Case Report/Case Series

Severe Cognitive Impairment Associated With Intrathecal Antibodies to the NR1 Subunit of the *N*-Methyl-D-Aspartate Receptor in a Patient With Multiple Sclerosis

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IMPORTANCE Some patients with multiple sclerosis (MS) can either present with or develop severe cognitive impairment during the course of their disease. However, the mechanisms underlying severe cognitive dysfunction in MS are not well understood.

OBSERVATIONS We report on a woman who was diagnosed as having MS at age 33 years and who after giving birth at age 37 years developed cognitive impairment with severe memory dysfunction as the leading symptom. Treatment with different immunotherapies, including cyclophosphamide and natalizumab, did not improve her cognitive deficits, necessitating admission to a nursing home at age 39 years. During a thorough reevaluation at age 43 years, analysis of current and stored cerebrospinal fluid and serum samples demonstrated an intrathecal synthesis of IgG antibodies to the NR1 subunit of the *N*-methyl-D-aspartate receptor, that is, the characteristic laboratory finding of anti–*N*-methyl-D-aspartate receptor encephalitis. Although the patient initially stabilized under therapy with corticosteroids, plasma exchange, and mitoxantrone, severe cognitive impairment persisted and she eventually died from the sequelae of her disease.

CONCLUSIONS AND RELEVANCE This report suggests that the occasional occurrence of severe cognitive impairment in patients with MS may, in some cases, be related to a superimposed antibody-mediated autoimmune encephalitis.

JAMA Neurol. 2015;72(1):96-99. doi:10.1001/jamaneurol.2014.1817
Published online November 10, 2014.

Supplemental content at jamaneurology.com

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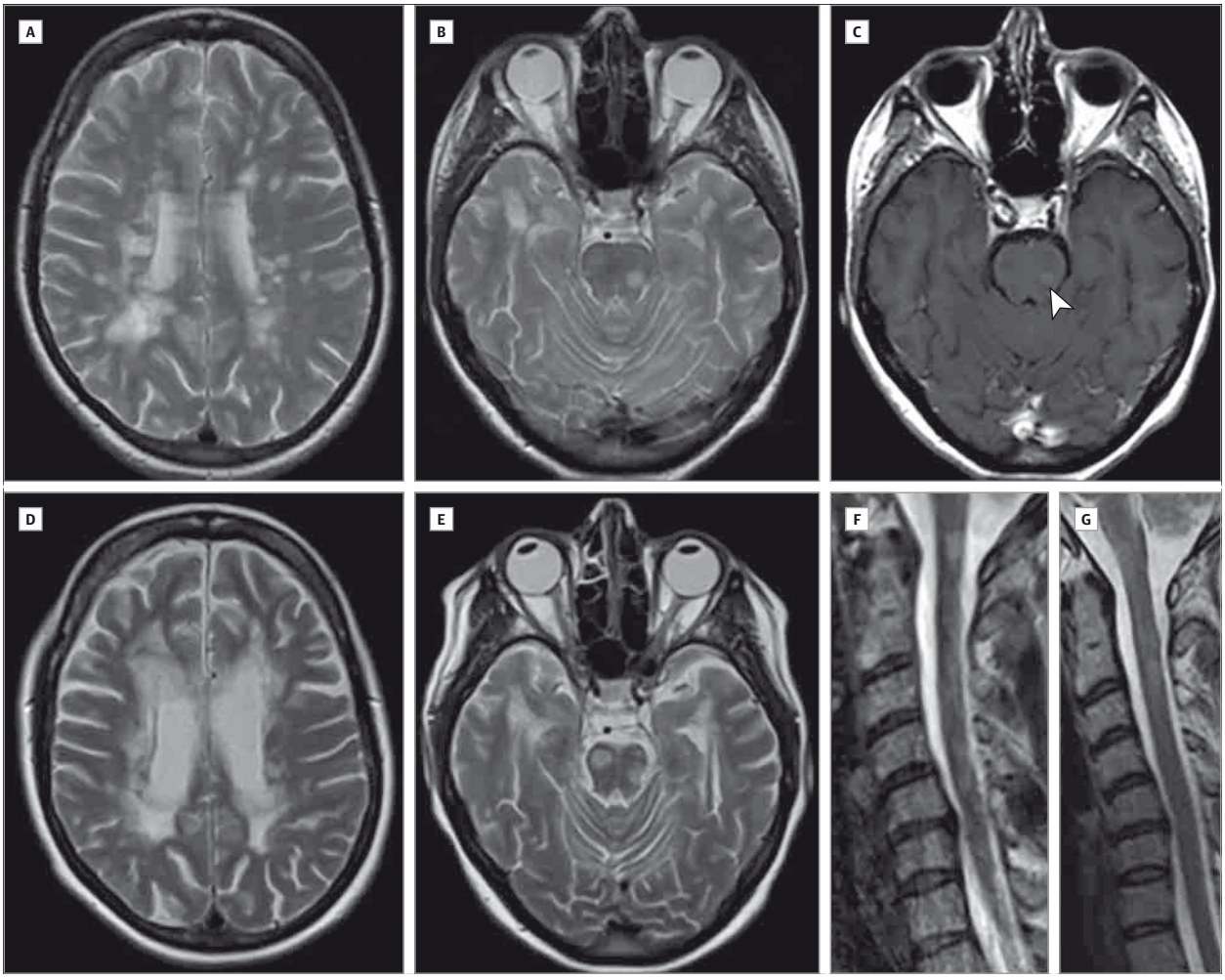
While it is well recognized that some patients with multiple sclerosis (MS) can either present with or develop severe cognitive impairment during the course of their disease, the mechanisms underlying severe cognitive dysfunction in MS are not well understood.[1] Here, we report on a patient with MS who developed severe cognitive impairment associated with intrathecal antibodies to the NR1 subunit of the *N*-methyl-D-aspartate receptor (NMDAR).

Report of a Case

A 33-year-old woman developed bilateral plantar paresthesia and numbness in her right leg in June 2002. Five years before, an episode of blurred vision in both eyes had resolved spontaneously. Neurological examination revealed a mild spastic paraparesis and hypesthesia of the right leg. Cranial magnetic resonance imaging (MRI) showed disseminated periventricular hyperintense lesions and cerebrospinal fluid (CSF) examination findings revealed a white blood cell count of 9/μL (reference range, <5/μL; to convert to $\times 10^9$ per liter, multiply by 0.001) and CSF-specific oligoclonal bands. She was diagnosed as having relapsing-remitting MS and was prescribed immunomodulatory therapy with glatiramer acetate, 20 mg/d subcutaneous. The patient had 2 further relapses with a left facial palsy in February 2003 and transient dysarthria in September 2004. Glatiramer acetate was discontinued in June 2004 because she wished to become pregnant. Findings from thorough neurological and psychiatric examinations performed in July 2005 were normal. Nevertheless, after the patient had given birth to a healthy child in March 2006, she developed a new relapse with gait ataxia and dysarthria and first noticed disorientation and memory problems, interfering with care for her child and activities of daily living. In a detailed neuropsychological examination in May 2006, she was oriented but had reduced processing speed and attention span, decreased working memory capacity, increased distractibility, and impairment of anterograde memory for figural more than for verbal contents, consistent with mild dementia. **Figure 1**A-C shows a cranial MRI performed at that time. Further thorough diagnostic reevaluation demonstrated moderately elevated antinuclear antibody (titer, 1:320; reference range <1:160) and posi-

Figure 1. Magnetic Resonance Imaging Findings



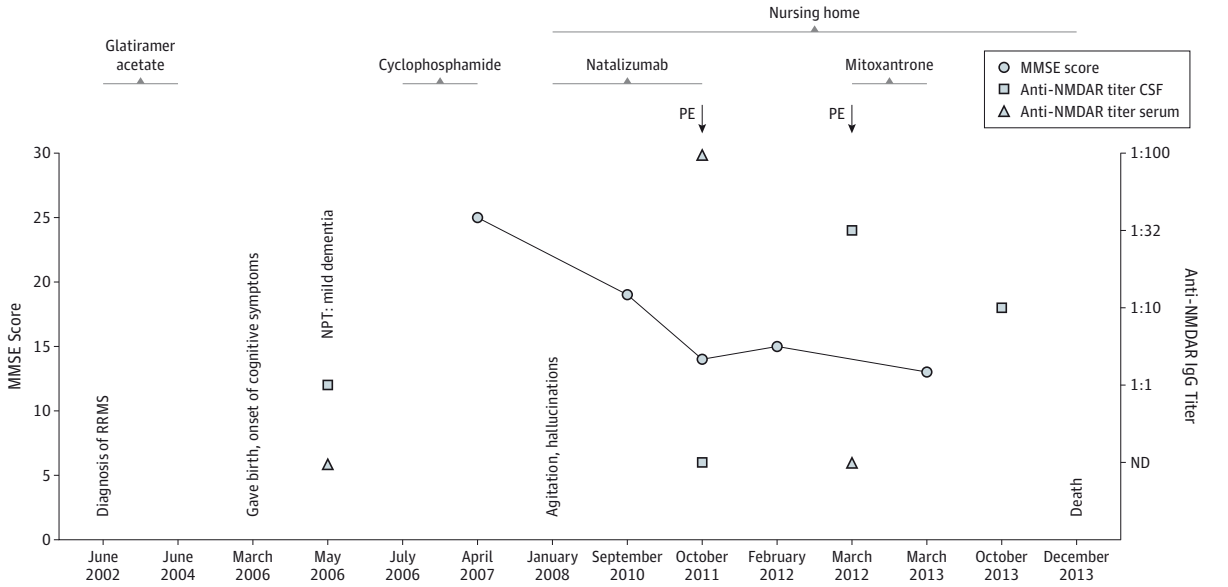
Cranial magnetic resonance imaging performed after the onset of cognitive impairments in July 2006 demonstrates multiple T2-hyperintense lesions typical of multiple sclerosis (A and B), with 1 left pontomesencephalic lesion showing contrast enhancement (C, arrowhead). Follow-up cranial and spinal T2-weighted magnetic resonance images obtained during a fulminant relapse in March 2012 show progressive generalized cerebral atrophy, large confluent periventricular lesions, a new right pontine lesion (D and E), and multiple new confluent lesions in the cervical cord (F), which were not visible in a prior spinal magnetic resonance image obtained in 2008 (G).

tive Sjögren syndrome antigen A antibody levels. A Schirmer test revealed reduced tear production, but salivary secretion (Saxon test) was normal. Findings from a lip biopsy showed mild chronic sialadenitis with 1 inflammatory focus (Chisholm and Mason grade 3), compatible with Sjögren syndrome.

In an attempt to reverse her cognitive deterioration, immunosuppressive therapy was initiated with high-dose intravenous corticosteroids, followed by oral corticosteroids and azathioprine, which was switched to monthly intravenous cyclophosphamide (700 mg/m^2 body surface) in July 2006. However, formal neuropsychological testing in January 2007 showed no improvement of her cognitive deficits and the patient stopped therapy owing to lack of efficacy in April 2007. Subsequently, her disease exacerbated at the end of 2007, when she developed intercurrent delusions, behavioral abnormalities, and progressive gait ataxia. A cerebral MRI demonstrated at least 5 contrast-enhancing lesions and she eventually started treatment with monthly natalizumab infusions in January 2008. This therapy was associated with improvement of motor functions but no significant effect on cognitive symptoms; therefore, she had to be taken care of in a nursing home starting in 2008.

In October 2011, after 33 months of natalizumab therapy, the patient was readmitted to our hospital because of progressive memory deficits and behavioral changes including aggressiveness. On examination, she was disoriented to place and time. She had a severe amnesic syndrome; for instance, she was unable to recall whether she had eaten half an hour after she had lunch. Her Mini-Mental State Examination score was 14 out of 30. No JC virus DNA was detectable in the CSF, arguing against progressive multifocal leukoencephalopathy. Given the unusual clinical picture, CSF and serum samples were tested for antibodies associated with autoimmune encephalitides. While no antibodies to Hu, Ri, Yo, Tr, Ma/Ta, glutamic acid decarbox-

Figure 2. Synopsis of Clinical Features and Anti-*N*-methyl-D-aspartate Receptor (NMDAR) IgG Antibody Titers in Cerebrospinal Fluid and Serum



MMSE indicates Mini-Mental State Examination; ND, not detectable; NPT, neuropsychological testing; PE, plasma exchange; RRMS, relapsing-remitting multiple sclerosis.

ylase, amphiphysin, CV2/CRMP5, myelin-oligodendrocyte glycoprotein, aquaporin 4, leucine-rich glioma-inactivated 1, contactin-associated protein-like 2, α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate receptor, γ-aminobutyric acid type B receptor, and glycin receptor could be found, anti-NMDAR IgG antibodies (titer, 1:100) were detected in serum, but not in CSF, by indirect immunofluorescence using human embryonic kidney 293 cells transfected with the NR1 subunit of the NMDAR (Euroimmun AG). Subsequent reexamination of stored CSF and serum samples obtained in May 2006, when memory problems first became apparent, revealed anti-NMDAR IgG antibodies in CSF (titer, 1:1), but not in serum, demonstrating an intrathecal synthesis of anti-NMDAR IgG. Whole-body fluorodeoxyglucose positron emission computed tomography and pelvic MRI showed no neoplasia. A diagnosis of anti-NMDAR antibody encephalitis superimposed on MS was made and the patient was treated with 5 courses of plasma exchange, with no significant improvement (Mini-Mental State Examination score of 15 out of 30 in February 2012). Because of the increased risk for progressive multifocal leukoencephalopathy after more than 2 years of natalizumab treatment and prior immunosuppressive therapy, natalizumab was discontinued.

Five months after natalizumab withdrawal, the patient developed a fulminant relapse with somnolence, inability to walk, and urinary retention. Cerebral and spinal MRI both revealed new lesions (Figure 1D-F). Findings from CSF examination showed an increased anti-NMDAR IgG titer (1:32; eFigure in the Supplement), but serum anti-NMDAR IgG was negative, again demonstrating intrathecal production of anti-NMDAR IgG antibodies. After intravenous corticosteroids and 6 courses of plasma exchange, the patient improved to her prerelapse level of functioning. She was subsequently treated with immunosuppressive therapy with mitoxantrone and tapered oral corticosteroids, which was associated with a certain stabilization and a reduction of anti-NMDAR IgG in CSF (titer, 1:10; October 2013). Still, her general condition deteriorated and she eventually died following urosepsis at the end of 2013. There was no postmortem examination. **Figure 2** summarizes her clinical course and anti-NMDAR IgG antibody findings.

Written informed consent for this report was obtained from the patient's family.

Discussion

The initial presentation of the patient described in this report appears typical of MS, and she fulfilled both current clinical and MRI diagnostic criteria for MS.[2] However, her subsequent disease course was characterized by an unusually severe and progressive cognitive decline, with marked impairment of anterograde memory as the most prominent deficit. Detection of intrathecally produced NMDAR IgG, which is highly specific for anti-NMDAR encephalitis,[3,4] at the time of symptom onset and during a relapse following natalizumab withdrawal suggests that the patient's cognitive impairment and further neuropsychiatric symptoms were related to these antibodies. Indeed, persistent cognitive impairments, mainly affecting memory and executive functions, were observed in 8 of 9 patients who underwent comprehensive neuropsychological assessment at a median of 43 months after acute anti-NMDAR encephalitis.[5]

Titulaer et al[6] described overlapping demyelinating syndromes in 23 patients with NMDAR encephalitis. While most of those patients (18 of 23) had antibodies to aquaporin 4 or

myelin-oligodendrocyte glycoprotein, suggesting that demyelinating syndromes in patients with NMDAR encephalitis might be associated with the co-occurrence of these antibodies, our patient had no antibodies to aquaporin 4 or myelin-oligodendrocyte glycoprotein. Nevertheless, because in 5 of 23 cases no antibodies other than to NMDAR were detectable, it remains possible that NMDAR antibodies themselves might be associated with demyelination.[6] Although we thus cannot exclude that our patient's entire disease process was related to NMDAR antibodies, we feel that given the characteristic initial course and the MS-typical paraclinical findings, our patient had a true co-incidence of MS and NMDAR encephalitis.

In the only other patient with MS and anti-NMDAR encephalitis described so far, diagnosis was based on the detection of antibodies to the NMDAR NR2B subunit in CSF.[7] Because anti-NMDAR antibodies in patients with anti-NMDAR encephalitis are directed against the NR1 subunit of the NMDAR and only rarely codetect NR2B,[3] to our knowledge, we believe this to be the first report of a patient with MS with the characteristic laboratory finding of anti-NMDAR encephalitis.

A diagnostic reevaluation at the onset of cognitive symptoms also revealed Sjögren syndrome. A thorough rheumatologic diagnostic performed at that time excluded systemic manifestations of Sjögren syndrome. In particular, there was no evidence of cerebral or other organ vasculitis. Altogether, we feel that MS and Sjögren syndrome coexisted in our patient, as previously described in other cases,[8] but consider it very unlikely that her disease was due to neurological manifestations of Sjögren syndrome rather than to MS.

The patient had a fulminant relapse after cessation of natalizumab, reminiscent of previous observations on rebound disease activity following natalizumab withdrawal.[9] This relapse was associated with an increase of the anti-NMDAR IgG titer in CSF. $CD138^+$ plasma cell levels in the CSF of natalizumab-treated patients with MS are significantly lower compared with patients with other neurological diseases and untreated patients with MS but increase after discontinuation of natalizumab.[10] Therefore, it seems plausible that natalizumab withdrawal facilitated entry of NMDAR antibody–producing plasma cells to the central nervous system.

Conclusions

This report opens the possibility that severe cognitive impairment or other neuropsychiatric abnormalities in patients with MS may in some instances be related to superimposed antibody-mediated encephalitides. The diagnosis of those patients will require a high degree of clinical suspicion as cognitive symptoms are rather frequent in MS and may mask or be confounded with features of antibody-mediated encephalitides. Nevertheless, testing for antineuronal antibodies appears warranted in patients with MS with unusual neuropsychiatric symptoms. Although various immunotherapies could not reverse cognitive impairments in our patient, antibody-mediated encephalitides can respond to treatment, and immunotherapy should be considered in such cases.

ARTICLE INFORMATION

Accepted for Publication: May 28, 2014.

Published Online: November 10, 2014. doi:10.1001/jamaneurol.2014.1817.

Author Contributions: Dr Ruprecht had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Fleischmann, Ruprecht.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Fleischmann, Ruprecht.
Critical revision of the manuscript for important intellectual content: Fleischmann, Prüss, Rosche, Bahnemann, Gelderblom, Deuschle, Harms, Kopp.
Administrative, technical, or material support: Fleischmann, Rosche, Deuschle, Harms.
Study supervision: Harms, Kopp, Ruprecht.

Conflict of Interest Disclosures: Dr Rosche has participated in meetings sponsored by Bayer Healthcare, Merck Serono, Biogen Idec, Novartis, Ovamed, and Teva Pharmaceuticals and has received lecture fees and research support from these companies. Dr Harms has received speaking fees from Novartis, Biogen Idec, Merck-Serono, Diamed, and Bayer; honoraria for serving on advisory boards from Novartis, Biogen Idec, and Genzyme; and travel grants from Teva Pharmaceuticals, Merck Serono, and Biogen Idec. Dr Ruprecht has received research support from Novartis as well as speaking fees and travel grants from Bayer Healthcare, Biogen Idec, Merck Serono, sanofi-aventis/Genzyme, Teva Pharmaceuticals, and Novartis. No other disclosures were reported.

Funding/Support: Dr Ruprecht is supported by the German Ministry of Education and Research (BMBF/KKNMS, Competence Network Multiple Sclerosis).

Role of the Funder/Sponsor: The German Ministry of Education and Research had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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