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Treatment-Refractory Autoimmune Glial Fibrillary Acidic Protein Meningoencephalomyelitis in a Young Adult Female

Janetta Arellano, Michael Sy

Objective

To describe a case of autoimmune glial fibrillary acidic protein (GFAP) astrocytopathy refractory to immunotherapy without evidence of malignancy or coexisting autoimmunity.

Background

Autoimmune GFAP astrocytopathy is an autoimmune disease of the central nervous system associated with the presence of GFAP-IgG in the CSF. Patients may present with acute or subacute onset of headache, encephalopathy, seizures, abnormal vision, weakness or numbness, postural tremor and cerebellar ataxia. GFAP astrocytopathy is usually corticocorticosteroid-responsive in the acute setting but may rarely require maintenance immunotherapy to prevent relapse. Treatment refractory cases should trigger work up for coexisting autoimmunity or malignancy.

Design/Methods

A 35-year-old female patient presented with subacute meningoencephalomyelitis with prodromal symptoms.

Results

Her cerebrospinal fluid revealed lymphocytic pleocytosis and elevated protein. Brain magnetic resonance imaging (MRI) with and without contrast showed perivascular radial enhancement and periventricular T2 FLAIR hyperintensity. Spinal MRI with and without contrast demonstrated longitudinal T2 FLAIR hyperintensity from T1-T2 to T7-T8. Despite high dose steroid treatment, her disease progressed with an enlarging periventricular lesion and worsening visual acuity. Biopsy of the enhancing periventricular lesion showed perivascular inflammation. After five cycles of plasma exchange along with a five-day course of intravenous methylprednisolone 1 gram daily, her symptoms stabilized. The CSF autoimmune encephalopathy panel (Mayo Clinic Laboratories) came back positive for GFAP-IgG antibody on tissue immunofluorescence assay, and was confirmed positive by GFAP cell-based assay. No neoplastic disease was identified using high resolution PET/CT scans. Based on the aggressiveness of her disease, she received one cycle of cyclophosphamide, and was discharged home on an oral corticosteroid taper. Even one year after addition of both mycophenolate mofetil and rituximab, MRI imaging continued to reveal new enhancing lesions.

Conclusions

Autoimmune GFAP astrocytopathy may sometimes require long-term immunosuppression even without presence of malignancy or other coexisting autoimmune disease.

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Autoimmune Encephalitis Misdiagnosis in Adults; A Multicenter Observational Study of Outpatient Subspecialty Clinics

Michael Geschwind, A. Sebastian Lopez-Chiriboga, Kyle Blackburn, Sanchit Turaga, Sophie Binks, Jennifer Zitser, Jeffrey Gelfand, Gregory Day, Steven Dunham, Stefanie Rodenbeck, Stacey Clardy, Andrew Solomon, Sean Pittock, Andrew McKeon, Divyanshu Dubey, Anastasia Zekeridou, Michel Toledano, Lindsey Turner, Steven Vernino, Sarosh Irani, Eoin Flanagan

Objective

To determine the diseases misdiagnosed as AE and potential reasons for misdiagnosis.

Background

Misdiagnosis of autoimmune encephalitis (AE) may harm patients.

Design/Methods

Patients with AE misdiagnosis were identified (1/1/2014-12/31/2020) from outpatient AE subspecialty clinics including: Mayo Clinic (n = 44); Oxford (n = 18); UT Southwestern (n = 18); UCSF (n = 17); Washington University (n = 6); University of Utah (n = 4). Inclusion criteria were adults (=18 years) with: 1) A prior diagnosis of AE; and 2) An alternative diagnosis made at a participating center. We collected data on clinical features, investigations, fulfillment of possible AE criteria, alternative diagnoses, and potential contributors to misdiagnosis.

Results

We identified 107 patients misdiagnosed with AE. Thirty (28%) fulfilled diagnostic criteria for "possible AE". Median onset age was 48 years (inter-quartile range, 35.5-60.5) and 65 (61%) were female. Correct diagnoses included: functional neurologic disorder, 27 (25%); neurodegenerative disease, 22 (21%); primary psychiatric disease, 19 (18%); cognitive deficits from comorbidities, 11 (10%); cerebral neoplasm, 10 (9%); and other, 18 (17%). Onset was insidious (>3 months) in 51 (48%). MRI brain was suggestive of encephalitis in 19/104 (18%) and CSF pleocytosis occurred in 16/84 (19%). Thyroid-peroxidase antibodies were elevated in 24/62 (39%). Positive neural autoantibodies were more frequent in serum (48/105[46%]) than CSF (7/91[8%]; p<0.001) and serum antibodies included: GAD65, 14; voltage-gated-potassium-channel-complex [LGI1, CASPR2 negative], 10; NMDA-receptor by cell-based assay only, 10 (6 negative in CSF); and other, 18. Immunotherapy adverse effects were observed in 17/84 (20%). Potential contributors to misdiagnosis included: over-interpretation of a non-specific positive serum antibody, 53 (50%); misinterpretation of functional, psychiatric, or non-specific cognitive dysfunction as encephalopathy, 41 (38%).

Conclusions

Red flags suggesting alternative diagnoses to AE include lack of fulfillment of "possible autoimmune encephalitis" criteria, positive non-specific serum antibody, and insidious onset. Avoiding AE misdiagnosis will prevent morbidity from unnecessary immunotherapies and delayed treatment of the correct diagnosis.

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Glial Fibrillary Acidic Protein (GFAP) Antibody-Associated Astrocytopathy in Systemic Sarcoidosis

Elizabeth Matthews, Ide Smets, Ryan Kammeyer, Maarten Titulaer, Amanda Piquet

Objective

To report two cases of glial fibrillary acidic protein (GFAP) antibody-associated meningoencephalitis in patients with biopsy-proven systemic sarcoidosis.

Background

GFAP astrocytopathy is an autoimmune neurologic disease first defined in 2016. To our knowledge, no association with systemic sarcoidosis has been previously reported.

Design/Methods

Case Series

Results

Patient 1 is a 47-year-old woman with pre-existing pulmonary sarcoidosis treated with steroids and methotrexate with remission 6 years prior. She subsequently developed new-onset epilepsy, progressive ataxia and vertical diplopia. GFAP antibodies were positive in the cerebrospinal fluid (CSF) by cell-based assay (CBA). Body PET scan showed diffuse FDG avidity in her lungs, spleen, and lymph nodes, suggesting simultaneous reactivation of her systemic sarcoidosis. She was treated with steroids followed by infliximab with resolution of her symptoms. Patient 2 is a 58-year-old man with known pulmonary sarcoidosis, who was off immunosuppression at the time of his presentation but had received steroids 17 years prior. He presented with progressive apathy, memory disturbance, dysarthria, and gait instability. MRI revealed widespread T2 hyperintensities. GFAP antibodies were positive in CSF on CBA and confirmed by tissue-based immunofluorescence assay. He received steroids with initial response but relapsed after steroid discontinuation. He improved after restarting steroids and was subsequently transitioned to infliximab with sustained neurologic recovery.

Conclusions

Sarcoidosis is a poorly understood multi-system disorder that is presumably an immune-mediated response to yet unidentified antigen(s). It is known to co-exist with other autoimmune diseases, with autoimmune thyroiditis being most common. GFAP astrocytopathy is also poorly understood. GFAP is found intracellularly and similar to other antibody-mediated diseases against intracellular epitopes, the antibodies are believed to be a biomarker of underlying autoimmunity but not directly pathogenic. We report these cases to highlight a potential association between production of intrathecal GFAP antibodies and systemic sarcoidosis, which may provide insights into the pathogenesis of these two diseases.

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Case of Anti-NMDA Receptor Encephalitis Presenting in a Toddler With Hemorrhagic Cavernomas

Kayla Jacques, Lydia Marcus

Objective

N/A.

Background

N/A.

Design/Methods

Introduction: Anti-N-methyl-D-aspartate (anti-NMDA) receptor encephalitis signifies an autoimmune antibody-mediated neuropsychiatric