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ALEMTUZUMAB AND INTRATHECAL METHOTREXATE FAILED IN THE THERAPY OF RASMUSSEN ENCEPHALITIS

OPEN

Rasmussen encephalitis (RE) is a rare but devastating unihemispheric brain disorder that often affects children.[1] The clinical picture is characterized by intractable focal epilepsy and progressive decline of functions associated with the affected hemisphere.[2] Despite its known inflammatory background and T-cell involvement, immunotherapy appears to slow rather than halt disease progression, and hemispherotomy appears to be the only solution for intractable epilepsy.[1–4] A potential early therapeutic window has been suggested, and new therapeutic agents have become available.[1] A monoclonal antibody targeting CD52 that leads to long-term depletion of lymphocytes (alemtuzumab) has previously been considered as a possible treatment option for RE, but clinical data are limited.[1,5]

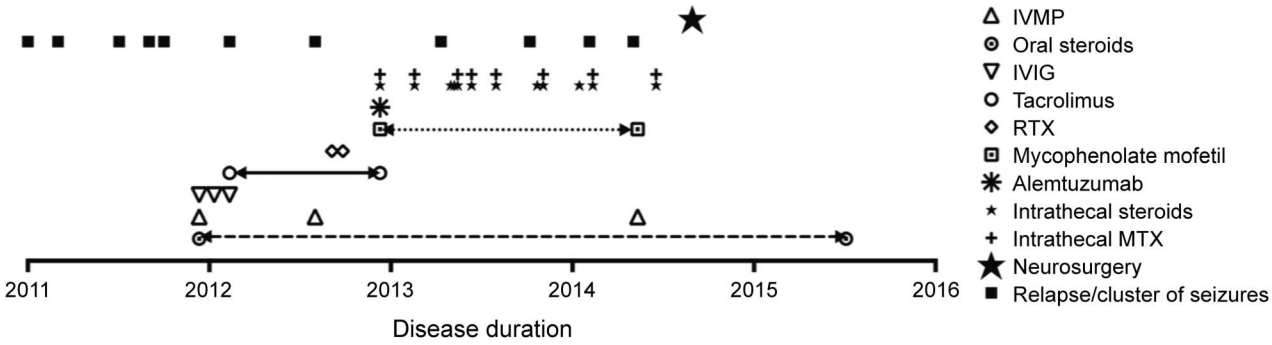
Case report. A previously healthy, right-handed boy developed refractory epilepsy at the age of 7 years. Based on clinical, electroencephalographic, and neuroimaging features,[3] he was diagnosed with RE of the dominant hemisphere at the age of 8 years. Unremarkable right-sided hemiparesis (pyramidal signs but no permanent weakness) and above-average intellectual capacity were described at that time. Video-EEG showed left-hemispheric epileptiform activity and multiple types of epileptic seizures, including epilepsy partialis continua (EPC) of the right hand. Brain MRI revealed mild left-hemispheric atrophy without any inflammatory signal changes or gadolinium enhancement (figure e-1A at Neurology.org/nn). Blood-brain barrier failure was observed, with no pleocytosis in the CSF. Common immunotherapy that was escalated as displayed in figure 1 was applied during the first year of the therapy. Despite this, brain MRI showed new signal changes (figure e-1B) and the boy suffered from refractory epilepsy and deteriorated.

Thus, further escalation of the immunosuppression was applied. According to our previous experience with a different diagnosis, IV treatment with alemtuzumab (total dose of 0.75 mg/kg for 3 consecutive days) was combined with intrathecal administration of methotrexate (MTX) (12 mg for a single dose).[6] Finally, tacrolimus was switched to mycophenolate mofetil because of its side effects and ineffectiveness.

The administration of alemtuzumab was complicated by an unexpected severe systemic reaction and hyperpyrexia that required intensive care for 21 days. Sedation, physical cooling, ventilation support, and high doses of IV immunoglobulin were required to manage this situation. After that, a change in disease course was observed. There were no clinical seizures apart from a fine EPC in the right hand, and overall cognitive performance (in particular psychomotor speed, attention, and verbal fluency) was improved. Brain MRI revealed a regression of the inflammatory changes (figure e-1C). An additional dose of intrathecal MTX was administered to strengthen the positive effect. Unfortunately, a clinical relapse characterized by clustering seizures, accented right-side hemiparesis (in terms of muscle weakness) and aphasia occurred 8 weeks later; however, repeating the intrathecal MTX led to prompt stabilization. Thus, we continued to repeat the intrathecal therapy with gradually extending intervals and clinical stabilization was reached for 6 months. Nevertheless, when we extended the intervals up to a maximum of 3 months, new flares of the disease occurred (figure 1, figure e-1D). Severe lymphopenia in the peripheral blood and the absence of lymphocytes in the CSF persisted throughout the entire time regardless of clinical relapses. Hemispherotomy was finally performed 2 months after the last dose of intrathecal MTX, when the boy reached 10 years of age and was in a phase of clinical stabilization. At the time of surgery, he had preserved function of the right hand, walked independently, spoke in sentences, and had no seizures apart from an EPC of the right hand. Brain MRI showed ongoing atrophy but no inflammatory signal changes (figure e-1E). Brain biopsies collected from different lobes showed similar unremarkable inflammatory changes, including mild astrogliosis and scattered lymphocytic perivascular infiltration with $CD8^+$ T-cell predominance (figure e-1G). Severe neurologic sequelae were

Supplemental data at Neurology.org/nn

Figure 1 Timeline of immunotherapy and clinical course



The timeline of multiple drugs is displayed in the figure. Clinical clusters of epileptic seizures with the need for hospitalization are marked. The concurrent treatment with antiepileptic drugs and anti-infective prophylaxis is not indicated. Common immunotherapy was applied at the beginning as follows: (1) IVMP followed by a slow oral steroid tapper, (2) high doses of monthly repeated IVIG, and (3) tacrolimus—the dose was titrated according its levels. Because of ongoing clinical deterioration and signs of neuroinflammation on MRI, (4) RTX was added. Despite this, the cognitive and motor deterioration slowly progressed. Thus, a novel approach of further escalation of the immunosuppression was applied as follows: (5) IV alemtuzumab, (6) intrathecal MTX with intrathecal steroid. In addition, tacrolimus was switched to (7) mycophenolate mofetil. Finally, (8) hemispherotomy was performed, and the medication has been gradually tapered down. IVIG = IV immunoglobulin; IVMP = IV methylprednisolone; MTX = methotrexate; RTX = rituximab.

observed after the neurosurgery, as expected (figure e-1F). At 18 months after the surgery, the patient has no functional use of the right hand, hardly walks, and speaks in very simple sentences. He is seizure free and attends school with special assistance.

Discussion. Extremely demanding therapeutic effort was performed in an attempt to prevent hemispherotomy of the dominant hemisphere in a boy with RE and a mild neurologic deficit. Although the cause of RE remains elusive, T cells are involved in the pathology.[1] The aim of our combined therapy was to deplete T cells from the peripheral blood and influence the inflammatory process behind the blood-brain barrier.[5] However, the boy experienced a life-threatening systemic reaction immediately after alemtuzumab administration and later on, the clinical stabilization seemed to be dependent on intrathecal MTX. It was not possible to continue with this therapy because of its known cumulative side effects and neurotoxicity. We believe the brain biopsy demonstrated that it was possible to temporarily control brain inflammation, but at the cost of inappropriate risks. We hypothesize that our aggressive immunotherapy failed for the following reasons: (1) we missed the early therapeutic window[1,7]; (2) the pathology of RE is more complex, and the immunosuppression was not enough to cure the disease.[1]

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