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Intravenous Immunoglobulin Treatment for Recurrent Optic Neuritis

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ABSTRACT

Introduction: Recurrent optic neuritis neuritis (rON) is an autoimmune inflammatory condition of unknown cause. Intravenous immunoglobulin (IVIg) treatment is used for many autoimmune disorders; however we do not have any information about its effect in rON, other than case reports. We aimed to evaluate our patients with rON who were treated with IVIg.

Methods: Data from all our patients with rON with or without anti aquaporin4 (AQP4) seropositivity, seen between April 2011 and October 2015, who received IVIg treatment were retrospectively evaluated.

Results: Nine patients (all female) with rON had received IVIg. These patients were aged between 34 and 65 years, and had started receiving monthly IVIg from 6 to 58 months after onset of disease. In three out of nine rON patients serum AQP4 antibody were positive. Under current treatments the patients had continued to have attacks, therefore monthly IVIg was given in addition to the existing immunosuppressant drug. The follow up duration was between 6 to 31 months. Three patients, each suffered one relapse under IVIg treatment. Mean number of relapses in the year prior to treatment was 1.4±0.72, whereas it was 0.3±0.5 during the year after IVIg therapy. During follow-up with IVIg administration only one patient had fever and no other adverse events were reported.

Conclusion: Monthly IVIg is well-tolerated and safe and it seems to be effective in rON as an add on treatment. However, since our study is a retrospective case series, future randomized controlled trials with IVIg are needed.

Keywords: Recurrent optic neuritis, neuromyelitis optica spectrum disorders, intravenous immunoglobulin

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INTRODUCTION

Optic neuritis (ON) is an inflammatory disease of the optic nerve characterized by painful visual loss, and it is usually associated with multiple sclerosis (MS), or neuromyelitis optica spectrum disorders (NMOSD). A distinct clinical subset of ON is characterized by multiple episodes that involve one or both optic nerves and do not involve any other associated clinical or radiologic findings. This entity, defined as either recurrent optic neuritis (rON), is typically corticosteroid-responsive and requires immunosuppressive therapy to prevent relapses, and permanent damage to the optic nerves (1). These patients should be carefully evaluated to exclude other underlying etiologies.

According to the international consensus diagnostic criteria for NMOSD, anti-aquaporin 4 (AQP4) antibody positive patients with isolated ON/rON relapses are now accepted as NMOSD (2). There are still rON patients without AQP4 seropositivity who do not fall within the rubric of NMOSD; however, they should also be treated like NMOSD patients to prevent relapses and permanent disability (3).

Attack treatment for NMOSD includes high dose intravenous corticosteroids; those who do not respond to steroids sufficiently should be given a chance of plasma exchange (4–6). However, it is not certain if intravenous immunoglobulin (IVIg) treatment could substitute plasma exchange, as in acute inflammatory demyelinating neuropathies or myasthenia gravis (7), in cases where plasmapheresis will not be accessible rapidly. On the other hand, attack prevention therapies for NMOSD include immunosuppressive drugs such as azathioprine, cyclophosphamide, methotrexate, mycophenolate mofetil and rituximab. When occasionally these current therapies are contraindicated or fail to prevent relapses, IVIg could be a relatively safe option for NMOSD. There are few case reports of favorable experiences with IVIg for relapse prevention for NMOSD (8–10) and we are not aware of any reports on the effect of IVIg treatment for rON relapses. We present our experience with IVIg treatment in our patients with rON with or without AQP4 seropositivity.

METHODS

We reviewed retrospectively all our patients who received at least 6 months of IVIg treatment among our rON cases seen at our center between April 2011 and October 2015, among a total of 86 NMOSD patients (11). Informed consent was obtained from all the patients. IVIg

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treatment was given to the patients with a permission for off-label IVIg use in rON patients from the Ministry of Health. Diagnosis of NMOSD was made according to the international consensus diagnostic criteria for NMOSD (2). Active disease was considered in the presence of at least 1 relapse in the previous year despite another treatment given in sufficient dose and duration. Optic neuritis attack was considered as sudden blurry vision, vision loss, loss of colour vision, pain on movement of eye and visual field defect, which lasted longer than 24 hours. A minor attack was considered as blurry vision, loss of colour vision, pain on eye movement or visual eye field defect without vision loss, which lasted longer than 24 hours. The patients' clinical and demographic data, cerebral and spinal cord magnetic resonance imaging (MRIs) and serum AQP4 antibodies and presence of oligoclonal bands (OCB) in cerebrospinal fluid (CSF) were recorded (Table 1). Prior clinical and paraclinical examinations were done including serum screenings for antinuclear antibodies, anti-phospholipid antibodies, anti-neutrophil cytoplasmic antibodies, anti-SSA, and anti-SSB to exclude other causes of optic neuritis. None of the patients were tested for MOG antibodies, since it was not available in our department.

All patients had previously been treated with high doses of intravenous methylprednisolone (IVMP) for exacerbations of optic neuritis. All of the patients were treated with an initial IVIg dose of 0.4 gr/kg/day for 5 consecutive days, and then 0.4 gr/kg for each month. Each infusion was administered in out-patient care; treatment was supervised by specialist nurses and overseen by a neurologist. All patients had normal baseline serum IgA levels. Patients were observed for relapses and possible adverse effects during IVIg treatment.

RESULTS

Patient Characteristics

Nine patients with rON were included in the study, three of them were full filling the new criteria for NMOSD (2); all the patients were female. All patients received IVIg for attack prevention; one also received IVIg as an attack treatment. Mean age of the patients was 48.6±9.9 years (median: 47 years, range: 34–65 years). Mean disease duration was 4.8±1.6 years (median: 5 years, range: 2–8 years). The patients' clinical and demographic characteristics are shown in Table 1. Brain and spinal MRIs were normal in all of the patients. Serum anti-AQP4 antibody testing was performed in all patients using a commercial kit (Euroimmune, Germany); 3 patients (33%) tested positive. In two patients the CSF examination had not been done. CSF oligoclonal bands were positive only in 2 patients with rON (22%). Serum screening for antinuclear antibodies, anti-neutrophil cytoplasmic antibodies, anti-SSA, and anti-SSB were negative in all cases. One patient was positive for antiphospholipid antibodies.

Follow-up Data with IVIg Treatment

A total of 266 cycles of IVIg were administered (median: 31; range: 10–40), during a mean follow up period of 25±9.5 months (median: 25 months; range: 6–36 months. Follow up data of the patients are summarized on Table 2. Mean time of onset of IVIg therapy from the first relapse was 31.2±17.9 months (median: 30; range: 6–58). The mean number of total relapses in the disease course before IVIg treatment was 4.3±2.8 (median: 4; range: 2–11) and the relapses in the year prior to treatment was 1.4±0.72 (median: 1; range: 1–3). Baseline immunosuppressive treatment was azathioprine in all of the patients. After a mean follow-up period of 25 months, three patients each suffered one relapse. In three patients with optic neuritis the relapses were occurred at month 3, at month 18, and at month 28. The mean number of relapses after IVIg therapy was 0.3±0.5 (median: 0; range 0–1). Visual acuity remained unchanged in 8 patients. One patient's visual acuity in one eye improved from 0.1 to 0.7 under IVIg therapy (Table 2). EDSS was 2.4±1.2 (median: 3; range: 1–4) before IVIg therapy and improved to 2.1±1.1 (median: 2; range: 1–3). During IVIg administration, only one patient had fever and no other adverse events were reported. In one patient with rON, the serum AQP-4 antibody testing result was changed from positive to negative during IVIg therapy.

DISCUSSION

Results of this study suggest that IVIg treatment is safe and well-tolerated in rON. After a total of 266 infusions and a median of 25 months of follow-up, no serious adverse events were recorded. Although we had a limited number of cases, and our follow-up duration was relatively short, there seems to be a substantial decrease in relapse rate. Visual acuity was preserved in 8 patients and improved from 0.1 to 0.7 in one patient. There was 0.3 point decrease in the mean EDSS score of the group with IVIg therapy.

NMOSD are uncommon and there are no randomized controlled trials demonstrating efficacy of the current drugs used in NMO treatment such as azathioprine, mycophenolate mofetil, rituximab and cyclophosphamide (12–17). The experience with these drugs are based on comparison of pre-treatment to post-treatment relapse rates in retrospective analyses or prospective open label studies which represents the highest level of evidence supporting their use. While these treatments have been shown to be partially effective, they are associated with the possibility of serious adverse events, which do not occur with IVIg (14). Adverse events associated with IVIg treatment are generally mild and transient, such as headaches, erythema, and dysgeusia. Potentially serious adverse events are uncommon and include acute tubular necrosis, aseptic meningitis or thrombotic complications. In our patient group there was only one patient with fever.

Table 1. Clinical characteristics of the patients with rON treated with IVIg

Patient number	1	2	3	4	5	6	7	8	9
Age	65	57	47	40	39	54	47	55	34
Disease duration (y)	5.5	5.5	2	5	5	3.5	8	5	4
Number of ON attacks Before IVIg/after IVIg	5/-	2/-	2/-	3/-	4/-	2/-	11/-	5/-	5/-
Other autoimmune diseases	-	-	-	-	-	-	-	-	-
Brain MRI	-	-	-	-	-	-	-	-	-
Spinal MRI	-	-	-	-	-	-	-	-	-
Serum AQP4-antibody	(+); After IVIg (-)	(+)	(+)	(-)	(-)	(-)	(-)	(-)	(-)
CSF OCB	(+)	(-)	NA	(-)	(-)	(+)	(-)	(-)	NA

ON, optic neuritis; IVIg, intravenous immunoglobulin; MRI, magnetic resonance imaging; AQP4, aquaporine 4; CSF, cerebrospinal fluid; OCB, oligoclonal band; (+), positive; (-), negative; NA, not available.

Table 2. Follow-up data of rON patients with IVIg treatment

Patient number	1	2	3	4	5	6	7	8	9
Treatment prior to IVIg	AZA CS CTX x6	AZA IVMP	PLEX AZA CS	CTX AZA IVMP	CTX x 6 PLEX x 2 CS AZA	AZA CS	AZA CS PLEX	AZA CS	AZA CS
Disease duration at IVIg onset (m)	30	47	6	47	40	12	58	15	26
Follow up time with IVIg	36 cyc 31 m	29 cyc 25 m	10 cyc 6 m	24 cyc 20 m	31 cyc 23 m	37 cyc 33 m	40 cyc 36 m	37 cyc 33 m	22 cyc 18 m
Adverse events	-	-	-	Fever	-	-	-	-	-
Attacks the year before IVIg	1	2	1	3	1	2	1	1	1
Attacks under IVIg	1	-	-	-	1	0	0	1	0
Therapy during IVIg	MM CS	AZA	AZA CS	AZA	MM MTX	AZA CS	AZA CS	AZA CS	AZA CS
EDSS before IVIg	3.0	2.0	4.0	3.0	4.0	1.0	1.0	3.0	1.0
EDSS after IVIg	3.0	2.0	4.0	3.0	1.0	1.0	1.0	3.0	1.0
VA before IVIg	R-NLP L-0.8	R-0.2 L-1.0	R-NLP L-1.0	R-1.0 L-0.6	R-0.1 L-1.0	R-0.9 L-0.9	R-0.9 L-0.6	R-LP L-1.0	R-1.0 L-1.0
VA after IVIg	R-NLP L-0.8	R-0.2 L-1.0	R-NLP L-1.0	R-1.0 L-0.6	R-0.7 L-1.0	R-0.9 L-0.9	R-0.9 L-0.6	R-LP L-1.0	R-1.0 L-1.0

IVIg, intravenous immunoglobulin; AZA, azathioprine; CS, oral corticosteroids; CTX, cylclophosphamide; PLEX, plasma exchange; IVMP, intravenous methylprednisolone; MM, mycophenolate mofetil; MTX, methotrexate; Cyc, cycle; m, month; VA, visual acuity; R, right; L, left; NLP, negative light perception; LP, light perception.

IVIg administration seems to be effective in rON patients. In three out of nine rON patients anti-AQP4 antibody was positive. One rON patient had an early attack under IVIg administration. However, she did not have any further attacks under IVIg treatment; which might suggest that an early relapse may not be the sign of unresponsiveness. The other rON patient had an attack on month 18 which recovered only with 5 days IVIg therapy. Also this patient expresses that every month before the IVIg dose she experienced blurry vision, which recover with the infusions however there is no objective proof for that. The third rON patient had a minor attack at month 28, and the vision did not change. The other six rON patients did not have an attack under IVIg administration although their previous attack rate was high under current immunosuppressant therapies. In only one of our patients IVIg was used in the treatment of an acute attack, and seemed to be beneficial. However, our data is even less sufficient to draw any conclusions in that aspect.

In NMOSD, antibody-and complement-related mechanisms appear to be principally involved in disease pathogenesis and AQP-4 antibody has been shown to have a pathogenic role. IVIg may potentially be effective for NMOSD, since it is efficacious in other humorally mediated disorders such as myasthenia gravis (18), which can also be seen as a comorbid disease with NMOSD (19, 20). It has been proposed that IVIg could plausibly reduce anti AQP-4 levels (21) and neutralize B cell activating factor, which is elevated in NMOSD (22). In one patient with rON, the serum AQP-4 antibody testing result was changed from positive to negative during IVIg therapy. Other suggested mechanisms of action of IVIg include interference with antigen recognition, downregulation of cytokine networks and adhesion molecules, and suppression of T-cell mediated mechanisms. All of these processes may be therapeutically relevant in NMOSD.

In conclusion, IVIg may be a safe treatment option in NMOSD for acute relapses when there is a failure of improvement with corticosteroids, and plasmapheresis is not available, or for relapse prevention where current therapies are contraindicated or not efficient enough to prevent relapses. Future randomized controlled studies are needed to confirm the beneficial effect and dose of IVIg.

Committee Approval: This retrospective study was conducted in accordance with the Helsinki Declaration.

Informed Consent: Informed consent was obtained from all the patients.

Peer-review: Externally peer-reviewed

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REFERENCES

1. Kidd D, Burton B, Plant GT, Graham EM. Chronic relapsing inflammatory optic neuropathy (CRION). Brain 2003;126(Pt 2):276–284.
2. Wingerchuk DM, Banwell B, Bennett JL, Cabre P, Carroll W, Chitnis T, de Seze J, Fujihara K, Greenberg B, Jacob A, Jarius S, Lana-Peixoto M, Levy M, Simon JH, Tenembaum S, Traboulsee AL, Waters P, Wellik KE, Weinshenker BG; International Panel for NMO Diagnosis. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology 2015;85:177–189. [CrossRef]
3. Bernard-Valnet R, Librau RS, Vukusic S, Marignier R. Neuromyelitis optica: a positive appraisal of seronegative cases. Eur J Neurol 2015;22:1511–1518. [CrossRef]
4. Keegan M, Pineda AA, McClelland RL, Darby CH, Rodriguez M, Weinshenker BG. Plasma exchange for severe attacks of CNS dmyelination: predictors of response. Neurology 2002;58:143–146.
5. Weinshenker BG, O'Brien PC, Petterson TM, Noseworthy JH, Lucchinetti CF, Dodick DW, Pineda AA, Stevens LN, Rodriguez M. A randomized trial of plasma exchange in acute central nervous system inflammatory demyelinating disease. Ann Neurol 1999;46:878–886.
6. Bonnan N, Valentino R, Olindo S, Mehdaoui H, Smadja D, Cabre P. Plasma exchange in severe spinal attacks associated with neuromyelitis optica spectrum disorder. Mult Scler 2009;15:487–492. [CrossRef]
7. Bascic-Kes V, Kes P, Zavoreo I, Lisak M, Zadro L, Corić L, Demarin V; Ad Hoc Comittee of the Croatian Society for Neurovascular Disorders, Croatian Medical Association. Guidelines for the use of intravenous immunoglobulin in the treatment of neurological diseases. Acta Clin Croat 2012;51:673–683.

8. Magraner MJ, Coret F, Casanova B. The effect of intravenous immunoglobulin on neuromyelitis optica. Neurologia 2013;28:65–72. [CrossRef]
9. Bakker J, Metz L. Devic's neuromyelitis optica treated with intravenous gamma globulin (IVIG). Can J Neurol Sci 2004;31:265–267.
10. Okada K, Tsuji S, Tanaka K. Intermittent intravenous immunoglobulin successfully prevents relapses of neuromyelitis optica. Intern Med 2007;46:1671–1672.
11. Altunrende B, Tavlı AM, Altınkaya A, Topcular B, Kocarslan M, Server S, Fırtına F, Yenice S, Akman Demir G. Neuromiyelitis optica and neuromiyelitis optica spectrum disorders: The evaluation of 86 patients followed by Istanbul Bilim University, Department of Neurology. Abstract of the 7th Congress of the Pan-Asian Committee for treatment and research in multiple sclerosis, Taipei, Taiwan, November 6–8, 2014.
12. Cree BA, Lamb S, Morgan K, Chen A, Waubant E, Genain C. An open label study of the effects of rituximab in neuromyelitis optica. Neurology 2005;64:1270–1272. [CrossRef]
13. Jacob A, Matiello M, Weinshenker BG, Wingerchuck DM, Lucchinetti C, Shuster E, Carter J, Keegan BM, Kantarci OH, Pittock SJ. Treatment of neuromyelitis optica with mycophenolate mofetil: retrospective analysis of 24 pateints. Arch Neurol 2009;66:1128–1133. [CrossRef]
14. Jacob A, Weinshenker BG, Voilich I, McLinskey N, Krupp L, Fox RJ, Wingerchuk DM, Boggild M, Constantinescu CS, Miller A, De Angelis T, Matiello M, Cree BA. Treatment of neuromyelitis optica with rituximab: retrospective analyses of 25 patients. Arch Neurol 2008;65:1443–1448. [CrossRef]
15. Costanzi C, Matiello M, Lucchinetti CF, Weinshenker BG, Pittock SJ, Madrekar J, Thapa P, McKeon A. Azathioprine: tolerability, efficacy, and predictors of benefit in neuromyelitis optica. Neurology 2011;77:659–666. [CrossRef]
16. Bichuetti DB, Oliveira EM, Boulos Fde C, Gabbai AA. Lack of response to pulse cyclophosphamide in neuromyelitis optica: evaluation of 7 patients. Arch Neurol 2012;69:938–939. [CrossRef]
17. Mandler RN, Ahmed W, Dencoff JE. Devic's neuromyelitis optica: a prospective study of seven patients treated with prednisone and azathioprine. Neurology 1998;51:1219–1220.
18. Patwa HS, Chaudhry V, Katzberg H, Rae-Grant AD, So YT. Evidence-based guideline: intravenous immunoglobulin in the treatment of neuromuscular disorders: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2012;78:1009–1015. [CrossRef]
19. Leite MI, Coutinho E, Lana-Peixoto M, Apostolos S, Waters P, Sato D, Melamud L, Marta M, Graham A, Spillane J, Villa AM, Callegaro D, Santos E, da Silva AM, Jarius S, Howard R, Nakashima I, Giovannoni G, Buckley C, Hilton-Jones D, Vincent A, Palace J. Myasthenia gravis and neuromyelitis optica spectrum disorder: a multicenter study of 16 patients. Neurology 2012;78:1601–1607. [CrossRef]
20. Jarius S, Paul F, Franciotta D, de Seze J, Munch C, Salvetti M, Ruprecht K, Liebetrau M, Wandinger KP, Akman-Demir G, Melms A, Kristoferitsch W, Wildemann B. Neuromyelitis optica spectrum disorders in patients with myasthenia gravis: ten new aquaporin-4 antibody positive cases and a review of the literature. Mult Scler 2012;18:1135–1143. [CrossRef]
21. Yu Z, Lennon VA. Mechanism of intravenous immune globulin therapy in antibody-mediated autoimmune diseases. N Engl J Med 1999;340:227–228. [CrossRef]
22. Okada K, Matsushita T, Kira J, Tsuji S. B-cell activating factor of the TNF family is upregulated in neuromyelitis optica. Neurology 2012;74:177–178. [CrossRef]