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Impact of additional intravenous methylprednisolone pulse therapy on the quality of life in patients with dysthyroid optic neuropathy

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ABSTRACT

Introduction. Dysthyroid optic neuropathy (DON) is a severe complication of Graves' orbitopathy (GO). Treatment of DON should involve immediate administration of intravenous methylprednisolone (ivMP) in very high doses. It is recommended to include additional 12 pulses of ivMP according to a weekly schedule as a further step of the treatment process. The purpose of this study was to evaluate the influence of a 12-week ivMP treatment on the quality of life (QoL) in DON patients.

Material and Methods. A retrospective study was conducted on 6 patients (the tests involved 8 individual eyes) with DON and treated with ivMP in very high doses, followed by orbital decompression in one patient. All patients were qualified for additional treatment with ivMP in a 12-week protocol and completed the Polish version of the GOQoL questionnaire before and after the therapy. Visual acuity (VA) and diplopia were examined prior to the administration of ivMP pulses for DON, as well as before and after the additional ivMP treatment.

Results. A minimal clinically important difference in QoL was observed in four patients at the end of the additional ivMP therapy. A significant increase in VA was observed following additional pulses of ivMP compared to the evaluation at the time of the DON diagnosis (p=0.04).

Conclusions. Applying additional 12 pulses of ivMP following DON therapy may impact QoL. Performing QoL assessment throughout the entire therapy in patients with DON is particularly important in the clinical practice. Final evaluation of QoL should be performed after completing the entire therapeutic process, which involves surgical treatment to correct diplopia.

Introduction

Graves' orbitopathy (GO) is an autoimmune orbital disorder manifested by disfiguring proptosis, diplopia, pain, redness and swelling of the eyelids [1,2]. The pathogenesis is based on inflammation, adipogenesis, and the production of glycosaminoglycans, which may lead to the expansion of the

orbital connective tissue and the enlargement of the eye muscles [3]. Approximately 5% of the GO patients suffer from dysthyroid optic neuropathy (DON). This sight-threatening complication results from optic nerve compression caused by swollen muscles and fat in the orbital apex [4,5]. The first-line treatment of DON recommended by the European Group on Graves' Orbitopathy (EUGOGO) consists of intravenous methylprednisolone (ivMP) pulse therapy (500–1000 mg for 3 consecutive days). In the case of poor or absent response within 2 weeks, urgent orbital decompression should be performed. Furthermore, it is recommended that patients with a complete recovery receive additional treatment with 12 pulses of ivMP scheduled every week [6].

Up to now, there are no data to verify the influence of additional therapy with ivMP in a 12-week protocol on the quality of life (QoL) in DON patients. Nevertheless, it has been found that moderate-to-severe GO negatively affects patients' well-being. Persons with GO suffer from poorer QoL, both with regard to vision problems and compromised appearance, compared to healthy individuals [7,8]. By means of the National Eye Institute Visual Function Questionnaire (NEI VFQ-25) Du Y et al. demonstrated that vision-related QoL tends to be more impaired in GO patients with DON than in those not suffering from DON [9]. However, NEI VFQ-25 is not a specific QoL questionnaire for patients with GO, and it does not concern some of the unique issues affecting patients with GO, such as altered appearance.

According to EUGOGO, the evaluation of QoL should constitute an integral part of management in patients with GO. Therefore, it is recommended to use specific GOQoL questionnaire, which has been proven to be valid, reliable, and culturally applicable[10]. In 2015 a validated Polish version of the GOQoL questionnaire (GOQoLpl) was developed and subsequently published by EUGOGO as the recommended version for the assessment of QoL among Polish patients with GO in the clinical practice [11]. Since the development of the GOQoLpl only a handful of studies evaluating QoL of GO patients have been conducted, and no study has been performed regarding DON.

The purpose of this study was to evaluate the impact of additional ivMP treatment in a 12-week protocol on the quality of life of DON patients.

Material and Methods

Patients

Six individuals diagnosed with DON were retrospectively recruited in the study. A total number of 8 eyes were affected by DON. Patients were treated in the Department of Internal Medicine and Endocrinology, Medical University of Warsaw, between 2015 to 2018. The diagnosis of DON was based on at least two features, such as deterioration of visual acuity (VA) (< 1.0) and/or colour vision, optic disc swelling and/or signs of DON in magnetic resonance imaging (optic nerve stretching and/or presence of apical crowding) [12]. The inclusion criterion was an additional treatment with ivMP in a 12-week protocol following the treatment of DON. The exclusion criteria were: a previous history of ivMP therapy for GO, as well as a lack of a completed GOQoL questionnaire before or after the additional treatment with ivMP.

Treatment

All patients were administered ivMP (3 × 1.0 g given within three consecutive days). Due to the poor improvement one individual received additional pulses of ivMP (3 × 1.0 g and 3 × 0,5 g – cumulative dose of 8 g) and another one underwent additional endoscopic intranasal orbital decompression. Subsequently each patient was qualified for treatment with 12 pulses of ivMP. Five patients received an additional cumulative dose of 4.5 g (0.5 g once weekly for 6 weeks, followed by 0.25 g once weekly for 6 weeks). One patient (treated with 8 g IVMP for DON) was qualified for 12 pulses of ivMP with a cumulative dose of 7.5 g (0.75 g once weekly for 6 weeks, followed by 0.5 g once weekly for 6 weeks), but due to the increased level of alanine and aspartate aminotransferases this patient received 9 pulses of ivMP.

Laboratory and ophthalmic evaluation

The serum levels of thyroid-stimulating hormone (TSH), free triiodothyronine (fT3), free thyroxine (fT4) and TSH binding inhibitory immunoglobulin (TBII) were evaluated with an electro-chemiluminescent immunoassay performed on a Cobas 6000 analyser from Roche Diagnostics (Mannheim, Germany).

VA of the patients' eyes diagnosed with DON was verified using Snellen charts and expressed

as a decimal fraction. The Gorman score was used to evaluate and classify diplopia graded from 0 – 3: 0–no diplopia, 1-intermittent diplopia, 2-inconstant diplopia, 3-constant diplopia [13]. Each parameter was assessed at three time points: prior to the administration of the first-line treatment with ivMP pulses for DON, before and after the additional ivMP treatment.

QoL questionnaire

At the beginning of and after the treatment with additional pulses of ivMP, all patients completed GOQoLpl. It consists of two subscales which assess: limitations in visual functioning (7 questions) and influence of the GO on appearance (8 questions). Each question is scored based on a 3-point scale referring to GO impact: 1–serious, 2-little, 3-no impact. The results are established on the basis of the following formula: (total score- #)/(2 × #) × 100 where # indicates the number of completed items. The total QoL score is expressed as a number between 0 to 100, where a higher result indicates better QoL.

According to Wiersinga et al., a minimal clinically important difference (MCID) in the GOQoL for immunosuppression and surgical decompression is a change of ≥ 10 points [14].

Statistical analysis

All the analyses were performed using SPSS statistical software version 22.0 (IBM SPPS Statistics, New York, US). The results were expressed as a mean (± standard deviation) except for the GOQoL score, which was expressed as a median (interquartile range). Categorical variables were expressed as numbers (n) and percentages (%). The Shapiro-Wilk test was applied to confirm or reject the normal distribution of each continuous variable. Comparisons between continuous data were performed using a paired t-test (for parameters with normal distribution), or the Wilcoxon rank sum test (for parameters with the distribution deviations). Statistical significance was established for the results with $p<0.05$.

Results

The demographic details and clinical characteristics are presented in Table 1. DON was diagnosed in 6 patients in the total of 8 eyes (2 patients with bilateral DON and 4 patients with unilateral DON). VA significantly increased following the additional treatment with ivMP compared to the baseline evaluation at the time of the diagnosis of DON

Table 1. Baseline demographic and clinical characteristics at three time points: prior to the administration of ivMP for DON, before and after the additional treatment with ivMP pulses

Demographics			
Age, years[a]	69.33 (±5.79)		
Male/female[b]	2/4		
Number of eyes with DON	8		
	0	**I PULSE**	**LAST PULSE**
Clinical characteristics of thyroid disease			
TSH (0.27–4.2 μIU/mL)[a]	1.14 (±1.42)	0.68 (±0.52)	1.21 (±0.79)
fT3 (3.1–6.8 pmol/L)[a]	4.64 (±1.80)	4.66 (±1.33)	4.33 (±0.94)
fT4 (12–22 pmol/L)[a]	19.06 (±4.28)	15.72 (±2.61)	17.37 (±3.33)
TBII (< 1.75 IU/L)[a]	10.44 (±7.17)	6.24 (±4.12)	3.47 (±2.53)
Clinical characteristics of orbital disease			
Gorman score[b]			
No diplopia	*3*	*1*	2
Intermittent diplopia	*1*	*1*	1
Inconstant diplopia	*1*	*1*	1
Constant diplopia	*1*	*3*	2
Visual acuity[a]	*0.58 (±0.27)*	*0.78 (±0.29)*	0.83 (±0.23)

[a] Data are presented as means (± standard deviation). [b] Data indicate the number of patients
ivMP: intravenous methylprednisolone, DON: dysthyroid optic neuropathy. 0: diagnosis of DON, I PULSE and LAST PULSE: before and after the additional treatment with ivMP pulses respectively

(p=0.04). A significant improvement has not been observed either between the assessment prior to the treatment of DON and the beginning of the additional therapy (p=0.125), or between the 1st and the last pulse of the additional therapy (p=0.18). Mean values of VA are shown in Figure 1.

All six patients completed GOQoLpl. The median GOQoLpl total score, as well as subtotals for visual functioning and appearance before and after the ivMP treatment are provided in Figure 2. MCID was observed in four patients (2 patients – an improvement of QoL, 2 patients – a dete-

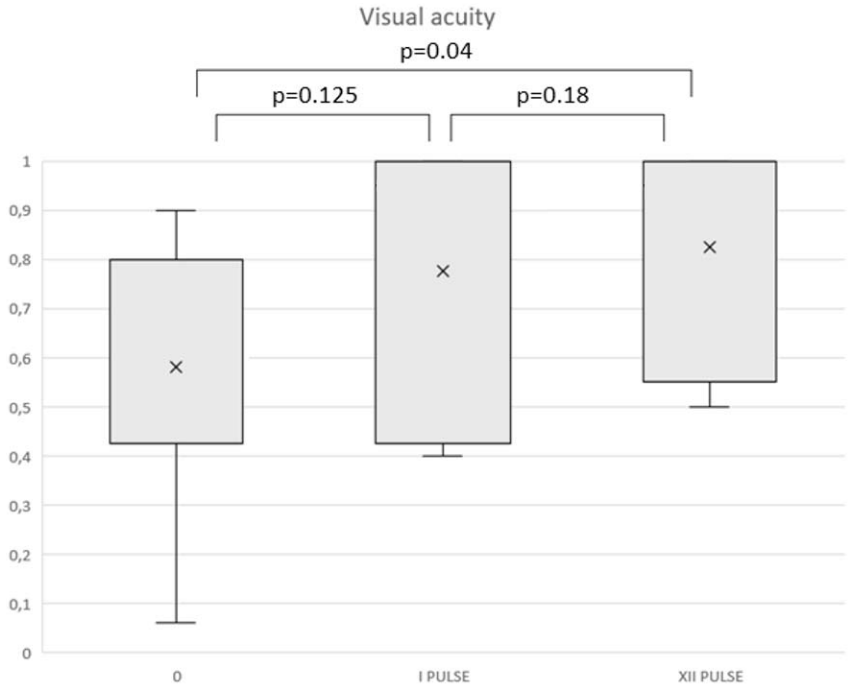

Figure 1. Visual acuity of 8 eyes in patients diagnosed with dysthyroid optic neuropathy (DON). A comparison of variables between the time of the diagnosis of DON (0), the 1ST and the last pulse of additional intravenous methylprednisolone treatment. Vertical line ranges from a maximum to a minimum value. Bold square presents a standard deviation. x – mean

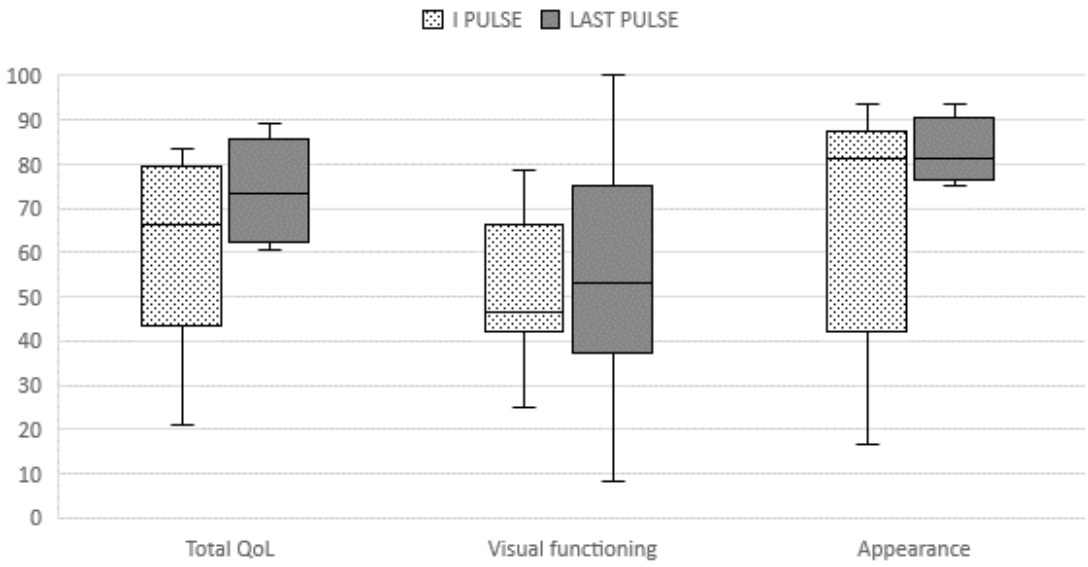

Figure 2. Total Graves' Orbitopathy Quality of Life (QoL) questionnaire score and its subscales: visual functioning and appearance were based on the following formula: (total score- #)/(2 × #) × 100 where # indicates the number of completed items. The total QoL score varies from 0 to 100. Higher result indicates better QoL. A comparison of variables between the 1ST and the last pulse of intravenous methylprednisolone treatment. Vertical line ranges from maximum to minimum value. Data are shown as median values (line across the box) with interquartile (25th – 75th percentile) range (the box)

rioration of QoL). In two patients MCID was not detected.

One of the patients with a deterioration of QoL after the additional treatment, who initially exhibited monocular vision in the course of DON, developed diplopia, due to the improvement of VA during the additional treatment. Furthermore, we found a reduction of eye motility with a deterioration of diplopia in another patient.

Discussion

According to the EUGOGO, the treatment of DON involves immediate administration of ivMP in very high doses followed by urgent orbital decompression as a second-line treatment in the case of poor, or absent response within 2 weeks. Subsequently, patients with a complete recovery should be qualified for additional ivMP pulses in a 12-week protocol [6]. The main purpose of the additional therapy is to maintain the clinical improvement and minimize the inflammatory process. Nevertheless, its impact on QoL of the patients with DON has not been investigated until now.

Our study, performed on 6 patients with DON, showed no significant influence of the additional ivMP therapy on QoL. Simultaneously, an improvement in VA following the treatment was observed. A detailed analysis revealed that a decreased QoL after the additional treatment was associated with an exacerbation of diplopia and reduced motility of the eye muscles, which possibly deteriorated QoL, despite the improved VA. Furthermore, in some cases, the use of ivMP in high doses may lead to various side effects which can also interfere with QoL following the treatment [15], although generally it is considered to be highly efficient and mostly safe [16].

Results

The results of this study indicate that an additional 12-week ivMP treatment should constitute an integral part of the strategy in the management of DON. In terms of analysing a comprehensive therapy of DON, we should also consider involving rehabilitative surgery of the extraocular muscles. As demonstrated in our study, some patients consider the presence of diplopia to be a more relevant factor when assessing QoL, rather than improved VA. Therefore, strabismus surgery may have a positive impact on QoL.

To our knowledge, it is the first report evaluating changes in QoL in DON patient following the treatment with 12 pulses of ivMP. The main limitations of our study are its retrospective character and the small sample size. Nevertheless, the following conclusions may be drawn.

Conclusions

Including the additional 12 pulses of ivMP into combined therapy of DON may impact QoL. The assessment of QoL is, therefore, particularly important and should constitute an integral part of routine clinical practice. For some patients, diplopia or decreased eye motility become the main factor deteriorating QoL following the therapy, despite increased VA. The final evaluation of QoL should be performed after completing the entire therapeutic process, which involves surgical treatment to correct diplopia.

Following the first and second-line treatments of DON, a multidisciplinary and individual approach is necessary to maximize the potential improvement of signs and symptoms of the disease.

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Conflict of interest statement
The authors declare no conflict of interest.

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