Optic Neuritis Unresponsive to Steroids: Prevalence, Characteristics and Plasma Exchange Treatment

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Abstract

**Background:** Neuromyelitis optica (NMO) is a demyelinating disease associated to the presence of anti-aquaporin 4 (AQP4) antibodies and damage to the optic nerve and spinal cord. Sometimes Steroids do not stop the autoimmune response. Plasma exchange (PE) is a purification technique used to remove high weight molecules (e.g. antibodies), and it has shown efficacy in NMO unresponsive to steroids. However, the role of PE in optic neuritis (ON) unresponsive to steroids secondary to NMO has been less studied.

**Objective:** We present our experience about ON unresponsive to steroids in NMO’s patients characteristics and PE treatment results.

**Materials and method:** retrospective study included 56 NMO medical records since January 2010 to May 2015. ON unresponsive to steroids cases and PE treatment were included. Visual acuity (VA) and EDSS score were recorded before and after the PE. Categorical variables were compared with Chi square, continuous variables were assessed using Wilcoxon’s test or Mans Whitney U test according to groups.

**Results:** We included 12 cases (10 females and 2 males). Prevalence of ON unresponsive to steroids was 0.21. We found a significant difference between VA pre and post PE in both eyes and in EDSS score. Bilateral ON was the most frequent presentation. Rate of response was of 75%.

**Conclusion:** We described the prevalence of ON unresponsive to steroids. Women were mostly affected and bilateral ON was the type more frequent. PE was effective up to 75%.

Keywords: Neuromyelitis optica: Optic neuritis; Steroid; Plasma exchange; Visual acuity; EDSS

Introduction

Neuromyelitis optica (NMO) is a chronic, demyelinating, inflammatory and autoimmune disease, which major symptoms are optic neuritis (ON) and/or myelitis [1-5]. It is more frequent in African, East-Asian and Latin American, while its prevalence in Europe and North America is low (less than 1 to 4.4 cases per 100,000 inhabitants) [4]. In 2004, Lenon and collaborators, identified high anti-aquaporin 4 (AQP4) antibodies levels in NMO’s patients. This finding explained the development of humoral response against optic nerve, spinal cord and periventricular spaces [6]. Clinical consequences of the NMO are: decrease of visual acuity, amaurosis, paresia or/sphincters dysfunction, all of them produce a negative influence in physical, emotional, productive and social patient’s life [2,3,7,8]. NMO’s acute treatment consists in intravenous methylprednisolone 1 or 2 g per day, 3 to 5 dose. [2,5,9]. Unfortunately, in some cases it is not enough and ON or myelitis become unresponsive to steroids. There are several reports in the literature regarding Plasma exchange (PE) treatment of patients with demyelinating diseases unresponsive to conventional steroids doses. Although, the American Society for Apheresis (ASFA) and others associations and authors have accepted PE for NMO as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment (recommendation grade IB) [10-13], but more information is necessary regarding ON events. PE is a purification technique used to remove high weight molecules (e.g., antibodies) [11-14]. PE treatment in NMO has been studied extensively, and several trials have showed its efficacy [10-13,15-19]. However, the roll of PE in ON unresponsive to steroids secondary to NMO has been less studied [15,16,20]. In 2004, Ruprecht and collaborators identified 10 isolated acute ON cases with a positive effect of PE, but all patients had Multiple Sclerosis, a disease with a ON less aggressive than ON caused by NMO [21]. Afterwards, other study compared the efficacy of PE against Immunoadsorption in MS patients with NO again [22]. Wang and colleagues studied 9 NMO unresponsive to steroids patients, but just one with ON attack [20]. Otherwise, a group of researchers documented 39 eyes with ON and PE treatment and they identified that early PE improves outcome [15]. While, another study reported 11 ON attacks in 8 patients [16]. The largest trial gathered 16 patients with NO, but the author compared the efficacy of steroids vs PE in acute relapses, not in ON resistant to steroids [23]. We present our experience about ON unresponsive to steroids in NMO’s patients characteristics and PE treatment results.

Patients and Methods

This retrospective study included 56 NMO medical records from the National Institute of Neurology and Neurosurgery since January 2010 to May 2015. All of them met NMO’s criteria [24] and had ON unresponsive to steroids, defined as patients with persistence or worsening of the visual acuity despite 5 g intravenous methylprednisolone doses. Characteristics registered were: gender, age, diagnostic disease date, time of disease (number of months since NMO’s diagnosis until the ON unresponsive to steroids relapse.), number of relapses, prophylactic treatment, interval days before PE, visual acuity (VA), Expanded Disability Status Scale (EDSS) before and after PE and complications.

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Plasma Exchange

All patients had a catheter Mahurkar two-way type in subclavian or jugular vein. An X ray control was performed in each subject. A machine continuous flow centrifuge (OPTIA machine BCT), was used for PE. The amount of plasma was calculated from the Kaplan formula: Volume of plasma= (0.065 x weight) (1-Hematocrit). Albumin (5%) and saline solutions (0.9%) were used for to replace volume, and citrate as anticoagulant. Patients received 5 sessions (one each every 48 hr, for a 2 week period). Outcome Principal outcome was VA measure, defined as the able to distinguish details (assessed by feet method trough Snellen card). The VA assessment was realized by a Neuro-Ophthalmology. We converted feet method to LogMAR method (log of the minimum angle of resolution) score [25], because decimal number improves the data management. For the comparison of visual acuity after treatment, we use the criteria of Keegan and collaborators [26], in order to maintain a consistent assessment performed in previous studies. But we modified as follow: “No improvement” was defined as no gain in neurologic function; ”mild improvement” was defined as definite improvement in neurologic status without impact on function (gain of 0.1 to 0.2 LogMAR points); ”moderate improvement” was defined by definite improvement in function (gain 0.3 to 0.5 LogMAR points); and ”marked improvement” was defined by a major improvement in function (gain of more than 0.6 LogMAR points), and we added “total recovery”. Treatment success was defined as moderate, marked improvement or total recovery. We used the visual functional system of EDSS. This evaluate: visual acuity, visual fields, scotoma and disc paller. Visual functional system score could reach 1 to 4 global EDSS points. EDSS was recorded as a secondary outcome [27].

Statistical analysis

Demographic and clinical variables were represented individually and in average, percentage and standard deviation values. Categorical variables were compared with Chi square. LogMAR and other continuous variables were assessed using Wilcoxon’s test or Mars Whitney U test according to groups. A logistic regression model was made for identify risk variables. Correlation between age, gender, time of diagnosis, interval days for PE, type of ON and VA recovery was calculated by Spearman test. Statistical significance established was p=0.05.

Results

We gathered 56 NMO medical records, but just 12 met all criteria (10 females and 2 males). Prevalence of ON unresponsive to steroids was 0.21 respect to total NMO patients. Clinically, we recorded time of NMO diagnosis, type of ON, treatment, number of total relapses and ON relapses before PE in each patient (Table 1). Average of follow-up was 21.2 months (SD ± 8.2), and only one record was not included, because the patient did not attending the medical appointments. Mean VA and EDSS before and after PE are illustrates in (Table 2). We found a significant difference between VA pre and post PE in both eyes and in EDSS score. Bilateral ON was the most frequent presentation, and it showed difference in VA in pre and post PE for the right eye (RE) p=0.04 and in EDSS p=0.04 (CI 95% 0.0-1.4), but not for left eye (LE). According to the Keegan’s classification, distribution of the patients was as follow: one patient showed no improvement, 2 (16%) had mild improvement; 3 (25%) moderate; 5 (41.6%) marked and one had completely recovery. At the same time, we divided groups in two categories: a) PE responders (9 total), and b) PE non responders (3 total). Rate of response was of 75%. A negative correlation was found between age/EDSS (-0.59, p=0.04) and age/V A (-0.65, p=0.02) after PE. There was no significant difference about age, time of NMO diagnosis, anti-AQP4 status, interval time to start PE, number of relapses and type of ON between both groups. We analyzed age, gender, time of disease, and gender, time of diagnosis, interval days for PE, type of ON and VA recovery was calculated by Spearman test. Statistical significance established was p=0.05.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age (years)</th>
<th>Time of NMO Diagnosis (months)</th>
<th>Anti-AQP4</th>
<th>Time for PE (days)</th>
<th>Previous relapses</th>
<th>ON relapses</th>
<th>Type of ON</th>
<th>Treatment</th>
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<tbody>
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<td>1</td>
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<td>ND</td>
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<td>37.1</td>
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<td>+7.1</td>
<td>11.3</td>
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<td></td>
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<td>ND4</td>
<td>SD.6.1</td>
<td>SD.2.6</td>
<td>SD.2.4</td>
<td>1</td>
<td>CFM, RTX1</td>
<td>B8</td>
</tr>
</tbody>
</table>

ON: Optic Neuritis; M: Male; F: Female; ND: No Data; SD: Standard Deviation; R: Right; L: Left; B: Bilateral; NT: No Treatment; AZT: Azathioprine; CPM: Cyclophosphamide; RTX: Rituximab.

Table 1: Demographic and clinical characteristic of patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before PE RE/LE</th>
<th>After PE RE/LE</th>
<th>p=</th>
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</thead>
<tbody>
<tr>
<td>VA</td>
<td>2.1 (SD ± 1.5)²</td>
<td>1.3 (SD ± 1.3)²</td>
<td>RE 0.01</td>
</tr>
<tr>
<td>EDSS</td>
<td>3.25 (0.7)³</td>
<td>3.25 (0.7)³</td>
<td>LE 0.03</td>
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</table>


Table 2: Improvement of visual accuracy after PE.
number of relapses and use of prophylactic treatment, but none of them showed to be a risk factor for to develop NO unresponsive to steroids. A total of 7 patients (58.3%) suffered adverse effects (AE): 3 (25%) slow flow (two times in the same patient), 2 (16.5%) hypotension, 1 (8.3%) neuromoraxia, and one more infection from catheter. The sever AE like neuromoraxia and infection was solved and no more complications was record. Just in one occasion the PE was stopped because slow flow.

**Discussion**

In our study we identify an important impact in the ON unresponsive to steroid VA improvement after PE, supporting previous reports. Significant recovery of VA in ON unresponsive to steroids patients after PE was seen, with a marked improvement in most of the cases. Others researchers have identified ameliorate mild or moderate, however inconsistencies in the methodology could explain this difference (not all studies used Keegan method and EDSS). Also, we have provided more information about patients with NO steroid-resistant. In our research, we identify an ON unresponsive to steroid prevalence of 21%. It mean, almost one in four NMO patients could not receive the therapeutic option of central nervous system. It is necessary to avoid bias, and clear up that we used to received NMO patients from all country, there for, it could explain the high prevalence of ON unresponsive to steroid. It was no surprise to find more women affected consequence of the female gender tendency viewed in NMO’s disease. Nevertheless, one study did not find significant difference in sex ratio. Mean age was similar to previous reports, affecting fourth and fifth decade of life. Kim and collaborators account one 12 years old child, who complained of two ON unresponsive to steroid attacks. It seems an isolated event with an extremely high inflammatory activity [16]. One important difference over other studies was the type of ON, because we recognized mostly bilateral affection, non-concordant to other study, which reported just one bilateral ON case. Until now, it is really difficult to answer why one or both eyes results injured, but we suggest that bilateral NO is a good candidate as risk factor to develop ON unresponsive to steroids. Unfortunately, we did not find a significant statistic value regarding this, just a tendency. There was no correlation between number of days until start PE and VA improvement. This draws attention, because Bonnan and collaborators had proposed early PE to obtain best results with a success rate of 100% at 11 days, 57% between 12 and 22 days and 52% from day 23 to 73. Analyzing our data, we find that the average time for to receive PE was 11.6 days, which falls on higher success rate. We encourage the application of PE in the first 11 days of NO, but the therapeutic window (at least 50% chance of improvement) could extend up to 8 weeks. However, a meta-analysis or more studies are needed to ensure this last. We propose age and gender as prognostic factors. Age had a negative correlation with VA and EDSS; this means that young patients suffer less visual impairment. Women were the most affected, so the male gender seems to have a good prognostic factor in NO unresponsive to steroids. AE were frequent, however just two of them were severe (neuromoraxia and infection) and solved. Unfortunately, these kind of inconvenient delay PE session, or perpetuate the inflammatory process. One past study mentioned anemia and leukocytosis after PE, but this are not frequent, and we did not found it. We recognize some limitation of our study, like small sample, non-comparable group and specialized reference center. For statistical purposes, of course the sample is really small, but considering NMO and ON unresponsive to steroids is seldom, we have presented one of the biggest series of cases until now. Otherwise, it is not ethic let the ON unresponsive to steroid patients without treatment, unless patient decides it. As you can see, it will be difficult to have a control group. A good option could be to compare immunoglobulin versus PE groups in ON unresponsive to steroids. Anyway, we recognize that future multicenter studies are necessary for to consolidate the response, risk and prognostic factors.

**Conclusion**

We described the prevalence of ON unresponsive to steroids. Women were mostly affected and bilateral ON was the type more frequent. PE is more successful in the first 11 days of NO unresponsive to steroids.

**References**


