Dr. Garg has received intellectual property interests from a discovery or technology relating to health care. Dr. Garg has received intellectual property interests from a discovery or technology relating to health care.

Rank Wise Effect of HLA-DQ5 Explains Risk for the Development of Anti-IgLON5 Disease

Selina Yogeshwar, Vicente Peris-Sempere, Sergio Muñiz-Castrillo, Guo Luo, Carsten Finke, Jerome Honnorat, Emmanuel Mignot, Anti-IgLON5 Disease Collaborators

Objective

To better characterize the genetic association between human leukocyte antigen (HLA) and anti-IgLON5 disease and to explore auto-antigen binding to associated HLA molecules and their functional involvement in pathophysiology.

Background

Anti-IgLON5 disease is a rare, but likely underdiagnosed type of autoantibody encephalitis with a heterogeneous clinical phenotype, including sleep, movement and brainstem dysfunction. Its pathophysiology remains elusive, although dominant association with HLA-DRB1*10:01-DQB1*05:01 strongly supports an autoimmune basis.

Design/Methods

A multicentric cohort of 62 patients and 433 controls matched by principal component analysis was included. Genome-wide association analysis was performed with 4-digit resolution HLA imputation and selected 8-digit resolution validation typing. A generalized logistic model was used to determine the association with individual alleles and haplotype counts to establish haplotype associations. Furthermore, we computationally predicted binding of IgLON5-derived peptides to risk-associated HLA-molecules.

Results

Our results indicate a rank wise effect of HLA-DQA1*01:05~DQB1*05:01 (heterozygotes: OR 46.6), HLA-DQA1*01:01~DQB1*05:01 (homozygotes: OR 26.9; heterozygotes: OR 2.5) and HLA-DQA1*01:04~DQB1*05:03 (homozygotes: OR 30.9; heterozygotes: OR 5.6), in order of descending relative risk predisposition. Differences between encoded heterodimers are minimal (a few amino acids outside the main HLA sequence binding region), suggesting a common function. Computational binding predictions support similar, high binding affinity for IgLON5275-283 in a post-translationally modified (N-deglycosylated) form by all three of these HLA-DQ molecules and other common binders. In contrast, association analysis suggests that effects of HLA-DR are likely explained by linkage disequilibrium.

Conclusions

This study is the, so far, largest genetic study on anti-IgLON5 disease. Our results strongly suggest HLA-DQ over HLA-DR association, with higher reactivity against post-translationally modified versus physiological peptides, in line with reduced T cell priming against these epitopes. Further studies should address the functional implications of these HLA associations.

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Cohort Study of Autoimmune Encephalitis (AIE) in Pediatric and Adult Population from India-A Single Tertiary Centre Experience

Nagashree Sharma, Tarishi Nemani, Radhika Manohar, Minal Kekatpure V, Harirama Acharya, Vikram Huded, Gopal Dash, Kuldeep Shetty S, Anirudh Kulkarni V, Mudasir Mushtaq Shah, Vivek J Philip

Objective

Study and compare clinico-epidemiological data and long-term outcomes in pediatric (<18 yrs) and adult AIE patients based on serostatus.

Background

India is a burgeoning hub for autoimmune diseases. Studies on AIE comparing seropositive and seronegative outcomes in pediatric and adult population are lacking. We highlight age and serostatus specific approach in low resource country settings.

Design/Methods

Retro-prospective study from Narayana Institute of Neurosciences, Bangalore (2016-2021) included AIE patients as per Autoimmune Encephalitis International Working Group and Autoimmune Encephalitis Alliance Clinicians Network. Serum and CSF autoimmune encephalitis panels, CSF meningitis panel was incorporated to exclude infections and other demyelinating disorders. With phone calls and outpatient follow ups (1-4 yrs), results were statistically analyzed and compared based on age and serostatus.

Results

Adult AIE was commoner than pediatric (75% vs 25%,n = 60) and seronegative than seropositive (56.7% vs43.3%) with overall male preponderance. NMDAR (11.7%), MOG (8.3%), LGI1 and GAD65 (5% each) were common antibodies (MOG commoner than NMDAR in children; NMDAR, LGI1 and GAD 65 equally predominant in adults). Common presentations included seizures (75%) and memory disturbances (66.7%) independent of serostatus. There were no differences in MRI and EEG parameters based on age or serostatus. Methylprednisolone mono-therapy (46.6%) was multitude than add on rescue immunosuppressants [IVIG (28.3%),rituximab (10%), PLEX & cyclophosphamide (3.3% each)]. Pediatric age, specific antibodies, status epilepticus and dysautonomia were markers requiring aggressive immunotherapy. Oral steroids (61.7%),mycophenolate (8.3%)and azathioprine (6.7%) were maintenance immunosuppressants. 10% patients (mostly seropositive) had poor outcome with Modified Rankin Scale (MRS) >3. Deaths (all adults) though rare was slightly preponderant in seronegative type owing to lack of consent for aggressive immunosuppression. Clinical relapse was noted in 10% (mostly seropositive). 86% patients were weaned off maintenance immunosuppression (earlier in seronegative).

Conclusions

Seronegative and pediatric AIE had better long term outcomes. Methylprednisolone mono-therapy is efficacious in majority of the cases when started early. Early recognition and aggressive management in high risk groups has pivotal role. Further multi-centric studies are needed to confirm these findings.

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Long-Term Psychiatric Symptoms in Autoimmune Encephalitis Remission

Ramy Gabarin, Julien Hébert, Seth Climans, Alexandra Muccilli, Sydney Lee, Gregory Day, Richard Wennberg, David Tang-Wai

Objective

To identify the prevalence of self-reported symptoms of depression and anxiety among patients in remission from autoimmune encephalitis (AE).

Background

Although prior studies have found a high prevalence of residual cognitive deficits among patients in remission from AE, there is a paucity of data on long-term psychiatric outcomes for this patient population. In normal populations, median Patient Health Questionaire-9 (PHQ9) and General Anxiety Disorder-7 (GAD7) scores were reported to be, respectively, around 3 and 2, with prevalence of depressive and anxiety symptoms on these questionnaires reported as around 24% and 23%.

Design/Methods

Retrospective cross-sectional cohort study at a tertiary center AE clinic between 2012-01-01 and 2021-12-31. Patients were contacted via phone or regular follow-up and completed the PHQ9 and GAD7.

Results

Forty-one patients were contacted; 29 responded (71%) and were included. Seventeen (59%) were female. Median age was 32.5 years (range 5-77). Autoantibody results were N-methyl-D-aspartate receptor (n = 14, 48%), negative (n = 7, 24%), leucine-rich glioma-inactivated 1 (n = 6, 21%), and contactin-associated protein-like 2 (n = 1, 3%). Median time from disease onset to questionnaire collection was 6.3 years (range 1.5-23.0). Ten patients (37%) were experiencing symptoms of depression as measured by the PHQ9, with six (60%) reporting moderate-to-severe symptoms. Median PHQ9 score was 3 (range 0-18). Six patients (22%) were experiencing symptoms of anxiety on the GAD7, with one (17%) reporting moderate-to-severe symptoms. Median GAD7 score was 2 (range 0-10). Eight patients (28%) reported a psychiatric history prior to the onset of AE, which was associated with increased PHQ9 scores ($p = 0.04$, Wilcoxon rank sum test).

Conclusions

The prevalence of self-reported depressive and anxious symptoms in this cohort in remission from AE was similar to general populations. Patients with a psychiatric history that preceded onset of AE had higher PHQ9 scores. These results may be affected by censoring bias and lower sensitivity of self-reported diagnostic tools.

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The Clinical Response of California Serogroup Virus Neuroinvasive Disease in a Pediatric Patient to Intravenous Immunoglobulin (IVIG) Therapy

Avni Sanghi, Grace Gombolay, Tuba Khan

Objective

NA.

Background

California serogroup (CSG) viruses are commonly associated with neurologic disease. There are few cases of CSG viruses where IVIG has been proven to help. We report a young child with neuroinvasive CSG virus encephalitis treated with IVIG and associated outcome.

Design/Methods

A retrospective chart review.

Results

A 6 year old boy, previously healthy presented with fluctuating mental status with vomiting, fatigue, and fever starting six days prior to presentation. He began to have repetitive movements of rubbing his nose, and twisting movements of the upper extremities with mild eye deviation to the left with no EEG correlate. He required PICU admission for desaturations and altered mental status requiring intubation with sedation. He was found to have positive serum IgG and IgM antibody titers 1:128 of CSG viruses. IgG and IgM antibody titers of CSG viruses was negative (<1:1) in CSF. Of note he was positive for human metapneumovirus IgM antibodies. His serum and CSF NMDA was negative suggesting California encephalitis is not likely associated with NMDA encephalitis. His MRI brain resulted with extensive diffusion restriction throughout the frontal, parietal, and temporal cortex as well as non-diffusion restricting signal abnormality involving the basal ganglia and brainstem, suggesting a parainfectious encephalitis. He received IVIG given his worsening mental status starting on day 14 of admission. Neurological symptoms gradually improved after IVIG treatment. Despite therapies he displayed difficulties with focus and attention. 6 months after initial presentation his routine EEG showed frequent, sleep activated, 1-3 seconds bursts of irregular generalized spikes-and-slow wave complexes. Patient was continued on levetiracetam with no seizures.

Conclusions

This report highlights a severe case of encephalitis with CSG viruses. Although it is not clear whether time or IVIG helped in this patient case, it seemed to have shortened his acute altered mental status although he still has long-term learning difficulties.

Disclosure: Dr. Sanghi has nothing to disclose. The institution of Dr. Gombolay has received research support from CDC. The institution of Dr. Gombolay has received research support from NIH. Tuba Khan, MD has nothing to disclose.

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Cohort Study of Autoimmune Encephalitis (AIE) in Pediatric and Adult Population from India-A Single Tertiary Centre Experience

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