ORIGINAL ARTICLE

UDC: 616.441-008.61:617.7]:615.357
DOI: 10.2298/VSP1203249J

Evaluation of the patients with Grave's ophthalmopathy after the corticosteroids treatment

Ocena bolesnika sa Grejvsovom oftalmopatijom posle lečenja kortikosteroidima

Mirjana Janićijević Petrović*†, Tatjana Šarenac*†, Sunčica Srećković*†, Marko Petrović*†, Dejan Vulović*†, Katarina Janićijević*†

***Ophthalmology Clinic, Clinical Centre Kragujevac, Kragujevac, Srbija; †Medical Faculty, University of Kragujevac, Kragujevac, Srbija**

Abstract

Background/Aim. Graves' ophthalmopthy is one of the most common causes of exophthalmos as well as the most common manifestation of Graves' disease. The treatment of Graves' ophthalmopathy includes ophthalmological and endocrinological therapy. The aim of this study was to clinically evaluate the patients with Graves' ophthalmopathy treated with corticosteroids. **Methods.** Evaluation of 21 patients was performed in the Ophthalmology Clinic and Endocrinology Clinic, Clinical Centre Kragujevac, in the period from 2009 to 2010. They were treated with pulse doses of intravenous corticosteroids. They were referred to ophthalmologist by endocrinologist in euthyroid condition in the active phase of Graves' ophthalmopathy (ultrasonography of orbit findings and positive findings of antithyroid stimulating hormone receptor antibody – anti-TSH R Ab). The clinical activity score (CAS) and NO SPECS classification for evaluation of disease severity were used. Ophthalmological examination includes: best corrected visual acuity, slit-lamp exam, Hertels' test, direct ophthalmoscopy and ultrasonography of the orbit. **Results.** According to our results 76.19% of the patients were female; mean age of the patients was 35.2 ± 5.6 years. According to CAS classification after 6 months of the treatment recovery was shown in 23.81% of the patients, partial amelioration in 47.62% and no clinical amelioration in 28.57% of the patients. We achieved better results with male, young patients with high clinical activity score. Good results were observed after the first dose of corticosteroids, much better CAS after the third dose, which maintained until 6 months after the first treatment. **Conclusion.** Our results signify that intravenous pulse dose of corticosteroids treatment of the patients with Graves' ophthalmopthy is safe, comfortable, clinically justified and accessible for the clinicians and patients. Positive results are achieved after the first dose with increasing trend up to the third dose, which was maintained for the next three months.

Key words:
graves ophthalmopathy; thyrotropin; antibodies; severity of illness index; classification; adrenal cortex hormones; convalescence.

Apstrakt

Uvod/Cilj. Grejvsova oftalmopatija najčešći je uzrok egzoftalmusa i najčešća ekstratireoidna manifestacija bolesti. Za lečenje aktivne faze bolesti koriste se kortikosteroidi. Cilj rada bio je evaluacija lečenja bolesnika sa Grejvsovom oftalmopatijom tretiranih kortikosteroidnom terapijom. **Metode.** Ispitivan je 21 bolesnik u aktivnoj fazi bolesti, koji su u eutireoidnom statusu tretirani pulsnim dozama intravenskih (*iv*) kortikosteroida u Klinici za oftalmologiju i Klinici za endokrinologiju Kliničkog Centra Kragujevac, od 01. 01. 2009. do 31. 12. 2010. Aktivnost Grejvsove oftalmopatije potvrđena je ultrazvučnim pregledom orbite (oftalmolog) i određivanjem koncentracije antitela na receptore tireostimulišućeg hormona (TSH) ab (endokrinolog). Procena aktivnosti bolesti određivana je skorom kliničke aktivnosti (*Clinical Activity Score* – CAS), a stepen težine bolesti NO SPECS klasifikacijom koja određuje kliničke aspekte ispitivanja i praćenja oftalmopatije. Klinički pregled oftalmologa obuhvatao je: određivanje vidne oštrine, biomikroskopski pregled, direktnu oftalmoskopiju, egzoftalmometriju i ultrazvučni pregled orbite. **Rezultati.** Među ispitanicima bilo je 76,19% pripadnika ženskog pola. Prosečna starost bolesnika bila je 35,2 ± 5,6 godina. Analiza podataka prema CAS klasifikaciji, posle šest meseci pokazala je: potpuni oporavak kod 23,81% bolesnika, a kod 47,62% parcijalni oporavak, dok kod 28,57% bolesnika nije bilo kliničkog poboljšanja. Bolji terapijski rezultati postignuti su kod pripadnika muškog pola, mlađih, sa većom kliničkom aktivnošću bolesti. Prvi pozitivni rezulati postižu se nakon prve doze kortikosteroida, bolji posle treće doze, a održavaju se na nivou, šest meseci posle prve doze lečenja. **Zaključak.** Naši rezultati ukazuju na visoku efikasnost lečenja bolesnika sa Grejvsovom oftalmopatijom primenom *iv* pulsnih doza kortikosteroida. Ovakav tretman je bezbedan i komforan i za lekara i za bolesnika. Pozitivni rezutlati vidljivi su već posle prve doze kortikosteroida uz tendenciju poboljšanja posle treće doze, što se održava tokom sledeća tri meseca.

Ključne reči:
gušavost, egzoftalmička; tireotropin; antitela; bolest, indeks težine; klasifikacioni indeksi; kortikosteroidni hormoni; oporavak.

Correspondence to: Mirjana A. Janićijević Petrović Ophthalmology Clinic, Clinical Centre Kragujevac, Kneza Miloša 3/1, 34 000 Kragujevac, Srbija. Phone: +381 66 013 691, +381 34 370 037. E-mail: mira.andreja@yahoo.com

Introduction

Graves' ophthalmopathy (GO) is one of the most common causes of exophthalmos and the most common cause of morbidity and discomfort in patients with Graves' disease [1]. The first document about Graves' disease was found in 1786 by Perry, but a complete clinical manifestation was described in 1835 by Basedow [2]. Ophthalmopathy is a manifestation of autoimmune process with the expressed extraocular myositis, glicosaminoglican production, orbital congestion and mononuclear orbital infiltration. The main causes of GO are genetic (positive findings of HLA-A8, HLA-DR3) and the influence of surroundings (stress, smoking cigarettes, infection) [3]. The disease is more frequent in female patients, with the ratio 3–10 : 1, and the mean age is 41 years, 2.5 years after the beginning of the disease. The more difficult form of the disease is described in male patients, at the age of 50 [3]. Clinical manifestation of the disease is typical and self-limited with active (progressive exacerbation) and inactive phase (regression and stagnation). Werner et al. [4] classified clinical signs of the disease in NO SPECS system, and classification was modified in 1981 to RELIEF classification. The clinical activity score (CAS) is based on 4 of the 5 classical signs of inflammation and has 10 well-known items. For each item, one point can be given. The sum of these points is CAS (range 0–10) [5, 6]. The diagnosis can be proved by endocrinologist and ophthalmologist. Computerized tomography (CT) and nuclear magnetic resonance (NMR) are reserved for unclear clinical manifestations of the disease [7]. Intravenous (*iv*) pulse doses of corticosteroids are used for the treatment of the active phase GO. Their action is mediated by inhibition of polymorphonuclear migration [8]. Side effects of corticosteroid treatment are rarely reported. Some of them like weight gain, hypertension, diabetes mellitus induction, pyloric ulcer, osteoporosis and the most difficult of them – fatal autoimmune hepatitis, can be notified [9]. Indications for this treatment are: euthyroid condition of patients, positive findings of anti thyroid stimulating hormone receptor anti-body (anti-TSH R Ab), extraocular muscle hypertrophy without fibrosing.

The aim of our study was to evaluate the patients with GO treated with corticosteroids *iv* pulse doses of.

Methods

We examined 21 patients with the active phase of GO in euthyroid condition, treated with *iv* pulse doses of corticosteroid therapy in the Ophthalmology Clinic and Endocrinology Clinic, Clinical Centre Kragujevac, from January 1, 2009 until December 31, 2010. The active phase of GO was confirmed by orbital ultrasonography, positive finding of anti-TSH R Ab and clinical activity was classified by CAS and disease degree was classified by NO SPECS classification (Tables 1, 2). Ophthalmological examination included: best corrected visual acuity (Snellen table), slit-lamp examination, direct ophthalmoscopy, Hertels' exophtalmometry and orbital ultrasonography. The patients were referred to ophthalmologist by endocrinologist with a detailed endocrinological status. All the patients were classified according to the duration of the disease into 3 groups: 1 – duration less than 1 year, 2 – duration from 1 to 2 years and 3 – duration for more than 2 years. The patients with active phase GO were treated with *iv* pulse doses of corticosteroids with Ethical Committee approval. We used *iv* pulse doses of corticosteroids (methylpredisolone 1 g/24 h for 3 days) followed by corticosteroides *per os*, 40 mg/24 h seven days, with a decreasing dose for 10 mg every week to the next pulse dose. Our patients were treated with 3 cycles of pulse dose every fourth week. Before the treatment the patients were examined for the clinical parameters: arterial pressure, glycemia and the serum liver enzymes level, as well as basic blood examination. During the treatment, there were no complications related to the corticosteroid therapy. The patients were ophthalmologically examined after 4 weeks, 3 and 6 months. We evaluated CAS and NO SPECS signs values in our patients analyzed by SPSS, version 13.

Table 1

NO SPECS (underlined first letter) and RELIEF (bolded first letter) categorization of Graves'ophthalmopathy

Classification	Signs and symptoms
0	No signs and symptoms
1	Only signs are upper eyelid retraction
2	Softe tissue signs and symptoms
	Resistance to retropulsation
	Edema of conjunctiva or caruncula
	Lacrimal gland enlargement
	Injection over the horizontal rectus muscle insertion
	Edema of eyelid
	Fullness of the eyelid
3	Proptosis
4	Extraocular muscle involvement
5	Corneal involvement
6	Sight loss

Table 2

Clinical Activity Score

Symptoms/Signs	Description
Pain	1 – Painfull, oppresive feeling on or behind the globe, during the last
	2 – Pain or attempted up, side or down gaze, during the last 4 weeks
Redness	3 – Redness of the eyelid(s)
Swelling	4 – Diffuse redness of the conjunctiva, covering at least one quadrant
	5 – Swelling of the eyelid
	6 – Chemosis
	7 – Swollen caruncle
	8 – Increase of proptosis of ≥ 2 mm during 1–3 minutes
Impaired function	9 – Decrease of eye movements in any direction ≥ 5°, 1–3 months
	10 – Decrease of visual acuity of ≥ 1 line on Snellen chart (using pinhole), 1–3 months

Results

According to our results, 16/21 (76.19%) of the patients were female, with a clinically significant manifestation of the disease ($\chi^2 = 5.762$, $p = 0.016$). The mean age of the patients was 35.2 ± 5.6 years. Clinical activity measured by CAS was ≥ 4 in 80.95%. According to NO SPECS classification, 71.43% of the patients had class 2 of the disease with a significant differences ($\chi^2 = 14$, $p = 0.001$). There were 14.28% of the patients in the third class and 19.04% patients in the first class. There were no patients in the lower class of the NO SPECS classification. After 4 weeks of the treatment there were no statistically significant differences about the distribution of patients by NO SPECS classification (in the class 0 – 19.04%, class 1 – 42.86%, class 2 – 33.33%, class > 3 – 4.76%; $\chi^2 = 7.0$, $p = 0.072$). After the third *iv* pulse dose of corticosteroids, a great number of the patients was in the class 1 – 38.10%, then in the class 2 – 33.33% with increasing number of patients in the class 0 – 28.57%, but with no statistically significant differences ($\chi^2 = 0.286$, $p = 867$). After 6 months, a great number of the patients was in the class 1 – 47.62%, in the class 2 – 23.81%, but without patients in the hardest class 3, with no statistically significant differences ($\chi^2 = 2.0$, $p = 0.368$) (Table 3). According to our results classified in CAS, best results were reached after 6 months – complete remission in 23.81%, partial remission in 47.62%, without remission in 28.57% of the patients, without statistically significant differences ($\chi^2 = 2.0$, $p = 0.368$). The results after 4 weeks were: complete remission in 19.04%, partial remission in 42.86%, without remission in 38.10% of the patients, with no statistically significant differences ($\chi^2 = 2.0$, $p = 0.368$). After 3 months we achieved complete remission in 23.81%, incomplete remission in 42.86%, no remission in 28.57%, without statistically significant differences ($\chi^2 = 2.0$, $p = 0.368$). It means that many clinical signs decreased in their manifestation after corticosteroid treatment. After 4 weeks of the beginning of the treatment we summarized the number of patients with a complete and incomplete remission, when we reached no statistically significant differences ($\chi^2 = 5.762$, $p = 0.275$), but after 3 and 6 months we got statistically significant differences in the number of patients with complete and incomplete remission ($\chi^2 = 3.857$, $p = 0.005$). There were no statistically significant differences in these analysis, but we were able to notify great changes in the variables during the examination, with a significantly better clinical status of the patients after the first dose of the *iv* pulse dose of corticosteroids, with increasing trend after the second and the third dose maintained until 6 months after the beginning of the treatment. A complete and incomplete remission was achieved in male patients. A complete remission was achieved in 19.04% of females, incomplete remission in 28.57%, without remission in 28.57%. According to these results we can notify that at the very beginning of the corticosteroid treatment a great number of patients had incomplete remission with trend for increasing effectiveness of the therapy. A complete remission was achieved in 14.28% of all patients younger than 40 years, followed by 33.33% with incomplete remission. All the patients without remission were older than 40 years. There was a significant difference related to the age of the patients and the results of the therapy. The group of the younger patients (< 40 years) had better results ($\chi^2 = 12.095$, $p = 0.02$). A complete recovery was noted in the group with CAS > 4, incomplete in 33.33 % of the patients with CAS > 4 and in 14.28% of patients with CAS ≤ 4, but all the patients without recovery had CAS ≤ 4 (Table 4). There were no significant differences between the duration of the disease and the results of the therapy. In the group of patients with the duration of the disease less than 2 years, complete recovery was achieved in 9.52%, incomplete in 19.05% and without recovery in 2 patients. In the group of patients with the disease

Table 3

Distribution of patients according to NO SPECS classification, after 4 weeks, 3 and 6 months

Duration of drug therapy	NO SPECS classification*			
	0	1	2	≥ 3
Before treatment		4	15	2
After 4 weeks	4	9	7	1
After 3 months	6	8	7	
After 6 months	5	10	6	

***see Table 1**

Table 4

Effects of the therapy according to the CAS classification, sex, age and disease degree

Parameters	Recovery (number of patients)			
	complete	incomplete	partial	no recovery
Duration of drug treatment				
after 4 weeks		4	9	8
after 3 months		5	9	7
after 6 months		5	10	6
Sex				
male	4		1	0
female	4		6	6
Age (years)				
> 40	2		3	5
< 40	3		7	1
CAS*				
≤ 4			3	6
< 4	5		7	

***see Table 2**

duration of one to two years, complete recovery was achieved in 9.52%, incomplete in 14.28% and without recovery in 9.52% of the patients. In the group of patients with the disease duration more than 2 years, complete recovery was noted in 4.76%, incomplete in 14.28% and without recovery in 2 patients.

Before the treatment all the patients were examined (arterial pressure, blood examination, liver enzimes). All the patients were treated with gastroprotective therapy. Cushingoid syndrome was detected in 18 (85.71%) patients, but after the treatment it was regulated. During the treatment transitorial hypertension was notified in 2 patients, but arterial preassure was regulated at the end of the treatment. We notified weight gain in all the patients, but after 3 months of the treatment it was also regulated. There were no elevation of the serum liver enzimes values.

Discussion

Rundle at all. [10] notified that Graves' ophthalmopathy has two phases, interrupted with a "plate" phase: initial phase with high activity after 6–24 months from the beginning of the disease and the phase of incomplete regression. Early symptoms are a consequence of autoimmune process and inflammation. The later ones are a consequence of the fibrosing process. Some earlier studies indicated that there is no correlation between the disease duration and the treatment effects as well as in our study [6]. The active phase of GO can be treated with corticosteroids and the late one can be treated with radiation and surgical therapies [11]. Peroral steroids were used for the treatment of the active phase of GO, but better results were achieved with intravenous steroids [11]. There are some data about using rituximab (anti-CD20), etancerot (anti-TNF), octreotide, somatostatin, plasmapheresis, etc. [3, 12]. Corticosteroid therapy in our opinion has many advantages, such as lower costs and lower number of side effects and contraindications [11]. Very important predictive factor for the efficiency of corticosteroid therapy are CAS values. Good results were noted in the group of patients with CAS > 4 and bad results in the group with CAS ≤ 4. In this fashion our results are similar to other records [13]. The majority of the patients were younger female patients (< 40 years). The best results were noted in younger male patients (< 40 years). The efficacy of the therapy in the female group was 66.66%. Incomplete recovery was noted in 76.19% of the patients with lower CAS values, according to other investigations [13]. The younger patients had better effects of the corticosteroid therapy. Euthyroid status of the patient was of great importance during the whole therapy in our investigation.

Conclusion

Our results signify that intravenous pulse dose of corticosteroids treatment of the patients with Graves' ophthalmopthy is safe, comfortable, clinically justified and accessible for the clinicians and patients. Positive results are achieved after the first dose with increasing trend up to the third dose, which was maintained for the next three months.

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Received on March 07, 2011.
Accepted on July 1, 2011.