Podcast

NMDA receptor encephalitis causing reversible caudate changes on MRI and PET imaging

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Practical Implications

NMDA receptor (NMDAR) antibodies may cause reversible caudate MRI and PET brain abnormalities associated with a restricted phenotype of NMDAR encephalitis.

Since the original description of the classic phenotype of memory deficits, psychiatric symptoms, decreased consciousness, and hypoventilation was described in association with NMDAR antibodies, the phenotype of NMDAR encephalitis has expanded to include patients with a pure psychiatric presentation, insomnia, isolated dystonia, paroxysmal limb weakness, and eye movement abnormalities.[1] Despite prominent dystonia and dyskinesias, reversible basal ganglia abnormalities on structural MRI and FDG-PET have not been reported to date, even in patients with isolated hemidystonia.[2]

Case report

A 21-year-old man presented with episodic anxiety, palpitations, diaphoresis, diarrhea, weight loss, and tinnitus of 1 month's duration. Over the next month, he developed bradykinesia, bilateral arm numbness, inappropriate laughter, psychosis, cognitive impairment, an exaggerated response to alcohol, and dysarthria. Spinal fluid analysis revealed 12 leukocytes per microliter (86% lymphocytes) and mildly elevated protein. Brain MRI 4 months after symptom onset demonstrated T2 fluid-attenuated inversion recovery high signal involving medial temporal lobes, caudate heads and bodies, and lentiform nuclei (figure, B). FDG-PET/CT scan demonstrated absent metabolism in the basal ganglia bilaterally, with otherwise normal brain activity (figure, A). No malignancy or tumor was found on whole-body FDG-PET/CT or testicular ultrasound.

Testing for the NMDAR antibody was positive in serum and spinal fluid using a transfected HEK293 cell-binding assay (Euroimmun, Lübeck, Germany; each sample scored positive or negative by 3 experienced readers). The patient's serum and CSF underwent comprehensive neural antibody evaluation with a standardized indirect immunofluorescence assay on a composite substrate of mouse cerebellum, midbrain, basal ganglia, thalamus, cerebral cortex, hippocampus, stomach, and kidney to detect immunoglobulin G (IgG) autoantibodies binding selectively to

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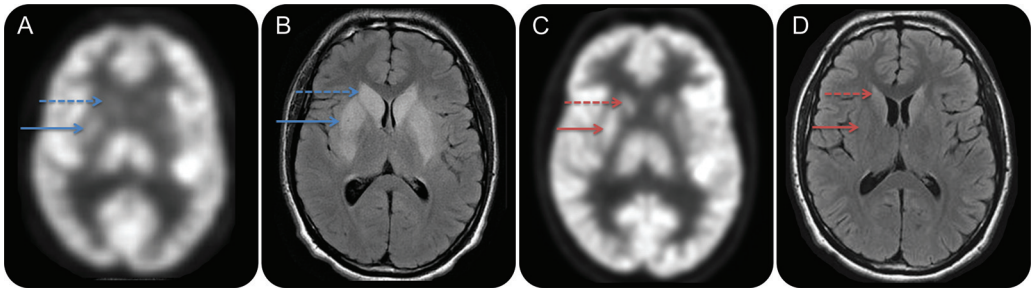
Figure Imaging



PET demonstrates hypometabolism in the caudate heads (dashed arrow) and lentiform nuclei (solid arrow) prior to treatment (A) and following 3 months of treatment with IV steroids and immunoglobulin (C). Brain MRI demonstrates T2 fluid-attenuated inversion recovery high signal in the caudate head (dashed arrow) and lentiform nuclei (solid arrow) prior to treatment (B) and following 3 months of treatment with IV steroids and immunoglobulin (D).

neuronal and glial nuclei (antineuronal nuclear antibodies, type 1 [anti-Hu], type 2 [anti-Ri], and type 3; antiglial/neuronal nuclear antibody, type 1 [AGNA or SOX 1 antibody]), neuronal cytoplasm (Purkinje cell antibodies [types 1 (anti Yo), 2, and -Tr], collapsin response–mediator protein 5-IgG and amphiphysin-IgG), or hippocampal and basal ganglionic synapses.

Antibodies reactive with neural cation channel complexes (neuronal voltage-gated calcium channels [P/Q type and N type], voltage-gated potassium channel complexes, nicotinic acetylcholine receptors of skeletal muscle type [α1 subunit] and neuronal ganglionic type [α3 subunit]) and glutamic acid decarboxylase 65 kDa isoform (GAD65) were sought using a radioimmunoprecipitation assay. Skeletal muscle striational antibodies were tested by ELISA. IgGs targeting other specific neurotransmitter receptors in hippocampal synapses (AMPA [GluA1 and GluA2] and GABA-B) were also sought by indirect immunofluorescence on HEK293 cells transfected with appropriate cDNAs (Euroimmun). The only other neural antibody detected was GAD65 antibody level at 0.03 nmol/L (normal range <0.02 nmol/L) in spinal fluid. No other antibody was detected.

Speech assessment demonstrated a mixed dysarthria, with primarily hypokinetic features as well as spastic/dystonic features (video 1 at Neurology.org/cp). The patient was treated with IV steroids, 1 g daily for 3 consecutive days, then once weekly for 5 weeks, followed by once every 2 weeks for 6 weeks. IV immunoglobulin was given concurrently at a dose of 0.4 g/kg daily for 3 days followed by 0.4 g/kg every week for 6 weeks and then every 2 weeks for 6 weeks. At the same time, he received mycophenolate 500 mg twice daily, increasing after 2 weeks to 1,000 mg twice daily.

Video
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Three months after commencing treatment, neuroimaging abnormalities had almost completely resolved (figure, C and D). Examination revealed a residual action dystonia in the patient's right hand, with associated mild bradykinesia. Neuropsychometric and speech testing were normal (video 2).

DISCUSSION

This is the first reported case of reversible caudate MRI and PET abnormalities in a patient with NMDAR antibody–associated encephalitis. A patient with isolated generalized dystonia, caudate MRI abnormalities, and NMDAR antibodies has been described previously,[3] although reversibility was not demonstrated despite treatment. Our patient had some unusual features including tinnitus and an exaggerated response to alcohol. His speech abnormalities were presumably caused by basal ganglia dysfunction, as evidenced by complete resolution in tandem with resolution of MRI changes. The patient's action dystonia correlated with a residual area of reduced metabolism on FDG-PET imaging, supporting a functional correlation. Brain MRI abnormalities are typically subtle or absent in patients with NMDAR

encephalitis.[4] In the largest case series of patients with NMDAR encephalitis, 5 out of 100 patients had basal ganglia abnormalities on brain MRI.[4] Other areas where MRI abnormalities have been described include the medial temporal lobe; frontal, parietal, and occipital lobe cortex; and cerebellar cortex.[4–6] FDG-PET global hypometabolism and cerebellar hypermetabolism, which subsequently became hypometabolic, has been reported in a 15-year-old boy with NMDAR encephalitis.[7] Advanced imaging techniques have demonstrated alterations of functional connectivity in patients with normal standard MRIs of the brain.[8] Orofacial dyskinesias, along with "piano playing" movements of the hands, are frequent, and isolated hemidystonia has been described, in the absence of MRI abnormalities.[2] The current case may represent the extreme end of a spectrum of basal ganglia abnormalities in this condition, and lends support to the theory of neuronal dysfunction, in the absence of neuronal destruction in the condition.

The patient demonstrated a dramatic recovery, typical of NMDAR encephalitis, despite moderately severe deficits prior to immunomodulatory treatment. The NMDAR antibody is directed against a cell surface antigen and is associated with a reduction in cell surface and synaptic NMDAR density[9] and is thought to be pathogenic, in contrast to antibodies directed against intracellular antigens.[9] In contrast to antibody-mediated inflammatory diseases such as neuromyelitis optica, binding of NMDAR antibodies does not lead to complement activation.[9] This may protect from neuronal death and allow a full recovery if treated appropriately, despite significant apparent structural changes in this case.

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