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ANTI-NMDA RECEPTOR ENCEPHALITIS ASSOCIATED WITH ATRIAL FIBRILLATION AND HEARING LOSS

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Case report. A 65-year-old man presented with left-sided weakness and right gaze deviation. He complained of left-sided chest pain, headache, lightheadedness, and diplopia. Five weeks prior to presentation he had a brief febrile illness with cough, vomiting, diarrhea, episodes of unresponsiveness, confusion, progressive hearing loss, and weight loss of 30 lb. Six days prior to presentation he had a syncopal event at home and was diagnosed with atrial fibrillation. His rhythm converted to sinus spontaneously, and the echocardiogram was normal. MRI of the brain was normal. Two days after discharge he returned to the Veterans Administration hospital with fever, chills, dizziness, worsening confusion, and staring episodes. Examination revealed orthostatic hypotension and mild difficulty with concentration but no focal neurologic deficits. Correction of hyponatremia (serum sodium of 127 mEq/L) cleared the confusion and he was discharged home.

Two days later he was agitated and perseverative but was able to follow simple commands. He had right-sided gaze deviation, weakness of the left upper and lower extremities, and left-sided sensory neglect. MRI of the brain revealed no evidence of stroke, and an angiogram of the chest was negative for aortic dissection. CSF analysis revealed a glucose concentration of 38 mg/dL (CSF: serum glucose ratio of 0.4), protein of 127 mg/dL, white blood cell count of 84/mm³ (95% lymphocytes), and red blood cell count of 2,535/mm³. Thyroid screening tests were normal (table). Repeat CSF analysis 4 days later revealed similar results and a negative viral panel (table). Serum paraneoplastic antibodies were normal (table), while serum immunoglobulin G antibodies to *Mycoplasma pneumonia* were significantly elevated at 606 U/mL (normal < 99). Serum screening tests for lupus, vasculitis, Sjögren syndrome, HIV, Lyme disease, and sarcoidosis were normal (table). CT scans of abdomen and pelvis were negative for malignancy. Notably, he had recalcitrant orthostatic hypotension requiring treatment with sodium chloride tablets. He received a short course of IV antibiotics for suspected viral meningitis and his mental status improved. He was discharged.

Two weeks later he developed intermittent left facial twitching with alteration of awareness and was started on levetiracetam with complete resolution of symptoms. An outpatient EEG was normal.

One month after discharge he was readmitted to our hospital with diplopia, gait instability, headaches, and vomiting. He had lost 50 lb since the beginning of his illness. A third MRI of the brain with contrast was normal and CSF analysis again showed mild elevation of protein (63 mg/dL) and a lymphocytic pleocytosis (22 white blood cells/mm³). Repeated selective serum paraneoplastic antibody assays and a paraneoplastic CSF panel were unrevealing. CSF was found to be positive for anti-NMDA receptor (NMDAR) antibodies but negative for other receptor autoantibodies (table). The patient was treated with a 5-day course of IV methylprednisolone (1,000 mg/day) with significant improvement of diplopia and headaches.

Four months after his last discharge, the patient complained of fatigue, memory deficits, recurrence of diplopia, and unsteadiness of gait. The examination revealed behavioral disinhibition, bilateral sensorineural hearing loss, and a slightly ataxic gait. He was started on oral prednisone but could not tolerate it due to psychomotor overstimulation. He was switched to IV immunoglobulin (IVIg) and received 0.4 mg/kg/day for 5 days. This treatment initially led to marked improvement of most symptoms, but 2 months later he developed debilitating fatigue, irritability, and blurry vision. He received another 5-day course of IVIg, but his symptoms failed to improve within 4 weeks. Seven months after his initial diagnosis he was started on a rituximab protocol (375 mg/m²/day), which he tolerated well. His current modified Rankin scale score is 2.

Discussion. We describe an unusual presentation of anti-NMDAR encephalitis associated with atrial fibrillation in a patient with no prior history of cardiovascular disease. The incidence of rhythm disturbances in anti-NMDAR encephalitis is high and varies from 30% to 90% in different case series reports.^{1–3} Most patients demonstrate sinus tachycardia with or without intermittent episodes of bradycardia, or independent sinus bradycardia,³ sometimes leading to sinus arrest and atrioventricular block; telemetry recordings support a vagal etiology.^{3–5} To our knowledge, atrial fibrillation has not been previously

Table Normal laboratory test results

Laboratory tests	Specific assays
Viral studies, CSF	Enterovirus, adenovirus, cytomegalovirus, herpes simplex 1 and 2, human herpes virus 6, Epstein-Barr virus, varicella-zoster virus, West Nile virus, JC virus
Paraneoplastic autoantibody studies, serum	Anti-neuronal nuclear antibody 1, 2, and 3, anti-glial nuclear antibody 1, Purkinje cell cytoplasmic antibody 1, 2, and Tr, amphiphysin antibodies, CRMP5 antibodies, striational antibodies, P/Q voltage-gated calcium channel antibodies, N-type calcium channel antibodies, ACh binding receptor antibodies, ACh antiganglioside antibodies, neuronal voltage-gated potassium channel antibodies, GAD-65 antibodies
Paraneoplastic autoantibody studies, CSF	Anti-neuronal nuclear antibody 1, 2, and 3, anti-glial nuclear antibody 1, Purkinje cell cytoplasmic antibody 1, 2, and Tr, amphiphysin antibodies, CRMP5 antibodies
Receptor autoantibodies, CSF and serum	AMPA, GABA _B , CASPR2, LGI1, mGluR1, mGluR5 receptor antibodies
Autoimmune disease, serum	Antinuclear antibodies, rheumatoid factor, anti-double-stranded DNA antibodies, anti-SSA and anti-SSB antibodies, cytoplasmic antineutrophil cytoplasmic antibodies, perinuclear anti-neutrophil cytoplasmic antibodies, atypical antineutrophil cytoplasmic antibodies, ganglioside GQ1b autoantibodies, angiotensin-converting enzyme
Infectious disease, serum	HIV-1 p24 antigen, HIV-1/HIV-2 antibodies, Lyme C6 antibodies
Thyroid disease, serum	Thyroid-stimulating hormone, free T4

reported in association with anti-NMDAR encephalitis. Sinus tachycardia is thought to be centrally mediated and to involve the loss of NMDAR-mediated augmentation of parasympathetic signaling in the brainstem vagal nuclei.³ Atrial fibrillation, which could also be vagally mediated in our patient,⁶ has not recurred. It remains unclear at this time whether his atrial fibrillation was coincidental to or part of an anti-NMDAR syndrome.

The other unusual feature of our patient's disease was progressive bilateral asymmetrical sensorineural hearing loss, which occurred within the first month of his symptoms. Once considered an immunoprivileged site, the inner ear is currently a well-recognized target of immune responses in various autoimmune diseases.⁷ Sensorineural hearing loss has been described in several rheumatologic conditions⁸ and paraneoplastic syndromes⁹; however, no such association has been described with anti-NMDAR encephalitis. NMDARs expressed in the inner ear¹⁰ could be a target for autoantibodies in encephalitis. Other manifestations of autoimmune inner ear dysfunction include vestibular symptoms, tinnitus, and aural fullness, which develop in up to 50% of patients^{7,8} but were not present in our patient. Notably, the immune-mediated hearing loss improves with immunosuppressive therapy (i.e., steroids, cytotoxic drugs) and plasmapheresis^{7,8}; however, this was not the case in our patient.

In summary, we present a 65-year-old male with anti-NMDA receptor encephalitis associated with atrial fibrillation and sensorineural hearing loss, possibly mediated by autoimmune mechanisms.

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