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LETTER TO THE EDITOR

Anti-*N*-methyl-D-aspartate receptor encephalitis with minimal cortical impairment

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Abstract Anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis has been recently identified as a fulminant encephalopathy, presenting with a variety of symptoms including behavioral change, amnesia and seizures suggesting cortical gray matter involvement. A 42-year-old woman presented with acute-onset clinical and magnetic resonance imaging (MRI) findings indicating brainstem and diencephalon involvement. Her neuropsychological examination revealed mild frontal dysfunction with no memory impairment. Detailed diagnostic workup proved negative except for serum/cerebrospinal fluid (CSF) NMDAR-antibodies and increased activity in inguinal and pelvic lymph nodes on positron-emission tomography (PET) examination. The symptoms and MRI findings completely resolved following steroid treatment. A 38-year-old woman presented with migraine-type headache and episodes of forgetfulness. Her brain MRI and neuropsychological examination were normal and diagnostic workup was unremarkable. *N*-methyl-D-aspartate receptor antibodies were identified in her sera and her symptoms spontaneously resolved within few months. Our cases suggest that anti-NMDAR encephalitis might present with minimal cognitive impairment, no apparent cortical gray matter involvement, a mild clinical course and without the classical clinical features of the disease.

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Dear Editors,

A severe and fulminant but treatable form of encephalitis associated with serum and/or cerebrospinal fluid (CSF) antibodies against NR1/NR2 heteromers of the *N*-methyl-D-aspartate receptor (NMDAR) has recently been identified. Anti-NMDAR encephalitis affects mostly females and is characterized by a well-defined set of clinical findings. Anti-NMDAR encephalitis is typically a multistage disorder. After a prodromal event, psychiatric symptoms develop, followed by amnesia or seizures, suggesting that cortical gray matter is preferentially affected. Subsequent subcortical involvement is observed in most patients leading to movement disorders, autonomic symptoms and brainstem findings [1–3].

A 42-year-old woman presented with frontal tension-type headache, fatigue, double vision and difficulty walking, which had steadily progressed over the previous 2 weeks. Neurological examination revealed severely limited upward vertical gaze that could be overcome with the doll's head maneuver, brisk deep-tendon reflexes in the legs and right extensor plantar response. Downward vertical gaze and horizontal gaze were intact. Pupils were equal and reactive. Although she did not report any memory or behavioral problems, her detailed neuropsychological examination revealed mild frontal dysfunction with no memory impairment (Table 1) and her Mini-Mental State Examination (MMSE) score was 27/30. Cerebrospinal fluid examination showed mild lymphocytic pleocytosis (18 leukocytes/μL), increased protein (52 mg/dl), normal glucose concentration and oligoclonal bands. Brain magnetic resonance imaging (MRI) T2/FLAIR sequences showed hyperintense lesions in

Table 1 A review of the neuropsychological test performances of the patients

	Case 1		Case 2
	First	Follow-up (2 months)	
Attention/concentration (digit span, mental control subtests of WMS-R)	Normal	Normal	Normal
Verbal memory (verbal memory processes test)	Normal	Normal	Normal
Visual memory (visual reproduction test of the WMS-R)	Normal	Normal	Normal
Executive functions (categorical verbal fluency, clock drawing, Stroop test)	Mildly impaired	Normal	Normal
Language and naming (Boston Naming Test)	Normal	Normal	Normal
Visuospatial functions (Benton Facial Recognition Test, clock drawing)	Normal	Normal	Normal

WMS-R Wecshler Memory Scale-Revised

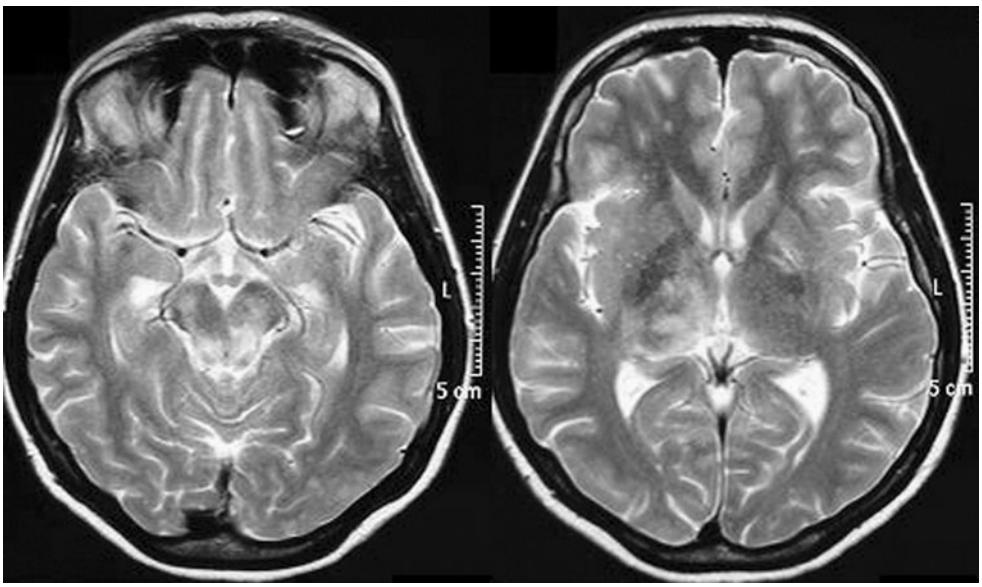

Fig. 1 Axial MR T2-weighted images of the brain show bilateral midbrain and right thalamic lesions

midbrain, thalamus (Fig. 1) and deep frontal white matter. Electroencephalography was normal. A comprehensive screening for infectious, metabolic and autoimmune vasculitic disorders was negative. Her serum and CSF were negative for Hu, Yo, Ri, Ma2, CV2, amphiphysin, glutamic acid decarboxylase, voltage-gated calcium channel and voltage-gated potassium channel antibodies. *N*-methyl-D-aspartate receptor antibodies were identified in serum and CSF samples using immunocytochemistry on HEK293 cells transfected with NR1 and NR2 subunits of NMDAR (Euroimmun, Lübeck, Germany). The antibody binding was visualized using a fluorescence microscope and both serum and CSF samples received a score of 3 [on a previously reported scale [2] from 0 (no binding) to 4 (very strong binding)] by two independent observers. The samples did not show any binding with non-transfected or aquaporin-4 transfected HEK293 cells (Euroimmun). An extensive oncologic workup, including total body computed tomography scan, tumor markers, pelvic ultrasonography, peripheral blood smear and mammography proved negative. Whole-body fluorodeoxyglucose-positron emission tomography (FDG-PET) showed increased FDG uptake in both inguinal and multiple pelvic lymph nodes, but no evidence of a tumor or altered metabolism in the central nervous system. An informed consent could not be obtained for biopsy of the inguinal lymph nodes. The patient remarkably responded to high-dose methylprednisolone (1,000 mg intravenously for 7 days) treatment and abnormal clinical, neuropsychological (Table 1) and MRI findings completely resolved in 2 months. The patient remains well with no treatment 26 months after initial symptom presentation.

This 38-year-old woman presented with complaints of migraine-type headache and episodes of forgetfulness that had started 2 months ago. The forgetfulness episodes occurred on a daily basis, did not appear to be associated with any precipitating factors such as sleep deprivation, depression or stress and mostly included difficulty finding words and people's names or remembering the location of personal

belongings. The neurological and a detailed neuropsychological examination did not yield any abnormal findings (Table 1) and her MMSE score was 29/30. Complete blood count, blood biochemistry tests, serum B12 and folate levels, thyroid function tests, sedimentation rate, brain MRI and electroencephalography examinations were all normal. During the screening of sera in the context of a research study, the patient's serum sample obtained during admission was found out to be positive for NMDAR-antibodies (with a score of 3). A second serum sample obtained during a follow-up visit 3 months after the first visit was also found to be NMDAR-antibody positive (with a score of 2) using NR1/NR2 subunit-transfected HEK293 cells (Euroimmun). None of the samples reacted with non-transfected or aquaporin-4 transfected HEK293 cells (Euroimmun). At that time, the patient reported that her complaints had subsided. The patient remains well with no symptoms or treatment 23 months after initial symptom presentation.

An additional home-made assay was utilized to confirm the antibody results. HEK293 cells were transfected with plasmids containing NR1 and NR2 subunits of the NMDAR. All cells were grown in the presence of 500 μM of ketamine after transfection. Transfected cells were then incubated with the sera (1:20) and the appropriate Alexa Fluor-secondary antibody (1:1,000), as described earlier [2]. The sera of herein presented patients and of six patients with typical clinical features of NMDAR encephalitis were found positive (with scores of 2–4), whereas sera of five voltage-gated potassium channel antibody-positive limbic encephalitis patients and eight healthy individuals did not show any reactivity with the NR1-/NR2-transfected cells. None of the samples reacted with non-transfected cells.

It has been postulated that the sequence of symptoms in anti-NMDAR encephalitis might be explained by preferential impairment of cortical gray matter neurons followed by the sequential involvement of subcortical neurons [2]. Patients presenting with only neuropsychiatric symptoms have been described, suggesting that the progression of disease might be restricted to the impairment of cortical neurons in some cases [2–4]. Alternatively, some NMDAR-antibody positive patients may display brainstem lesions or oculomotor findings such as inverse ocular bobbing, one-and-a-half syndrome and opsoclonus, suggesting that subcortical regions are preferentially involved [5, 6] or may present with milder or incomplete forms of the disorder [3]. However, in these variant forms, at least one of the classical components of the disease such as psychiatric symptoms, seizures or amnesia occur later during the course of the disease. Also these patients often develop cortical lesions [3, 5, 6]. By contrast, our patients presented with very minimal cognitive impairment and no clinical or MRI findings suggesting cortical involvement. As an exception, case 1 displayed mild frontal dysfunction, which could also be explained by deep frontal white matter involvement. A similar NMDAR-antibody positive patient with isolated hemidystonia, normal MRI and no cortical findings has recently been reported, corroborating the presence of the fruste forms of anti-NMDAR encephalitis that do not affect cortical functions [7].

Case 2 might represent another fruste form of anti-NMDAR encephalitis. Her headache might be a prodromal symptom often observed in anti-NMDAR encephalitis and episodes of forgetfulness might plausibly be associated with non-convulsive seizures that have also been described in association with NMDAR-antibodies [8]. Another intriguing finding was the increased FDG activity observed in the pelvic and inguinal lymph nodes of case 1; a similar case has been recently reported and lymph node and bone marrow aspiration biopsies have only shown reactive changes [9]. This finding might plausibly be explained by the fact that the anti-NMDAR immune response may trigger an exaggerated lymph node cell proliferation or a local inflammation in certain susceptible individuals.

In conclusion, our cases imply that anti-NMDAR encephalitis might present with minimal cognitive impairment, no apparent cortical gray matter involvement, a mild clinical course and without the classic clinical features of the disease, indicating that anti-NMDAR encephalitis is still an expanding concept.

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