Anti–NMDA Receptor Encephalitis Associated With Transient Cerebral Dyschromatopsia, Prosopagnosia, and Lack of Stereopsis

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Abstract: A 20-year-old woman suffered from anti–*N*-methyl-D-aspartate receptor (NMDAR) encephalitis and was treated with removal of an ovarian teratoma and retroperitoneal ganglioneuroma in addition to immunotherapy. She was incapable of face recognition, had difficulty with object recognition, and lacked color sensation and stereo perception during recovery. These symptoms were transient and completely resolved over 4 months. Our report documents additional aspects of visual impairment associated with anti-NMDAR encephalitis and suggests that the disease can lead to diffuse cerebral dysfunction including the cortical visual system.

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Anti–*N*-methyl-D-aspartate receptor (NMDAR) encephalitis is an autoimmune disorder characterized by the temporal progression of a variety of clinical features including psychiatric symptoms, seizures, movement disorders, reduced consciousness, central hypoventilation, and dysautonomia (1,2). Anti-NMDAR encephalitis was initially described as paraneoplastic syndrome affecting young women with ovarian teratomas (3). Subsequently, it has been observed in patients of all ages and both sexes, with or without teratomas (1,4). The concept of disease was established with the identification of antibodies against NMDAR (2,5). Since then, the characteristic clinical features have been defined (1,2). However, impairment of visual function associated with anti-NMDAR encephalitis has not been well described. We present a case of anti-NMDAR encephalitis displaying transient symptoms of dyschromatopsia, prosopagnosia, partially impaired visual object recognition, and dysfunction of stereopsis during the recovery period.

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CASE REPORT

A 20-year-old woman was admitted to hospital with generalized seizures that developed following headache, fever, memory disturbance, and psychosis. She had dyskinesia of her upper limbs, hypersialosis, and hypoventilation requiring sedation and intubation with ventilation. One month later, she was transferred to our institution. On admission, cerebrospinal fluid examination showed mild lymphocytic pleocytosis (11 cells mm^3) with a protein of 29 mg/dL (normal: 15–40 mg/dL), and a glucose of 74 mg/dL (normal: 50–70 mg/dL). Magnetic resonance imaging (MRI) of the brain only showed a small hyperintensity in the white matter close to the left insular gyrus (Fig. 1). Because the patient's clinical course was highly suspicious for anti-NMDAR encephalitis, she underwent screening for an ovarian tumor and began on high-dose methylprednisolone (1000 mg/d for 3 days). Abdominopelvic MRI, computed tomography, and transrectal ultrasound revealed a mass in the left ovary and retroperitoneal space. Two weeks later, antibodies against GluN1/GluN2 heteromers of the NMDAR were detected in the patient's serum and cerebrospinal fluid. No other anti–neuronal antibodies were found including anti-amphiphysin, anti-Yo, anti-Ri, anti-Hu, anti-Ma1, anti-Ma2 (Ta), or anti-recoverin.

The patient underwent removal of the ovarian and retroperitoneal tumors, which were, on pathological examination, mature cystic ovarian teratoma and retroperitoneal

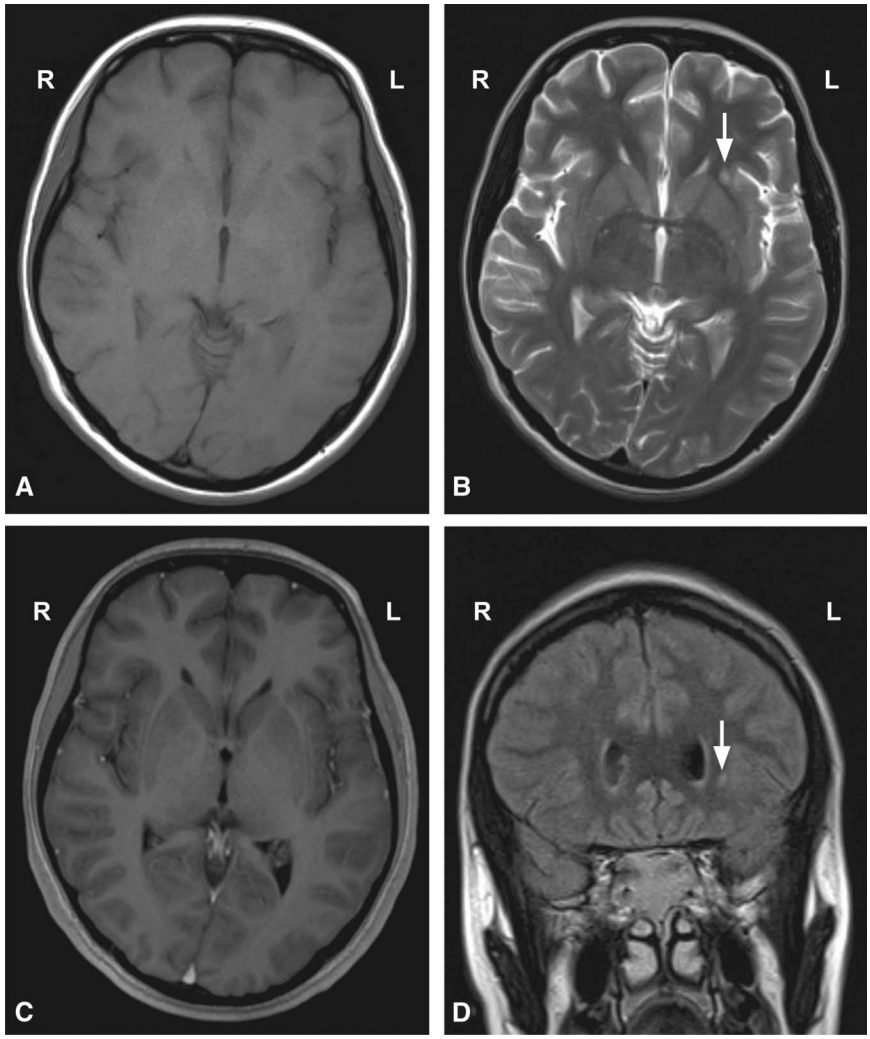

FIG. 1. Brain magnetic resonance imaging includes noncontrast axial T1 (**A**), T2 (**B**), postcontrast T1 (**C**), and coronal fluid-attenuated inversion recovery (FLAIR) (**D**) images. An area of increased signal (*arrows*) is present on the T2 (**B**) and FLAIR (**D**) scans.

ganglioneuroma, respectively. In addition, she received immunotherapy comprising high-dose methylprednisolone (1000 mg/d for 3 days; 3 courses), intravenous immunoglobulin, and cyclophosphamide (750 mg/m^2; 3 courses).

The patient's consciousness gradually improved, and she was weaned off the ventilator 15 weeks after admission. Upon awakening, she reported lack of color sensation, inability to recognize faces, and impairment of object recognition and stereo perception. The frontal assessment battery (FAB) and revised Hasegawa dementia scale (HDS-R) were performed. She scored 16/18 on the FAB and 26/30 on the HDS-R (normal >21/30 points). She also took the visual perception test for agnosia (VPTA). In this test, a score of 0 indicates 100% correct answers and full points indicate 100% incorrect answers. A score of more than 50% indicates severe impairment of the function examined. The VPTA demonstrated severely impaired object recognition by sight (score 13/16 vs 4/16 for object recognition by touch) and face recognition (score 16/16) in both naming familiar persons from photographs and pointing at photographs of familiar persons. The VPTA also demonstrated mild or severe impairment reading "kana" or "kanji" characters (scores 4/12 and 8/12, respectively) and describing the topography of familiar surroundings (score 2/2). The results of the visual search (scores 1/20), solid line bisection (1/6), and judgment of line orientation (0/6) tasks in the VPTA ranged from normal to slightly abnormal.

Initial neuro-ophthalmic testing revealed visual acuity of 20/125, right eye, and 20/50, left eye. Pupillary reaction, extraocular movements, and anterior and posterior segment examination were normal. In evaluating color perception using the Farnsworth dichotomous test (Panel D-15), the patient could not arrange the color stimuli; all test stimuli were recognized in a monochromatic fashion in both eyes (Fig. 2A). She also demonstrated difficulty in recognizing familiar objects by visual inspection alone, such as pens,

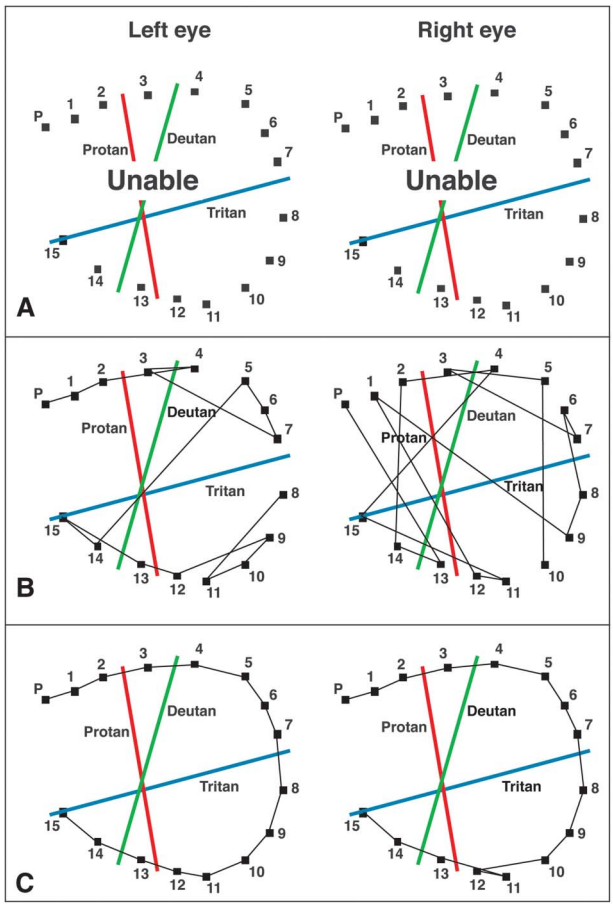

FIG. 2. Sequential results of Farnsworth dichotomous test (Panel D-15). **A**. Initially, this patient was unable to arrange the color stimuli in order. **B**. Four weeks later, the patient arranged the stimuli but random crossing occurred in both eyes. **C**. At 14 weeks, there are minor transpositional errors in the right eye with a perfect arrangement in the left eye.

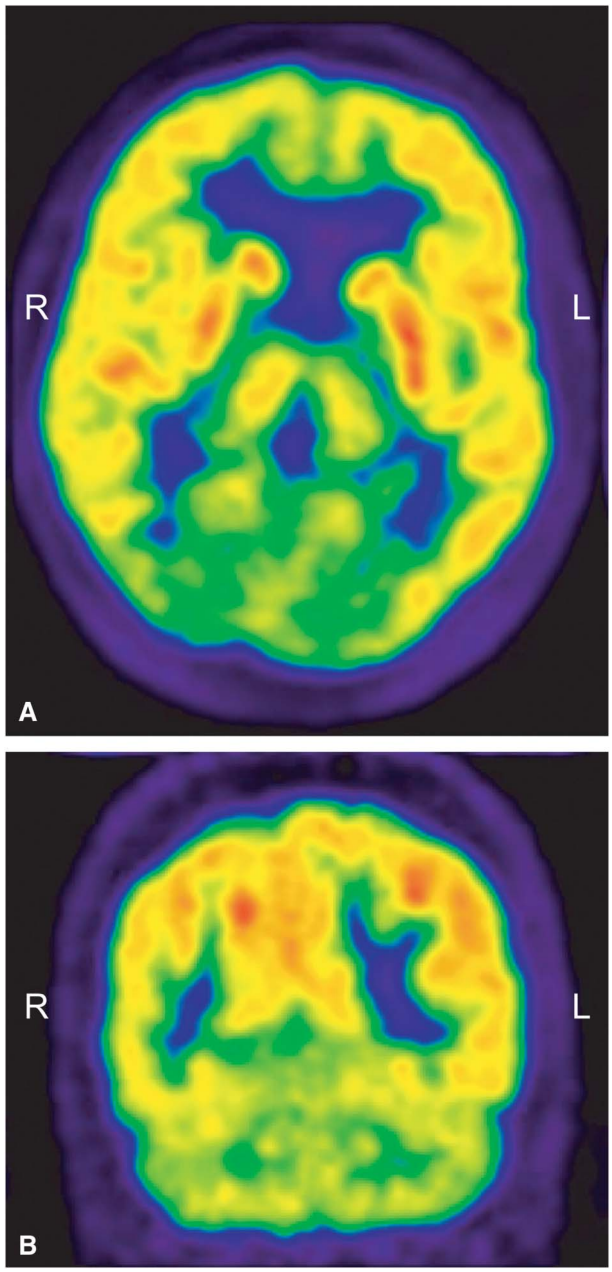

FIG. 3. Positron emission tomography with ^{18}F-fluoro-2-deoxy-D-glucose shows hypometabolism in the occipital cortex bilaterally on axial (**A**) and coronal (**B**) sections.

scissors, or bottles of eye drops. While follow-up brain MRI was unchanged, ^{18}F-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) revealed hypometabolism in both occipital lobes (Fig. 3).

Four weeks later, the patient's visual acuity was 20/25, right eye, and 20/20, left eye. Panel D-15 testing revealed random crossing in both eyes (Fig. 2B). The patient lacked all stereo perception with the Titmus stereo test and was still unable to recognize faces (VPTA score 12/16), even her family members. Voice recognition allowed her to recognize her family and distinguish men from women. The patient demonstrated partially impaired visual object recognition (VPTA score 7/16), but could recognize an object correctly when holding it in her hands (VPTA score 1/16). Kinetic perimetry revealed small paracentral scotomas in each eye, and optical coherence tomography (3D-OCT 2000; Topcon Corp., Tokyo, Japan) revealed no abnormal findings of the macula or optic nerve. Fourteen weeks after her referral to our institution, the patient's visual acuity was 20/20 in both eyes, and kinetic perimetry was normal. She could recognize colors, faces, and objects. Panel D-15 testing revealed a normal minor transpositional error in the right eye and normal perfect arrangement in the left eye (Fig. 2C). Titmus tests revealed that her stereo acuity had improved to 40 seconds of arc. VPTA results were in the normal range for object recognition, face recognition, reading, and describing topography. Over 1 year of follow-up, the patient has remained stable and brain MRI findings remained unchanged.

DISCUSSION

Anti-NMDAR encephalitis has characteristic clinical features of memory disturbance, psychiatric symptoms, seizures, involuntary movements, abnormal eye movements, central hypoventilation, and dysautonomia (1,2,6). Recent reports have suggested that the pathogenesis of anti-NMDAR encephalitis involves antibodies against the GluN1 subunit of the NMDAR, which deplete the NMDAR clusters on neurons, resulting in dysfunction of signal transmission mediated by glutamatergic synapses (1,2,7–10). Involvement of cortical or subcortical structures is postulated to cause specific clinical symptoms: memory disturbances, psychiatric symptoms, and seizures are likely due to dysfunction in the cortical frontal and/or temporal lobes (1,2,11,12), and involuntary movements and central hypoventilation due to dysfunction in the subcortical structures of the basal ganglia or brainstem (3,13,14).

Our patient demonstrated a variety of visual impairments. Color sensation, face recognition, object recognition, and stereopsis are higher-order visual functions in which information is processed in distinct regions of occipital, occipitotemporal, and occipitoparietal cortices and segregated dorsal and ventral streams (15–19). Damage to these cortical visual processing regions causes specific clinical findings depending on which part of the cortex is involved (20,21). For example, loss of stereopsis is caused by bilateral occipitoparietal lesions (21), while prosopagnosia and cerebral dyschromatopsia are caused by bilateral lesions of the fusiform gyri (16,21). Our patient may have developed complex visual impairments due to prolonged dysfunction of signal transmission in occipitotemporal and occipitoparietal cortices. PET revealed hypometabolism in both occipital lobes, a pattern previously reported in anti-NMDAR encephalitis (22). We postulate that the hypometabolic regions included the fusiform gyri bilaterally contributing to our patient's visual impairment. The white matter hyperintensity detected on MRI is unlikely a cause of visual dysfunction as it remained unchanged throughout the clinical course.

Kruer et al (23) described retrochiasmatic optic neuritis in a 15-year-old girl during a relapse of anti-NMDAR encephalitis. Because bilateral paracentral scotomas were observed on kinetic perimetry in our case, optic nerve involvement is conceivable. However, we did not detect a relative afferent pupillary defect, fundus changes, or signs of optic nerve abnormalities on MRI. The pattern of visual field loss is inconsistent with involvement of the lateral geniculate nucleus, which also appeared unremarkable on MRI. The cause of the visual impairments in our patient was ascribed to dysfunction of the cerebral visual system. The possibilities of anoxia and nonconvulsive seizures are unlikely because the patient had no episodes of severe hypoxemia, no cortical laminar necrosis or edema in the white matter on MRI, no epileptiform discharges on electroencephalography, and no focal hyper- or hypometabolism revealed by PET.

Tumor removal and immunotherapy are proposed treatments for anti-NMDAR encephalitis in patients with neoplastic disease (2,23). Early tumor removal results in a better clinical outcome (2,11), especially within 4 months of the appearance of neurological symptoms (1). In our case, removal of the ovarian teratoma and retroperitoneal ganglioneuroma was performed within 2 months of symptoms onset. In patients that lack response to first-line therapy or failure to detect a tumor, additional management options include rituximab (2,24,25).

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