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Plasma exchange in severe acute relapses of multiple sclerosis – Results from a Portuguese cohort

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ABSTRACT

Background: Relapses in Multiple Sclerosis (MS) are often associated with significant disability impairment which is resultant from poor response to corticosteroids. In such severe cases, plasma exchange (PLEX) may be used, although only a few studies with MS patients have been reported. Our objective was to evaluate the effectiveness of PLEX in severe relapses of MS.

Methods: Retrospective study of MS patients treated with PLEX in acute relapses. Data regarding EDSS, annualized relapse rate (ARR), treatment with corticosteroids, number of PLEX sessions, adverse events, and gadolinium enhancement in brain MRI were analysed.

Results: Included 46 patients, 76.09% female (n = 35) with mean age of 38.76 years and mean disease duration of 5.99 years, of which 84.78% had a Relapsing Remitting MS (n = 39), 15.22% Secondary Progressive MS (n = 7). The previous ARR was 1.1 and in 28.26% of the cases (n = 13) PLEX was used in the relapse that led to MS diagnosis. The majority of relapses had motor impairment (69.6%, n = 32), with a median EDSS increase of 1.5 points from baseline (maximum of 6.5) and higher than 1.5 points in 45.65% of cases (n = 21). Brain MRI was available in 69.57% of the cases (n = 32), and gadolinium enhancing lesions were present in 68.75% of cases (n = 22). Corticosteroids were used before PLEX in all patients for a mean of 6.09 days, without any immediate benefit in 41.30% of cases (n = 19), with the remaining cases showing only mild disability recovery. After a mean of 7.39 PLEX sessions, there was clinical benefit with complete EDSS recovery in 41.30% of patients (n = 19), and partial in 39.13% (n = 18). There were no adverse events related to PLEX in 89.13% of patients (n = 41) and in the remaining patients the reported adverse events included deep venous thrombosis (n = 1), anaemia (n = 1), fever (n = 1), hypoalbuminemia (n = 1) and arterial hypotension (n = 1).

Conclusion: Our results support the use of PLEX in severe relapses unresponsive to corticosteroids, since it was an effective and relatively safe treatment for most of our patients.

1. Introduction

Multiple Sclerosis (MS) is the most common demyelinating inflammatory disease of the central nervous system (CNS), and the leading cause of non-traumatic neurological disability in young adults in North America and Europe, affecting more than two million people worldwide (Dutta and Trapp 2011).

Most patients experience a relapsing remitting MS (RRMS), with acute episodes of neurologic dysfunction named relapses, followed by periods of partial or complete remission with clinical stability between episodes, although patients with secondary progressive MS (SPMS) and primary progressive MS (PPMS) may also experience relapses during evolution of the disease (Confavreux et al., 2000; Lublin et al., 2014).

Although in the past 20 years an important progress has been made in the field of multiple sclerosis treatment, the available treatments are yet incapable of completely preventing relapse occurrence, and its treatment is still a major component of the management of MS patients, in all phases of the disease (Comi et al., 2017). Relapses with incomplete remissions are an important contributor for the increase in neurologic disability and decreased health-related quality of life, and therefore aggressive relapse treatment is critical (Confavreux et al., 2000; Berkovich, 2013).

The gold standard treatment for MS relapses are corticosteroids. Several mechanisms have been proposed to justify its efficacy: decrease

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of oedema due to anti-inflammatory component; reduction of B-lymphocyte counts and their availability at the inflammatory lesions resulting in a decreased number of immunoglobulin (Ig) G synthesizing cells in the CNS; reduction of the blood–brain barrier abnormally increased permeability resulting in less gadolinium enhancing lesions (Berkovich, 2013; Frohman et al., 2007; Durelli et al., 1986; Martinelli et al., 2009).

Frequently, severe relapses are unresponsive to corticosteroids and in such cases, several options have been studied and used, such as plasma exchange (PLEX), cyclophosphamide, intravenous immunoglobulin G (IVIG) and natalizumab (Berkovich, 2013).

Several reports of PLEX efficacy have been published and although most studies have small cohorts and different evaluation methods, (Dau et al., 1980; Valbonesi et al., 1981; Weiner et al., 1989; Palm et al., 1991; Weinshenker et al., 1999; Weinshenker, 1999; Keegan et al., 2002, 2005; Bennetto et al., 2004; Ruprecht et al., 2004; Schilling et al., 2006; Linker et al., 2007; Llufriu et al., 2009; Trebst et al., 2009; Habek et al., 2010; Roesner et al., 2012; Ehler et al., 2015; Ikeda et al., 2015; Deschamps et al., 2016, 2017) due to the available evidence, European and American guidelines consider that some patients with MS, who have not responded to treatment with methylprednisolone may benefit from PLEX (Sellebjerg et al., 2005; Cortese et al., 2011).

Our objective was to evaluate efficacy and safety of PLEX in a cohort with severe relapses of MS refractory to corticosteroids treatment, in order to reinforce its importance in the management of MS relapses.

2. Materials and methods

2.1. Participants

This was a retrospective study. The start date for inclusion was January 1, 2000 and the last date for data introduction was 31 December 2015. The inclusion criteria were: patients followed in the Neurology Department of our Portuguese University Hospital with the diagnosis of RRMS (all patients met the criteria for diagnosis according to the McDonald Criteria of 2010); (Polman et al., 2011) treatment with Plasma Exchange (PLEX) during an acute relapse; and age above 18 years. Exclusion criteria were incomplete medical records.

This study was approved by the local ethics committee.

2.2. Clinical assessment

A relapse was defined as current patient-reported symptoms or objectively observed signs, typical of an acute inflammatory demyelinating event in the central nervous system, lasting at least 24 h, in the absence of fever or infection (Polman et al., 2011).

Data regarding MS subtype, EDSS, annualized relapse rate (ARR), previous and following treatment, treatment with corticosteroids, number of PLEX sessions, adverse events, and gadolinium enhancement in brain MRI were analysed.

2.3. MRI acquisition and analysis

Data from 1.5 T MRI reports were obtained. The presence of gadolinium enhancement lesions in brain MRI was analysed.

2.4. Statistical analysis

Demographic characteristics were presented as means and standard deviations for continuous variables, and as frequencies and percentages for categorical variables. The ARR and the EDSS were described as the mean and standard deviation. Safety outcomes were reported descriptively. In our sample all the variables have a non-normal distribution, so nonparametric tests were used. The Wilcoxon Signed Ranks Test was used to compare related continuous and related ordinal samples, and the Mann-Whitney Test is used to compare different groups of patients.

Table 1
Patient characteristics previous to PLEX treatment.

Female gender, % (n)	76.09% (n = 35)
Mean age, years (min-max, SD)	38.76 (19–71, 10.30)
Mean disease duration, years (min-max, SD)	5.99 (0–19, 6.0)
Subtype MS	
• RRMS, % (n)	84.78% (n = 39)
• SPMS, % (n)	15.22% (n = 7)
Annual relapse rate in the previous year, mean (min-max, SD)	1.13 (0–4, 1.11)
Baseline EDSS, median (min-max, IQR)	2.49 (0–6.5, 2.9)
Baseline MS treatment	
• Naïve - without previous MS diagnosis % (n)	28.26% (n = 13)
• Glatiramer acetate, % (n)	13.04 (n = 6)
• Interferon beta, % (n)	34.78 (n = 16)
• Fingolimod, % (n)	8.70 (n = 4)
• Natalizumab, % (n)	2.17 (n = 1)
• Azathioprine, % (n)	4.35 (n = 2)
• Micophenolate mofetil	2.17 (n = 1)
• Mitoxantrone	2.17 (n = 1)
• Cyclophosphamide	4.35 (n = 2)

Abbreviations: n – number; MS- Multiple Sclerosis; RRMS – relapsing-remitting multiple sclerosis; min - minimum; max - maximum; SD - standard deviation; IQR – interquartile range.

P values (2-tailed) < 0.05 were considered statistically significant; in the graphs 95% confidence intervals were used.

3. Results

3.1. Demographic characteristics of the patients

Among the MS population regularly followed in our outpatient department (n = 1014 patients), 47 patients were treated with PLEX, of which one was excluded due to incomplete medical records, with a final population of 46 patients. Patient baseline characteristics are summarized in Table 1.

The diagnosis of MS was performed in the relapse leading to PLEX treatment in 28.26% of the cases (n = 13). In 23.91% of the cases (n = 11) patients were treated with fingolimod, natalizumab or other immunosuppressive therapies. In the particular case of other immunosuppressive therapies, azathioprine was used in two patients (RRMS and SPMS) in 2007, micophenolate mofetil was used in one RRMS patient in 2014, mitoxantrone was used in one RRMS patient in 2009, cyclophosphamide was used in one RRMS patient in 2007 and in another with SPMS in 2014. These treatments were used in all cases after approved disease modifying treatments failure.

3.2. PLEX in our cohort

3.2.1. Relapse characteristics

The relapse characteristics that led to PLEX may be consulted in Table 2.

Table 2
Relapse characteristics that led to PLEX.

Symptoms	
• Motor impairment, % (n)	47.83% (n = 22)
• Severe optic neuritis, % (n)	4.35% (n = 2)
• Ataxia, % (n)	4.35% (n = 2)
• Brainstem symptoms, % (n)	4.35% (n = 2)
• Multifocal symptoms, % (n)	39.13% (n = 18)
EDSS during relapse, median (min-max, IQR)	4.0 (1.5 – 8.0, 3.0)
EDSS increase during relapse, median (min-max, IQR)	1.5 (0 – 6.5, 2.0)
Gadolinium enhancing lesions in brain MRI[a], % (n)	68.8% (n = 22)

Abbreviations: PLEX – plasma exchange; n – number; min - minimum; max - maximum; IQR – interquartile range; MRI – magnetic resonance imaging.
[a] - MRI available in 32 patients.