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Rituximab as a treatment for limbic encephalitis associated with leucine-rich glioma inactivated-1: A case report and literature review.

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Abstract

Leucine-rich glioma-inactivated-1 (LGI1) protein antibody-associated limbic encephalitis (LE) is a treatable autoimmune disease. This report is about the administration of rituximab in two patients with LGI1 antibody-associated LE. Both patients had progressive confusion, behavioral alteration, memory impairment and temporal lobe seizures. Treatment included steroids, intravenous immunoglobulin (IVIG) and rituximab. Patients showed a positive response to the therapy. Both patients satisfactorily tolerated rituximab and neither experienced side effects. We also reviewed the recommended treatments for the LGI1 LE. Based on the recent reports, rituximab has the potential to become one of the treatment options for LE. Nevertheless, more evidence is necessary in order to accurately evaluate its efficacy.

Keywords: Rituximab, Leucine rich glioma inactivated protein 1, Limbic encephalitis, Treatment.

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Introduction

Leucine-rich, glioma inactivated 1 (LGI1) is a glycoprotein in the voltage-gated potassium channels (VGKCs) which binds to the presynaptic protein, ADAM23, and the postsynaptic protein, ADAM22 [1]. LGI1 plays a major role in synaptic transmission, therefore antibodies directed against this synaptic neuronal protein disrupt synaptic conduction.

Patients who suffer LGI1 limbic encephalitis (LE) have various clinical manifestations including facial-brachial dystonic seizures (FBDS), memory loss, confusion and hyponatremia [2]. Although hyponatremia is commonly found in patients with LGI1 LE, the condition is not a specific finding [3]. Seizures are the most common manifestation of LGI1 LE and FBDS has recently been identified as a characteristic feature [4].

Precise diagnosis of LGI1 LE requires the detection of LGI1 antibodies in the cerebrospinal fluid (CSF) or serum. Prior studies have been reported hyperintensity of the mesial temporal lobe in magnetic resonance imaging (MRI). However, it has also been reported that some patients did not have MRI evidences of temporal lobe inflammation [1]. Electroencephalography (EEG) and functional imaging with positron emission tomography (PET) of the brain are other possible adjuncts to the immunologic tests [5]. Most patients, but not all of them, will respond favorably to the first line immunotherapy [6]. Currently, rituximab and cyclophosphamide are considered as second line therapies for these patients. These treatments are associated with improvement of the disease and patient independence for activities of daily living [7].

Rituximab has recently been suggested for the treatment of refectory autoimmune encephalitis [6]. Here we report of two patients with LGI1 LE. Both patients had progressive confusion, behavioral alteration, memory impairment and temporal lobe seizures. The patients were treated with rituximab after their failure to respond to IV steroids and IVIG.

Case Presentation

This study was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent before screening. This study was approved by the Ethical Committee of the Shahid Beheshti University of Medical Sciences.

Case 1

A 67-year-old right-handed man was admitted for progressive dementia and paroxysmal episodes of behavioral alteration, staring, and several attacks of dystonic posturing of his head, neck and left arm which in some instances were accompanied by episodes of generalized tonic-clonic seizures (GTCS) over a six-month period. He was being medicated orally with levetiracetam and carbamazepine (500 mg and 400 mg twice daily, respectively). His past medical history was unremarkable and general examination was normal. The neurological examination indicated a significant decrease in the patients Mini Mental State Examination (MMSE: 19/30). A brain MRI showed increased bilateral T2-weighted intensity in the medial temporal lobe. The clinical manifestations and MRI findings raised our suspicion of autoimmune encephalitis.

Results from laboratory tests, including a complete blood count (WBC: 8000 × 10^3/µl, hemoglobin: 14 g/dl, Platelet: 250000 × 10^3/µl) renal tests (BUN: 18 mg/dL, creatinine: 1.1 mg/dL), liver function tests (AST: 20 IU/L, ALT: 25 IU/L, INR: 1.2), and thyroid function tests (T3: 3.5 mmol/L, T4: 9.4 pmol/L, TSH: 4.6 ml U/L), were within normal limits. The lumbar puncture showed no abnormalities.

In order to rule out other diseases, the patient underwent work ups for infections, collagen-vascular disease, and neoplastic and paraneoplastic diseases. These included blood antinuclear antibody, rheumatoid factors, serum and CSF immunoglobin levels (IgA, IgM, and IgG), CD4 count (350 cells/mm^3), human immunodeficiency virus and human T lymphotropic virus antibodies, anti-*Mycobacterium tuberculosis* antibody, herpes simplex virus antibody, CA-125 20 U/ml (normal<35), CEA 2 µg/L (normal<5.0), CA19.9 10 U/ml (normal<37), computed tomography (CT) scans of the chest, abdomen and pelvis and a whole body PET scan. While all of the tests were unrevealing, radioimmunoassay showed an elevated VGKC-complex antibody level (850 pmol/L, normal range<450 pmol/L). Cell-based assay with immunofluorescence staining showed positive LGI1 antibody in serum and CSF.

Finally, LGI1 LE was diagnosed. Treatment consisted of intravenous (IV) methylprednisolone, 1 g daily, plus oral prednisolone, 50 mg daily, for 2 weeks followed by an IVIG of 400 mg/kg, divided over five days. Since the primary response was insufficient, rituximab, 2 g, was delivered twice in two-week intervals. 24 hours after the first dose of rituximab he showed marked decrease in seizure frequency and improvement in cognition. In two weeks the patient had no FBDS and his MMSE score was 22/30. The second dose of rituximab resulted in a remarkable resolution of symptoms with MMSE of 25/30. Six months after discharge in the last follow up visit, the patient had no seizures and his MMSE was 27/30.

Case 2

A 54-year-old right-handed man was admitted for progressive dementia and psychotic symptoms including paranoia and auditory hallucinations accompanied by frequent paroxysmal episodes of involuntary right face and arm twitching motions. Similar to the former case, the patient's past medical history and physical examination were unrevealing. His initial neurological examination indicated an MMSE of 5/30 in absence of other significant neurological deficits.

An MRI of the patient's brain indicated increased bilateral T2-weighted intensity in the medial temporal lobe. Primary laboratory tests, including a complete blood count (WBC: 6500 × 10^3/µl, hemoglobin: 15.5 g/dl, platelet: 165000 × 10^3/µl) renal tests (BUN: 12 mg/dL, creatinine: 0.9 mg/dL), liver function tests (AST: 14 IU/L, ALT: 25 IU/L, INR: 1), and thyroid function tests (T3: 4 mmol/L, T4: 9.2 pmol/L, TSH: 5 m; U/L), were within normal limits.

As the prior case, the patient underwent complete work up for other immunologic or infection disorders which was unremarkable. Screening test using radioimmunoassay showed an elevated VGKC-complex antibody level (670 pmol/L, normal range<450 pmol/L).

Detection of LGI1 antibody in serum and CSF confirmed the diagnosis of LGI1 LE. The patient was treated with antiepileptic drugs (levetiracetam, 750 mg/twice daily) as well as IV methylprednisolone (1 g daily for five days). Since the primary response was not sufficient, the treatment continued with rituximab, 2 g, administered in two sessions in two-week intervals. The patient showed a dramatic response.

24 hours after the first dose of rituximab the frequency of seizures decreased and he became more communicative. In two weeks the patient had 2 attacks of FBDS and his MMSE score was 25/30. The second dose of rituximab resulted in resolution of paranoid thoughts and hallucinations. He had followed up visit after six months, his MMSE was 28/30 and he had a few monthly FBDS attacks and psychotic symptoms were resolved. Despite the fact that rituximab treatment started late in both cases, neither patient experienced side effects of immunotherapy or relapse of their disease.

Discussion

The currently recommended first line treatments for LGI1 LE are corticosteroids, intravenous immunoglobulin (IVIG) and plasmapheresis (Table 1). LE is associated with antibodies against paraneoplastic antigens, or neuronal surface antigens, including the voltage-gated potassium channels (LGI1 and Caspr2), N-methyl- D-aspartate receptor, and glutamic acid decarboxylase [8]. Immunotherapy in autoimmune LE has a good prognosis with a reported 80% of patients having a full recovery [9]. Table one describes the reported LGI1 encephalitis patients with their treatments regimens. In a few

cases, patients have shown spontaneous recovery without treatment [10].

Table 1. *Clinical manifestations and treatment plans of LGI1 associated LE in the current reports.*

Patient characteristics	Treatment regimen	Reported outcome
48-year-old, male	First line: IVIG+prednisolone	Good recovery
	Second line: cyclophosphamide	
41-year-old, female	IV methyl prednisolone	After 3 months patient remained free FBDS memory had been partially restored.
	Maintenance: oral prednisolone for 8 weeks	
75-year-old female	IV prednisolone+IVIG	cognitive disorders, epilepsy, and SIADH corrected in 9 months
	Maintenance: oral prednisolone+oral azathioprine+oral levetiracetam for 9 month	
8yearold, female	First line: levetiracetam+IVIG	Gradual recovery
	Second line: IV methylprednisolone+oral prednisolone (duration of therapy is not reported)	
34-year-old male	Methyl prednisolone	At a 6 months follow-up seizures were resolved, MMSE score was 30
53-year-old, male,	observation without immunotherapy for 3 years	Symptoms disappeared completely without immune therapy
10 patients were reported	8 patients were treated with IVIG+oral prednisolone for one month	One patient was seizure free after prednisone treatment alone.
4 males and 5 females	One patient was diagnosed with lung cancer and did not continue the therapy.	8 patients were seizure free after treatment with IVIG and prednisone.
Age (Median, range) 61, 34-78	One patient was treated with prednisone alone for 1month	One patient showed no response to IVIG
62-year-old male	IVIG+maintenance IVIG q 3 month	Mental status and cognitive function improved within a few weeks. He was able to perform daily activities.
45-year-old female	IV methylprednisolone+IVIG	After 1 month the patient had had no ischemic events and memory had improved
	Maintenance treatment: with mycophenolate mofetil and an oral prednisone (duration is not reported)	
16 patients are reported	First line treatment:	After 6 months 1 patient died due to unknown etiology
9 males, 7 females	IV methylprednisolone+IVIG or plasma exchange in 5 patients	After one year MMSE improved (median of 23.5/30 to 30/30 only two patients reported seizure
Age (median, Range) 62, 29-84	Second line treatment: azathioprine in 5 patients	
14 patients were reported	oral prednisolone	13 patients were received immunotherapy.
Age (median, Range) 60, 43-78	IV methylprednisolone	After one year 11 patients had near complete recovery and 2 patients had relapse of the disease.
8 males and 6 females	Methylprednisolone+IVIG	
	IV methylprednisolone, IVIG and rituximab	
	IV methylprednisolone, IVIG and tacrolimus	
	IV methylprednisolone plus azathioprine	
	Oral prednisolone+IVIG, azathioprine, cyclophosphamide, Rituximab	
	Methylprednisolone, IVIG, plasmapheresis, rituximab, tacrolimus	

Although primary response to immunotherapy is remarkable, there are reports of the long-term sequelae of LGI1 LE. Based on research conducted by Finke and colleagues [11], in the long term, LGI1 LE can cause structural damage in the hippocampal system and may produce various degrees of cognitive impairment. Therefore, rapid diagnosis and early effective treatment is imperative to decreasing the risk of long-term brain damage. Considering a good prognosis after

immunotherapy, neurologists should be vigilant about the possibility of LE when a progressive cognitive disorder is associated with epileptic seizures [9].

Rituximab is a monoclonal antibody that targets CD20 positive B-cells, causing B-cell death and new B-cell production [12]. Rituximab has been utilized to treat various autoimmune neurologic disorders including multiple sclerosis, neuromyelitis optica, and myasthenia gravis [13-15]. Rituximab does not block the activity of T-cells or the production of immunoglobulin, so the risk of related opportunistic infection is low [6,15]. The exact mechanism of rituximab in LGI1 LE patients is still unclear. One possible explanation is that rituximab can attenuate B-cells and deplete antibodies [16-18].

As an increasing number of autoimmune non-paraneoplastic encephalitis cases are being recognized, it is important to screen suspected patients for the presence of neuronal surface antibodies, including LGI1 antibodies, along with conducting a search for systemic malignancy to rule out paraneoplastic disease. Early diagnosis and treatment with immunotherapy, such as IVIG, expedites the resolution of clinical symptoms in these patients.

In the present report, both of the patients had positive responses to therapy after rituximab infusions as measured by a remarkable increase in MMSE scores. Rituximab also decreased episodes of FBDS. Additionally, it should be noted that psychotic symptoms in the second patient were also resolved following rituximab infusions. Both patients satisfactorily tolerated rituximab and neither experienced side effects after infusion. In summary, these two case reports are successful examples of treatment of LE with rituximab.

Conclusion

Although there are reports about the successful treatment of LE with retuximab, there is still inadequate data to recommend rituximab as a first line therapy. In addition, it should be noted that most cases were improved by steroids or IVIG.

Conflict of Interest

None

References

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