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Дозвіл комісії з біоетики щодо проведення досліджень: Дослідження було схвалено Комітетом з етики Клінічного госпітального центру Осієка, реєстраційний номер: 25/01:10359-5/2014, і всі учасники дали письмову інформовану згоду.

Фінансування: Це дослідження не потребувало фінансування.

Стан неураженого ока є передвісником швидкого одужання в хорватській когорті пацієнтів із монокулярним невритом зорового нерва

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Мета. Визначити клінічний профіль пацієнтів з одностороннім невритом зорового нерва (ОНЗН) у нашій клініці та основні клінічні ознаки й демографічні дані, пов'язані з результатами гостроти зору за місяць.

Методи. Пацієнтів із підозрою на неврит зорового нерва, які звернулися в нашу клініку, послідовно оглядали для включення в дослідження з лютого 2017 року до листопада 2019 року. Гостроту зору вимірювали за допомогою таблиць Снеллена. Клінічні та демографічні дані, а також початкові дані й показники через один місяць було проаналізовано на основі багатовимірної моделі.

Результати. Загалом було включено 71 пацієнта, шість із яких вважали втраченими для подальшого спостереження. Середній вік пацієнтів – 50 років (міжкартильний розмах – 37-57 років), а співвідношення жінок до чоловіків становило 3:1. 14.1% пацієнтів мали серйозний напад, а 83.1% пацієнтів повністю одужали через місяць після встановлення діагнозу. Багатовимірний аналіз даних 65 пацієнтів виявив, що початкова гострота зору ураженого ока (P=0.011) і другого ока (P=0.015) були чинниками, які пов'язані з гостротою зору ураженого ока під час контрольного спостереження.

Висновок. Наша когорта пацієнтів була старшою за віком, мала вищий показник співвідношення жінок і чоловіків, і загалом менш серйозні клінічні прояви невриту зорового нерва порівняно з доповідями з інших країн. Початкова гострота зору ураженого та другого ока є провісниками відновлення гостроти зору через один місяць.

Ключові слова: оцінювання, результати пацієнтів, неврит зорового нерва, гострота зору.

The status of the unaffected eye is a predictor of short-term recovery in a croatian cohort of patients with monocular optic neuritis

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Aim. To define the clinical profile of patients with unilateral optic neuritis (ON) presented to our clinic and to identify baseline clinical features and demographic data associated with one-month visual acuity (VA) outcome.

Methods. Patients with suspected ON referred to our clinic were consecutively assessed for inclusion between February 2017 and November 2019. VA was measured using Snellen charts. Clinical and demographic, baseline and after one-month follow-up data were analyzed in a multivariate model.

Results. Overall, 71 patients were included, of which six were considered lost to follow-up. The median age was 50 years old (interquartile range 37-57 years old) and the female to male ratio was 3:1. 14.1 % had a severe attack and 83.1 % recovered completely one month after the diagnosis. Multivariate analysis of data from 65 patients showed that baseline VA of the affected eye (P=0.011) and fellow eye (P=0.015) were factors associated with VA of the affected eye at follow up.

Conclusion. Our cohort was older, had a higher female to male ratio and on average, a less severe ON clinical presentation compared to reports from other countries. Baseline VA of both the affected and fellow eye are predictors of one-month VA recovery.

Keywords: assessment, patient outcome, optic neuritis, visual acuity.

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Introduction

Optic neuritis (ON) is an inflammation of primary the optic nerve, typically represented with acute loss of vision combined with dyschromatopsia in predominantly one eye [1]. Loss of vision progresses over several days and is often followed by painful eye movements. Less common, ON can affect both eyes at the same time [2]. It is the most common first episode (clinically isolated syndrome) of multiple sclerosis (MS) and there is a 50% chance of developing MS in 15 years [3, 4]. Both of the conditions share inflammatory pathophysiology, which leads to demyelination and loss of neural cells [5]. It can be categorized as typical or atypical, based on clinical features. It takes on several forms depending on the affected structure, including retrobulbar neuritis, papillitis, perineuritis, and neuroretinitis [5]. ON diagnosis is made on the basis of history and clinical manifestations. Apart from systemic and neurological examinations, ophthalmological examinations are undertaken to quantify symptom severity. These include measures of visual acuity, color vision, contrast sensitivity, visual field determination, and additional diagnostic tests [5]. Although more than 80% of patients recover spontaneously within weeks, ON recurs in one-third of patients within 10 years and permanent visual loss is seen in 40-60 % of patients. There is no known cure for ON and, as in MS, steroid and immunomodulatory therapies are used to reduce the attack severity and prevent future episodes [1, 5, 6]. Current treatment regimens for ON are based on findings and recommendations from the Optic Neuritis Treatment Trial (ONTT) [7].

There are several known causes of ON, although most cases remain idiopathic [5]. Healthy female young adults make up the majority of five new yearly cases per 100 000, while the prevalence is 115 per 100 000 [1]. ON incidence was shown to be linked to geographical latitude, so that higher latitude countries have a higher incidence, a phenomenon also observed in MS [2]. As well, it was reported that MS incidence is linked to longitude, suggesting that ON incidence could vary between eastern and western parts of the world [2]. MS and ON are not considered to be hereditary diseases but genetic variations have been associated with greater risk and infectious agents have been considered as triggers [8, 9].

The aim of this study was to identify clinical predictors for short-term visual outcomes among patients with ON visiting our clinic.

Methods

Setting

This study was conducted at the outpatient ophthalmological clinic at Osijek Clinical Hospital Center. Eligible patients with suspected typical ON referred to our clinic were consecutively assessed for inclusion between February 2017 and November 2019. The study was approved by the Institutional Ethics Committee and all participants gave written informed consent.

Participants

Inclusion criteria were complaints of acute onset of monocular or binocular loss of visual acuity, pain during eye movement, and difficulty perceiving colors. All patients meeting the criteria underwent a clinical examination carried out by an experienced ophthalmologist followed by a systemic and neurological examination. Baseline demographic data were collected upon initial clinical examination. Ophthalmologic evaluation of both eyes included measuring best-corrected distance visual acuity (BCDVA) using a Snellen chart, contrast sensitivity and color vision testing, fundoscopy, afferent pupillary defect testing, and visual field (VF). The severity of ON attack was measured by loss of VA (mild ≤20/40, moderate 20/50-20/190, and severe ≥20/200) and recovery, respectively (complete ≤20/20, fair 20/40, and poor ≥20/50).

To assess exclusion criteria, additional diagnostic evaluation was performed, including visual evoked potential (VEP), optical coherence tomography (OCT), and magnetic resonance imaging (MRI) of the brain and orbit. Prolonged latency of the P100 response on the VEP was considered a necessary inclusion criterion and the assessment was performed following the previously established standard [10]. To assess the thickness of the retinal nerve fiber layer (RNFL), OCT was performed using the Copernicus HR (OPTOPOL Technology Sp. Zoo, Zawiercie, Poland) instrument. All MRI studies were performed on a 3T de-

vice (Magnetom Verio, Siemens Healthcare). Exclusion criteria included the presence of one or more of the following conditions: optic neuritis manifested on both eyes; hereditary, toxic, traumatic, ischemic, compressive, or infectious optic neuropathy; and other ocular and brain conditions that affect vision. Cases with incomplete data were excluded from the multivariate analysis.

All patients received intravenous methylprednisolone (250 mg every six hours for three days) followed by oral prednisone (1 mg per kilogram per day for 11 days, with subsequent tapering for four days). All examinations during follow-up visits included Snellen's VA, pupil evaluation, contrast sensitivity, color vision, and Goldman visual field (GVF).

Patients were scheduled for a follow-up examination one month after the initial examination.

Statistical analysis

Data were summarized as median (interquartile range – IQR) for continuous variables (none of the continuous variables had a normal distribution), and frequency (with 95% confidence interval (CI)) for categorical variables. Distribution normality was assessed using the Shapiro-Wilk test. Differences between medians were tested using the Mann-Whitney *U* test. We used a generalized linear model (multivariate analysis of variance) to assess predictors of outcome of interest. All variables included in the univariate analysis were also included in the multivariate model, regardless of their significance in the univariate comparisons, to identify the interaction between any of the variables (all interactions were considered biologically plausible). *P*-values <0.05 were considered statistically significant. All analyses were performed using the Statistical Package for the Social Sciences (SPSS) software version 17 (IBM Software, NY, USA).

Results

Seventy-one patients with clinically definite optic neuritis were included, of which 18 (25.4 %) were male. Their median age was 50 years old (IQR 37-57). Fifty-seven (80.3 %) had an MS diagnosis prior to developing ON. The baseline median VA on the affected eye was 0.70 (IQR 0.20-1.00) and 1.00 (IQR 1.00-1.00) on the fellow eye. Fifty-two (73.2 %) had a mild attack, nine (12.7 %) – moderate, and 10 – (14.1 %) severe attacks. The median main defect size of the affected eye (measured in 68 patients) was 5.65 (IQR 2.98-9.12) and

Table 1

Patient characteristics. Data are median (interquartile range) or count (proportion, 95% CI)

	N	Summary data		
Age (years)	71	50 (37-57)		
Sex (male)	71	18 (25.4; 15.8-37.1)		
MS at baseline	71	57 (80.3; 69.1-88.8)		
Baseline ophthalmological data				
VA of the affected eye	71	0.70 (0.20-1.00)		
VA of the fellow eye	71	1.00 (1.00-1.00)		
main defect of the affected eye	68	5.65 (2.98-9.12)		
main defect of the fellow eye	69	2.20 (0.60-5.85)		
attack severity		mild	moderate	severe
	71	49 (69.0; 57.0-79.5)	9 (12.7; 6.0-22.7)	13 (18.3; 10.1-29.3)
Follow-up data		*P*-value*		
VA of the affected eye	67	1.00 (0.80-1.00)	<0.005	
VA of the fellow eye	67	1.00 (1.00-1.00)	0.363	
the main defect of the affected eye	65	2.50 (1.20-4.85)	<0.001	
the main defect of the fellow eye	65	1.50 (0.20-2.75)	0.047	
recovery	67	complete	fair	poor
		59 (83.1; 72.3-91.0)	2 (2.8; 0.3-9.8)	6 (8.5; 3.2-17.5)

MS – multiple sclerosis; VA – visual acuity; *compared to baseline, Mann-Whitney *U* test

on the fellow eye (measured in 69 patients) – 2.20 (IQR 0.60-5.85). Follow-up data were complete for 65 patients, of which 59 (83.1 %) recovered completely. Median VA of the affected eye and mean main defects on both eyes significantly changed one month after diagnosis (data are summarized in Table 1).

Multivariate analysis showed that baseline VA of the unaffected and affected eye were statistically significant predictors of VA of the affected eye at the follow-up examination (Table 2).

Following GVF examination, 11 patients (15.5 %) had a centrocecal scotoma, 10 (14.1 %) had paracentral scotoma, eight had an enlarged blind spot (11.27 %), and eight had a defect of nerve fiber bundles (11.27 %), while other types of defects were less common.

Discussion

Our results from this study indicate that VA of the healthy eye could help predict visual acuity of the eye affected with ON one month after the diagnosis. Sex, age, MS at baseline, size of the main defect of the affected and unaffected eye were not significantly associated with VA of the affected eye on follow-up.

Research on the patient profile and factors associated with short-term outcomes is scarce and findings are diverse. It was shown earlier that clinical profiles of ON patients differ significantly between regions and countries and some geographic areas have been known for endemic distinctions in the clinical presentation of MS and ON [2]. To the best of our knowledge, this is a first prospective study on ON patients from Croatia (and the broader geographical region of southeastern Europe), which contributes data on initial clinical findings, patient characteristics, and early outcome of ON and analyzes factors associated with one-month recovery of VA. Although most ON patients recover spontaneously, those who fail to recover have permanent and severe eye damage. It was shown on animal models that corticosteroid treatment could prevent loss of retinal ganglion cells and affect long term outcomes [11]. In humans, the Optic Neuritis Treatment Trial (ONTT) results showed that corticosteroid treatment shortens the recovery period, but does not affect six-month or one-year visual outcomes [12].

Compared to reports from the ONTT, the milestone publication in this area of research, and Asian publications, our patients were significantly older [13-15]. Female preponderance was higher (3:1) than in the ONTT and Asian patients, but not as high as in African patients [16]. One recent report from China had a cohort with more male subjects [17]. In 2004, a group of Croatian authors described 127 cases over a 16-year period, which were younger and had a lower female/male ratio than our group [18].

Over 83% of our patients recovered completely one month after being diagnosed with ON. Although the follow-up in our study was much shorter than in other comparable published research, we can assume recovery rates would be close to the ONTT reports (93.3 % recovery after six months) [19]. Research from other countries showed much lower recovery rates. The Indian study reported a 64% recovery, Chinese – 52%, and only 27% of patients from the African cohort regained complete vision. In our study, 14.1% of patients had

Table 2

Factors affecting visual acuity of the affected eye after one month of treatment – summary of multivariate analysis on 65 patients with complete follow-up data

	Estimate (95% CI)	*P*-value
Age (years)	0.398 (-0.013 – 0.808)	0.058
MS (yes)	-0.041 (-0.119 – 0.037)	0.304
Male sex	-0.010 (-0.125 – 0.105)	0.864
VA of the affected eye	0.200 (0.045 – 0.355)	0.011
VA of the contralateral eye	0.463 (0.090 – 0.835)	0.015
the main defect of the affected eye the main defect of the contralateral eye	0.000 (-0.013 – 0.012) -0.010 (-0.029 – 0.009)	0.935 0.290

CI – confidence interval; MS – multiple sclerosis; VA – visual acuity.

a severe attack, a proportion lower than in other comparable studies [16, 17].

In the multivariate model, with one-month visual acuity set as a dependent variable, we found that VA of both the affected and the fellow eye were significantly associated with short term recovery of VA. This finding is consistent with ONTT findings, but we did not find the age to be associated with the outcome [19]. A Chinese study on bilateral ON similarly found VA at presentation, alongside disc swelling, to be significantly associated with VA recovery [16]. Likewise, a study on American patients showed that VA at presentation and in females are associated with more favorable outcomes of ON in patients with MS [20]. Apart from clinical findings, imaging and electrophysiological findings are likely to be predictive of ON outcomes as well [21].

Our study has some limitations since it had a short-interval follow-up and we included only patients with unilateral ON. Also, results of VEP testing, MRI, and OCT, all known to be related to outcomes, were only used for the assessment of exclusion criteria, and not included in the analysis. Nevertheless, the study results provide valuable data on the Croatian ON patient profile and its results suggest that VA of the unaffected eye could be predictive of the recovery of VA of the affected eye.

To sum up our study, we were able to show that our ON patients in Croatia have different sociodemographic characteristics, as compared to other countries. Moreover, the severity of clinical presentation seems to differ as well. However, we are cautious in drawing strong conclusions in this respect, due to the limited sample size and the resulting fragility of estimates. Finally, we have shown that baseline VA of both the affected and fellow eye are predictors of one-month VA recovery.

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