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## PEDIATRIC ANTI-HU-ASSOCIATED ENCEPHALITIS WITH CLINICAL FEATURES OF RASMUSSEN ENCEPHALITIS

### OPEN

Anti-Hu antibodies (anti-neuronal nuclear antibodies, type 1) are associated with paraneoplastic encephalomyelitis in adults, especially those with small cell lung cancer. Anti-Hu antibodies are extremely rare in children, but they have been observed in neuroblastoma with or without opsoclonus-myoclonus syndrome or in limbic encephalitis without associated malignancy.<sup>1</sup> However, anti-Hu antibodies are not typically associated with clinical features of Rasmussen encephalitis (RE).

**Case history.** We present a 5-year-old right-handed girl meeting clinical, EEG, and MRI diagnostic criteria for RE<sup>2</sup> but with elevated serum and CSF anti-Hu antibodies. She was asymptomatic until age 4, when she developed simple partial seizures with right face and arm clonic movements without epilepsy partialis continua (EPC). She then developed right lower facial weakness, dysarthria, and stagnation in cognition and learning. EEG showed left hemispheric slowing and left frontotemporal focal seizures. Serial MRIs showed progressive left-greater-than-right hemispheric atrophy and left frontal, temporal, insular and caudate greater than right frontal and temporal T2 signal hyperintensity (figure). She had no personality changes, ataxia, opsoclonus, movement disorders, dysautonomia, neuropathy, or myopathy.

Diagnostic evaluation 1 year after symptom onset included serum and CSF inflammatory markers and antibodies (including anti-glutamic acid decarboxylase, anti-NMDA receptor, anti-contactin-associated protein 2, and anti-leucine-rich glioma-inactivated 1 protein). Results were notable for elevated anti-Hu antibody titers (Mayo Clinic Paraneoplastic Antibody Panel immunofluorescence assay<sup>3</sup>) in serum (1:960, normal <1:240) and CSF (1:16, normal <1:2), 13 CSF oligoclonal bands, and CSF neopterin of 67 nmol/L (normal 7–40 nmol/L) without significant pleocytosis (2 white and 0 red blood cells per mm<sup>3</sup>) or high titers of other anti-neuronal antibodies. Serum striational

antibody titer was 1:3,840 (normal <1:120) with normal anti-acetylcholine receptor (AChR) antibody and normal collapsin response-mediator protein 5 immunoglobulin (CRMP-5-IgG). Serum thyroperoxidase (TPO) antibody was 15.6 IU/mL (normal <15 IU/mL) with normal thyroid function. Head magnetic resonance angiogram and malignancy workup including whole-body MRI, urine homovanillic acid, and urine vanillylmandelic acid were unremarkable.

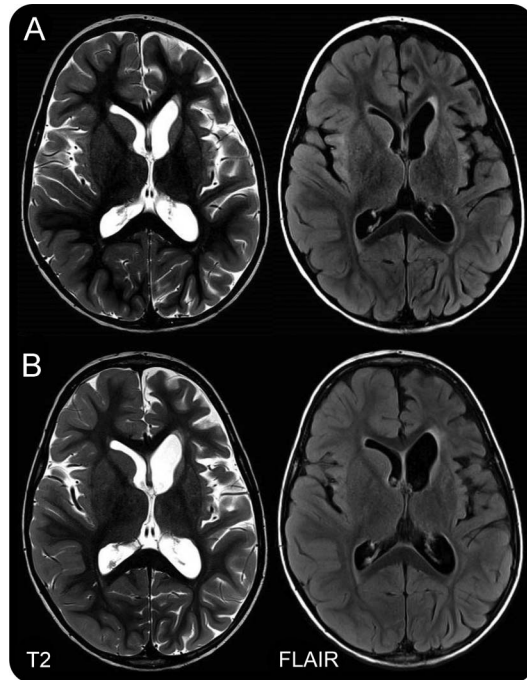
Treatment has included 3 courses of methylprednisolone 30 mg/kg/mo, 7 courses of cyclophosphamide 750 mg/m<sup>2</sup>/mo, and maintenance immunotherapy with mycophenolate mofetil 600 mg/m<sup>2</sup>/d. Eleven months after her diagnosis, her seizure frequency has improved from once daily to once weekly on levetiracetam and lacosamide, her right facial weakness has resolved, and her mother notes improvement in school performance.

**Discussion.** We describe a novel presentation of anti-Hu–associated encephalitis with features of RE.<sup>2</sup> Cases of anti-Hu–associated EPC have been reported with focal cortical lesions but without hemispheric atrophy or other RE features.<sup>4–6</sup> Notably, our patient has no malignancy, opsoclonus-myoclonus, or limbic encephalitis, which are typically seen in pediatric anti-Hu–associated encephalitis.<sup>1</sup>

Anti-Hu antibodies are not thought to be directly toxic but have been associated with the presence of Hu-specific T cells.<sup>1</sup> This could direct T cell–mediated cytotoxicity considered to be a pathophysiologic mechanism of RE.<sup>2</sup> Anti-Hu–associated encephalitis, as in our patient, is most commonly treated with IV immunoglobulins, cyclophosphamide, and/or methylprednisolone. Since both anti-Hu–associated encephalitis and RE involve T cell–mediated cytotoxicity, T cell–directed treatments may be particularly useful. Furthermore, as anti-Hu–associated cytotoxicity could further affect her contralateral hemisphere, hemispherectomy alone may not be sufficient to control her seizures and may not be curative.

Our patient has predominantly unilateral hemispheric atrophy, but she also has mild contralateral atrophy and T2 hyperintensity. Diffuse cerebral

**Figure** Progressive unilaterally predominant brain atrophy



Brain MRI with predominantly left-greater-than-right hemispheric atrophy and T2 hyperintensity involving the caudate that has progressed between 2 months (A) and 10 months (B) after seizure onset. FLAIR = fluid-attenuated inversion recovery.

damage may be due to the fact that Hu antigens are expressed by all neurons.<sup>1</sup> The pathophysiology underlying unilaterally predominant atrophy is unclear given that Hu antigens are ubiquitously expressed. In a previous case of anti-Hu encephalitis, Hu antigen neuronal expression variability was hypothesized to underlie focal pathologic features.<sup>4</sup>

In addition to high anti-Hu titers, our patient also had mild elevation of 2 other autoantibodies, as has been noted previously.<sup>3</sup> Anti-TPO levels in Hashimoto thyroiditis and encephalopathy are >100–1,000 IU/mL. An anti-TPO level of 15.6 is likely not pathogenic. Anti-striated muscle antibodies are classically elevated in thymoma-associated myasthenia, although they are nonspecific and may be a generic marker of autoimmunity. Absence of myasthenic features and normal anti-AChR antibody and CRMP-5-IgG make thymoma-associated myasthenia unlikely.<sup>7</sup> Anti-Hu antibodies may also be a nonspecific inflammatory marker. Noting the difficulty of comparing titers across labs, our patient's serum anti-Hu titer is lower than in previous pediatric cases (>1:10,000), but it is still 4 times the upper normal limit.<sup>1</sup>

This case provides insights into the anti-Hu-associated neurologic disorder spectrum. New-onset

refractory focal seizures or focal cerebral atrophy, including RE, could be a presentation of anti-Hu-associated encephalitis. Thorough evaluations for autoimmune etiologies should be strongly considered, especially because this could potentially guide treatment.

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