Brain & Development 38 (2016) 613–622

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Review article

Plasma exchange in pediatric anti-NMDAR encephalitis: A systematic review

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Received 16 October 2015; received in revised form 19 January 2016; accepted 25 January 2016

Abstract

Objective: To clarify the most frequent modalities of use of plasma exchange (PE) in pediatric anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis and to establish the most effective association with other immunotherapies.

Methods: Systematic literature review on PE in pediatric anti-NMDAR encephalitis (2007–2015).

Results: Seventy-one articles were included (mostly retrospective), reporting a total of 242 subjects (73.2%, 93/127 females; median age at onset 12 years, range 1–18). Median time to immunotherapy was 21 days (range 0–190). In most cases, PE was given with steroids and IVIG (69.5%, 89/128), or steroids only (18%, 23/128); in a minority, it was associated with IVIG only (7%, 9/128), or was the only first-line treatment (5.5%, 7/128). In 54.5% (65/119), PE was the third treatment after steroids and IVIG, in 31.1% (37/119) the second after steroids or IVIG; only in 14.3% (17/119) was it the first treatment. Second-line immunotherapies were administered in 71.9% (100/139). Higher rates of full/substantial recovery at follow-up were observed with immunotherapy given $\leqslant$30 days from onset (69.4%, 25/36) compared to later (59.2%, 16/27), and when PE was associated with steroids (66.7%, 70/105) rather than not (46.7%, 7/15). Significant adverse reactions to PE were reported in 6 patients.

Conclusion: Our review disclosed a paucity of quality data on PE in pediatric anti-NMDAR encephalitis. PE use in this condition has been increasingly reported, most often with steroids and IVIG. Despite the limited number of patients, our data seem to confirm the trend towards a better outcome when PE was administered early, and when given with steroids.

Keywords: Anti-NMDAR; Encephalitis; Plasma exchange; Plasmapheresis; Apheresis; Children; Immune therapy

1. Introduction

Since its description in 2007, anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis has been increasingly recognized also in pediatric age, even in the absence of tumor. Although treatment strategies have

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http://dx.doi.org/10.1016/j.braindev.2016.01.009
0387-7604/

been suggested in adults [1], to date there is no established treatment algorithm in children.

A direct pathogenic role of antibodies against the GluN1 subunit of the NMDAR has been demonstrated in anti-NMDAR encephalitis, resulting in immunoglobulin-induced NMDAR internalization [2,3], and supporting the rationale of antibody removal for the treatment of the disease.

Therapeutic plasma exchange (PE) is an established intervention as a first-line, often life-saving treatment in several conditions [4]. In view of its potential for removal of the pathogenic antibodies, PE is one of the immune therapies so far commonly used in pediatric anti-NMDAR encephalitis. Though, the extent of PE use, timing, and therapeutic protocols in pediatric anti-NMDAR encephalitis vary greatly in the literature. The use of PE in children partly relies on the expertise of the individual centers [1].

We searched the literature for children with anti-NMDAR encephalitis treated with PE, in order to clarify the most frequent modalities of use of PE in this disease and to investigate the most effective protocols, especially as regards the association with other immune therapies and the relative timing. In particular, we studied the relationship between outcome at last follow-up and overall first-line immune therapy strategy, use of second-line immune therapy, and timing of initiation of the first immune therapy, regardless of the type.

2. Materials and methods

2.1. Systematic review criteria

We performed an extensive search of the literature for children with anti-NMDAR encephalitis treated with PE. The literature search was conducted through MEDLINE, updated to December 2015, using the search terms "NMDAR", "Anti-N-methyl-D-Aspartate Receptor Encephalitis", "N-methyl-D-Aspartate receptor", "anti-NMDAR encephalitis" and "NMDA receptor encephalitis". No randomized controlled trials are available on the use of PE for anti–NMDAR encephalitis. Given the retrospective nature of published data, and the variable reporting in the publications, the data regarding treatment and timing was not always available. Therefore, the number of reported patients with available data is provided in brackets for each criteria. When the same patients reported in different articles were clearly identifiable, we counted them only once to avoid duplication.

2.2. Inclusion and exclusion criteria

We included in the present study published pediatric patients (age $\leqslant$18 years) with anti-NMDAR encephalitis treated with PE. Exclusion criteria were lack of treatment with PE, negative search for anti-NMDAR antibodies, or age >18 years.

2.3. Demographics and clinical data

We searched in the literature cohort a comprehensive set of data, including gender, age at onset, presence of tumor and symptoms of anti-NMDAR encephalitis. Based on the pertinent literature, we categorized symptoms in: prodromal flu-like symptoms; behavioral/psychiatric symptoms; movement disorder; speech disturbances/aphasia; psychomotor agitation; paroxysmal spells/epileptic seizures; consciousness disturbances/unresponsiveness/bed ridden/catatonia; autonomic instability.

2.4. Immune therapy

First-line immune therapy was defined as steroids, intravenous immunoglobulin (IVIG) and/or PE; second-line immune therapy included cyclophosphamide, rituximab, mycophenolate mofetil, azathioprine, methotrexate or other. Timing of initiation of immune therapy with respect to disease onset was registered, when explicitly reported in the original papers or when it could be inferred with a certain degree of confidence from the available data.

To enable comparison between treatment strategies involving PE, these were categorized according to the timing of PE compared to other first-line immune therapies (PE as first treatment; PE after steroids; PE after IVIG; PE after steroids and IVIG), and to the overall first-line immune therapy strategy, regardless of the order (PE + steroids + IVIG; PE + steroids; PE + IVIG; PE only). We defined the time point for "early" immune therapy as $\leq$30 days, in order to split the literature cohort in two similar sized subgroups – similar time thresholds have been used in other previous studies of autoimmune encephalitis [5–7].

2.5. Outcome

Based on the explicit comments of the authors, or to the best of our interpretation of the case description, clinical response to treatment in three major categories was performed by MN: full/substantial recovery (modified Rankin Scale (mRS) 0–2, asymptomatic or only mild deficits), similarly to the "good outcome" category used in one of the major studies on treatment in this condition [8]; partial improvement (mRS 3, moderate impairments); and limited/no improvement (mRS 4–6, severe deficits or death). Outcome was assessed at three different time stages: immediately after PE (regardless of the administration of other therapies), after completion of all first-line treatments, and at last available follow-up.

The clinical outcome was evaluated with respect to overall first-line immune therapy strategy, use of