular pain, near activities, distance activities, driving, colour vision, peripheral vision and vision specific social functioning, mental health, role difficulties and dependency. Scores range from 0 to 100 with lower scores indicating worse vision related quality of life. Averaging all subscale scores excluding the general health item generates a final composite score. The questionnaire was answered self-administered whenever possible. If patients were not able to read the questionnaire due to blindness, it was filled in by interview.

### 2.4. Optical coherence tomography

Each participant underwent retinal examination with optical coherence tomography (Spectralis SD-OCT, Heidelberg Engineering, Heidelberg, Germany) with automatic real time (ART) function for image averaging. Peripapillary retinal nerve fibre layer (pRNFL) was evaluated using a 3.4 mm ring scan around the optic nerve head (12°, 1536 A-scans 16≤ART≤100). The combined ganglion cell and inner plexiform layer thickness (GCIP) and inner nuclear layer (INL) thickness (only available for NMOSD patients) were derived from a 6 mm diameter cylinder around the fovea from a macular volume scan (25°×30°, 61 vertical B-scans, 768 A-scans per B-scan, ART=15). Retinal layers were segmented automatically by the device's software (Eye Explorer 1.9.10.0 with viewing module 6.0.9.0) and reviewed for scan quality and segmentation errors by an experienced grader. Segmentation errors were corrected whenever necessary prior to analysis.

### 2.5. Visual function

Visual function was tested monocularly under best corrected or habitually corrected conditions with the Functional Vision Analyzer Optec 6500 P system (Stereo Optical Co., Chicago, Illinois) with a simulated distance of 20 ft. High-contrast visual acuity was tested using the device's Early Treatment Diabetic Retinopathy Study (ETDRS) charts. Contrast sensitivity was tested using the device's Functional Acuity Contrast Test (FACT) under photopic (85 $cd/m^2$) conditions without glare. Contrast sensitivity was calculated as the area under the curve (AUC) as previously described (Bock et al., 2012).

### 2.6. Data analysis

Statistical analyses were performed with R version 3.3.0 using the packages geepack and ggplot2(R Development Core Team, n.d.). Differences in demographics and clinical data between the cohorts were tested with Pearson's $Chi^2$ test for sex and Mann-Whitney *U* test for age, disease duration and EDSS. Group comparisons of NEI-VFQ composite score between the NMOSD and MS cohorts were performed with linear regression models for simple group analysis and multivariate linear regression models with NEI-VFQ items set as dependent variable, accounting for influences of diagnosis (NMOSD or MS), ON status (no ON, unilateral ON, bilateral ON), and an interaction effect of diagnosis and ON status. The results of the twelve NEI-VFQ subscores were only investigated descriptively to avoid multiple testing errors in this study with low sample size. NEI-VFQ items of NMOSD patients were also compared to published control data using *t*-tests (Franke et al., 1998). OCT and visual function data was compared between groups using generalized estimating equation models (GEE) accounting for within-subject inter-eye dependencies. GEE models included