Letters

OBSERVATION

Bortezomib Treatment for Patients With Anti-*N*-Methyl-D-Aspartate Receptor Encephalitis

Anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis, an autoimmune disease associated with ovarian teratoma, predominantly affects young females.[1] Because antibodies against subunits of the NMDAR contribute to the pathogenesis, methods targeting humoral immunity are therapeutically efficacious.[2] However, some patients have an unsatisfactory outcome after high-dose corticosteroids, apheresis therapies, or CD20-targeted B-cell depletion with rituximab.[2] We describe 2 patients with severe anti-NMDAR encephalitis who received the proteasome inhibitor bortezomib (Velcade), which was well tolerated and followed by marked remission.

Report of Cases | *Case 1.* A black woman in her early 30s was admitted with acute agitation, hallucinations, and catatonia. She developed autonomic instability and central hypoventilation. Anti-NMDAR encephalitis was diagnosed, and paraneoplastic staging revealed an ovarian teratoma that was surgically removed. Although the patient received plasma exchange, rituximab, cyclophosphamide, and high-dose corticosteroids, no clinical improvement occurred (**Figure**, A). She was mechanically ventilated for 7 months and transferred to our clinic. She was nonresponsive and had orofacial dyskinetic movements and tetraparesis. Her CD19-positive B cells were completely depleted. She only slightly improved after receiving plasma exchange, corticosteroids, and intravenous immunoglobulins. Because of severe residual deficits, she was subsequently treated with bortezomib (4 subcutaneous injections of 1.3 mg/m^2 on days 1, 4, 8, and 11; comedication with 400 mg of acyclovir sodium twice a day and 960 mg of cotrimoxazole twice a day, 3 times a week for 2 months) after obtaining informed consent for off-label use from her legal guardian. Her therapy was well tolerated with no adverse effects. In the following months, clinical deficits and serum anti-NMDAR antibody titers markedly improved. Until her last follow-up, she remained stable and had only minor cognitive impairment of alertness and nonverbal short-term memory (**Table**).

Case 2. A white woman in her early 20s exhibited behavioral changes, hallucinations, and gait ataxia. Owing to her rapid deterioration with central hypoventilation, she was mechanically ventilated, and anti-NMDAR encephalitis was diagnosed. No teratoma was found. After receiving plasma exchange, her condition improved, and she could resume her vocational education (Figure, B).

Twenty months later, she experienced a relapse with gait ataxia, confusion, hallucinations, and sexual disinhibition. No significant improvement was achieved after receiving plasma exchange and rituximab. She further deteriorated with impulsive behavior and was transferred to our hospital. She presented with severe dysarthria, perioral dyskinetic automatisms, and gait ataxia. Her CD19-positive B cells were still completely depleted. She was treated with corticosteroids, plasma exchange, and intravenous immunoglobulins with no significant improvement. Owing to her refractory deficits, she was treated with bortezomib (for dosing and regimen, see case 1). Six months later, she showed marked improvement with regard to ataxia and dysarthria. A second treatment cycle of bortezomib was given and again was well tolerated with no adverse effects. Until her last follow-up, she had not relapsed and had clinically improved further with remaining minor neurocognitive deficits, particularly memory impairment (Table).

Discussion | We describe 2 women with a severe course of anti-NMDAR encephalitis. Both lacked a therapeutic response to corticosteroids, plasmapheresis, immunoglobulins, and rituximab, all given at sufficient doses and followed up for a sufficient time. Remission did occur only after treatment with bortezomib. Importantly, bortezomib was well tolerated and safe for these severely disabled patients (both with a modified Rankin Scale score of 5). Potential adverse effects, particularly neuropathy, were not observed during follow-up. Because spontaneous improvement of anti-NMDAR encephalitis may occur in rare cases, clinical remission could have been partly due to the natural course of the illness or to preceding therapies. Two additional patients who improved after receiving a combination of rituximab and bortezomib are described by Titulaer et al.[5]

Bortezomib is approved for the treatment of multiple myeloma and mantle cell lymphoma. It interferes with proinflammatory signaling cascades in immune cells and reduces the number of plasma cells and antibody production.[6] This is also the proposed mechanisms of action in anti-NMDAR encephalitis, where B cells and plasma cells are abundant in brain lesions.[7,8] We suggest that bortezomib may be used for patients with severe anti-NMDAR encephalitis who are nonresponsive to established treatment regimens.

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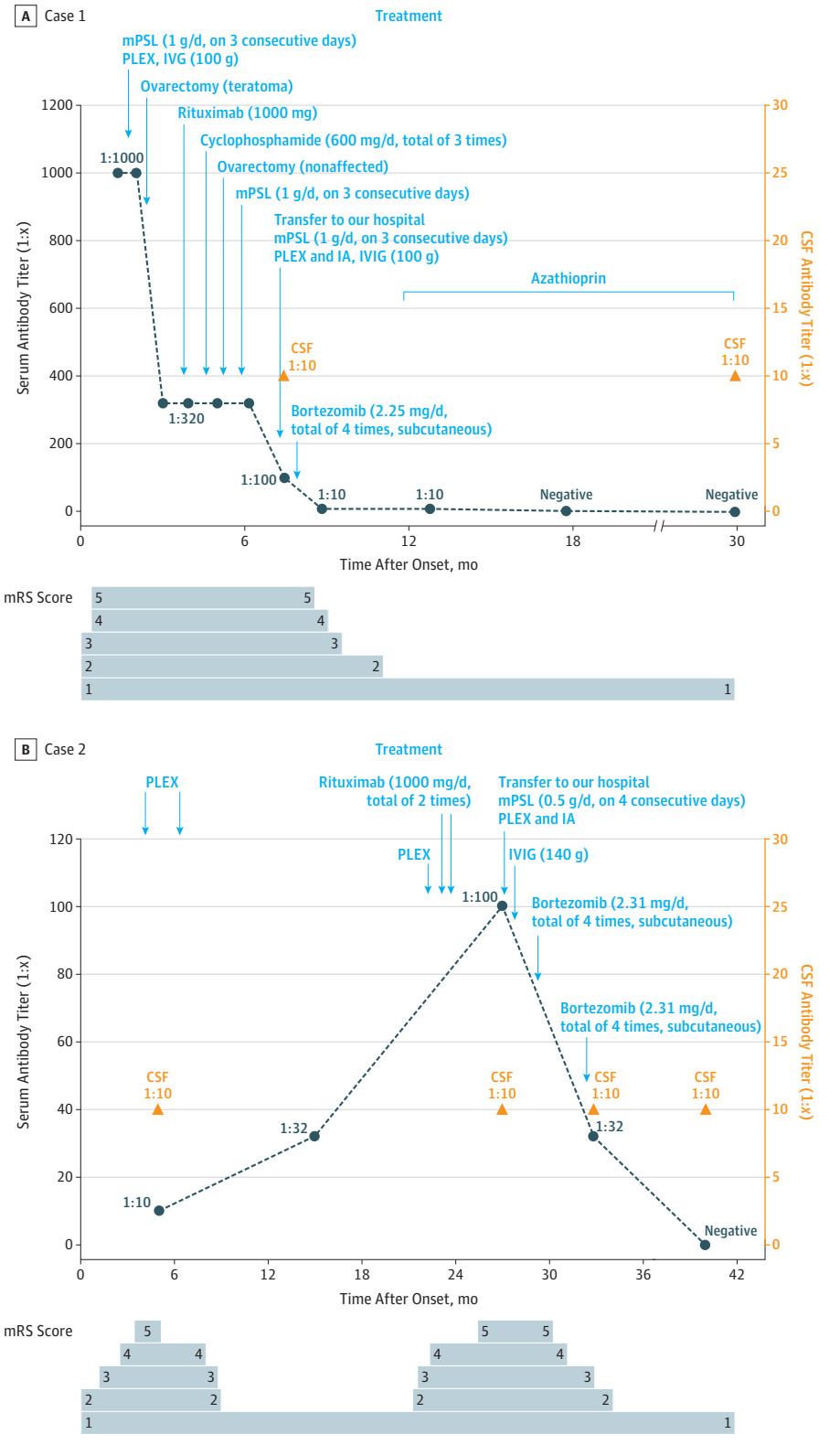
Figure. Clinical Course and Treatment in Cases 1 (A) and 2 (B)



The x-axis indicates the number of months after disease onset. The y-axis indicates the anti-*N*-methyl-D-aspartate receptor antibody titer measured by a standard cell-based assay in the cerebrospinal fluid (CSF [triangles]) and serum (connected by dashed line). The clinical course is documented by the modified Rankin Scale (mRS) score depicted as horizontal bars below the graph. IA indicates immunoadsorption; IVIG, intravenous immunoglobulins; mPSL, methylprednisolone; and PLEX, plasma exchange.

Table. Results of Neuropsychological Assessment Transformed Into *z* Scores[a]

Test	Case 1 (18 mo After Onset)	Case 2	
		40 mo After Onset	43 mo After Onset
Digit span (WMS-R)			
Forward	−0.1	−1.6	−1.6
Backward	0.1	−1.6	0.2
Letter fluency (RWT)	0.7	Not performed[b]	Not performed[b]
Semantic fluency	Not performed[c]	Not performed[b]	Not performed[b]
Word memory (AVLT)	3.0	<−1.8	−1.7
Block span	−1.1	Not performed	Not performed
Deductive Reasoning (LPS test 3)	−0.3	0.3	1.1
Visuospatial function (LPS test 7)	0.0	0.3	−0.6
Alertness (d2 test)[3]	−3.1	0.8	0.3
PASAT	Not performed[c]	−0.5	−1.7

Abbreviations: AVLT, Rey Auditory Verbal Learning Test (German adaption: Verbaler Lern- und Merkfähigkeits-Test); LPS, Leistungsprüfsystem[4]; PASAT, Paced Auditory Serial Addition Test (3 seconds); RWT, Regensburger Wort-Flüssigkeits-Test; WMS-R, Wechsler Memory Scale–Revised.

[a] A *z* score between −1 and 1 means that the performance of an individual is within 1 SD from the performance of a normal control of the same age and education.

[b] Too difficult for the patient (expected value <−3).

[c] No test in maternal language available.

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Conflict of Interest Disclosures: Dr Behrendt reports having received personal fees from Genzyme. Dr Krogias reports having received honoraria for oral presentations and travel grants for scientific meetings from Bayer Vital, Bristol-Myers Squibb, and Boehringer Ingelheim. Dr Reinacher-Schick reports having received speaker's and board honoraria from Roche, Celgene, Merck Serono, Amgen, Sanofi, and Pfizer and grant support from Roche, Sanofi, and Celgene. Dr Gold reports having received speaker's and board honoraria from Baxter, Bayer Health Care, Biogen Idec, Chugai, CLB Behring, Genzyme, Merck Serono, Novartis, Talecris, Teva, and Wyeth and grant support from Bayer Health Care, Biogen Idec, Genzyme, Merck Serono, Novartis, and Teva. Dr Kleiter reports having received honoraria for consultancy or speaking and travel reimbursement from Bayer Health Care, Biogen Idec, Chugai, and Novartis and grant support from Biogen Idec, Novartis, Chugai, and Diamed.

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COMMENT & RESPONSE

Spectrum of Movement Disorders in Mitochondrial Disorders

To the Editor With interest we read the article by Martikainen et al[1] about 42 genetically or biochemically confirmed adult (n = 30) and pediatric (n = 12) patients with a mitochondrial disorder (MID) who also presented with various types of an extrapyramidal movement disorder. We have the following comments and concerns.

The types of movement disorders found in this study were parkinsonism, dystonia, restless leg syndrome, tremor, and chorea.[1] However, there are several other types of movement disorders, which have been occasionally described in patients with MID, such as Tourette syndrome due to mutations in the *IMMP2L* gene,[2] tics,[3] athetosis,[4] dyskinesias, or progressive supranuclear ophthalmoplegia.[5] Additionally, there are ballism and paroxysmal nocturnal limb movements, which have not been reported in MIDs. Were any of these other movement disorders also detected?

We also should be informed about the family history. How often was the family history positive for movement disorders? Was there phenotypic heterogeneity between the generations? How many of the parents of the 42 patients were consanguineous? In how many patients carrying a mutation was the mutation also found in first-degree relatives?

Were patients investigated for movement disorders only clinically and with magnetic resonance imaging or single-photon emission tomography or did patients also undergo positron emission tomography with ^{18}fluorodeoxyglucose, sleep laboratory investigation, or gait analysis? In patients with Leigh syndrome, mitochondrial encephalomyopathy with lactic acidosis and strokelike episodes, or mitochontrial neurogastrointestinal encephalopathy diseaselike presentation, positron emission tomography with ^{18}fluorodeoxyglucose studies have shown glucose hypometabolism in the basal ganglia and cerebellum, the occipital lobes, or the frontotemporal lobes, respectively, which not always complies with the magnetic resonance imaging lesions. Were positron emission tomography with ^{18}fluorodeoxyglucose studies also carried out in any of the 42 patients with movement disorder?