Intrathecal Rituximab as a Rescue Therapy in Refractory Pure CSF Positive, Non-Teratomatous Type Anti-NMDAR Encephalitis

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Abstract

NMDAR antibody encephalitis is the most common autoimmune encephalitis characterized by a myriad of neuropsychiatric symptoms. It predominantly affects females and is associated with ovarian teratoma (58%). Nineteen percent do not respond to treatment and are left with serious neurological deficits. A subset of NMDAR encephalitis with antibody positivity in CSF alone without ovarian teratoma is often found to be refractory to treatment. We name them ***Pure CSF positive, non-teratomatous type anti-NMDAR encephalitis***. We report two such cases who responded to intrathecal rituximab, to highlight a novel treatment as a rescue therapy to prevent long-term disability and improve clinical outcomes.

Keywords: Anti NMDA receptor encephalitis, intrathecal injection, non-paraneoplastic anti-NMDAR encephalitis, rituximab

Introduction

Autoimmune encephalitis (AE) is a debilitating neurological disorder that causes a range of neurological and psychiatric symptoms.[1] N-methyl-D-aspartate receptor antibody encephalitis (NMDARE), the most common form of AE, is characterized by abnormal behavior, cognitive dysfunction, seizures, movement disorders, reduced consciousness, mutism, autonomic dysfunction, hypoventilation, and memory deficits.[1-5] Clinical presentation is determined by the degree of active CNS inflammation, and therefore, the mainstay of treatment is immunosuppression. Early commencement of immunotherapy may prevent major disability.[2,6,7]

We report two cases of severe NMDARE refractory to treatment that responded to rescue therapy with low-dose intrathecal rituximab. Rituximab is a chimeric monoclonal antibody against CD20-positive B lymphocytes (B cells) inducing B-cell depletion.[2,6]

Case History

Case no 1

A 15-year-old girl presented with sub-acute encephalopathy, severe orofacial dyskinesias, new onset status epilepticus, psychosis, and severe autonomic dysfunction. She later became mute and non-communicative. Her clinical presentation was classical of NMDARE, but serum autoimmune panel was negative. CSF showed markedly elevated titers of NMDAR antibody. Serial search for ovarian teratoma with ultrasound, CT, and MRI pelvis turned up negative. MRI brain was normal. EEG showed diffuse generalized slowing. She was initiated on first-line immunotherapy with intravenous methylprednisolone and intravenous immunoglobulin (IVIg). Despite treatment initiation, she continued to deteriorate, and hence, 5 cycles of plasma exchange (PLEX) were given. Her condition further deteriorated with severe respiratory disturbance and status epilepticus requiring mechanical ventilation. Even after 2 months of second-line therapy with intravenous rituximab, she continued to be mute, non-communicative, and bedbound with recurrent seizures. Although we were not able to demonstrate ovarian teratoma, exploratory laparotomy was performed and suspicious cysts were removed. Histopathological examination was normal. We then administered IV cyclophosphamide, but she continued to deteriorate. After getting informed consent, we gave 25 mg intrathecal rituximab weekly for 4 weeks. Second day after intrathecal rituximab patient started improving with increased responsiveness and seizure control. She became normal by 3-4 weeks. She continues to be in clinical remission after 8 months of administration of intrathecal rituximab.

Case no 2

A 16-year-old student presented with sub-acute onset encephalopathy with severe psychosis and recurrent orofacial

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brachial dyskinetic seizures. Her serum NMDA antibody was negative; however, her CSF NMDA antibody was strongly positive. Workup for teratoma was negative. Her MRI brain and CSF parameters were normal. She was treated initially with IV methylprednisolone and IVIG followed by PLEX. Subsequently, we treated her with two doses of intravenous rituximab followed by cyclophosphamide. As there was no response, we then treated her with 25 mg rituximab intrathecally for 4 weeks after getting informed consent. She showed rapid improvement with more alertness and started vocalizing 2–3 days after first dose of intra-thecal rituximab. She recovered fully and continues to remain so at the end of 8 months.

Discussion

Anti-NMDARE is the most common non-infectious autoimmune limbic encephalitis.[8] The disease mainly affects young females (median 21 years, range 1-85 years).[9] Fifty-eight percent of cases are associated with ovarian teratoma.[2] Teratomas contain neuronal cells that induce immunologic sensitization against NMDA receptors. These antibodies reach CNS, cause crosslinking, internalization, and reversible reduction in the number of NMDA receptors leading to the clinical picture of anti-NMDA receptor encephalitis.[10] Diagnosis of NMDAR encephalitis is confirmed by detection of IgG antibodies to the GluN1 subunit of NMDA receptor in CSF, while serum testing is less reliable.[11]

Clinical therapy includes first-line immunotherapy (corticosteroids, IVIg, and PLEX), second-line immunotherapy (intravenous rituximab, cyclophosphamide, azathioprine, and mycophenolate mofetil), and tumor removal.[2,9] The use of second-line immunotherapies in AE due to autoantibodies against cell surface antigens is associated with a better outcome and lower rates of relapse. The death rate in anti-NMDARE ranges from 2% to 5%.[2,6] With early appropriate therapy, 81% patients show good recovery.[2,9] Plasma cells secreting high amount of NMDAR antibodies found in perivascular, interstitial, and Virchow Robin spaces of brain are responsible for intrathecal synthesis of antibodies in anti-NMDAR encephalitis.[10] Hence, the ideal therapy should eliminate the intrathecal antibody. Preserved integrity of blood brain barrier (BBB) in anti-NMDARE along with limited penetration of IVIG, steroids, rituximab, and cyclophosphamide may be responsible for the restricted response to immunotherapy seen in patients with high levels of synthesized antibodies in CSF.[2,10,12,13]

Anti-NMDARE in children is less associated with teratomas, and failure of first-line therapies is more frequent among children without tumor.[2,6,12] This non-teratomatous, non-paraneoplastic type, pure CSF positive anti-NMDARE seems to be a separate entity often refractory to treatment. Intrathecal methotrexate and dexamethasone have been successfully tried in refractory cases of anti-NMDARE.[14,15] Intravenous rituximab has only 1% penetration into CSF and may be less effective against the long living intracranial memory B cells.[10] Casares *et al.*[12] administered intrathecal rituximab in a patient with CSF NMDA antibody positivity with good clinical improvement and reduction in antibody titers.

Antibody titer changes in CSF rather than in serum are more closely related to clinical outcome in patients with anti-NMDARE.[12,14,15]

In the absence of prospective and randomized data, therapeutic strategies in anti-NMDARE are based on observational studies and clinical experiences. We report 2 children who had anti-NMDAR antibodies present only in CSF and no associated ovarian teratoma. Both patients were refractory to first- and second-line immunotherapy, and we tried intra-thecal rescue therapy with rituximab after ethical committee clearance. We postulate that intrathecal rituximab has a direct impact on inflammatory environment and suppresses the intrathecal synthesis of antibodies resulting in rapid clinical improvement and sustained clinical response. This can be considered as a rescue therapy in refractory cases. Long-term follow-up is essential as a relapse in NMDAR encephalitis is seen in up to 25% cases and may even occur after several years.[1,9] We plan to closely follow up our patients clinically and ascertain the need for future treatment.

We have not ascertained serial quantitative titers of NMDA in our patients. Quantitative NMDA titers pre- and post-intrathecal rituximab administration (which have been documented in other studies) may further help in validating this novel approach.

Advantages of intrathecal rituximab include low dosage, cost effectiveness, rapid onset of action, negligible side effects, and sustained response.[12,16] Anticipated side effects of intrathecal rituximab are mild and dose related. These include nausea, vertigo, paresthesia, and refractory hypertension.[12,17] However, low dosage—25 mg as a 1:1 dilution is safe and can avoid hypertension which may be encountered at higher dosages.[12,14]

Pure CSF positive non-teratomatous, non-paraneoplastic type of anti-NMDARE is a subset of autoimmune encephalitis seen more commonly in young girls, often refractory to conventional therapy. Low-dose intrathecal rituximab (25 mg x 4 doses) seems to be safe with good clinical outcome and can be considered a ***rescue therapy in those refractory to conventional therapy***.

Key messages

Pure CSF positive – non-teratomatous type anti-NMDAR encephalitis is often treatment refractory and low-dose intrathecal rituximab provides a safe, effective treatment option with rapid and sustained clinical response.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other

clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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