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Protective Association of HLA-DRB1*04 Subtypes in Neurodegenerative Diseases Implicates Acetylated Tau PHF6 Sequences

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Objective

To explore genetic association between human leukocyte antigen (HLA) and neurodegenerative diseases and investigate mechanisms behind the association.

Background

Pathophysiology of Alzheimer's disease (AD), Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS) involves accumulation of tau (neurofibrillary tangles) and amyloid-ß-rich (amyloid plaques) aggregates in AD, a-synuclein-rich aggregates (Lewy bodies) in PD and TDP-43 aggregates in ALS, although these aggregates may also co-occur. Likewise, consensus is growing that tau may play a key role in PD and ALS as well.

Design/Methods

We analyzed HLA associations in ~176,000 individuals with PD or AD versus controls across ancestry groups. Pursuing this, we also compared postmortem brain density of neurofibrillary tangles and amyloid plaques in brain, tau and Aß42 levels in cerebrospinal fluid (CSF) of ~8,000 individuals (controls and AD), and examined association of HLA in ~2,500 patient with pathologically demonstrated Lewy Body Dementia. This was followed by HLA binding and tetramer T cell studies.

Results

A shared genetic association was observed across AD and PD at rs601945 (PD: odds ratio (OR) = 0.84; 95% confidence interval, [0.80; 0.88]; p = 2.2 x 10-13; AD: OR = 0.91[0.89; 0.93]; p = 1.8 x 10-22) and with a protective HLA association recently reported in ALS. Hierarchical protective effects of HLA-DRB1*04 subtypes best accounted for the association, strongest with HLA-DRB1*04:04 and HLA-DRB1*04:07, intermediary with HLA-DRB1*04:01 and HLA-DRB1*04:03 and absent for HLA-DRB1*04:05. The same signal was associated with decreased neurofibrillary tangle (but not neuritic plaque) density postmortem and was more associated with lower tau levels than Aß42 level changes in CSF. Furthermore, protective HLA-DRB1*04 subtypes strongly bound the aggregation-prone tau PHF6 sequence, but only when acetylated at K311, a modification central to aggregation. T cells recognizing this epitope were identified, showing relevance of this immune response in patients with neurodegenerative disorders.

Conclusions

An HLA-DRB1*04-mediated adaptive immune response, potentially against tau, decreases PD, AD and ALS risk, offering the possibility of new therapeutic avenues.

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Real-World Resource Utilization and Productivity Loss Among Patients With Myasthenia Gravis in Sweden: A Nationwide Population-Based Study

Qiaoyi Zhang, Qian Cai, Nurgul Batyrbekova, Lilla Di Scala, Shane Kavanagh

Objective

To assess annual healthcare resource utilization including inpatient admission and outpatient visits, employment status, and sickness absence associated with myasthenia gravis (MG).

Background

MG is a rare, chronic and debilitating autoimmune neuromuscular disease characterized by muscle weakness and fatigue that leads to hallmark symptoms including ptosis, dysphagia, dyspnea and limb weakness. Nearly 10% of patients are estimated to have treatment-refractory MG.

Design/Methods

Data were linked from four longitudinal nationwide population-based registries in Sweden. Patients with = 1 diagnosis of MG (ICD-10 G70.0) from 01/01/2001 to 12/30/2017 were selected. Date of 1st MG diagnosis in the national patient register was designated as index date. The healthcare resource use, employment status, and sickness absence for all cause and associated with MG within 1-year post-index period were evaluated.

Results

A total of 4,339 patients with newly diagnosed MG were identified from 2001 and 2017. Mean (±SD) age at index date was 59.8 (±19.5) years; 54% were female. During the first year post-MG diagnosis, 50.6% of patients) had = 1 MG-related inpatient admission and 23.6% spent >1 month as an inpatient. Most patients (89.3%, n = 3,875) had = 1 specialist visits for MG and 16.1% had >5 visits during 1-year post-index period. 58.9% of patients had = 1 all-cause inpatient admission and 97.5% of patients used = 1 outpatient specialist services in the same period. Among patients of working age with =1-year follow-up (n = 2,006), 37.3% of them were not employed; among those in employment (n = 1,250), 44.6% reported = 1 sickness absences within 1-year post-index period.

Conclusions

Patients with MG require considerable care both for MG and comorbidities over a period of years. An important sub-population of patients (e.g., those with MG crisis) may be the intensive users of both inpatient and outpatient care. Future research needs to detail treatment pattern and outcomes in this population.

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Anti-myelin Oligodendrocyte Glycoprotein Antibody-Associated Disorder (MOGAD) in a Pediatric Patient with Rare Presentation of a Cerebellar Tumefactive Lesion

Avni Sanghi, Grace Gombolay, Tuba Khan

Objective

NA.

Background

Anti-myelin oligodendrocyte glycoprotein (MOG) antibodies have been commonly associated with optic neuritis, myelitis, and acute disseminated encephalomyelitis but rarely with tumefactive lesions, especially in children. We report a young child with MOGAD presenting with a tumefactive cerebellar demyelinating lesion.

Design/Methods

A retrospective chart review

Results

A 3-year-old developmentally appropriate boy with fever for five days prior presented for gait changes and a self-resolved seizure lasting less than 5 minutes. Neurologic examination showed abnormal finger to nose on the left side, weakness of the left lower extremity and an ataxic gait. The differential at the time was Todd's paralysis versus an intracranial process. MRI showed a non-enhancing, ill-defined T2 hyperintense tumefactive lesion with mass effect within the left cerebellum concerning for tumor, abscess, or demyelination. On EEG, a lack of a well sustained and modulated posterior dominant rhythm and lack of a well-developed anterior to posterior gradient, with moderate background slowing was seen. Cerebrospinal fluid showed 8 white blood cells, 0 red blood cells, 55 mg/dl glucose, 31 mg/dl protein, 0.61 IgG index, and 0 oligoclonal bands. The Mayo Clinic cell-based assay detected anti-MOG IgG antibody in the serum with titer of 1:100. Neurological symptoms gradually improved after steroid pulse therapy.

Conclusions

This report highlights the novel spectrum of radiologic manifestations associated with MOGAD in pediatric patients and MOGAD should always be considered in the differential diagnosis of tumefactive lesions.

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Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) as a novel presentation of CNS autoimmunity in a pediatric patient with Wiskott-Aldrich syndrome (WAS)

Vivien Xie, Alexandra Kornbluh

Objective

Report a novel case of myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) presenting as relapsing bilateral optic neuritis in a pediatric patient with Wiskott-Aldrich syndrome (WAS).

Background

WAS is a rare X-linked primary immunodeficiency caused by mutations in the WAS gene that leads to increased susceptibility to infections, thrombocytopenia, eczema, malignancies, and autoimmunity. Known CNS autoimmune manifestations include cerebral vasculitis, but optic neuritis, CNS demyelination, and MOGAD have not been previously reported.

Design/Methods

Chart review

Results

A 5-year-old boy with a history of chronic immune thrombocytopenia, hypogammaglobulinemia, anemia, and focal epilepsy developed binocular vision loss. MRI of the brain demonstrated enlargement of bilateral optic nerves with marked enhancement of the nerve sheaths consistent with optic neuritis, as well as multiple small enhancing supratentorial lesions. He was treated with pulse methylprednisolone followed by oral steroid taper, and he returned to baseline with no reported residual visual deficits. Five months later, he experienced a relapse of bilateral vision loss, and repeat MRI re-demonstrated bilateral optic neuritis as well as resolution of prior brain lesions. He was treated with repeat course of steroids and experienced moderate improvement in his vision. Rituximab was then initiated to prevent further relapses of optic neuritis while treating his chronic suspected immune-mediated thrombocytopenia. Myelin oligodendrocyte glycoprotein antibody (MOG-IgG) via serum fluorescence-activated cell sorting assay was positive (titer 1:100), confirming a diagnosis of MOGAD. At age six, molecular panel testing for genes associated with primary immunodeficiency identified a missense WAS gene variant. He was subsequently found to have decreased WAS protein expression consistent with a diagnosis of WAS.

Conclusions

We describe a case of pediatric MOGAD presenting with multiphasic bilateral optic neuritis in a patient with WAS. This case expands the reported spectrum of CNS autoimmunity associated with WAS and may help to inform indications for therapeutic options such as bone marrow transplant.

Disclosure: Dr. Xie has nothing to disclose. Dr. Kornbluh has nothing to disclose.

MOGAD in the Mountain West: Epidemiology and Outcomes in Pediatric and Adult Patients at Two Large Academic Referral Centers

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Objective

To describe the characteristics and outcomes in adult and pediatric patients diagnosed with myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) at the two major referral centers in the Mountain West of the United States, a geographic area encompassing roughly 15% of the land mass of the continental US.

Background

Since the development of commercial assays, MOGAD has become increasingly recognized as an etiologic diagnosis for several CNS demyelinating phenotypes, yet the epidemiological characteristics, relapse rates and outcomes of large populations are not well-described

Design/Methods

A retrospective chart review for patients within the health systems at the University of Utah and the University of Colorado, and affiliated children's hospitals, was conducted. To identify MOGAD patients, we queried the ICD10 codes corresponding to demyelinating disease of CNS, neuromyelitis optic spectrum disease, optic neuritis, transverse myelitis, and acute disseminated encephalomyelitis. These patients were then cross matched against antibody testing results and existing research databases at each institution. Search dates included 1/1/2016-12/1/2021 to encompass the period of commercially available MOG IgG testing. Patients were cross referenced with a list of positive MOG IgG assays at each institution.

Results

We describe the characteristics of over 50 patients (adults and children) with MOGAD, including age of onset, gender, symptoms at onset, associated autoimmunity, antibody titers, response to therapies and relapse rates.

Conclusions

This is a comprehensive characterization of a diverse population of pediatric and adult MOGAD patients seen at the two major referral

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