Lečenje retrobulbarnog neuritisa u sklopu multiple skleroze kortikosteroidima i interferonom $\beta 1b$

Treatment of retrobulbar neuritis in multiple sclerosis with corticosteroids and interferon $\beta 1b$

Mirjana A. Janićijević-Petrović^{1,2}, Tatjana Šarenac-Vulović¹, Katarina M. Janićijević², Dejan Vulović^{1,2}

1. Klinika za oftalmologiju, Klinički centar "Kragujevac", Kragujevac
2. Fakultet medicinskih nauka Univerziteta u Kragujevcu, Kragujevac

PRIMLJEN 28.11.2012.
PRIHVAĆEN 22.02.2013.

APSTRAKT

Cilj. Retrobulbarni neuritis je zapaljenje očnog nerva koje se lokalizuje iza očne jabučice. Pacijenti sa multiplom sklerozom su adekvatni za naše ispitivanje, zbog dobro poznate povezanosti ove dve bolesti.

Metode. U studiju je uključeno 64 pacijenta, podeljenih u 4 grupe, poslednjih 5 godina, tokom hospitalizacija i ambulantnih kontrola. Analizirali smo demografske karakteristike, neurooftalmološku kliničku simptomatologiju, dijagnostičke testove i efektivnost lečenja.

Rezultati. Najveći broj pacijenata su bile mlađe žene, urbanih regiona, lečene pretežno u zimskom periodu kalendarske godine. Temporalno bledilo glave optičkog živca bio je uvek prisutan klinički status. Pad vidne oštine zabeležen je kod 64% ispitanika, pozitivan MRI nalaz nađen je kod 56%, a pozitivan nalaz u likvoru kod 43% ispitanika. Pozitivan VEP - nalaz bio je kod 84%, očne sekvele kod 67%, a neurološki poremećaji kod 48% ispitanika. Incidenca recidiva retrobulbarnog neuritisa zabeležena je kod 16% pacijenata sa normalnim MRI nalazom tokom pet godina. Nakon kortikosteroidnog tretmana pojava plakova bila je odložena za oko 2 godine kod gotovo svih pacijenata. Klinički oporavak pacijenata bio je za 2 - 3 nedelje posle kortikosteroidne terapije. Efektivnost interferonske terapije sa interferonom beta-1b zabeležena je kod 76% ispitanika. Kod naših ispitanika elongacija relapsing-remiting perioda kod neuritisa retrobulbarisa u sklopu evolucije multiple skleroze je bila oko 2 godine.

Zaključak. Retrobulbarni neuritis je značajan zdravstveni problem kod mnogih bolesnika sa multiplom sklerozom.

Ključne reči: optički neuritis; multipla skleroza; interferoni.

Mirjana A. Janicijevic-Petrovic^{1,2}, Tatjana Sarenac-Vulovic¹, Katarina M. Janicijevic², Dejan Vulovic^{1,2}

1. Clinic of Ophthalmology, Clinical Centre "Kragujevac", Kragujevac, Serbia
2. Faculty of Medical Sciences University of Kragujevac, Kragujevac, Serbia

RECEIVED 28.11.2012.
ACCEPTED 22.02.2013.

ABSTRACT

Objective. Retrobulbar neuritis is the inflammation of optical nerve which is localized behind the eye. Patients with multiple sclerosis are adequate for our examination, because of well-known association between these two diseases.

Methods. The study included 64 patients, divided in 4 groups, during last five years, during hospitalizations and outpatient controls. We analyzed demographic characteristics, neuro-ophthalmological clinical symptoms, diagnostic tests and the effectiveness of therapy.

Results. The greatest number of patients was young women, from urban regions, treated primarily during the winter time of the year. Temporal pallor of optic head was always present in clinical status. The loss of visual acuity appeared in 64%, MRI findings were positive at 56%, positive cerebrospinal fluid findings were at 43% subjects. VEP examination was positive at 84%, ocular sequels at 67% and neurological disturbances occurred in 48% subjects. Incidence of relapse of retrobulbar neuritis was found in 16% of patients with normal MRI in the period of five years. After the treatment with corticosteroids, the appearance of plaques was delayed for 2 years at almost all patients. A good recovery of patients appeared after 2-3 weeks of corticosteroid treatment. The good results with interferon beta-1b therapy were achieved in 76% of patients. In our patients, prolongation of relapse-remitting status of retrobulbar neuritis during multiple sclerosis evolution was about 2 years.

Conclusion. Retrobulbar neuritis is an important health problem in many patients suffering from multiple sclerosis.

Key words: optic neuritis; multiple sclerosis; interferons.

KORESPONDENCIJA / CORRESPONDENCE

Prof. dr Mirjana A. Janićijević-Petrović, Kneza Miloša 3/1-1, 34000 Kragujevac, Tel: 034370073, 066013691, E-mail: mira.andreja@yahoo.com

Prof. Mirjana A. Janicijevic-Petrovic, MD, PhD, Kneza Milosa 3/1-1, 34000 Kragujevac, Serbia, Phone: +38134370073, +38166013691, E-mail: mira.andreja@yahoo.com

INTRODUCTION

Retrobulbar neuritis is mainly an inflammatory disease of the optic nerve. Medical and social interests for this disease are in great expansion. At the first phase of the disease, there are no clear clinical signs on the optic nerve head, but at the later stage we can find temporal pallor of the optical nerve head (PNO), with clear borders, presence of lower visual acuity, which depends on the number of lost nerve fibers.¹ The vascular component of retrobulbar neuritis is explained with clinical anatomy of Haller-Zinnia ring. Ophthalmologist describes pallor of the PNO, reduction of the PNO vessels, regional or diffused thinning of the nerve fibers, according to the etiology and the level of lesions.² The most common type of the disease is multifocal demyelization neurodegenerative process. Fibrous multifocal acute or chronic plaque, formed by atrocities reduces conduction in terminal synapse of the optical nerve. The same process is in the brain and spinal cord. The travel of the cytoplasmic organelles of the peripheral nerves is still preserved. MS is still the great challenge for neurology-ophthalmologists, as a hereditary, autoimmune, unpredictable and complex disease. The clinical subtypes of MS are isolated, primary or secondary progressive and remitting disease.³ Kurtzke's Functional Systems Scale and Expanded Disability Status Scale (EDSS) with score from 0 to 10 is used for standardization of the disease progression.⁴ The complexity of the medical treatment includes, besides the corticosteroids, oral interferon's therapy, treatment with monoclonal antibodies, stem cell transplantation, adjuvant therapy, etc. Interferon, like nonspecific cytokine, suppressed autoimmune reaction with antiviral, antibacterial, antiproliferative and antitumor action.⁵

The recognizable trend of this disease is a well-known trend among physicians. Therefore main goal of our study was to examine the efficiency of corticosteroid and the interferon's therapy at patients with retrobulbar neuritis and multiple sclerosis. Achieved perpetual therapy is very important for neurology-ophthalmologist and is the guaranty for better quality of life of the patients.

PATIENTS AND METHODS

We analyzed 64 patients, divided in four groups, in our region, in the period from 2005 to 2010. We made standardized clinical protocol for each patient. We did check-up of every patient in the cyclic for 1 to 3 months, for correlation of the treatment efficiency. We also analyzed demographic characteristic, neurology-ophthalmo-

logical and others clinical manifestation of the disease, diagnostic and laboratory tests. The examination of the visual acuity was performed by Jigger's table. The color examination was done by Ichihara's table. The visual field was examined by Humphrey's perimeter. We also performed the examination by Amsler's test, Hess-Lancaster test, fluorescent-angiography, measuring the intraocular pressure, Hertel's ophthalmometry as well as optical coherence tomography. Our patients underwent complete examination. The examination of the liquor includes IgG, IgG index and myelin basic protein level, examination of oligoclonal band and complete immunological analysis of the blood. MRI was done for every patient, with T1 and T2 profiles. We performed VEP investigation with 100-flash stimulation, with evaluation of the latency time and amplitude of the reaction. We started our treatment at patients with visual acuity less than 0.1 - 0.5. The first group of patients was treated with corticosteroids (methylprednisolone-sodium-succinate, 2g/24h, i.v. for 3 - 7 days, then prednisolone 1mg/kg/24h p.o. for more than 11 days), second group with interferon therapy (Betaseron®, 8 - 16 million IU/mL, s/c for every second day), third group with adjuvant therapy (vasoactive drugs, minerals, vitamins) and the fourth group with combined therapy (combination of the corticosteroids and adjuvant therapy).

RESULTS

Distribution according to sex among our patients showed that women prevailed (38 patients), figure 1.

Figure 1. Distribution of the patients according to sex

Distribution according to age showed that the great number of patients were between 30-45 years old, figure 2.

Figure 2. Distribution of the patients according to age

Most of patients were from industrialized region (urban). We noticed that the incidence of disease was higher during winter, with disease peak in December, statistically significant (T test, $p < 0.05$), figure 3.

Figure 3. Peak of the disease per months

Temporal pallor (unilateral or bilateral) of the optic head was present in all patients. Visual acuity distribution was L+P at 26 patients, 0.1-0.2 at 15 patients, 0.3-0.5 at 16 patients, >0.5 at 7 patients. Other visual disturbances were distributed as: disturbances in color vision - 62 patients, scotoms - 61 patients, painful eye movement at 49 patients, late recidivate at 28 patients, figure 4. (T test, $p < 0.01$).

Figure 4. The clinical symptoms

MRI showed demyelization plaques at 56 patients, figure 5.

Figure 5. Magnetic resonance imaging – diagnosis

Analysis of focus was detected at 8 patients, as the background for the disease, liquor presented oligoclonal bands at 43 patients, figure 6, (x2test, $p < 0.01$).

Figure 6. Liquor – diagnosis

Pathological results of VEP were inherent at 89%. Eye sequels were positive at 60% and neurological sequels were positive at 40%. 18% of patients had intellectual alteration with dementia, (x2test, $p < 0.01$). The effects of therapy showed that methyl-prednisolone-succinate (2g/24h, i.v., 3-7 days), with prednisolone (1mg/1kg/24h, p.o., more than 11 days) was justified for 98% patients. This treatment accelerated clinical revival in 2 to 3 weeks, delayed recidivate for 2 years (T test, $p < 0.05$). The positive results of interferon $\beta 1b$ were notified at 76% (8-16 million IU / mL, s.c., 3 per week). It was manifested like prolonged relapse-remitting status at these patients (T test, $p < 0.05$). The therapy effects showed that steroid treatment, without prolonged effects had positive effect at 98%; interferon $\beta 1b$ treatment presented relative remission with prolonged effects (>2 years), at 76% of patients; the adjuvant therapy with positive effect, but without total remission was presented at 30%. Combined treatment was effective at 98% of patients, figure 7. (T test, $p < 0.05$).

Figure 7. The effects of the therapy

The early recidivate were noticed at 30%, late recidivate at 60%, without recidivate were 10% of all patients, figure 8. (T test, $p < 0.05$).

Figure 8. Recidivate of disease - late, early and without recidivates

DISCUSSION

Patients with retrobulbar neuritis and with negative MRI have 16% lower incidence of multiple sclerosis for 5 years.⁶ Sex distribution showed female domination (2:1). Most of the patients are either young or middle age. The highest incidence of the disease was in winter ("peak" in December), just like other viral infections.⁷ Temporal pallor was presented at all patients, some of them had bilateral manifestation. Decreasing of visual acuity, color defects, scotomas were notified at almost 20%.⁸ Painful eye movement was present at half of all patients.⁹ Late recidivate were more frequent than early ones (2:1). Infective genesis of the disease was detected at 8 patients. We found in literature that at 1/4 of patients, infective genesis was positive. Negative effects of the steroids and interferon therapy were the reason for cyclic controls of other specialists (endocrinologists, cardiologist, gastroenterologists). Immunological and blood analysis were performed on monthly basis. Neurological, gastroenterological, urological and other examination was regularly done every month. The relapse of the disease was delayed for 2 years (MRI, liquor analysis, VEP examination).^{10,11} Optimal treatment effects were achieved, but with specific char-

acteristic. The good treatment is the treatment which results in prolonged remitting time and without new, quick nerve damages. We must bear on our minds all unwanted effects of the current treatment (interferon's antibodies, osteoporosis, menopause, cardiovascular or gastrointestinal discharges, increase of immunity status, etc. Steroid therapy is our choice made according to the social and economic state of our country.¹² Negative MRI results after steroid treatment in acute stage of the disease indicates the positive effect of this therapy, without delayed clinical effects.¹³ Interferon therapy is also good treatment modality. Authentic, five years study indicates that patients, who were treated with steroids or interferon therapy, had better life quality and prolonged remitting-relapse status.¹⁴ This finding corresponds to the dates from other authors.¹⁵

Retrobulbar neuritis is among the first signs of the multiple sclerosis. It is a joined mission for the ophthalmologist and neurologist. This joined struggle for the better quality of life of the patients is hard and uncertain. At the end of the era of one therapy, a new one appears.

We must make our decision what to use. Consulting the literature in this field and relying on one's own experience are the basis for good practice.

REFERENCES

1. Roodhooft JM. Ocular problems in early stages of multiple sclerosis. *Bull Soc Belge Ophtalmol* 2009; 65-8.
2. Fisher JB, Jacobs DA, Markowitz CE, et al. Relation of visual function to retinal nerve fiber layer thickness in multiple sclerosis. *Ophthalmology* 2006; 113: 324-32.
3. Miller D, Barkhof F, Montalban X, et al. Clinically isolated syndromes suggestive of multiple sclerosis, part I: natural history, pathogenesis, diagnosis, and prognosis. *Lancet Neurol* 2005; 4:281-8.
4. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an Expanded Disability Status Scale (EDSS). *Neurology* 1983; 33: 1444-52.
5. Plosker GL. Interferon β 1b: review of its use in multiple sclerosis. *CNS Drugs* 2011; 25: 62-88.
6. Swanton JK, Fernando KT, Dalton CM, et al. Early MRI in optic neuritis: the risk for disability. *Neurology* 2009; 72: 542-50.
7. Balashov KE, Pal G, Rosenberg ML. Optic neuritis incidence is increased in spring months in patients with asymptomatic demyelinating lesions. *Mult Scler* 2010; 16: 252-4.
8. The Optic Neuritis Study Group. Multiple sclerosis risk after optic neuritis: final optic neuritis treatment trial follow-up. *Arch Neurol* 2008; 65: 727-32.
9. Bermejo PE, Oreja-Guevara C, Diez-Tejedor E. Pain in multiple sclerosis: prevalence, mechanisms, types and treatment. *Rev Neurol* 2010; 50: 101-08.
10. Weinstock-Guttman B, Baier M, Stockton R, et al. Pattern reversal visual evoked potentials as a measure of visual pathway pathology in multiple sclerosis. *Mult Scler* 2003; 9: 529-34.
11. Jacobs LD, Kaba SE, Miller CM, et al. Correlation of clinical, magnetic resonance imaging, and cerebrospinal fluid findings in optic neuritis. *Ann Neurol* 1997; 41: 392-8.
12. Beck RW, Cleary PA, Anderson MM, et al. A randomized, controlled trial of corticosteroids in the treatment of acute optic neuritis. The Optic Neuritis Study Group. *N Engl J Med* 1992; 326: 581-8.
13. Swanton JK, Fernando KT, Dalton CM, et al. Early MRI in optic neuritis: the risk for disability. *Neurology* 2009; 72: 542-50.
14. Oliver BJ, Kohli E, Kasper LH. J. Interferon therapy in relapsing-remitting multiple sclerosis: a systematic review and meta-analysis of the comparative trials. *J Neurol Sci* 2011; 302: 96-105.
15. Warnke C, Leussink VI, Kieseier BC, Hartung HP. Interferon β for multiple sclerosis. How much is good enough?. *Nervenarzt* 2010; 81: 1476-82. (in German)