folia medica

Folia Medica 62(4):861-5
DOI: 10.3897/folmed.62.e50349

Case Report

Treatment of Corticosteroid Non-responsive Relapse of Neuromyelitis Optica with Intravenous Gamma Globulin – a Case Report

Maria Dimitrova, Dobromir Iliev

NI Pirogov University Hospital for Emergency Care, Sofia, Bulgaria

Corresponding author: Maria Dimitrova, Department of Neurology, NI Pirogov University Hospital for Emergency Care, Sofia, Bulgaria; E-mail: dr.m.i.dimitrova@gmail.com; Tel.: +359 886 850 961

Received: 21 Jan 2020 ♦ **Accepted:** 18 May 2020 ♦ **Published:** 31 Dec 2020

Citation: Dimitrova M, Iliev D. Treatment of corticosteroid non-responsive relapse of neuromyelitis optica with intravenous gamma globulin - a case report. Folia Med (Plovdiv) 2020;62(4):861-5. doi: 10.3897/folmed.62.e50349.

Abstract

We report a case of a patient with a relapse of neuromyelitis optica. The relapse was initially treated with intravenous corticosteroids. A therapy with intravenous gamma globulin was started as there was no symptomatic improvement. The patient responded well to the treatment with no significant side effects. Worldwide experience with gamma globulin treatment of neuromyelitis optica is limited and randomised control trials are lacking, therefore accumulation of data from case reports is of paramount importance.

Keywords

corticosteroid, intravenous gamma globulin, neuromyelitis optica, relapse

INTRODUCTION

Neuromyelitis optica (NMO, also known as Devic's disease) is a severe idiopathic immune-mediated demyelinating and necrotizing disease that mainly affects the optic nerve and spinal cord.

Historically, the diagnosis of NMO has been limited to a state of single-phase bilateral optic nerve involvement and myelitis. Currently, NMO is classified as a recurrent autoimmune CNS disease with clinical, neuroimaging, and laboratory characteristics other than those found in multiple sclerosis (MS). Besides, NMO-immunoglobulin G (NMO-IgG or aquaporin 4 antibodies), an antibody that binds to the Aquaporin 4 water channel (AQP4), in combination with other diagnostic criteria, supports the differentiation of NMO from other autoimmune CNS disorders.[1]

The natural course of the disease in untreated patients is considerably less favourable than in people with MS. This is the reason why rapid diagnosis and treatment plans for acute attacks and long-term disease-modifying treatment are required. Unfortunately, many of the studies and treatment findings reflect the experience of individual experts in the field as a result of studies with few participants.

CASE REPORT

We present the case of a 58-year-old woman who was admitted urgently to our department due to complaints of weakness in the lower limbs, urinary retention, an impossibility to walk unassisted, a painful tightness in the muscles of the lower limbs and a tightening around the abdomen. The onset of the disease involved back pain and weakness in the right leg one month prior to hospitalization. She had been treated at another hospital, where a CT scan of the thoracic spine was performed with evidence of degenerative changes. The patient had no past medical history, nor any concomitant diseases.

Diagnostic approach

Objectively, we found a syndrome of severe lower paraplegia, anesthesia from the level of Th11 downward on the right side, and from Th12 on the left side, and urine retention. The score on the expanded disability status scale (EDSS) was 6.5.

Diagnostic tests revealed myelopathy as a result of degenerative stenosis in the thoracic spine, a space-occupying lesion in the thoracic spine, transverse myelitis with a viral etiology or associated with NMO, spinal or cerebrospinal multiple sclerosis.

No clinical laboratory abnormalities were detected. A lumbar puncture was performed. CSF analysis showed WBC 4, protein 0.97 g/L, sugar 2.87 mmol/L, chlorine 132 mmol/L. Microbiology studies showed no abnormality. Tests for enteroviruses, HSV, VZV, EBV, and Lyme disease of CSF were negative. In order to exclude pathology due to a somatic disease, a CT scan of the abdominal organs was performed. The magnetic resonance imaging of the brain was normal. Magnetic resonance imaging of the cervical, thoracic, and lumbar spinal cord showed lesions in the craniospinal segment at C2-C4, C5, C7-Th3, Th7, Th9, and Th12. Signal amplification was detected after intravenous gadolinium administration. The lesions had demyelinating characteristics. Serum levels of the NMO-IgG / AQP4 antibody revealed a positive titer.

Therapeutic approach

Initial therapy with intravenous administration of high doses of methylprednisolone was administered: 1000 mg daily for three days, 500 mg at days 4 and 5, and the next two days - 250 mg daily. The patient tolerated the medication with no adverse events, but no significant improvement was observed. Plasmapheresis was suggested but the patient refused. Then intravenous immunoglobulin (IVIG) treatment was started for 5 days with a dose of 0.4 g/kg daily. There was partial improvement of the neurological symptoms, improving the strength of the lower limbs and the loss of sensory symptoms. Urinary retention was not improved. No side effects were registered. The patient was discharged with lower paraparesis, moderate hypesthesia from Th10. EDSS 5,0. Symptomatic therapy was prescribed and rehabilitation recommended. Control serum examination of NMO-IgG / AQP4 antibodies was performed with persistent high titer at 3 months. The patient revealed lower spastic paraparesis and urinary retention, no evidence of impaired sensory neurological symptoms. EDSS 4.0. The second course of intravenous immunoglobulin (IVIG) therapy was administered for 5 days at a dose of 0.4 g/kg. Over the next month, there was a significant improvement in the clinical presentation of the patient EDSS 3.5. On the third-month follow-up examination, the patient was prescribed immunomodulatory therapy with azathioprine with leukocyte count control and control of NMO-IgG/AQP4 antibodies.

DISCUSSION

Clinical features of the disease are possible manifestations with optic neuritis and/or myelitis. Optical neuritis (ON) is more pronounced at NMO. Spinal cord involvement is usually presented in the form of transverse myelitis with para- or tetraparesis, almost symmetrical sensory level, and sphincter dysfunction. Radicular pain, paroxysmal tonic spasms, and a sign of Lhermitte develop in one-thirds of patients with recurrent relapses but are absent or rare in patients with a single attack.[2] Symptoms such as nausea, vomiting, dizziness, hearing loss, weakness of facial muscles, trigeminal neuralgia, diplopia, ptosis, and nystagmus have been observed in patients with brainstem involvement or patients with recurrent attacks of NMO.[2] As a result of the involvement of brainstem centers responsible for neuromuscular respiratory control, respiratory failure and the subsequent lethal outcome may occur.[2,4,5]

Diagnostic tests

- Magnetic Resonance Imaging (MRI) - The most pronounced finding in the MRI is a spinal cord lesion extending to more than three spinal segments with almost complete transverse distribution, visible on T2-sequence. In brain MRI, the finding is most often missing.
- Cerebro-spinal fluid (CSF) - CSF analysis is a necessary complement to the diagnosis of NMO and is recommended to be acquired during or shortly after a seizure. The finding of lymphomononuclear pleocytosis > 50 cells/l and the lack of oligoclonal chains is suggestive of the diagnosis but nonspecific and of low sensitivity for NMO and NMO spectral disorders.
- Visual evoked potentials (EPs), somatosensory EPs, and stem auditory EPs in NMO patients often show changes while peripheral nerve conduction studies are normal.
- AQP4-IgG. The presence of NMO-IgG/AQP4 antibodies confirms the diagnosis of NMO (level A) and is a prognostic marker for the high-risk syndrome (level A); unfortunately, there is still no proven link between antibody concentration and the expected severity of the disease. The NMO-IgG/AQP4 antibody serum test is an important element in the diagnostic process, but there are cases of seronegative patients with a clinically probable diagnosis for NMO.

The diagnostic criteria are accepted by MS Working Group on Differential Diagnosis[6] and include: 1. Optical neuritis in one or two eyes; 2. Transverse myelitis, clinically complete or partial but associated with imaging data for a spinal cord lesion spanning over three spinal cord segments visible in the T2 sequence. 3. Lack of evidence of sarcoidosis, vasculitis, and clinical manifestation of systemic lupus erythematosus (SLE) or Sjogren syndrome (SS). Diagnosis requires all the basic criteria, but they can be distributed over time without a fixed interval.[7] Secondary criteria, at least one of which must be met: 1. The most recent MRI examination of brain must be normal or indicate abnor-

malities that do not meet the Barkhof criteria used for the McDonald diagnostic criteria. 2. Positive serum or CSF for NMO-IgG/AQP4 antibodies.

Therapeutic approach

Treatment of relapses

- Corticosteroids: primary or recurrent exacerbations are usually treated with high doses of intravenous methylprednisolone (IVMP) - 1 g/day for 3-5 consecutive days. This recommendation is part of studies on MS and idiopathic ON but it is not confirmed in guidelines of NMO due to the lack of controlled therapeutic studies on the efficacy of corticosteroid therapy in patients with NMO. Positive response to therapy, with good tolerance (class IV), was observed in 80% of patients within the first 1-5 days.[2] However, this first choice of treatment is not sufficient to reduce the inflammatory process in some patients. This requires the use of other approaches in therapy, and most often it is plasmapheresis.
- Plasmapheresis: the plasmapheresis technique consists of separating the blood plasma from the cellular elements by using centrifugation or filtration. Blood is filtered through pores up to 0.2 μm in diameter, resulting in the filtration of substances with a molecular level up to 3106 Da, namely circulating immunoglobulins and immune complexes targeting components of the central and peripheral nervous system. By plasmapheresis, the concentration of IgG, IgM, and complement can be reduced respectively to 63.4%, 68.9% and 57.1% after a single administration and 80.1%, 79.5% and 59.7% after five administrations. Therapeutic plasmapheresis is an effective method of treatment in patients with severe disease symptoms that do not respond to corticosteroid treatment.[7] In some cases, high doses of intravenous methylprednisolone (IVMP) contribute to a moderate level of neurological improvement from an acute NMO relapse. But the combination of plasmapheresis and high doses of IVMP improves the outcome of the disease in the early and late periods after treatment. Plasmapheresis is effective and leads to complete recovery of neurological deficits in some corticosteroid non-responders and is even more effective in patients with immunomodulatory therapy at the time of a new relapse.[8] Prognostic factors for better outcome of the disease are: male gender repeated and early plasmapheresis. A positive result can be expected between 10-90 days.[9] In some cases of NMO-IgG seropositive patients, non-responding to high-dose corticosteroid improvement occurs after more than one course of plasmapheresis.[10]
- Intravenous immunoglobulin (IVIG): intravenous immunoglobulin (IVIG) treatment has not been fully studied in patients with optic neuritis/longitudinal transverse myelitis in NMO/NMO spectral disorders, hence its use in corticosteroid non-invasive steroid patients.[11] IVIG is mainly used to prevent a new relapse of the disease.[12]

Relapse prevention

Immunosuppressive and immunomodulatory therapies used in the treatment of MS have also been tested in clinical trials in patients with NMO.

- Immunomodulation involves the use of the aforementioned treatment with intravenous immunoglobulin (IVIg), interferon-beta (IFNβ), or Glatiramer acetate (GA).
- Immunosuppressive therapy is oral and intravenous. It involves the use of drugs that suppress the cell-mediated and humoral immune response by its effects on B- and T-cells, as well as by reducing the secretion of cytokines (IFN-gamma, IL-12, TNF-alpha) such as azathioprine (AZA), mycophenolate mofetil (IMF), cyclophosphamide (CYC), mitoxantrone (MITO), rituximab (RTX).[13,14]

Devic's disease or neuromyelitis optica is a disease that differs from multiple sclerosis and is manifested by the presence of different types of autoantibodies.[15-17] This fact classifies NMOs into the group of autoimmune diseases, which calls for the first choice of treatment for this disease to be the administration of high doses of corticosteroid, intravenous immunoglobulin or plasmapheresis.

Our patient meets current clinical criteria, MRI data and laboratory tests to diagnose neuromyelitis optics. Severe disability of patients requires a more aggressive approach in the treatment of relapses and the application of preventive treatment with immunomodulators or immunosuppressants. IVIG has been successfully used in patients not responding to high doses of corticosteroid.

The reported case describes a patient with NMO who does not respond to the administration of corticosteroid therapy in a severe onset of the disease but undergoes clinical improvement after IVIG use.

In 2004 Jacqueline Bakker and Luanne Metz presented a similar case of a 58-year-old woman with Devic's disease for three years who had 5 relapses of the disease in the first 16 months of its onset. In their case, the monthly administration of IVIG for one year was associated with complete cessation of progression and significant improvement in the neurological status.[18]

In 2013, Magraner MJ, et al. presented 8 patients meeting the updated Wingerchuk's diagnostic criteria treated with IVIG every 2 months (0.7 g/kg per day for 3 days). The presence of serious side effects, but described in the NIH protocols for clinical studies was declared at first. The follow-up of 83 IVIG infusions resulted in changes in relapse frequency (from 1.8 in the previous year to 0.006 during the monitoring period; $z = -2.5$, $p=0.01$) and improvement of neurological disability measured with the Expanded Disability Status Scale (EDSS) (decreasing from 3.3 to 2.6; $z=-2.0$, $p=0.04$).[19,20]

CONCLUSIONS

Treatment with high doses of intravenous methylprednisolone (IVMP) results in the improvement of the neurologi-

cal symptoms in the acute relapse of NMO. The use of intravenous immunoglobulin (IVIG) is an effective method of treatment in patients not responding to corticosteroid therapy, leading to improvement of neurological function, especially in cases with severe onset of the disease. The previously described cases and the present case have shown that the use of IVIG is a safe and well-tolerated approach for management in patients with NMO and also suggests the benefit of IVIG not only as a treatment option in relapses but also as preventive therapy.

Funding

The authors have no funding to report.

Conflict of Interests

The authors declare that no competing interests exist.

REFERENCES

1. Roemer SF, Parisi JE, Lennon VA, et al. Pattern-specific loss of aquaporin-4 immunoreactivity distinguishes neuromyelitis optica from multiple sclerosis. Brain 2007; 130:1194–205.
2. Wingerchuk DM, Hogancamp WF, O'Brien PC, et al. The clinical course of neuromyelitis optica (Devic's Syndrome). Neurology 1999; 53:1107–14.
3. de Seze J, Blanc F, Jeanjean L, et al. Optical coherence tomography in neuromyelitis optica. Arch Neurol 2008; 65:920–3.
4. Bichuetti DB, Oliveira EM, Souza NA, et al. Patients with neuromyelitis optica have a more severe disease than patients with relapsing remitting multiple sclerosis, including higher risk of dying of a demyelinating disease. Arq Neuropsiquiatr 2013; 71:275–9.
5. Cabre P, Gonzalez-Quevedo A, Bonnan M, et al. Relapsing neuromyelitis optica: long term history and clinical predictors of death. J Neurol Neurosurg Psychiatry 2009; 80:1162–64.
6. Miller DH, Weinshenker BG, Filippi M, et al. Differential diagnosis of suspected multiple sclerosis: a consensus approach. Mult Scler 2008; 14:1157–74.
7. Weinshenker BG, O'Brien PC, Petterson TM, et al. A randomized trial of plasma exchange in acute central nervous system inflammatory demyelinating disease. Ann Neurol 1999; 66:878–86.
8. Hesham A, Alexandria E, Alex P, et al. Treatment of acute relapses in neuromyelitis optica: Steroids alone versus steroids plus plasma exchange. Mult Scler 2016; 22(2):185–93.
9. Llufriu S, Castillo J, Blanco Y, et al. Plasma exchange for acute attacks of CNS demyelination: predictors of improvement at 6 months. Neurology 2009; 73:949–53.
10. Watanabe S, Nakashima I, Misu T, et al. Therapeutic efficacy of plasma exchange in NMO-IgG-positive patients with neuromyelitis optica. Mult Sclr 2007; 13:128–32.
11. Wingerchuk DM, Weinshenker BG. Neuromyelitis optica. Curr Treat Options Neurol 2008; 10:55–66.
12. Noseworthy JH. A randomized trial of intravenous immunoglobulin in inflammatory demyelinating optic neuritis. Neurology 2001; 56(11):1514–22.
13. Weiner HL, Cohen JA. Treatment of multiple sclerosis with cyclophosphamide: critical review of clinical and immunologic effects. Mult Scler 2002; 8:142–54.
14. Weinstock-Guttman B, Ramanathan M, Lincoff N, et al. Study of mitoxantrone for the treatment of recurrent neuromyelitis optica (Devic disease). Arch Neurol 2006; 63:957–63.
15. Birnbaum J, Kerr D. Optic neuritis and recurrent myelitis in a woman with systemic lupus erythematosus. Nat Clin Pract Rheumatol 2008; 4:381–6.
16. Arabshahi B, Pollock AN, Sherry DD, et al. Devic disease in a child with primary Sjogren syndrome. J Child Neurol 2006; 21:285-6.
17. Bonnet F, Mercie P, Morlat P, et al. Devic's neuromyelitis optica during pregnancy in a patient with systemic lupus erythematosus. Lupus 1999; 8:244–7.
18. Bakker J, Metz L. Devic's neuromyelitis optica treated with intravenous gamma globulin (IVIG). Can J Neurol Sci 2004; 31:265–7.
19. Magraner MJ, Coret F, Casanova B. The effect of intravenous immunoglobulin on neuromyelitis optica. Neurologia 2013; 28(2):65–72.
20. Hahn AF, Bolton CF, Zochodne D, et al. Intravenous immunoglobulin treatment (IVIg) in chronic inflammatory demyelinating polyneuropathy (CIDP): a double-blind placebo-controlled cross-over study. Brain 1996; 119:1067–78.

Лечение рецидива оптического нейромиелита без ответа на кортикостероиды с помощью внутривенного гамма-глобулина – клинический случай

Мария Димитрова, Добромир Илиев

УМБАЛСМ „Пирогов", София, Болгария

Адрес для корреспонденции: Мария Димитрова, Отделение неврологии, УМБАЛСМ „Пирогов", София, Болгария; E-mail: dr.m.i.dimitrova@gmail.com; Тел.: +359 886 850 961

Дата получения: 21 января 2020 ♦ **Дата приемки:** 18 мая 2020 ♦ **Дата публикации:** 31 декабря 2020

Образец цитирования: Dimitrova M, Iliev D. Treatment of corticosteroid non-responsive relapse of neuromyelitis optica with intravenous gamma globulin – a case report. Folia Med (Plovdiv) 2020;62(4):861-5. doi: 10.3897/folmed.62.e50349.

Резюме

Мы сообщаем о пациенте с рецидивом оптического нейромиелита. Рецидив первоначально лечили внутривенными кортикостероидами. Была начата внутривенная терапия гамма-глобулином, но симптоматического улучшения не наблюдалось. Пациент хорошо поддаётся лечению без значительных побочных эффектов. Международный опыт лечения оптического нейромиелита гамма-глобулином весьма ограничен и рандомизированных контролируемых исследований нет, поэтому данные этого клинического случая чрезвычайно важны.

Ключевые слова

кортикостероид, внутривенный гамма-глобулин, оптический нейромиелит, рецидив