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Management of Neuropsychiatric Symptoms of Anti-NMDA Receptor Encephalitis

Review Article

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Abstract

Introduction: Anti-NMDA receptor (NMDAR) encephalitis is a significant cause of novel autoimmune and paraneoplastic encephalitis, Affect one out of 1.5 million people per year. Females are four times more affected as compared to males. Patients present with a prodromal phase of constitutional symptoms followed by a spectrum of clinical manifestations eventually leading to death if left untreated. However, rapid recognition and treatment can lead to survival and a return to the baseline level of functioning in most patients. It was diagnosed by the presence of Anti-NMDAR antibodies that are directed to the extracellular domain of the GluN1 subunit in the CSF and serum.

Methods: In this review article, we have examined the treatment of Anti-NMDA encephalitis in the past ten years, based on references retrieved from PubMed, NCBI publications.

Result: Treatment of Anti-NMDAR encephalitis is based on first-line immunotherapy [corticosteroids, plasmapheresis, and intravenous immunoglobulin] and second-line immunotherapy (rituximab and/or cyclophosphamide). Early treatment leads to rapid improvement in motor skills, responsiveness, self-care, and speech, additionally in the paediatric population dramatic resolution of neurologic and psychiatric symptoms was noted. In the case of complement deficiency, plasmapheresis was found to be highly effective. When first-line treatment was ineffective, intravenous rituximab has shown noteworthy clinical improvement. In cases refractory to intravenous rituximab, the use of intrathecal rituximab has shown marked improvement mainly associated with homozygous C4B deficiency. The use of cyclophosphamide helped resolve movement disorder and brought significant improvement in the domains of cognition, language, and behaviour. When given with rituximab it demonstrates remarkable improvement. in drug-resistant status epilepticus. Methotrexate, when given intrathecally along with steroids showed tremendous improvement in some paediatric cases. Bortezomib has proven to be a reserve when second-line immunotherapy is refractory. Electroconvulsive therapy reported a vigorous response in resolving neuropsychiatric symptoms. The use of oral perampanel , an α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor antagonist, illustrated considerable improvement in seizure activity and abnormal behaviour. Recently the use of ACTH therapy in patients with paralysis associated with choric dyskinesia of limb recovered.

Conclusion: It was observed that early initiation of combined immunosuppressive therapy in higher dosage for a prolonged duration shortens the clinical course and potentiates the possibility for complete recovery in the case of Anti-NMDAR Encephalitis. In the last decade, only 9 drugs have shown some beneficial effects. Therefore, further studies which involve more participants and evaluate newer medications are needed..

Keywords: Anti-NMDAR Encephalitis; Neuropsychiatric symptoms; Rituximab; Bortezomib; Perampanel

Introduction

Anti-NMDA receptor (NMDAR) encephalitis is a significant cause of novel autoimmune and paraneoplastic encephalitis. Although this is a rare disease, one affected out of 1.5 million people per year but is the most common cause of non-viral encephalitis. Females are four times more commonly affected as compared to males. Patients present with a prodromal phase of constitutional symptoms followed by a spectrum of clinical manifestations consisting of behavioural and psychiatric symptoms, autonomic disturbances, movement disorders, and seizures, even leading to death if left untreated. However, rapid recognition and treatment can lead to survival and a return to the baseline level of functioning in most patients and is based on a multidisciplinary approach [1]. Diagnosis of the disease is confirmed by the presence of Anti-NMDA receptor Antibodies, these antibodies are directed at the extracellular domain of the GluN1 subunit in the CSF and serum. Anti NMDAR encephalitis was previously known to be associated with teratoma but recent studies have shown its relationship with other tumours and autoimmune diseases [2]. In this review article, we have examined the treatment of Anti-NMDA encephalitis in the past ten years, it is based on references retrieved from PubMed publications [3].

Review

Treatment of Anti-NMDA encephalitis is based on first-line immunotherapy (corticosteroids, plasmapheresis and intravenous immunoglobulin) and second-line immunotherapy (rituximab and/or cyclophosphamide) [4,5,6]. Treatment with steroid (methylprednisolone) and intravenous immunoglobulins (IVIG) leads to rapid improvement in motor skills, responsiveness, self-care, and speech, additionally in the paediatric population with the use of cyclophosphamide dramatic resolution of significant neurologic and psychiatric symptoms was noted [7,8]. In the case of complement deficiency, plasmapheresis was found to be highly effective [9,10]. When first-line treatment was ineffective, intravenous rituximab has shown noteworthy clinical improvement [11]. In cases refractory to intravenous rituximab [12], the use of intrathecal rituximab has shown marked improvement [13,14]. Besides, this therapy was also found to be helpful in Anti-NMDA encephalitis associated with homozygous C4B deficiency. The use of cyclophosphamide helped resolve movement disorder and brought significant improvement in the domains of cognition, language, and behavior. Cyclophosphamide when given with rituximab in drug-resistant status epilepticus demonstrated remarkable improvement [15]. A promising alternative immunomodulator was methotrexate when given intrathecally in combination with steroids showed tremendous improvement in some paediatric cases of Anti NMDAR encephalitis. Bortezomib (proteasome inhibitor) proved to be a useful reserve when second-line immunotherapy is refractory [16,17,18].

Electroconvulsive therapy reported a vigorous response in resolving neuropsychiatric symptoms such as catatonia [19], especially in the paediatric population [20,21]. In a few studies use of oral perampanel, an α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptor antagonist, illustrated considerable improvement in seizure activity and abnormal behavior [22]. Some patients with paralysis associated with choric dyskinesia of limb in cases of Anti-NMDA encephalitis recovered with the use of ACTH therapy [23].

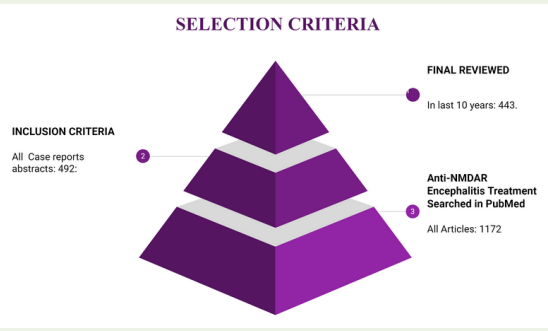

Figure 1: Selection Criterion for the study, treatment of Anti-NMDAR Encephalitis.

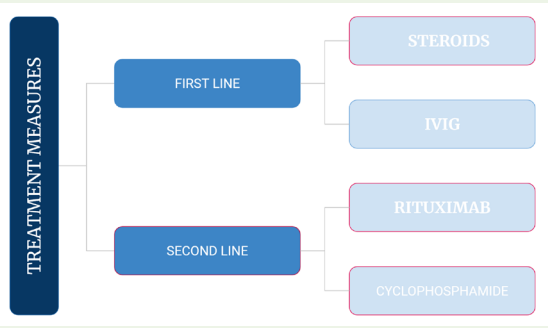

Figure 2: Treatment measures for Anti-NMDAR Encephalitis .

Conclusion

Early initiation of combined immunosuppressive therapy which includes both first and second line in higher dosage for a prolonged duration shortens the clinical course and potentiates the possibility for complete recovery in the case of Anti-NMDAR Encephalitis [24]. There have been many new drugs used for the resolution of various symptoms in the past decade in total 9 medicines have shown some beneficial effects. However, other than 4 drugs including first-line immunotherapy [corticosteroids, plasmapheresis, and intravenous immunoglobulin] and second-line immunotherapy (rituximab and/or cyclophosphamide) no other drug is approved. Further studies which involve more participants and evaluate newer medications are needed.

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