Progressive multifocal leukoencephalopathy and granule cell neuronopathy with novel mutation flanking VP1 C-terminus in natalizumab-extended interval dosing

Torge Rempe, MD, Qin Wang, PhD, Qi Wu, PhD, Varalakshmi Ballur Narayana Reddy, MD, Zachary Newcomer, DO, Augusto Miravalle, MD, and Yang Mao-Draayer, MD, PhD

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Correspondence

Dr. Rempe
torge.rempe@neurology.ufl.edu
or Dr. Mao-Draayer
maodraay@umich.edu

Reactivation of a dormant infection with the John Cunningham virus (JCV) can lead to the rare neurologic disorders progressive multifocal leukoencephalopathy (PML) and granule cell neuronopathy (GCN), a cerebellar syndrome with progressing cerebellar atrophy.¹ Here, we present a case of infratentorial PML with concomitant GCN in extended interval dosing (EID) of natalizumab associated with a novel mutation at 7th position after the C-terminus of viral capsid protein VP1 in addition to the common noncoding regulatory region (NCRR) mutation.

Case report

In March 2018, a 65-year-old woman presented with progressive symptoms of holocephalic headache, dizziness, nausea, and psychomotor slowing as well as balance difficulties and left hemibody weakness that started 2 weeks before admission. Her medical history was significant for relapsing-remitting MS initially diagnosed in 2000 with mild residual right-sided weakness. Because of the side effects of previous disease modifying therapy with interferons (flu-like symptoms) and glatiramer acetate (injection site reactions), natalizumab treatment was initiated in August 2010 and discontinued in March 2014 in light of her initial positive anti-JCV serostatus. Owing to the gastrointestinal side effects of subsequent therapy with teriflunomide and dimethyl fumarate (short treatment duration without associated lymphopenia), natalizumab therapy was reinitiated in August 2015 and infusion frequency was changed to EID (initially every 8 weeks, then every 6 weeks) for >2 years before the symptom onset.

On admission, mild tetraparesis (4/5) more evident on the left, diffuse 3+ hyperreflexia, positive bilateral Babinski reflexes, and impaired balance with inability to walk were present. Initially observed left-sided hemiataxia evolved into bilateral dysmetria pronounced on the left. MRI of the brain showed abnormal T2/fluid-attenuated inversion recovery hyperintensities in bilateral cerebellar hemispheres with extension into the left middle cerebellar peduncle and the cerebellar atrophy (figure).

The patient's most recent anti-JCV antibody indices (Quest Diagnostics, San Juan Capistrano, CA) were 3.32 (July 2016) and 3.42 (October 2017). Her absolute lymphocyte count ranged between $2.18\text{--}5.24 \times 10^3/\mu\text{L}$. JCV multiplex quantitative PCR analysis performed by the NIH was positive for 1,156 copies/mL in the CSF and 1,070 copies/mL in plasma of the NCRR variant most commonly associated with PML.² VP1 mutational analysis of the patient's plasma and CSF (supplementary material 1, links.lww.com/NXG/A250) did not show previously published common mutations at positions L55, K60, S61, D66, S267/S269, or Q271 nor in the C-terminus. However, a novel mutation at 7th position after VP1 C-terminus was detected in the patient's

From the Department of Neurology (T.R., V.B.N.R., Z.N., A.M.), University of Florida, Gainesville; and Department of Neurology (Q. Wang, Q. Wu, Y.M.-D.), University of Michigan, Ann Arbor.

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(A) Axial T2-weighted section showing hyperintensity in the white matter of the bilateral cerebellar hemispheres with extension into the middle cerebellar peduncle on the left (incidental mucosal thickening and an air-fluid level are present in the left sphenoid sinus); (B) axial gadolinium-enhanced T1-weighted section without evident contrast enhancement of the lesion; (C) axial FLAIR-weighted section with multiple periventricular foci of hyperintensity consistent with the patient's previous MS lesions; (D, E) diffusion-weighted imaging (D) and apparent diffusion coefficient (E) with central area of T2 shine-through and rim of diffusion restriction; and (F, G) sagittal FLAIR-weighted sections 13 months before presentation (February 2017; F) and at the time of presentation (March 2018 = most recent image; G) depicting interval development of cerebellar atrophy. FLAIR = fluid-attenuated inversion recovery.

plasma and CSF (nucleotide triplet ATA isoleucine/I [hydrophobic amino acid] to AAA lysine/K [hydrophilic amino acid]).

The patient received a 3-day course of apheresis for natalizumab removal. She was subsequently started on a 5-day course of 1,000 mg IV-methylprednisolone, maraviroc 150 mg twice daily, and nightly mirtazapine 15 mg. After discharge to acute rehab, the patient developed a severe aspiration pneumonia nonresponsive to antibiotics. She was transitioned to hospice care, and she passed away from aspiration pneumonia/sepsis approximately 2 months after discharge. An autopsy was not performed.

Discussion

Although EID has been shown to significantly lower the risk of PML,³ the reported case emphasizes that natalizumab-associated PML can also occur in EID. Furthermore, the case demonstrates concurrent cerebellar atrophy and infratentorial white matter changes associated with coexistence of the common NCRR variant and a novel mutation in the noncoding region after the VP1 C-terminus.

VP1 BC (amino acids 57-90) and HI (amino acids 268-278) loop mutations occur frequently (81%–93%) in JCV isolates of patients with PML.⁴ Deletions, duplications, and mutations in the VP1 C-terminus named JCV_{GCN1-8} have been associated with JCV-GCN.⁵ Although we did not identify the previously described VP1 mutations, we detected a novel mutation at 7th position after the VP1 C-terminus that we termed JCV_{GCN9}.

Concomitant cerebellar/pontine white matter changes have been observed in GCN, and it has been postulated that this could be because of a coinfection with 2 different JCV strains.⁶ While the NCRR variant is responsible for the PML-typical white matter changes, a different JCV strain with a VP1 C-terminus mutation leads to JCV-GCN with its characteristic cerebellar atrophy.⁷ The current case demonstrates an association between the concurrence of PML-lesions and JCV-GCN and the coinfection with the virulent NCRR variant and a novel mutation in the noncoding region flanking the VP1 C-terminus. The discovered mutation differs from the previous GCN mutations because it is located in the noncoding region after the VP1 C-terminus, and its potential pathogenicity will need to be further evaluated. A limiting factor is also the possibility that additional JCV strains with previously reported GCN mutations

might not have been captured without the sequencing of multiple clones if they only represent a minority strain.⁵ Future research is needed to further characterize the relationship between various JCV mutations in GCN and PML.

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Disclosure

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Appendix Authors

Name	Location	Contribution
Torge Rempe, MD	University of Florida	Draft of the manuscript
Qin Wang, PhD	University of Michigan	Mutational analysis, revision and critique of the manuscript

Appendix (continued)

Name	Location	Contribution
Qi Wu, PhD	University of Michigan	Revision and critique of the manuscript
Varalakshmi Ballur Narayana Reddy, MD	University of Florida	Treatment of patient, revision and critique of the manuscript
Zachary Newcomer, DO	University of Florida	Treatment of patient, revision and critique of the manuscript
Augusto Miravalle, MD	University of Florida; University of Colorado	Treatment of patient, revision and critique of the manuscript
Yang Mao-Draayer, MD, PhD	University of Michigan	Mutational analysis, revision and critique of the manuscript

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