Anti-Nmda Encephalitis treatment in Children: An Integrative Review

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Abstract. Anti-Nmda Encephalitis is one of the main autoimmune encephalitis diseases which can present with a wide range of symptoms, from psychological to motor, at first proving to be non-specific and difficult to diagnose. However, even with adequate therapy, many patients can still relapse and their symptoms return, or even fail to respond to the first-choice therapies (corticosteroids and immunoglobulins), making it necessary to quickly look for other forms of treatment that have emerged over the years, such as second-line or third-line drugs. In this way, the aim of the paper was to analyze the most conventional (main) drugs and those that have emerged in recent years for the treatment of Anti-Nmda Encephalitis in children.

Keywords. Anti Nmda encephalitis treatment, Anti Nmda encephalitis new treatment, anti Anti-N-Methyl-D-Aspartate Receptor Encephalitis, anti Nmda encefalitis in children.

1.Introduction

Anti-Nmda encephalitis is one of the main autoimmune encephalitis diseases, with an estimated incidence of 1.5 per million population per year worldwide, affecting mainly women. It also has a mortality rate of between 5% and 11% [1,2,3]. The condition is characterized by the presence of antibodies (IgG) against GluND1 (NMDA receptor subunit 1), leading to antibody-mediated inflammation and internalization of NMDA receptors. The pathology can start due to teratomas (mainly ovarian in women), after viral infection and idiopathic causes [1,2,3,4].

The symptoms are: amnesia, a series of subacute, severe, complex neuropsychiatric symptoms such as cognitive impairment, amnesia, mental behavioral disorder, epileptic seizures, autonomic nervous dysfunction, consciousness change, behavioral disturbances, seizures, disordered speech, dystonic movements, decreased responsiveness and central hypoventilation. Apparently, children have more seizures and epileptic states. Another characteristic symptom is amnesia of the disease period, which the authors associate with a reversible reduction of NMDA receptors in the central nervous system [3,5].

Treatment is currently divided into first-line (corticosteroids, intravenous immunoglobulin or plasma exchange), second-line immunotherapy (rituximab, cyclophosphamide, azathioprine, tocilizumab, and bortezomib and methotrexate) and third-line (bortezomib and tocilizumab) [4,5,6,7,8,9]. In view of these drugs, many children relapse after being cured, demonstrating the need for continuous therapy [4,5,6,7,8,9].

Finally, it is clear that there is a need for a review of the drugs already approved and other possible modalities that will benefit children who are unresponsive to standard initial treatment or whose symptoms have relapsed.

2. Methodology

2.1 Inclusion criteria

The integrative method was chosen to promote critical analysis of the recent studies in the field and gain insights.

This review was carried out by searching Pubmed from 2018 to 2023 with the keywords: Anti nmda encephalitis, treatment, Anti Nmda encephalitis new treatment, Anti-N-Methyl-D-Aspartate Receptor Encephalitis, anti Nmda encephalitis in childreen. In the first stage, the key words were used and the papers found in Pubmed were downloaded into a literature review manager and 3,564 articles were found. Of these, 521 were excluded because they had no duplicates.

In the second stage, the title was read, reducing the number of articles to 228. In the third stage, the introduction and abstract were read, reducing the number of articles to 86. In the fourth stage, the conclusion of these papers was read, leaving 36 articles. In the fifth stage, the papers were read in full, leaving only 14 to be used in the review.

The criteria were as follows: The papers should have been published in the last 5 years,Included studies must have compared first and second line treatments according to the refractory response of each case, observational, intervention or review studies, papers should talk about the management of children with Anti Nmda Encephalitis. Finally, both review and empirical studies (clinical trials and observational) were included.

2.2 Exclusion criteria

The criteria were Study published more than 5 years ago, Study published in a language other than English, Spanish and Chinese, papers that could not be accessed online or were duplicates and papers that dealt with adults.

3. Results

Fifteen articles were selected for their relevance to the topic. 7 retrospective cohort (observational studies), one analyzed 6 patients with refractory anti-NMDA receptor encephalitis who did not improve after first and second-line therapy and received monthly intra-thecal methotrexate [1], one analyzed Effectiveness of Mycophenolate Mofetil in the Treatment of Pediatric Anti-NMDAR Encephalitis: A Retrospective Analysis of 6 Cases [4],a study that analyzed 135 patients with autoimmune encephalitis, with Short-Term First-Line Treatment [5],one study that analyzerd Heterogenous treatment for anti-NMDAR encephalitis in children leads to different outcomes 6-12 months after diagnosis [7], a study that analyzed 111 cases in patients with anti-NMDA encephalitis, in south china[8], for long-term outcome in patients with anti-NMDA receptor encephalitis [11] and one analysis of four cases of a severe form of encephalitis due to anti-NMDA receptor antibody [13]. Five articles were literature reviews, one taht analyzed epidemiological differences and common challenges in the popuation with Anti-Nmda Encephalitis [2], another epidemiological differences and common challenges in the population withe Anti-Nmda Encephalitis [3], one Current Knowledge on Subtypes and Disease Mechanisms and Treatment. CNS Neurol Disord Drug Targets [6], one that addresses a paediatric population [9], one that summarizes current immunotherapy regimens and, at the same time, looks forward to optimizing immunotherapy regimens [10]. Three case report papers, one with patients refractory to conventional treatment [12], a case report on an 18-month-old boy who presented with seizures, movement disorder, cognitive impairment and behavioral disorders [14] and one on plasma exchange in patients with Anti-Nmda encephalitis [15].

4. Discussion

The treatment of Anti-Nmda receptor encephalitis consists of Immunotherapy, divided mainly into First Line, Second Line and Third Line, reducing the progression of the disease and potentially leading to a cure. Patients need to change their treatment due to intolerance of side effects or non-responsiveness to the drugs. In addition, the timing of the start of treatment is essential for a better prognosis and delay has been associated with persistent neurological deficits [9,10].

4.1 First line

The drugs used are corticoesteroids, in particular methylprednisolone or prednisone in adjuvant with immunoglobulins or not. The corticoesteroids have the best effect due to their immunosuppression and, consequently, reducing the production of antibodies and inflammation [2,7,10]. Corticosteroids are introduced either in the acute phase of the disease (leading to remission) or maintenance. In the acute phase, intravenous methylprednisolone is administered, at doses of 30mg/kg for 3-5 days. In the maintenance phase, oral prednisolone is generally used, with doses of 1-2mg/kg per day [2,7,10].Despite the beneficial effects of corticosteroid therapy, prolonged use can lead to side effects, even at low doses, such as atrophy of the adrenal gland, proteolysis, insulin resistance, neurological changes and loss of muscle mass [2,7,10]. Furthermore, the sooner the patient is medicated, the better their prognosis and the less chance there is of symptoms returning in a short period of time [3,10,11].

Immunoglobulins (IVIG)can be given initially with or without corticosteroids, depending on the individual's response, depending on the improvement or worsening of the condition with immunoglobulin alone. In general, IVIG treatment can prevent the binding of the Antibody to the receptor by removing circulating Nmda receptor antibodies, and steroids provide additional support by attenuating antibody production. The dosage of the Antibody (gamma globulin) is 1 g/kg daily for 2 d or 0.4 g/kg daily for 5 d [2,7,10].

Plasma exchange is less commonly used due to a lack of data, but its benefit is that it removes the antibodies present in the blood. In addition, it can be given together with corticosteroids and should not be used after gamma globulin. However, there is still a lack of studies to systematically prove its effectiveness for the treatment of this disease [10].

4.2 Second line

Second-line drugs are used when there is no response or when cases are refractory to the first treatment. In relation of these drugs, the first choice is Rituximab, which is a chimeric monoclonal antibody against CD20, significantly reducing the

levels of Cd20 and Cd19 (target of 0.05%) and reducing the production of anti-Nmda receptors, due to its action on B lymphocytes, leading to a decrease in these. It is generally indicated for patients unresponsive to the first phase (drugs of first choice) and its dosage is low (a cumulative value of 1200mg/m2), showing a good long-term prognosis, but it is necessary to evaluate Cd19 levels after each dose to observe the cumulative effect of the drug. Furthermore, the combination of rituximab and cyclophosphamide has shown positive effects in certain studies [4,6,7,10,12,13,14]

Cyclophosphamide is not commonly used due to its side effects (myelosuppression, hemorrhagic cystitis, reproductive toxicity) and lower tolerability compared to rituximab. Its shock dose is around 0.5-1mg;/m2, followed by a lower maintenance dose of 0.4-0.5mg/m2, leading to immunosuppression [4,5,10,13].

With regard to Azathioprine, an inhibition of deoxyribonucleic acid (DNA), ribonucleic acid (RNA), and protein synthesis, some doctors believe that it can be used orally for a prolonged period after initial treatment with rituximab and also to avoid prolonged use of corticosteroids [2,10].

Finally, Methotrexate acts as inhibition of DHFR by folate antagonists (methotrexate) results in a deficiency in the cellular pools of thymidylate and purines and thus in a decrease in nucleic acid synthesis. In view of this, it has proved to be an excellent drug to alleviate symptoms and reduce relapse 7.5-12.5 mg/m2 once a week, with the maximum single dose not exceeding 15 mg, and it can be used for several months to several years.The administration of this drug can be done differently from intravenous, being intrathecal, which began to be used in children who showed an insufficient response or relapse to first- and second-line immunotherapy, and can be administered together with a corticosteroid. This route removes the factor that hinders the concentration of the drug in the brain, which is the need to pass through the blood-brain barrier[1,2,10].

4.3 Third Line

The drugs in this line are used when the patient has no resolution with the others. They currently include Tocilizumab and bortezomib, both of which are relatively new drugs in Anti-Nmda encephalitis and have shown positive effects in some studies, but require further studies to prove their effects [10,13,15].

Tocilizumab is an anti-IL6 monoclonal antibody, which blocks IL-6-mediated signal transduction. Anti-IL-6 inhibits the differentiation of regulatory T-cells, which is crucial for maintaining the balance against IL-17-producing T-helper cells in the regulation of autoimmune processes [10,13,15].

Bortezomib binds to the chymotrypsin-like subunit of the 26S proteasome, resulting in its inhibition and preventing the degradation of various pro-apoptotic factors. Its dosage is generally 1.3 mg/m2 per dose. One of the hypotheses that bortezomib has a beneficial effect is that early administration of bortezomib may allow it to reach plasma cells before they cross the blood-brain barrier, since bortezomib has limited penetration into the central nervous system. Particularly in the case of a refractory autoimmune disease, it is possible that the antibody response is mediated by long-lived plasma cells. These cells do not respond to traditional immunosuppressive therapies, such as B-cell depletion regimens, because they do not express the CD20 cell surface antigen targeted by rituximab. However, they may be susceptible to being targeted by proteasome inhibitors such as bortezomib [9,12,13,14,].

Finally, both drugs can be given in conjunction with corticosteroids [5,9,13,14,].

4.4 Treatment of Symptoms

The treatment of symptoms consists of the introduction of antiepileptic drugs, antipsychotics, benzodiazepines or electroconvulsive therapy. Currently, trials have been carried out with Ketamine, but more studies are needed to prove its effectiveness [9].

4.5 Recovery

Firstly, patients begin to see an improvement in disturbances of consciousness, followed by an improvement in autonomic dysfunction and a reduction in dyskinesias. Finally, verbal and motor contact with patients gradually improves, as do executive function and memory, which are the last to improve [9].

4.6 Prognosis

Most patients, in the children population, if diagnosed early and treated, have a 75-87% chance of remission or a few symptoms that don't affect their daily lives. Relapses of symptoms are seen in 10-15% of patients [9,10].

Finally, 20-30% of patients have permanent neurological damage and apparently children have a worse prognosis with impaired executive functions and memory, due to the involvement of the hippocampus and subcortical nuclei, which have a high concentration of Nmda receptors. However, if treatment is delayed, there is a tendency for patients to suffer relapses of the disease [9,10].

5. Conclusion

Since the emergence of Anti-Nmda encephalitis, the greatest attention has been paid to its psychological, motor and even central nervous system depressive symptoms, especially in children who can suffer

severe and permanent damage for the rest of their lives. For this reason, it is essential to diagnose the patient early, along with first-line therapy and, if necessary, quickly assess whether the patient is unresponsive, to implement second-line or even third-line therapy. With regard to refractory patients, it is essential to manage them as efficiently as possible and, if necessary as last resourse, use therapies that are still experimental and require more robust studies, but which have been showing beneficial effects on curing the patient, with certain drugs such as: Cyclophosphamide, Azathioprine, Methotrexate, Tocilizumab or even Bortezomib. Finally, that therapy in Anti-Nmda Encephalitis should be individualized and in relation to the child population, it is more sensitive to the damage caused by Anti-Nmda encephalitis, requiring greater care, as well a faster and more effective management.

6. References

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