The earlier, the smaller, the better for natalizumab-associated PML: In MRI vigilance veritas?

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Neurology 2012;79;1067; Published online before print August 22, 2012;
DOI 10.1212/WNL.0b013e31826846b4

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THE EARLIER, THE SMALLER, THE BETTER FOR NATALIZUMAB-ASSOCIATED PML: IN MRI VIGILANCE VERITAS?

Natalizumab-associated progressive multifocal leukoencephalopathy (N-PML) in multiple sclerosis (MS) is due to CNS infection by the opportunistic JC virus (JCV). As of December 2011, 193 confirmed cases of N-PML have been observed, giving rise to an overall risk of approximately 0.202%.[1] N-PML pathogenesis remains partially elusive although risk factors have now been clearly delineated.[2] In patients with prior JCV infection detected by serum anti-JCV antibodies,[3] duration of therapy and prior use of immunosuppressants (IS) increase the risk of N-PML. The clinical outcome of patients with MS who developed N-PML was highly variable, ranging from asymptomatic case[4] to varying degrees of neurologic disability or even death.[5] It was also observed in real-life setting that the earlier N-PML was diagnosed and treated, the better was the clinical outcome.[5] Clinical vigilance is now considered as the established cornerstone of PML risk-management algorithm.[2]

Here we present early MRI features of 4 out of 8 N-PML cases, which were observed in Wallonia-Brussels and Northern France in more than 4 years of postmarketing utilization of natalizumab for both regions. We are not aware of the specific context and outcome of the 4 other N-PML cases, which were diagnosed and treated in other centers. The reported cases emphasize that 1) N-PML can have a long presymptomatic course while still being clearly detectable with MRI, 2) N-PML can have a benign outcome provided it is diagnosed and treated early, 3) a clinically symptomatic N-PML may be a further advanced infection with a poorer prognosis, and 4) periodic brain MRI scans, particularly in high-risk situations, are likely to provide earlier detection of N-PML[4] and better outcomes.

Written informed consent was obtained from all 4 patients.

Case discussion. We describe in the figure the clinico-radiologic features of 4 N-PML cases in which early preclinical MRI signs were captured. Case 1 was a left cerebellar peduncle lesion[4] (Liège, Belgium). Cases 2, 3 (Lille, France), and 4 (Brussels, Belgium) were left occipital, left posterior parietal, and right anterior frontal lesions, respectively. Case 4 emphasizes how slow and long can be the preclinical phase of N-PML and to what extent the size of the lesion at diagnosis is indicative of the duration of preclinical infection. The early MRI signs of supratentorial cases 2, 3, and 4 were all located in the cortical/juxtacortical white matter. Consistent with previous data, the Expanded Disability Status Scale status, the size of the MRI lesion, and the age of the patient at the time of diagnosis may correlate with the clinical outcome.[4] In cases 2, 3, and 4, the emergence of N-PML symptoms was concurrent with the development of T1 hypointensity (dark) within the lesion due to immune reconstitution inflammatory syndrome (IRIS) occurrence in cases 2 and 3 (not shown) and at the time of a late-stage clinical diagnosis in case 4 (figure).

The 4 N-PML cases were confirmed by PCR detection of JCV DNA in the CSF (all performed at Focus Diagnostics, Cypress, CA). Natalizumab infusions were interrupted and plasma exchanges (PLEX) were immediately performed in all cases at the time of diagnosis. IV methylprednisolone (IVMP) followed by an oral MP tapering course (starting with 1 mg/kg, slowly tapered down over 1 to 6 months, table e-1 on the *Neurology*® Web site at www.neurology.org) was administered at the time late IRIS occurred for 3 out of 4 cases, whereas case 1 concurrently started steroid therapy together with PLEX and was the only case with no late IRIS occurrence. Early gadolinium enhancement of the PML lesion in case 1 as early as 28 days after the last natalizumab infusion may be linked to infection-related blood–brain barrier (BBB) disruption or inflammation triggered by an early immune reconstitution. The presence of such early BBB disruption before PLEX-induced acceleration of natalizumab clearance may also have mitigated the risk of late IRIS occurrence.

This case series advocates for the use of frequent brain MRI and especially fluid-attenuated inversion recovery scans as a monitoring tool for patients with MS at higher risk of developing N-PML. Since PML is a progressive disease[6] and MRI signs of N-PML tend to develop over several months[7] before symptoms (as illustrated here and in other reported cases[6,7]), brain MRI scans every 3–4 months could be considered for interval MRI vigilance.

A thorough radiologic follow-up with periodic brain MRI and strict comparison with prior images is expected to be more effective than clinical vigilance alone in order to improve the prognosis of N-PML through preclinical/early diagnosis and treatment. The generation of homogeneous and controlled settings to ascertain this hypothesis will be highly challenging but further studies remain warranted, while the costs and access to periodic MRI should be part of the trade-off analysis.

Supplemental data at www.neurology.org

Supplemental Data

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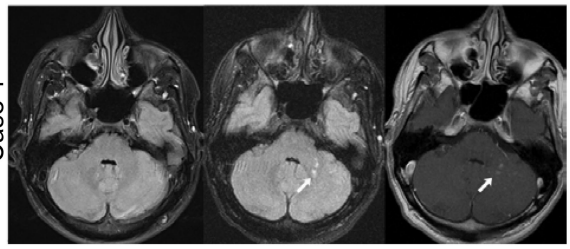
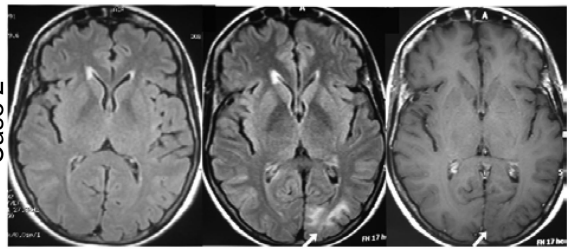
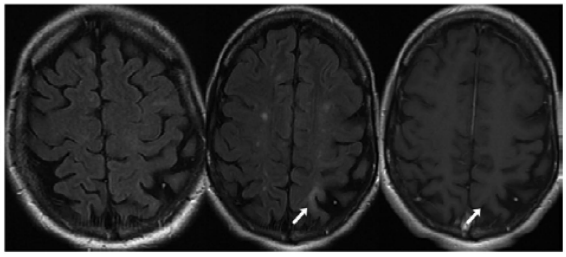
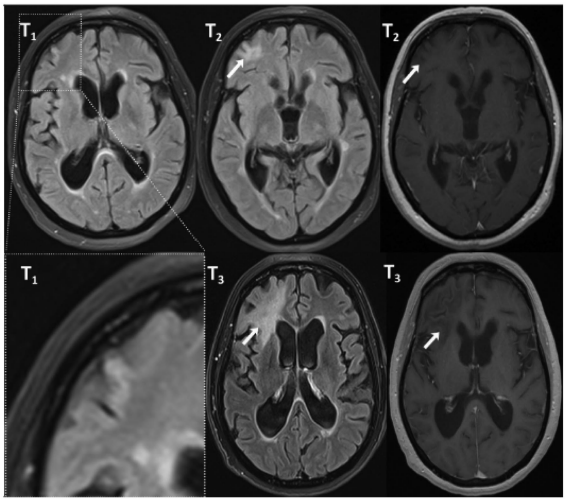
From the MYelin Disorders REseArch teaM (MYDREAM) (R.P.-B., S.B.), Liège; Department of Neurology (R.P.-B., S.B., G.M.), University and C.H.U. of Liège, Liège, Belgium; Department of Neurology (O.O., P.V.), Salengro Hospital, Université de Lille Nord de France, CHRU Lille; Service de Neurologie (C.S.), Cliniques Uni-

Figure **Clinical, MRI, diagnostic, and therapeutic features of the 4 natalizumab-associated progressive multifocal leukoencephalopathy (N-PML) cases**

	Last MRI before PML (FLAIR)	First radiological signs of PML (FLAIR, T1+Gd)	PML diagnosis and management	Outcome
Case 1			• 29 yo male, 38 infusions, EDSS 4.0 • No new symptoms • Gd-enhancement of initial MRI lesion, 28d after last natalizumab (NTZ) infusion • Prior IS (mitoxantrone) • Unknown JCV Ab status prior to PML • JCV PCR on CSF: 712 copies/mL • PLEX and IVMP (5x1gr) at time of Dx 7w after last NTZ infusion, followed by 24w oral MP tapering course	• No new symptoms (stable EDSS and MSFC course), no late-IRIS development • Negative JCV DNA PCR on CSF 12w after PLEX initiation • No hypointense T1 lesion, long-lasting Gadolinium enhancement vanishing 33w after PLEX and coalescence of T2 lesions.
Case 2			• 45 yo female, 33 infusions, EDSS 4.0 • No new symptoms of which patient is aware but inferolateral right quadranopsy on formal visual testing • No Gd-enhancement of initial MRI lesion, 15-20d after last NTZ infusion • Prior IS (mitoxantrone) • Unknown JCV Ab status prior to PML • JCV PCR on CSF: 284 copies/mL • PLEX at time of Dx 3w after last NTZ infusion + Cidofovir + Probenecid	• Negative JCV DNA PCR on CSF 12w after PLEX initiation • Development of an hypointense T1 lesion and disappearance of late-IRIS associated gadolinium enhancement after 24w
Case 3			• 40 yo female, 44 infusions, EDSS 3.5 • No new symptoms • No Gd-enhancement of initial MRI lesion, 18d after last NTZ infusion • No prior IS • Positive JCV Ab prior to PML • JCV PCR on CSF: 15016 copies/mL • PLEX at time of Dx 3w after last NTZ infusion + Norset + Mefloquine	• Right hemihypoesthesia and dyspraxia concurrent of late-IRIS development with edema 3-4w after PLEX, treated with IVMP (10x1g) followed by a short oral MP tapering course. Persistent right sensory deficit and dyspraxia. • No further control CSF analysis for DNA PCR detection • Development of an hypointense T1 lesion and slow disappearance of late-IRIS associated gadolinium enhancement.
Case 4			• 60 yo female, 49 infusions, EDSS 6.5. • No new symptoms at the time of first MRI signs of PML. T1 timepoint was considered stable but a linear hyperintense cortical/juxta-cortical lesion was retrospectively suspected. T2 was misinterpreted as a new plaque. Despite monthly clinical evaluation, a progressive cognitive and behavioral disturbance with increase in lower left limb paresis was only captured at T3 timepoint, i.e., 35w after T1 and 20w after T2. At the time of diagnosis (T3), PML FLAIR lesion volume had massively increased. • No Gd-enhancement of initial unequivocal MRI lesion (T2), nor at the time symptoms were detected (T3, 27d after last NTZ infusion) when PML lesion was then hypointense in T1-weighted sequence • No prior IS • Unknown JCV Ab status prior to PML • JCV PCR on CSF: 253 copies/mL • PLEX at time of Dx 4,5 weeks after last NTZ infusion but 20w after T2 and 35w after T1	• No obvious worsening of cognitive and motor symptoms concurrent of late-IRIS development 5w after PLEX, then treated with IVMP (2x5x1g) followed by an oral MP tapering course. Persistent major cognitive impairment and moderate lower left limb paresis • Development of a persistent hypointense T1 lesion and slow disappearance of late-IRIS associated gadolinium enhancement • JCV PCR on CSF still weakly positive (25 copies/mL) 12w after T3

MRI data include fluid-attenuated inversion recovery (FLAIR) and postgadolinium T1-weighted images. White arrows point toward the PML lesion in all cases. Early MRI signs of N-PML were highly detectable in the FLAIR sequence in all cases.

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Author contributions: Dr. Phan-Ba: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data. Pr. Belachew: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data. Dr. Outteryck: drafting/revising the manuscript, analysis or interpretation of data, acquisition of data. Pr. Moonen: drafting/revising the manuscript. Pr. Sindic: drafting/revising the manuscript, analysis or interpretation of data. Dr. Vokaer: drafting/revising the manuscript, analysis or interpretation of data, acquisition of data. Pr. Vermersch: drafting/revising the manuscript, analysis or interpretation of data.

Acknowledgment: The authors thank Inge Declercq, MD (Neurology Department, Europaziekenhuis, Belgium) for sharing the MRI and clinical data of case 4 and for reading and commenting on the manuscript.

Disclosure: R. Phan-Ba has received funding for travel from Bayer Schering Pharma, Sanofi-Aventis, and Biogen Idec. S. Belachew serves on scientific advisory boards for Bayer Schering Pharma, Biogen Idec, Genzyme-Sanofi Aventis, Novartis Pharma, and Merck-Serono; has received funding for travel and speaker honoraria from Bayer Schering Pharma, Biogen Idec, Genzyme-Sanofi Aventis, Novartis Pharma, TEVA, and Merck-Serono; and has received research and/or educational grant supports from Biogen Idec, Merck-Serono, Sanofi-Aventis, TEVA, and Novartis Pharma. O. Outteryck has received funding for travel from Biogen Idec, Bayer Schering Pharma, Merck Serono, Novartis, Teva Pharmaceutical Industries Ltd, and Sanofi-Aventis and for speaker honoraria from Bayer Schering Pharma, Biogen Idec, and Sanofi-Aventis. G. Moonen reports no disclosures. C. Sindic has received honoraria for consultancy, board membership, and lectures from Bayer Schering, Biogen Idec, GSK Biological Vaccines, Merck Serono, Novartis, and Sanofi Aventis, and research grants from Bayer Schering, Merck Serono, and Novartis. M. Vokaer has participated in (or is currently participating in) several industry-sponsored clinical trials in the field of multiple sclerosis. The sponsoring pharmaceutical companies for these trials have included (or do include) Biogen-Idec, Merck-Serono, Bayer Healthcare, GlaxoSmithkline, Sanofi-Aventis, and Novartis. He has received research support from Biogen-Idec, Merck-Serono, Novartis, Sanofi-Aventis, and Bayer Healthcare; received travel expenses for attending meetings from Bayer Healthcare, Biogen-Idec, Merck-Serono, Pfizer, and Sanofi-Aventis; personal compensation for activities with Bayer Healthcare, Novartis, and Biogen-Idec as a scientific advisory board member and as a consultant; personal compensation for activities with Bayer Healthcare, Merck-Serono, and Biogen-Idec as a speaker. P Vermersch serves on scientific advisory board for Biogen Idec, Bayer Schering Pharma, Merck Serono, Novartis, Teva Pharmaceutical Industries Ltd, and Sanofi-Aventis; has received funding for travel and speaker honoraria from Biogen Idec, Bayer Schering Pharma, Novartis, Teva Pharmaceutical Industries Ltd, Sanofi-Aventis, and Merck Serono; and receives research support from Biogen Idec, Merck Serono, Sanofi-Aventis, Teva Pharmaceutical Industries Ltd, and Bayer Schering Pharma. ***Go to Neurology.org for full disclosures.***

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Received January 6, 2012. Accepted in final form April 6, 2012.

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