

Balint syndrome in anti-NMDA receptor encephalitis

Aude Metzger, MD, PhD, Laure Pisella, PhD, Alain Vighetto, MD, PhD, Bastien Joubert, MD, Jérôme Honnorat, MD, PhD, Caroline Tilikete, MD, PhD, and Virginie Desestret, MD, PhD

Correspondence

Dr. Metzger
aude.metzger@chu-lyon.fr

Neurol Neuroimmunol Neuroinflamm 2019;6:e532. doi:10.1212/NXI.000000000000532

We report 2 cases of NMDA receptor (NMDAR) encephalitis with classic signs and symptoms of encephalitis, but in whom Balint syndrome was a predominant manifestation in the evolution of the disease.

Patient 1, a 24-year-old woman, presented initially with catatonia, mutism, unusual anxiety, and generalized epileptic seizures. She received 3 months of intensive care. She had no psychosis, no movement disorders, no sleep disturbance, or dysautonomia. Cerebral MRI was normal. Based on a large workup (table) and positivity of CSF anti-NMDAR antibodies, a diagnosis of NMDAR encephalitis was made, and she was accordingly treated for encephalitis and seizures (table). No teratoma was detected. One year after disease onset, neuropsychological assessment found deficits in executive functions (working memory, planning, and mental flexibility), constructive apraxia, and left spatial neglect; Balint syndrome was not assessed at this time. She was evaluated again 2 years after disease onset because of visual complaints, such as misreaching when grasping objects and difficulty to judge distances. Ophthalmologic examination and visual field were normal. Neurologic examination highlighted difficulties to reach and grasp a pen introduced in the patient's peripheral visual fields related to bilateral optic ataxia¹; lateralized spatial attention disorder attested by a rightward bias in manual line bisection and left omissions related to left hemineglect; and partial descriptions of complex pictures and embedded shapes, inability to detect the contour of dotted lines and to perform visual labyrinth tests, and inability to enumerate dots with a revisiting phenomenon consistent with simultanagnosia.² Eye movements were normal. A full Balint syndrome was therefore diagnosed on the association of optic ataxia, psychic paralysis of gaze (simultanagnosia), and lateralized disorder of attention (left hemineglect).³ At this time, cerebral MRI remained normal, 18 fluorodeoxyglucose PET (¹⁸F-FDG PET/CT) found a mild left fronto-temporo-parietal and insular hypometabolism, and EEG found diffuse posterior slow waves without epileptiform abnormalities. She was treated with 2 new infusions of rituximab. Anti-convulsants were not modified.

Patient 2, a 19-year-old woman, presented with severe limb apraxia and aphasia, behavioral disorders such as emotional lability and psychomotor slowing, associated with signs of Balint syndrome. The patient had no movement disorders, no epileptic seizure, sleep disturbance, or dysautonomia. Based on a large workup (table) and the positivity of CSF anti-NMDAR antibodies, a diagnosis of NMDAR encephalitis was made, and she was accordingly treated (table). No teratoma was found. At this time, cerebral MRI was normal, ¹⁸F-FDG PET/CT showed left temporo-occipito-parietal and bilateral insular hypermetabolism, and EEG found bilateral occipital and parietal slow waves without epileptiform abnormalities. She was re-evaluated 2 months after diagnosis at a rehabilitation center owing to the persistence of visual symptoms after recovery from aphasia and apraxia. Ophthalmologic examination and visual

From the Service de neuro-ophtalmologie et neuro-cognition (A.M., A.V., C.T., V.D.), Hospices Civils de Lyon, hôpital neurologique Pierre Wertheimer; IMPACT—Integrative, Multisensory (L.P., A.V., C.T.), Perception, Action and Cognition Team, Centre de recherche des Neurosciences de Lyon (CRNL); Université Claude Bernard Lyon 1 (A.V., B.J., J.H., C.T., V.D.); Centre de référence français des syndromes paranéoplasiques (B.J., J.H.), Hospices Civils de Lyon, hôpital neurologique Pierre Wertheimer; and Institut NeuroMyoGene INSERM U1217/CNRS UMR 5310 (B.J., J.H., V.D.), équipe synaptopathies et anticorps (SYNATAC), Lyon, France.

Funding information and disclosures are provided at the end of the article. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/NN.

The Article Processing Charge was funded by the Université de Lyon.

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND), which permits downloading and sharing the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Table Description of patients

	Patient 1	Patient 2
Age	24 years	19 years
Initial clinical presentation	Aphasia	Apraxia
	Catatonia	Aphasia
	Generalized seizures	Behavioral disorders (emotional lability and psychomotor slowing)
CSF analysis	At disease onset:	At disease onset:
	19 WBC	12 WBC
	Normal protein level	Normal protein level
	Oligoclonal bands	Oligoclonal bands
	Positive anti-NMDAR antibodies in serum and CSF	Positive anti-NMDAR antibodies in CSF
	Two years after disease onset:	Two months after disease onset:
	Normal cell count	Normal cell count
	Normal protein concentration	Normal protein concentration
	No oligoclonal bands	No oligoclonal bands
	Positive anti-NMDAR antibodies in CSF	Positive anti-NMDAR antibodies in CSF
Treatment	Methylprednisolone 1,000 mg daily for 5 days	Prednisolone 180 mg daily for 1 month
	IV immunoglobulin (2 courses, 0.4 g/kg daily for 5 days)	IV immunoglobulin (1 course, 0.4 g/kg daily for 5 days)
	Rituximab (1,000 mg per infusion, 4 infusions)	Rituximab (1,000 mg per infusion, 2 infusions)
	Cyclophosphamide (600 mg/m ² /infusion, 9 infusions)	Cyclophosphamide (600 mg/m ² , 5 infusions)
	Levetiracetam 1500 mg per day	
	Lacosamide 250 mg per day	
Follow-up	26 months	6 months
Balint syndrome assessment²	Two years after disease onset:	Two months after disease onset:
	Bilateral optic ataxia (left > right)	Bilateral optic ataxia
	Simultanagnosia	Simultanagnosia
	Inability to identify superimposed figure identification	Inability to identify superimposed figure identification
	Inability to perform visual labyrinth tests	Inability to perform visual labyrinth tests
	Inability to identify the contour of dotted lines	Inability to identify the contour of dotted lines
	Partial description of a complex picture	Partial description of a complex picture
	Erroneous counting with overestimations of the number of dots	Erroneous counting with underestimations of the number of dots
	Elementary visual-perceptual impairment: length comparison, size comparison, angle comparison task, midline localization, comparison of dot position, and dot position among distractors research. Total: 58/72 (impaired)	Elementary visual-perceptual impairment: length comparison, size comparison, angle comparison task, midline localization, comparison of dot position, and dot position among distractors research. Total: 52/72 (impaired)
	Left visual neglect	Left visual neglect
Systematic rightward bias at manual line bisection (mean deviation: 0.8 cm)	Systematic rightward bias at manual line bisection (mean deviation: 0.8 cm)	

Continued

Table Description of patients (continued)

	Patient 1	Patient 2
	Omission of elements displayed on the left side (map, complex scene picture)	Omission of elements displayed on the left side (map, complex scene picture)
Other neuropsychological symptoms	One year after disease onset:	One month after disease onset:
	Constructive apraxia	Mild constructive apraxia
	Working memory deficit (digit span and symbol digit modalities test)	Working memory deficit (digit span and symbol digit modalities test)
	Limitation of cognitive flexibility (Trail Making Test)	

Abbreviations: NMDAR = NMDA receptor; WBC = white blood cell.

field were normal. Full Balint syndrome was diagnosed on the association of optic ataxia, simultanagnosia, and lateralized disorder of attention (left hemineglect) (table).^{2,3} Eye movements were normal. Balint syndrome recovered over the next 4 months.

Discussion

These 2 cases show the occurrence of Balint syndrome, in addition to other symptoms, in NMDAR encephalitis. Balint princeps description included optic ataxia, psychic paralysis of gaze (now called simultanagnosia), and lateralized disorder of attention (left spatial neglect), as observed in our 2 patients.³ Oculomotor apraxia as described later in addition to the triad was not observed in our 2 patients.

Balint syndrome is a reliable marker of bilateral parieto-occipital dysfunction. Accordingly, posterior slow waves were observed on EEG in our 2 patients. Such posterior EEG abnormalities have been previously reported in NMDAR encephalitis.⁴

While in most vascular or degenerative Balint syndrome, bilateral parieto-occipital hypo metabolism is reported; metabolic imaging in our patients showed different patterns. Occipital hypometabolism has been highlighted in NMDAR encephalitis, but other patterns have been described, such as focal and lateralized hypo- or hypermetabolism.⁵ Furthermore, seizures and psychotropic treatment may also contribute to the metabolic pattern variability.

The pathophysiologic mechanisms leading to these clinical, EEG, and imaging changes remain unclear. They could involve a direct pathogenic role of anti-NMDAR antibodies leading to NMDAR internalization and a consecutive change in neuronal activity.⁶ They could also involve a thalamo-cortical disconnection, as such damage in connectivity has been identified among users of ketamine, an NMDAR antagonist.⁷

Our clinical observations highlight that posterior tropism of functional and metabolic changes reported in NMDAR encephalitis^{4,5} can be symptomatic. Future studies are needed to assess the prevalence and pathophysiology of Balint syndrome in NMDAR encephalitis.

Study funding

No targeted funding reported.

Disclosure

A. Metzger, L. Pisella, A. Vighetto, and B. Joubert report no disclosures. J. Honnorat receives royalties from licensing fees to Athena Diagnostics, Euroimmun, and Ravo Diagnostika for a patent for the use of CV2/CRMP5 as diagnostic tests and received research support from CSL Behring France. C. Tilikete received travel funding and/or speaker honoraria from Santhera, Novartis, and Teva; served on the editorial boards of the *Journal of Neuro-Ophthalmology*, *Frontiers in Neurology*, and *Neuro-ophthalmology*; and receives publishing royalties from Elsevier Masson. V. Desestret reports no disclosures. Full disclosure form information provided by the authors is available with the full text of this article at Neurology.org/NN.

Publication history

Received by *Neurology: Neuroimmunology & Neuroinflammation* July 2, 2018. Accepted in final form November 8, 2018.

References

1. Perenin MT, Vighetto A. Optic ataxia: a specific disruption in visuomotor mechanisms. I. Different aspects of the deficit in reaching for objects. *Brain* 1988;111(pt 3): 643–674.
2. Pisella LBD, Vighetto A. Combination of attentional and spatial working memory deficits in Balint-Holmes syndrome. *Ann N Y Acad Sci* 2015;1339:165–175.
3. Harvey M. Psychic paralysis of gaze, optic ataxia, and spatial disorder of attention. *Cogn Neuropsychol* 1995;12:265–281.
4. Goldberg EM, Taub KS, Kessler SK, Abend NS. Anti-NMDA receptor encephalitis presenting with focal non-convulsive status epilepticus in a child. 2011;42:188–190.
5. Probasco JC, Solnes L, Nalluri A, et al. Decreased occipital lobe metabolism by FDG-PET/CT: an anti-NMDA receptor encephalitis biomarker. *Neuro Neuroimmunol Neuroinflamm* 2018;5:e413.
6. Mikasova L, De Rossi P, Bouchet D, et al. Disrupted surface cross-talk between NMDA and Ephrin-B2 receptors in anti-NMDA encephalitis. *Brain* 2012;135(pt 5): 1606–1621.
7. Liao Y, Tang J, Liu J, et al. Decreased thalamocortical connectivity in chronic ketamine users. *PLoS One* 2016;11:e0167381.

Appendix 1 Author contributions

Name	Location	Role	Contribution
Aude Metzger, MD, PhD	Hôpital neurologique Lyon CRNL	Author	Drafting and revising the manuscript for intellectual content and clinical evaluation of patients
Laure Pisella, PhD	CRNL	Author	Major role in the acquisition of data, drafting and revising the manuscript for intellectual content, analysis and interpretation of the data, and clinical evaluation of patients
Alain Vighetto, MD, PhD	Hôpital neurologique Lyon	Author	Major role in the acquisition of data, drafting and revising the manuscript for intellectual content, analysis and interpretation of the data, and clinical evaluation of patients
Bastien Joubert, MD	Hôpital neurologique Lyon	Author	Drafting and revising the manuscript for intellectual content
Jérôme Honnorat, MD, PhD	Hôpital neurologique Lyon	Author	Drafting and revising the manuscript for intellectual content
Caroline Tilikete, MD, PhD	Hôpital neurologique Lyon, CRNL	Author	Design and conceptualization of the study, analysis and interpretation of the data, drafting and revising the manuscript for intellectual content, and clinical evaluation of patients
Virginie Desestret, MD, PhD	Hôpital neurologique Lyon	Author	Design and conceptualization of the study, analysis and interpretation of the data, and drafting and revising the manuscript for intellectual content
