Objective

To describe a novel autoantibody biomarker of Immune mediated rippling muscle disease (iRMD).

Background

iRMD is a rare immunotherapy-responsive myopathy characterized by wave-like muscle contractions (rippling) and percussion/stretch-induced muscle mounding. However, serological biomarker of this disease is lacking.

Design/Methods

A Retrospective review was done to identify iRMD patients with stored sera in Mayo Neuroimmunology laboratory. Archived sera from IRMD patients were evaluated for a common biomarker of IRMD using phage immunoprecipitation sequencing (PhIP-Seq).

Results

Archival sera from 10 patients with clinical diagnosis of iRMD were retrieved. Whole human proteome PhIP-Seq identified peptides corresponding to different regions of the cavin-4 in sera of iRMD patients. Eight of the ten iRMD cases were positive for cavin-4 IgG by immunofluorescent cell-based-assay (CBA) using cavin-4-transfected COS7 cells. The cavin-4-reactive IgG in all 8 positive sera was of IgG1 subclass. None of the disease control sera (98 immune-mediated myopathy/neuromuscular junction disorders, 20 autoimmune CNS diseases and 123 healthy subjects) contained cavin-4-reactive IgG. Furthermore, none of the iRMD patients' sera were positive for caveolin-3 IgG. The majority of seropositive cases were males (6/8, 75%) with median age of 51 years (range 18-76). Three seropositive patients had co-existing myasthenia gravis (38%). Creatine Kinase was elevated in 6/7 tested patients (median 771 U/L, range: 132-2625 U/L). Muscle biopsy was performed in 7 of the 8 cavin-4 IgG seropositive patients; 6/6 specimens analyzed immunohistochemically revealed a mosaic pattern of sarcolemmal cavin-4 immunoreactivity. Three of 6 seropositive patients who received immunotherapy had complete resolution of symptoms; one had mild improvement and two had no change.

Conclusions

Cavin-4 IgG is a novel and specific serological autoantibody biomarker identified in iRMD. Depletion of cavin-4 expression in iRMD patient muscle biopsies suggests the potential role of this autoantigen in disease pathogenesis.

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Anti-Neuronal Nuclear Antibody 3 Autoimmunity Targets Dachshund Homolog 1

Anastasia Zekeridou, Binxia Yang, Vanda Lennon, Guo Yong, Liang Wu, Claudia Lucchinetti, Andrew McKeon, Sean Pittock, Eoin Flanagan

Objective

To identify the autoantigen defined by Anti-Neuronal Nuclear Antibody-type 3 (ANNA3)-IgG and describe the clinical phenotype of seropositive patients.

Background

ANNA3 was described in 11 patients with multifocal neurological presentations and cancer; its detection is based on the characteristic immunofluorescence staining on mouse tissue sections; ignorance of the antigen's molecular identity has precluded its ready detection in clinical practice.

Design/Methods

This study was performed at the Mayo Clinic Neuroimmunology Laboratory. The ANNA3-IgG antigen, identified by immunoprecipitation and mass spectrometry as Dachshund-homolog 1 (DACH1), was confirmed by using a commercial DACH1-specific IgG for immunohistochemical colocalization, antigen-specific Western blot, transfected cell-based immunofluorescence, and immune absorption experiments. Clinical data were abstracted from patients' medical records or provided by referring physicians.

Results

IgG in 32 ANNA3 seropositive patient sera, but in none of 145 controls, bound to DACH1. Clinical information was available for 30 patients (median age, 63.5 years [range, 49-88]; 67% female). Neurological manifestations included neuropathy, 12; cognitive difficulties or encephalitis, 11; ataxia, 8; dysautonomia, 7 (two additionally had diarrhea and esophageal spasm); chorioretinopathy, 1. Clinical improvement was noted in 8 of 11, all treated with immunosuppressants or oncologic treatment. In two patients, the neurological syndrome appeared or worsened during immune checkpoint inhibitor cancer immunotherapy. A neoplasm was found in 27 patients (90%); fourteen were of neuroendocrine lineage. Coexisting neural autoantibodies were detected in 14 patients (47%), and most predicted a neuroendocrine tumor (specific for neuronal intermediate filaments, collapsin response-mediator protein-5, voltage-gated calcium channel [P/Q-type], ANNA1, SOX1, Purkinje-cell cytoplasmic autoantibody type 2/microtubule-associated-protein-1B).

Conclusions

IgG specific for DACH1 is a serological biomarker of neurological autoimmunity and cancer in patients of middle-age or older. DACH1-IgG is a valuable addition to comprehensive autoimmune and paraneoplastic neural antibody evaluations in clinical practice.

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Examining the Differences in Biomarkers of Neuronal and Glial Injury Between Autoimmune Neurologic Disease Patients and Healthy Controls

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Objective

To evaluate differences in concentrations of serum-based biomarkers obtained from a screened healthy control (HC) population compared to age and sex matched autoimmune and inflammatory neurologic disease (AIND) patients.

Background

Protein markers of neuronal and glial injury have become important, minimally invasive biomarkers for understanding the impact of disease in various neurological disorders, including ongoing research into AINDs. Levels of these proteins in healthy individuals remain unclear.

Design/Methods

Neurofilament light (NfL), glial fibrillary acidic protein (GFAP), ubiquitin carboxyl-terminal hydrolase L1 (UCH-L1), and total tau (Tau) levels in AIND and HC participants will be compared. Multiple Sclerosis (MS) patients, as inflammatory controls, will be analyzed as

Anti-Neuronal Nuclear Antibody 3 Autoimmunity Targets Dachshund Homolog 1

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