Bortezomib-Responsive Refractory Anti-N-Methyl-D-Aspartate Receptor Encephalitis

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Abstract

Background

Anti-N-methyl-d-aspartate receptor encephalitis is a central nervous system inflammatory autoimmune disease affecting adults and children. The use of first- and second-line immunotherapies is supported. Recent reports suggest the efficacy of bortezomib in severe anti-N-methyl-d-aspartate encephalitis in adult patients not responsive to second-line treatment; there are no data about pediatric patients.

patient description

We describe an eight-year-old child with anti-N-methyl-d-aspartate encephalitis not responsive to first- and second-line treatments who experienced marked clinical improvement after bortezomib administration.

Discussion

Bortezomib is a selective and reversible inhibitor of the 26S proteasome, which is used to treat oncologic and rare autoimmune disorders in pediatric patients. As observed in adult patients, bortezomib administration induced anti-N-methyl-d-aspartate antibody titer decline and clinical improvement with an acceptable risk profile.

Conclusion

This is the first report of the use of bortezomib in children with anti-N-methyl-d-aspartate encephalitis; it could be a useful therapeutic option in children with refractory anti-N-methyl-d-aspartate encephalitis.

Keywords

Autoimmune encephalitis

Anti-N-methyl-d-aspartate receptor (NMDAR) antibodies

Immunosuppressive therapy

Proteasome inhibitor

Cell-based assay

Arterial spin labeling (ASL)

Refractory status epilepticus

Introduction

Autoantibody-mediated encephalitis (AE) is a group of inflammatory brain diseases with variable clinical presentation and severity. Common clinical features include acute changes in behaviour, seizures, memory and cognitive deficits, and progressive decline in consciousness.1 Anti-N-methyl-d-aspartate receptor (anti-NMDAR) encephalitis is the most common form of AE. It is characterized by a typical multistage progression of symptoms (psychiatric changes, speech dysfunction, movement disorder, seizures, sleep-wave disruption, consciousness impairment, catatonia, dysautonomia).2 The disease can be severe, and over 50% of the patients require intensive care support. Approximately 40% of the cases present under age 18 years, surpassing the frequency of the most common viral etiologies in young individuals.3 Psychosis, seizures, and movement disorder are the primary presenting symptoms in children and adolescents.4

Currently, no definitive treatment guidelines are available, but a number of expert recommendations support the use of first-line and, in non-response patients, second-line

immunotherapy.5 Although around 80% of the patients improve with the administration of immunotherapy, the disease course can be long and the recovery incomplete, especially regarding the cognitive functions. In addition, some patients are refractory to drugs such as rituximab and cyclophosphamide, agents that are routinely used as second-line treatment.2,5,6 In such patients, recent reports suggest the efficacy of bortezomib in adult patients.7-9

Bortezomib is a selective and reversible inhibitor of the 26S proteasome, which is a component of cell growth and apoptosis, with more specific activity on plasma cells.8 Here we report an eight-year-old child with refractory anti-NMDAR encephalitis in which bortezomib administration led to rapid and complete clinical recovery. Monitoring of serum and cerebrospinal fluid (CSF) anti-NMDAR antibodies titers during the disease course and after bortezomib administration is provided.

Patient description

This previously healthy eight-year-old girl developed left focal motor epileptic seizures, asthenia, and dysarthria. Ten days later, she was hospitalized for rapidly worsening behavioural abnormalities with psychomotor agitation alternating with catatonia followed by progressive decline in consciousness, movement disorder with dystonia, buccal and eyelid myoclonus, orobuccal dyskinesia, tachycardia, and loss of sphincter control over the following two weeks. Electroencephalography (EEG) on admission showed right hemisphere slowing and right focal seizures. Conventional brain magnetic resonance imaging (MRI) did not reveal abnormalities, whereas perfusion imaging with arterial spin labeling (ASL) demonstrated increased perfusion in the right parietal lobe (Fig 1A-D).

Anti-NMDAR antibodies were detected in CSF using a commercial cell-based assay (Euroimmun, Lübeck, Germany) and immunohistochemistry on lightly fixed rat brain tissue optimized for neuronal surface antibodies (undiluted CSF; end point titration 1:30), as previously described,6 and were negative in serum. The tests were performed in the Pavia Neuroimmunology Laboratory as part of the approved clinical protocol.

Pelvic ultrasound was negative for ovarian teratoma. Two weeks after admission she required intubation and transfer to the intensive care unit (ICU). A follow-up brain MRI with ASL showed persistent areas of increased perfusion on the right parietal lobe and mild increased perfusion on the left parietal lobe, with evidence of mild restricted diffusivity on diffusion-weighted imaging (DWI) involving the left parietal region and ipsilateral thalamic pulvinar (Fig 1E-H).

High-dose intravenous steroids (30 mg/kg/day methylprednisolone for seven days) and intravenous immunoglobulins (2 g/kg over three days) followed by plasma exchange were ineffective, as well as rituximab administration (four weekly intravenous doses 375 mg/m2) started two weeks after the first-line treatments.

Antiseizure drugs (levetiracetam, valproate, phenobarbital, lacosamide) and ketogenic diet were not effective, so continuous infusion with midazolam or thiopental was started. She underwent gastrostomy and tracheostomy (Fig 2).

Because of the relapse of status epilepticus following attempt of reduction of midazolam infusion and because of the increase of antibody titers in serum and CSF, intrathecal methylprednisolone (10 mg) plus rituximab (10 mg) once a week was administered five times. At the same time immunomodulatory treatment with sirolimus (rapamycin) was started. We obtained an initial decrease in CSF antibody titers but very poor clinical response (reduction in the frequency of discharges at EEG monitoring) (Fig 2).

Four months after symptom onset and four weeks after the last immunomodulatory treatment, bortezomib was administered (four doses, 1.3 mg/m2 intravenously every three days) and the patient showed clinical improvement with resolution of the status epilepticus, disappearance of electrical discharges after the fourth bortezomib dose and progressive improvement in consciousness. She was discharged from the ICU seven days after the completion of bortezomib treatment. Brain MRI revealed symmetric normal perfusion of the cerebral hemispheres on ASL and no other brain abnormalities on conventional imaging (Fig 1I-L). A second cycle of bortezomib was administered four weeks later because of an increase of serum antibody titer (Fig 2).

Four months later she was able to breathe and eat autonomously with interactive speech. After 16 months of persistently negative serum anti-NMDAR antibody titers, a mild increase of anti-NMDAR in serum was observed with no clinical symptoms or EEG changes. Another titer two months later was unremarkable (Fig 2).

Eighteen months after the onset of the disease, she was able to return to school and resume age-appropriate activities.

Discussion

In recent years, a number of expert recommendations have been published on immunotherapy for anti-NMDAR encephalitis, but definite treatment guidelines are still lacking.10,11 First-line treatments include intravenous methylprednisolone and intravenous immunoglobulins followed by plasma exchange. In case of absent or unsatisfactory response, second-line treatment with rituximab and/or cyclophosphamide is often utilized.5 Maintenance immunosuppressive regimen is also recommended for a long time with steroids or steroid-sparing agents such as oral azathioprine, mycophenolate mofetil, or cyclosporine to minimize the risk of relapse.12 In some patients, intrathecal methotrexate plus prednisone, or occasionally intrathecal rituximab, have been administered.13

Recent reports of adult cases suggest that severe anti-NMDAR encephalitis not responsive to second-line treatment can benefit from the use of bortezomib, which induces anti-NMDAR antibody titer decline and clinical improvement with an acceptable risk profile.8 Bortezomib is a selective and reversible inhibitor of the 26S proteasome, which is a component of cell growth and apoptosis, approved for multiple myeloma treatment. In clinical practice, bortezomib is also used to treat a variety of other hematological malignancies and more recently to treat autoimmune conditions.14,15 Data on the use of bortezomib in pediatric patients are limited to oncologic patients and rare autoimmune disorders.14

In our patient, intrathecal methylprednisolone plus rituximab led to significant reduction of antibody titers in CSF, but no clinical improvement was noted. This is possibly related to intrathecal anti-NMDAR antibody production by long-living plasma cells that do not express CD20 and are not targeted by rituximab. On the contrary, bortezomib administration induced a marked clinical improvement with resolution of the status and progressive return of consciousness.

In addition, bortezomib should contribute to the improvement of symptoms by inhibition of nuclear factor-KB and blocking the proinflammatory cytokine production, thus reducing brain inflammation. Bortezomib administration was well tolerated with no adverse events.

Maintenance therapy with sirolimus, a mammalian target of rapamycin (mTOR) inhibitor, has a long-term effect because it inhibits effector T cells but does not impair the survival and function of regulatory T cells, thus promoting perduring immunosuppressive action.

Refractory AE are a heterogeneous group of challenging diseases with significant morbidity and mortality. The bortezomib-induced response we observed in our pediatric case with anti-NMDAR encephalitis could be applicable in other individuals with AE refractory to first- and second-line immunomodulatory treatment, where other types of biological agents such as tocilizumab should also be considered.16

Little has been reported on the phenomenon of elevated cerebral blood flow in the setting of anti-NMDAR encephalitis.17 Possible mechanisms of hyperperfusion in patients with encephalitis may include both seizures and inflammation. Considering the high frequency of seizures at onset and subsequent evolution to super-refractory status epilepticus, the ASL and DWI findings at admission and during follow-up were attributed to the seizure activity. These ASL and DWI changes abated after resolution of the electrical status epilepticus.

Conclusions

Our observations in this one patient suggest that bortezomib administration can be an effective and safe therapeutic option for children with anti-NMDAR encephalitis that is refractory to standard treatments. Further studies should investigate the efficacy and safety profile of bortezomib for the acute phase and of oral sirolimus for prolonged treatment to minimize the relapse risk of this and other forms of refractory autoantibody-mediated encephalitis.

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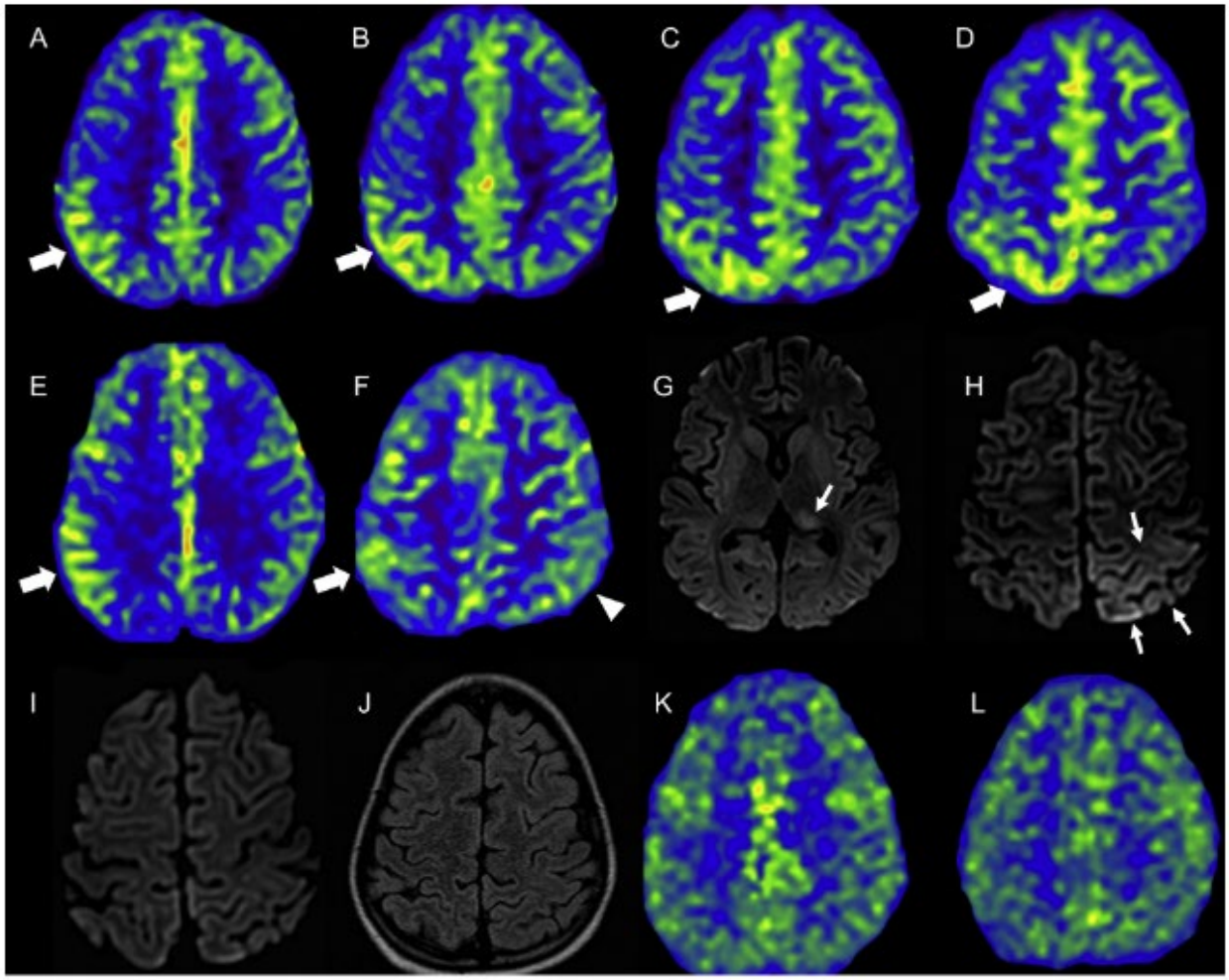

FIGURE 1 Imaging findings. (A-D) Brain magnetic resonance imaging (MRI) performed at admission. Axial arterial spin labeling (ASL) perfusion imaging shows increased signal in the right parietal lobe (thick arrows, A-D). (E-H) Brain MRI performed 1 month later. Axial ASL imaging shows areas of persistent increased perfusion in the right parietal lobe (thick arrows, E and F) and mild increased perfusion in the left parietal lobe when compared with the prior examination (arrowhead, F). Diffusion-weighted imaging (DWI) shows mild hyperintensity in the left parietal cortex and in the ipsilateral thalamic pulvinar (thin arrows, G and H) suggestive of peri-ictal restricted diffusivity (apparent diffusion coefficient maps, not shown, demonstrated hypointense signal in the corresponding areas). (I-L) Brain MRI performed at 6 months, after bortezomib treatment. Axial DWI (I) and fluid-attenuated inversion recovery (J) images do not show abnormalities or sequelae in the previous areas of increased perfusion or restricted diffusivity. ASL imaging shows symmetric normal perfusion of the cerebral hemispheres.

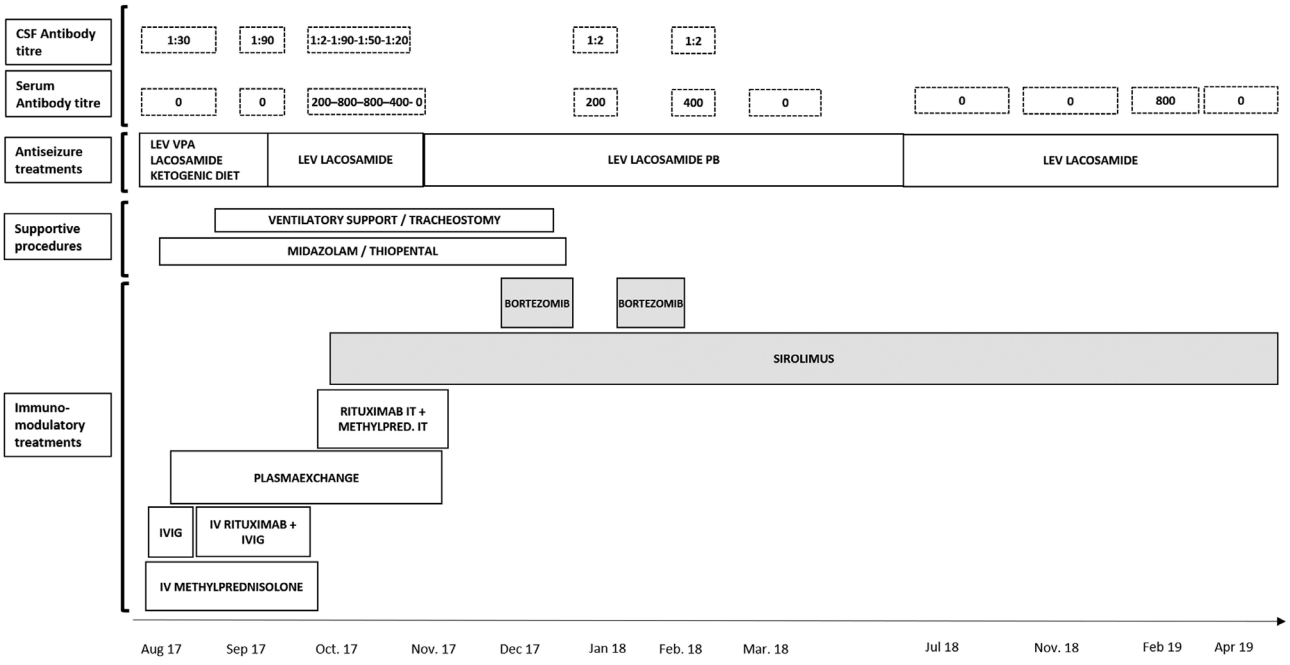

FIGURE 2 Type and timing of the different treatments from onset until the end of follow-up and evolution of anti-N-methyl-d-aspartate receptor antibody titers in cerebrospinal fluid (CSF, continuous line) and serum (dotted line).