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Long-term effect of rituximab in a case with late-onset Rasmussen´s encephalitis with anti-ganglioside IgGQ1b and anti-GAD antibodies positivity

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Abstract

Rasmussen's encephalitis is a rare autoimmune encephalitis usually involving one brain hemisphere, presenting with refractory epileptic seizures, and neurological and cognitive decline. Only 10% of cases start later in adolescence/adulthood. The only effective treatment for refractory seizures in childhood is hemispherectomy. For late-onset cases with mild neurological deficit the hemispherectomy is usually postponed because of its severe consequences. Immunotherapy shows some temporal effect for seizure control and slowing the brain atrophy, mainly in late onset Rasmussen's encephalitis.

We report a patient with late onset Rasmussen´s encephalitis with anti-ganglioside IgGQ1b and anti-GAD antibodies positivity, who failed immunotherapy with cytostatics, immunoglobulins and steroids. Anti-ganglioside IgGQ1b antibodies are typically associated with a Miller-Fisher variant of Guillain-Barre syndrome and Bickerstaff's brainstem encephalitis. The association with Rasmussen´s encephalitis was not described before. Patient´s neurological deficit was mild and hemispherectomy was refused. The treatment with rituximab, an anti-CD20+ monoclonal antibody, led to 36-month control of seizures without any signs of progression of neurological deficit and MRI brain atrophy. Although the treatment is associated with long term B-cells depletion, patient doesn´t suffer from any clinically relevant infection.

The biological treatment with monoclonal antibodies might be the way to stabilize patients with Rasmussen´s encephalitis, mainly late-onset, to prevent them from harmful and devastating hemispherectomy.

CASE REPORT

Abbreviations:

AED	- antiepileptic drug
BBF	- Bickerstaff´s brainstem encephalitis
CD	- cluster of differentiation
CNS	- central nervous system
CSF	- cerebrospinal fluid
CT	- computerized tomography
EPC	- epilepsia partialis continua
GAD	- glutamate decarboxylase
GBS	- Guillaine-Barre syndrome
IVIG	- intravenous immunnoglobulins
MFS	- Miller-Fisher syndrome
MRI	- magnetic resonance imaging
PS	- partial seizure
RTX	- rituximab
SE	- epileptic state
SGTCS	- secondary generalized tonic-clonic seizure

INTRODUCTION

Rasmussen´s encephalitis (RE) is rare brain inflammatory disease leading to progressive cerebral hemiatrophy. It is characterized by refractory epilepsy, progressive hemiparesis and cognitive decline (Rasmussen *et al.* 1958; Bien *et al.* 2005). The disease starts usually with polymorphic focal epileptic seizures. Up to 20% of cases start as epilepsia partialis continua (EPC) (Mastrangelo *et al.* 2010). Seizures may predominate the clinical picture in a patient, but they may be less dominant in another one (Sheybani *et al.* 2011). Apart from seizures, RE leads to an irreversible loss of cerebral functions. RE starts usually in children (range 1–13 years). In around 10% of cases of RE, the disease starts later than 13 years, with onsets occurring as late as 37 years (Cheong *et al.* 2009). The disorder is rare with about 100 cases reported.

MRI of the brain has become a mainstay for diagnostic assessment and follow-up in RE (Bien *et al.* 2002a; Yamazaki *et al.* 2011). Most patients show unilateral cerebral atrophy with enlargement of the ventricular system and/or a T2/FLAIR hyperintense signal in cortical or subcortical regions. The perisylvian region is a predilection site for signal change and volume loss.

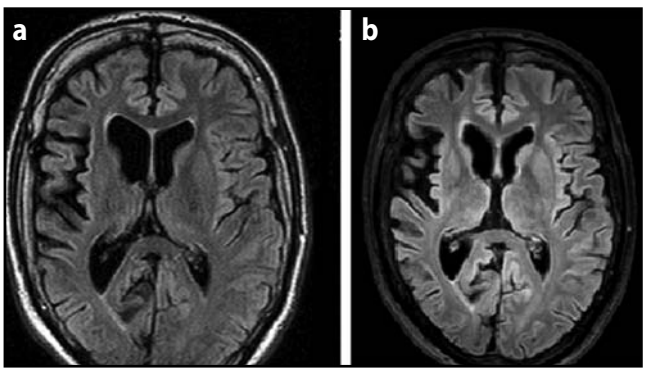

Fig. 1. FLAIR MRI of patient in year 2012 (a) and 2015 (b). No significant progression of atrophy of right hemisphere is present.

Serial MRIs typically show progression of signal change and atrophy. No specific EEG abnormalities can distinguish RE from other causes of focal epilepsy. The etiology of RE still remains unknown. The hypothesis about its etiology include an autoimmune process triggered through a viral agent or a primary autoimmune process (Bien *et al.* 2005; Mastrangelo *et al.* 2010).

Treatment of RE aims to reduce seizures and to improve functional outcome. Antiepileptic drugs (AED) are of limited value, as they are unable to control the epileptic seizures associated with RE. Case reports or small patient series of immunosuppressive or immunomodulatory treatments for RE showed temporarily effective experience with long-term corticosteroids, intravenous immunoglobulins, plasma exchange, protein A immuno-absorption and cytostatics tacrolimus and azathioprine (Granata *et al.* 2003; Hart *et al.* 1994; Bien *et al.* 2004; Bien *et al.* 2013). In childhood cases the only effective control of seizures is achieved with hemispherectomy. The discrepancy between slowing the degeneration with inefficient control of seizures might lead to the situation in which these patients with mild dysfunctions are unable to be referred for hemispherectomy despite having severe epilepsy. Therefore, the search continues for immunotherapy that could stop both the neurological deficit progression and the seizures. Promising candidates might come from other autoimmune diseases treatments (Bien *et al.* 2013). The main candidates are monoclonal antibodies targeting antibodies presenting B cells and T cells entry into the CNS. We present a patient with hemispherectomy contraindication who was treated successfully with rituximab (MabThera), a monoclonal antibody, what led to B-cells depletion. This case provides evidence that rituximab significantly reduced seizure frequency in a patient with RE for more than three years.

CASE REPORT

This male patient was born in 1981. He had his first secondary generalized tonic-clonic epileptic seizure (SGTCS) about age 17, and one year later he went into his first epileptic state (SE). Therapeutic attempt with cyclophosphamide and plasma exchange didn´t lead to seizure control. The patient had recurrent focal epileptic seizures. Later mild left sided hemiparesis was described and an MRI revealed marked atrophy of the right hemisphere with central predominance (Figure 1). The diagnosis of RE was postulated. He started his first course of intravenous immunoglobulins (IVIG) in a one-month interval regimen. 5 years later he had recurrent refractory focal SE. Cerebrospinal fluid (CSF) viral panel and Borrelia antibodies were negative, oligoclonal bands were not present, cytology and total proteins were normal, but mild elevated IgG was present. In the serum was found combined positivity of anti-ganglioside IgGQ1b antibodies (qualitative EUROLINE strip test, EUROIMMUN) without any

sign of peripheral or cranial nerve involvement and slight positivity of anti-GAD antibodies (1.3 U/ml, normal ≤0.9 U/ml, ELISA EUROIMMUN). He continued on combined therapy of high-dose IVIG (30 g) and steroids (1 g methylprednisolone) once per month. 4 years later he had recurrent focal and secondary generalized SE twice a month. Patient was readmitted to our department. No active viral infection was verified, and a repeated panel of autoantibodies at the time was negative. Immunophenotypisation of lymphocytes in peripheral blood revealed normal level of CD4+ (64%; 1.41×10^9/l) and low level of CD8+ lymphocytes (12.6%; 0.28×10^9/l; normal values 21–33%; $0.30–0.95\times10^9$/l) with elevated CD4+/CD8+ ratio (4.02–5.09; normal values 0.95–2.60) and slightly elevated CD19+ lymphocytes (17.1%; 0.38×10^9/l; normal values 7–15%; $0.2–0.59\times10^9$/l). AED regimen was a combination of levetiracetam (3 000 mg/d), valproic acid (2 000 mg/d), phenytoin (200 mg/d) and lamotrigine (300 mg/day). No clinically relevant neurological deficit or cognitive decline was present. The hemispherectomy was refused and due to severe refractory epilepsy therapeutic trial with rituximab (RTX), monoclonal anti CD20+ antibody was suggested.

After informed consent from patient and agreement from local Ethical Committee and Health Ministry of Slovakia was obtained, he started his first course of RTX in April 2013. The single therapeutic dose of RTX was 375 mg/m^2 (700 mg total) administered according to therapeutic schema for lymphoma treatment (4 times once a week). The fourth dose was not applied because total depletion of CD19+ lymphocytes in peripheral blood was achieved with three therapeutic doses. RTX induced a reduction of epileptic seizures with 2–3 PS per week and no SGTCS. Therapeutic effect lasted for 18 months, and we were able to withdraw phenytoin. Resolution of patient´s severe acne and hepatopathy was the result. The B-cells (CD19+) reappeared in his peripheral blood 6 month later. The frequency of PS rose to 6 per day when number of CD19+ lymphocytes in the peripheral blood rose to 0.05×10^9/l. The second cycle of RTX was introduced 22 months after the first one, when the level of the CD19+ lymphocytes was 0.07×10^9/l. Depletion of peripheral B-cells (CD19+) was achieved with one single dose 375 mg/m^2 (700 mg). This led to control of his seizures, with one PS per day and no SGTCS, still lasting (Figure 2). CD19+ cells reappeared in the peripheral blood 5 months after the second cycle of RTX. Though the treatment is associated with B-cells depletion, patient doesn´t suffer from any clinically relevant infection, and he evaluates the treatment as very beneficial.

DISCUSSION

In our case typical clinical picture, course of disease and typical MRI fulfilled the formal criteria of European Consensus Panel for the diagnosis of RE (Bien *et al.* 2005), and the diagnosis of RE could be postulated without biopsy of the brain. Evidence for an immunopathological basis of RE is growing. Cytotoxic T lymphocytes seem to play the most important role in the pathogenesis of RE. Brain tissue studies revealed an oligoclonal granzyme B-mediated T-cell immunoreaction against neurons and astrocytes (Bien *et al.* 2002b; Bauer *et al.* 2007; Schwab *et al.* 2009). Over the past 10 years it has become clear that there are a number of CNS diseases associated with pathogenic antibodies to neuronal surface and intracellular proteins. The first autoantibody identified in patients with RE was against GluR3, but later it was found in only a few RE patients, and plasma exchange helped only a few patients (Mantegazza *et al.* 2002). GluR3 antibodies were found in sera of many patients with severe epilepsy, so it is not believed to be specific for RE. Other identified antibodies, such as against the alpha-7 nicotinic acetylcholine receptor or Munc-18-1, were found in few patients, and later not reported (Watson *et al.* 2005; Alvarez-Baron *et al.* 2008). One case of RE with positivity anti Hu/Yo antineuronal antibodies without neoplasm and ANA antibodies successfully treated with RTX was described recently (Capobianco *et al.* 2015). Our patient presented in intermediate phase of the disease with serum positivity anti-ganglioside GQ1b antibodies and anti-GAD antibodies. The clinical picture of anti-GAD positivity involves diabetes mellitus type I, stiff person, autoimmune encephalitis, refractory epilepsy, ataxia and cerebellar degeneration. Mild elevation of anti-GAD in serum of our patient was probably associated with severe refractory epilepsy rather than a causal relation to RE. To the best of our knowledge, never before has positivity of anti-ganglioside GQ1b antibodies in association with epilepsy or RE been described. Classical syndromes associated with this type of antibodies are Guillain-Barre syndrome (GBS), Miller-Fisher syndrome (MFS) and rare Bickerstaff ´s brainstem encephalitis (BBE). The myelin of peripheral and cranial nerves is supposed to be a target of autoimmune response, with about 60% positivity in MFS, and BBE also. In BBE were described T2 hyperintensities in MRI in the brainstem, in basal ganglia and thalamus (Mondejar 2002), thus suggesting more than cranial nerves involvement in BBE. The presence of anti-

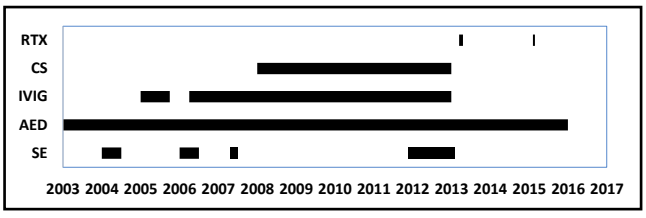

Fig. 2. Course of the disease and treatment attempts in patient in relation to control of epileptic seizures between years 2003 and 2016. SE – epileptic state, AED – antiepileptic drugs, IVIG – intravenous immunoglobulins, CS – corticosteroids, RTX – rituximab

ganglioside GQ1b antibodies in BBE and in our patient with RE suppose, that gangliosides might be an autoimmune target in predominantly central nervous system affections without clinically relevant expression in peripheral nerve system. It is not known if other types of autoimmune encephalitis could be associated with its expression. Occurrence of different types of antibodies in patients with RE points to an autoimmune process underlying the disease. Because none of the autoantibodies have been found in more than a small number of patients with RE, the role of autoantibodies in the pathogenesis of RE is still unclear.

Typically, no therapies have provided effective control of both seizures and functional decline. Immunosuppression with steroids, IVIG, plasmapheresis, and drugs such as tacrolimus and azathioprine produce good functional outcomes, but have poor efficacy against seizures. Only one case of treatment of RE with natalizumab, monoclonal antibody targeting the T-cell entry into the brain was described (Bittner *et al.* 2013). RTX is established for the treatment of lymphoma, rheumatoid arthritis and granulomatous angiitis (Wegener´s granulomatosis). It was successfully used in an off-label manner for the treatment of different autoimmune diseases. One case of successful treatment of refractory BBE not responding to plasma exchange and IVIG with RTX was described recently (Hardy 2012). Case reports of RE treated with RTX were referred before, with mixed results (Strozzi *et al.* 2008; Thilo *et al.* 2009; Prüfer *et al.* 2013; Lockmann *et al.* 2013). Our patient has shown excellent sustained response to RTX treatment for three years. There exists no data of long term safety of high dose RTX treatment (lymphoma regimen), but reduced doses are usually well tolerated in patients with rheumatoid arthritis. The depletion of peripheral CD19+ lymphocytes usually lasts 5–6 months (Thilo *et al.* 2009), and the same is true for our patient. Increased seizure frequency in our patient was associated with peripheral CD19+ cells reappearance. The pathophysiological rationale underlying the use of a B-cell-depleting therapy, rituximab, was to suppress B cells, which have a key role in T-cell activation through their antigen-presenting and cytokine-producing activities. Rituximab might, therefore, also be viewed as an indirect anti-T-cell treatment. Additional therapeutic effects might be produced by a reduction of antibodies produced by plasma cells that originate from CD20+cells (Bien *et al.* 2013). The potential toxic and adverse effects of long term B-cells depletion are concerning.

CONCLUSION

Rituximab and similar drugs that work in other chronic autoimmune conditions might be worth attempting in RE patients instead of taking half the patient's brain out. Today, from this case and small case and cohort reports we have some evidence that we can interfere with the process that causes a progressive inflammation of the brain in RE patients. There are some drugs, monoclonal antibodies in particular, that we can use to stop the progression of the disease. RE is a very rare condition, so numbers of patients who could enter trials are limited. What we have to do is larger trials, which would have to be multinational and cooperative in nature to get meaningful sample sizes.

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