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LETTER TO THE EDITORS

Spontaneous recovery from anti-NMDAR encephalitis

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Dear Sirs,

Encephalitis associated with antibodies (Abs) to the *N*-methyl-D-aspartate receptor (NMDAR) can occur in a paraneoplastic or non-paraneoplastic form. It is characterized by a broader clinical spectrum than typical limbic encephalitis, generally presenting with psychiatric symptoms, progressing to seizures and movement disorders, up to coma with hypoventilation [1, 2]. Although early treatment, based on tumor removal, when appropriate, and immunotherapy is associated with positive outcome, many patients require prolonged hospitalization and respiratory assistance [3]. We report a young woman with non-paraneoplastic anti-NMDAR encephalitis who experienced spontaneous recovery.

Neuropsychological evaluation was performed with a test battery including mini mental state examination and tests exploring episodic memory (Rey's auditory verbal learning test), short-term memory (digit and visual–spatial span), language [phonological word fluency, semantic word fluency (SWF)], object naming, executive functions (Stroop test), constructional praxis (copy of figures with and without landmarks), attention (multiple features targets cancellation) and intelligence tasks (Raven's colored matrices '47). Abs in samples taken at presentation were assayed by Prof. Vincent; these and subsequent samples were re-tested with a commercial assay (Euroimmun, Lübeck, Germany).

In September 2007, a 27-year-old Romanian woman was admitted to another hospital on the grounds of mild fever, confusion, extreme anxiety, and fear, followed, in a few days, by tonic–clonic seizures. Brain MRI was unremarkable and CSF analysis showed a mild increase in protein content (76 mg/dl) and lymphocytosis (25 cells/field). The patient was transferred to our hospital Department of Infectious Diseases, where a new CSF evaluation showed normal glucose, proteins 84 mg/dl, 2 cells/field; no oligoclonal bands. Treatment with phenobarbital and carbamazepine was started and, after exclusion of an infectious etiology (negative PCR for *Mycobacterium tuberculosis*, VZV, HSV, enterovirus, EBV, CMV on both CSF and serum; negative HIV-serology), the patient was admitted to our department. Brain MRI detected a T2 and FLAIR signal hyperintensity in the left temporal mesial lobe and insula (Fig. 1a). EEG showed slow activity in the left hemisphere. Neurological examination was unremarkable except for confusion, ideomotor slowing, and verbal reduction; dyskinesias, dystonia, rigidity, autonomic and breathing instability were not detected. Neuropsychological evaluation showed a multitask cognitive impairment mainly consisting of retrograde amnesia and lexical and semantic language disorder (see Table 1). In the following weeks, the patient's cognitive status and brain MRI improved spontaneously. Of an extensive Ab panel, including anti-Hu, -AMPAR, -CASPR2, -GABAR1 and -LGI1 Abs, NMDAR Abs were positive in CSF and serum. At the first control visit, in November 2007, the patient still showed an impairment of language abilities, with partial recovery of memory function (see Table 1). The patient's conditions remained stable until January 2008, when two generalized seizures occurred, possibly because of therapy

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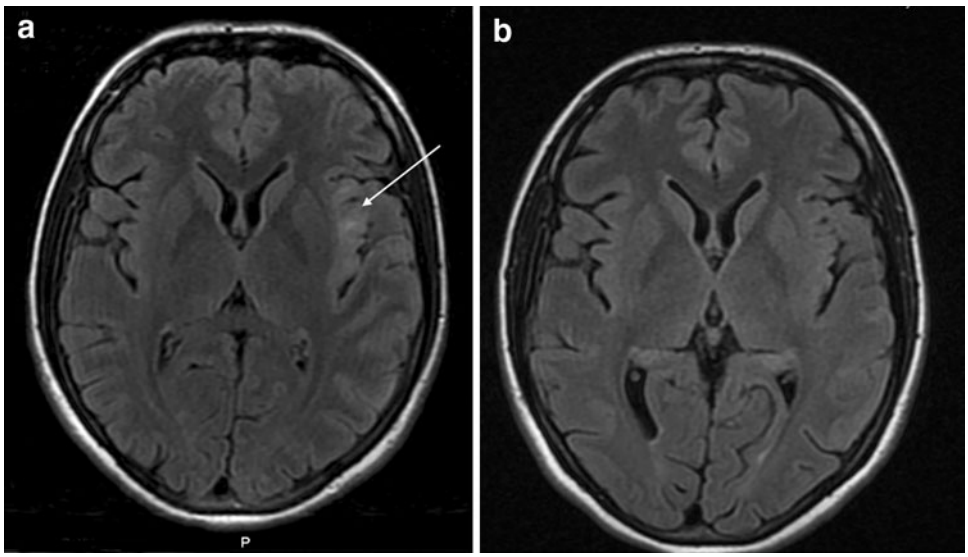

Fig. 1 Brain MRI at presentation (**a**) and at the last control (**b**). **a** T2 and FLAIR signal hyperintensity in the left temporal mesial lobe and insula (*arrow*). **b** No signal alteration evidence

Table 1 Cognitive profile during follow-up

	Oct 2007	Nov 2007	Jan 2008	Jul 2008	Mar 2011
MMSE	**4**	24	27	29	29
RAVLT-immediate	**0**	**26**	37	27	42
RAVLT-delayed	**0**	**7**	**6**	12	9
RAVLT-recognition/false alarms	Not done	1	1	0	1
RAVLT-recognition/accuracy	Not done	95	97	97	97
PWF (phonologic verbal fluency)	**0**	**17**	**9**	19	36
SWF (semantic verbal fluency)	**0**	**8**	**3**	**10**	**9**
Object naming	**13**	**18**	**9**	**19**	27
Copy of figures	9	10	11	12	10
Copy with landmarks	60	69	69	70	70
Digit span forward	**3**	7	5	5	5
Digit span backward	**0**	7	4	4	4
Spatial span forward	5	6	7	6	6
Spatial span backward	**0**	4	5	6	5
RCM '47	**17**	30	33	34	35
MFTC-false alarms	2	0	0	0	0
MFTC-accuracy	97	98	98	99	98
MFTC-time	40	35	22	46	30
Stroop-interference time	**180**	40	33	27	27
Stroop-interference errors	**30**	2	0	0	0

Abnormal results are in *bold*

MMSE mini mental state examination, *RAVLT* Rey's auditory verbal learning test, *RCM* Raven's colored matrices, *MFTC* multiple features targets cancellation

withdrawal. A new brain MRI showed a reduction of temporal hyperintensity and EEG detected slow activity and sharp waves on both hemispheres. Neuropsychological examination revealed a mild residual linguistic deficit with slightly lower scores compared to the previous control (see Table 1). The patient was discharged with carbamazepine treatment, gradually reduced, and finally suspended in 2009. At the last control in March 2011, the patient showed only mild SWF impairment, possibly related to the fact that Italian was not her mother tongue (see Table 1); EEG and brain MRI (Fig. 1b) were normal. Investigations for an associated tumor, performed with total-body CT scan, PET/CT scan and neoplastic biomarkers (NSE, beta-hCG, alpha-fetoprotein, CEA, CA 19.9, CA125, CA 15.3, CYFRA 21.1) was negative through the whole follow-up. Serum anti-NMDAR Abs were still clearly positive in January 2008, while only a faint immunoreactivity was detected in March 2011.

Anti-NMDAR encephalitis is generally a severe multi-stage disease, in which Ab-induced NMDAR reduction leads to progressive functional alterations involving different levels of CNS, followed by a prolonged recovery

phase of executive dysfunction [3, 4]. Despite good response to treatment, persistent cognitive dysfunction mostly concerning executive functions and memory has been reported [5]. Our patient appears to have suffered from a self-limiting disease that did not progress to the late, most severe stage. Consistent with the involvement of left insula, verbal tasks were prevalently affected and mild impairment in semantic verbal fluency was the only residual deficit. This case report confirms that anti-NMDAR encephalitis can rarely occur in a relatively benign form [6–8] and residual cognitive deficit can vary according to prevalent disease localization.

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Conflicts of interest The authors declare that they have no conflicts of interest.

Abbreviations

AMPAR	Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
beta-hCG	Beta subunit of human chorionic gonadotropin
CA 19.9	Carbohydrate antigen 19.9
CA125	Carbohydrate antigen 125
CA 15.3	Cancer antigen 15.3
CASPR2	Contactin-associated protein 2
CEA	Carcino-embryonic antigen
CMV	Cytomegalovirus
CNS	Central nervous system
CSF	Cerebrospinal fluid
CT	Computed tomography
CYFRA 21.1	Cytokeratin fragment 21.1
EBV	Epstein–Barr virus
EEG	Electroencephalogram
FLAIR	Fluid attenuated inversion recovery
GABAR1	Gamma-aminobutyric acid receptor 1
HIV	Human immunodeficiency virus
HSV	Herpes simplex virus
LGI1	Leucine-rich glioma inactivated 1
MRI	Magnetic resonance imaging
NSE	Neuron-specific enolase
PCR	Polymerase chain reaction
PET	Positron emission tomography
VZV	Varicella-zoster virus

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