Clinical/Scientific Notes

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ANTI-DPPX ENCEPHALITIS: PROMINENT NYSTAGMUS REFLECTED BY EXTRAOCULAR MUSCLE FDG-PET AVIDITY

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A 43-year-old Caucasian man developed persistent nystagmus after 10 months of weight loss, diarrhea, insomnia, and 5 months of agitation, memory impairment, and vision changes consisting of nystagmus and double vision. Ocular motor examination demonstrated left-beating nystagmus (LBN), upbeating nystagmus (UBN), and torsional (toward the left ear) nystagmus components (video at Neurology.org/nn), as well as a left hypertropia from a skew deviation. There was also gaze-evoked nystagmus (GEN) horizontally. General neurologic examination revealed postural tremor in his arms, brisk reflexes, mild dysmetria with finger to nose, and wide-based gait. Detailed neurocognitive testing demonstrated deficits in recall and attention. He had previously been healthy, and his family history was notable only for multiple sclerosis in his brother. Brain MRI showed no abnormalities, and CSF studies showed elevated protein. A broad screen for infections, toxins, and systemic autoimmune disorders was negative. Peripheral blood cell counts were normal. Whole-body 18-fluoro-deoxyglucose PET (^{18}FDG-PET-CT) did not reveal a malignancy, but showed asymmetric avidity of the extraocular muscles (figure). Testing for neuronal autoantibodies revealed a serum dipeptidyl-peptidase-like protein-6 (DPPX) antibody IgG titer of 1:15,360 (Neuroimmunology Laboratory, Mayo Clinic), providing evidence for immune-mediated encephalitis. DPPX antibody from CSF was not tested because of inadequate sample quantity before the initiation of treatment.

He was treated with IV methylprednisolone, plasma exchange, and rituximab, with improvement in hyperreflexia, gait, memory, sleep, mood, and appetite. His nystagmus and skew deviation also improved markedly (video). The UB-torsional nystagmus (which had an LBN component) seen at presentation was believed to result mainly from either semicircular canal (SCC) pathway imbalance at the level of the medulla or, in light of the skew deviation, disruption of the utricle-ocular motor pathways. In support of the latter, in follow-up months later, spontaneous downbeat nystagmus (DBN) was seen, and it was noted that changes in head orientation relative to gravity (head tilt and supine position) transitioned his DBN to UBN, a feature that can be seen with utricle pathway damage.[1] Overall, in our patient's case, ocular motor signs would be best explained by involvement of the perihypoglossal nuclei (UBN and GEN), paramedian tract cell groups, or their connections with the vestibulocerebellum (DBN), and vestibular nuclei (causing SCC and utricle imbalance, right more than left-sided dysfunction given skew deviation with left hypertropia and LBN).

DPPX, a recently recognized neuronal surface autoantigen, is a regulatory subunit of the voltage-gated Kv4.2 potassium channel complex expressed on neuronal dendrites and soma, dysfunction of which may result in neuronal hyperexcitability.[2–4] Kv4.2 channels and DPPX proteins are distributed throughout the nervous and enteric systems, including the cortex, cerebellum, brainstem, and myenteric and submucous plexus.[2,3,5] The widespread expression of DPPX is believed to underlie the broad manifestations of anti–DPPX-associated disease, including neurocognitive deficits, sleep disturbance, central hyperexcitability, and diarrhea. The majority of patients described have gastrointestinal symptoms, including diarrhea, constipation, and weight loss, and these symptoms as well as neurologic symptoms may present insidiously, thus making diagnosis challenging. Eye movement disturbances are common. Of 20 seropositive anti-DPPX patients, diplopia, oscillopsia, or blurred vision was reported in 8 patients, with one case of upbeat-torsional nystagmus.[3] Additional described visual disturbances include saccadic pursuit gaze movements in all directions; spontaneous downbeat and gaze-evoked nystagmus, broken pursuit, and incomplete suppression of vestibulo-ocular reflex on fixation; and broken pursuit and GEN with diplopia on lateral gaze.[3,6] Cerebellar and pontine targets by autoantibodies resulting in CNS hyperexcitability may underlie these ocular manifestations.

Although FDG-PET is often used to assess malignancy in patients with autoimmune encephalitis, may demonstrate abnormalities in brain metabolism, and has been reported to reflect muscle hyperactivity in

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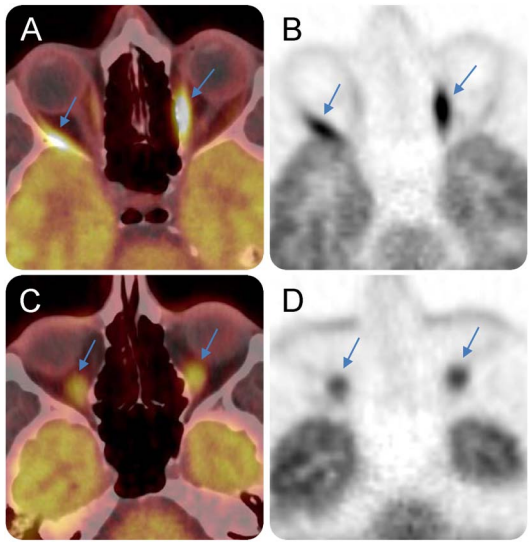
Figure F18-FDG-PET/CT



F18-FDG-PET/CT demonstrates normal size of extraocular muscles but markedly asymmetric increased FDG activity localizing to the left medial rectus and right lateral rectus (A and B, arrows), and inferior recti bilaterally (C and D, arrows).

other autoimmune neurologic conditions, little is known of PET findings in anti-DPPX encephalitis.[6] The FDG-PET in our case did not show evidence of malignancy, but did demonstrate asymmetric metabolism in extraocular muscles correlating with the slow (pathologic) phases of nystagmus. In particular, FDG-PET showed increased FDG activity in the left medial rectus, right lateral rectus, and bilateral inferior recti, correlating with the slow phases of his horizontal (LB) and vertical (UB) nystagmus, respectively. Although FDG-PET correlates of nystagmus have not been previously characterized, increased avidity of bilateral medial recti has been reported in a case of convergence spasm due to brain tumor.[7]

Overall, our case highlights the prominent eye movement abnormalities that can occur in the setting of anti-DPPX encephalitis, points to specific pontine and medullary nuclei that may be impacted, and highlights that FDG-PET can demonstrate correlates of nystagmus in this disease.

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