Expanding Our Knowledge of the Immunogenetic Characteristics of Anti-LGI1 Encephalitis—A Study of an Israeli Cohort Suggests Additional Significant HLA Associations With DQ Alleles

Yahel Segal, Michal Nisnboym, Keren Regev, Arnon Karni, Hadar Kolb, Firas Fahoum, Orna Aizenstein, Yael Paran, Yoram Louzoun, Sapir Israeli, Ron Loewenthal, Nina Svetlicky, Yifat Alcalay, Avi Gadoth

Objective

Exploring the clinical characteristics and HLA associations of patients with anti-leucine–rich glioma-inactivated 1 encephalitis (LGI1E) from a large single center in Israel

Background

Anti-LGI1E is one of the most commonly diagnosed antibody-associated encephalitic syndromes in adults. Recent studies of various populations reveal significant associations with specific Human Leukocyte Antigen (HLA) genes. We examined the clinical characteristics and HLA associations of a cohort of Israeli patients.

Design/Methods

Seventeen consecutive anti-LGI1E patients diagnosed at Tel Aviv Sourasky Medical Center between the years 2011-2018 were included. HLA typing was performed using NGS methodology at the tissue typing laboratory of Sheba Medical Center and compared to data from the "Ezer Mizion" Bone Marrow Donor Registry, containing over 1,000,000 samples.

Results

Our cohort displayed a male predominance and median age of onset in the 7th decade, as previously reported. All patients responded to immunotherapy, though residual damage was not uncommon (23% with MRS >1). HLA analysis revealed overexpression of DRB1*07:01 (OR 13, CI 0.6 p < 1.e-10) and DRB1*04:02 (OR 12, CI-0.6 p < 1.e-10), as previously reported, as well as of the DQ alleles DQB1*02:02 (OR 12, CI 0.6 p < 1.e-10), DQB1*03:03 (OR 27, CI 0.9 p < 1.e-10), previously attributed to linkage disequilibrium (LD) with the mentioned DR alleles. An additional allele overexpressed among our patients was the DQB1*03:02 allele (OR 12, CI 0.6 p < 1.e-10), which appeared in complete LD with DRB1*04:02. Linkage disequilibrium analysis performed on patients and controls suggests these DR-DQ associations are unique to anti-LGI1E patients. In silico predictions performed for the overexpressed DQ alleles reveal them to be strong binders of LGI1 derived peptides, and suggest a correlation between peptide binding sites of paired DR-DQ alleles.

Conclusions

Our findings shed additional light on the complex role of immunogenetics in the pathogenesis of anti-LGI1E, implying the possible relevance of certain DQ alleles as well as DR-DQ interactions.

Disclosure: Dr. Segal has nothing to disclose. Michal Nisnboym has nothing to disclose. Dr. Regev has nothing to disclose. Dr. Karni has received personal compensation in the range of $500-$4,999 for serving on a Scientific Advisory or Data Safety Monitoring board for Neopharm. Dr. Karni has received personal compensation in the range of $500-$4,999 for serving on a Scientific Advisory or Data Safety Monitoring board for BMS. Dr. Karni has received personal compensation in the range of $5,000-$9,999 for serving as an Expert Witness for Israeli Court. The institution of Dr. Karni has received research support from Medison. The institution of Dr. Karni has received research support from Sanofi. The institution of Dr. Karni has received research support from Novartis. The institution of Dr. Karni has received research support from Roche. Hadar Kolb has received personal compensation in the range of $500-$4,999 for serving as a Consultant for Novartis. Hadar Kolb has received personal compensation in the range of $500-$4,999 for serving as a Consultant for Marck. Firas Fahoum has received personal compensation in the range of $500-$4,999 for serving as a Consultant for LivaNova. Firas Fahoum has received personal compensation in the range of $500-$4,999 for serving on a Scientific Advisory or Data Safety Monitoring board for LivaNova. Orna Aizenstein has nothing to disclose. Yael Paran has nothing to disclose. Prof. Louzoun has nothing to disclose. Miss Israeli has nothing to disclose. Dr. Loewenthal has nothing to disclose. Dr. Svetlicky has nothing to disclose. Yifat Alcalay has nothing to disclose. Dr. Gadoth has received intellectual property interests from a discovery or technology relating to health care.

Broadening the Differential of Autoimmune Encephalitis: Diagnostic and Therapeutic Considerations in Down Syndrome Disintegrative Disorder

Aisha Elfasi, Torge Rempe

Objective

To assess clinical features of Down Syndrome Disintegrative Disorder (DSDD) in trisomy 21 (T21) patients with a presumed diagnosis of autoimmune encephalitis (AE) and analyze immunotherapy regimens and timing.

Background

DSDD is characterized by acute to subacute developmental regression in social and functional skills with emergence of autistic behaviors in T21. In contrast to AE, brain imaging, cerebrospinal fluid (CSF) testing and AE antibody panels are often unremarkable in DSDD. However, anti-thyroid antibody seropositivity in the majority of DSDD patients as well as reported positive immunotherapy responses raise the question of an autoimmune etiology.

Design/Methods

Retrospective analysis of T21 patients with progressive social, cognitive, and/or functional decline referred to the University of Florida neuroimmunology clinic for establishment of care for suspected autoimmune encephalitis.

Results

Two female T21 patients were included with onset of autism, cognitive decline, insomnia, and psychosis at 12 (P1) and 16 (P2) years of age. Catatonia was present in one patient (P1). Diagnostic work-up was pertinent for anti-thyroid antibody-seropositivity in both cases (anti-microsomal and anti-thyroid peroxidase) and positive oligoclonal bands in one patient (P2). Otherwise, MRI, EEG, CSF and comprehensive serum/CSF AE antibody panels were negative. Both patients were treated with intravenous corticosteroids, intravenous immunoglobulins, and additional immunosuppressive agents (azathioprine [P2]; plasmapheresis, rituximab, cyclophosphamide [P1]). Earlier initiation of immunotherapy (9 months after symptom onset) was associated with partial sustained improvement (P2) while later initiation of immunotherapy (12 months after symptom onset) was associated with partial but non-sustained improvement (P1).

Conclusions

Both reported cases align with diagnostic features of DSDD and had partial response to immunotherapy. Sustained improvement was associated with earlier immunotherapy initiation. DSDD should be a diagnostic consideration in T21 patients with presumed AE diagnosis in setting of functional decline and developmental regression. Early initiation of immunotherapy should be considered for better chance of sustained recovery.

Disclosure: Dr. Elfasi has nothing to disclose. Dr. Rempe has nothing to disclose.

Understanding Correlation of Electroclinical Findings With Functional and Neuropsychiatric Outcomes in Patients with LGI1-Encephalitis

Carol Swetlik, Amy Kunchok, Brittany Lapin, Yadi Li, Vineet Punia

Objective
To evaluate the interplay between seizures, quality of life (QoL), and neuropsychiatric outcomes in patients with leucine-rich glioma-inactived 1 antibody encephalitis (LGI1-Ab-E).

Background
Patients with LGI1-Ab-E experience varied seizure semiologies, but their potential differing impact on long-term outcomes remains under-explored.

Design/Methods
We conducted a single-center retrospective cohort study of patients with antibody-confirmed LGI1-Ab-E with seizures. Patients were categorized as having faciobrachial dystonic seizures (FBDS) or non-faciobrachial dystonic seizures (non-FBDS). Patient Health Questionnaire-9 (PHQ-9), Neuro-QoL, Patient Reported Outcomes Measurement Information System (PROMIS), and modified Rankin Scale (mRS) were abstracted. Outcomes were compared using two-tailed independent sample t-tests for continuous variables and chi-square and Fisher's exact test for categorical variables. Change over time was evaluated using Wilcoxon signed-rank test.

Results
21 patients (33% female, median 65 years) were included, 10 (47.6%) with FBDS and 11 (53.4%) with non-FBDS. Levetiracetam (66%), lacosamide (42.9%), and valproate (19.0%) were the most common anti-seizure medications; 19 (90.5%) underwent immunotherapy. In patients with at least one year of follow-up, all patients with FBDS (n = 7) and 75% with non-FBDS (n = 6) achieved seizure freedom (p = 0.48). From 8 months to 30 months post-diagnosis, PHQ-9 improved in the FBDS cohort (median 6, IQR 5.5—9.5 to median 2.5, IQR 2.0—4.5, p = 0.06), but remained stable in the non-FBDS cohort (median 5.5, IQR 2.3—9.3 to median 5, IQR 3.0 to 8.0, p = 0.75). Both groups had similar mRS baselines (median mRS 1 for both, p = 0.91) and experienced similar significant mRS worsening at median 23 months post-symptoms onset (median increase 1, p < 0.001 over time). Neuro-QoL and PROMIS scores were similar between groups (for all, p > .05).

Conclusions
Patients with LGI1-Ab-E who experience exclusively non-FBDS may be at higher risk of sustained depressive symptoms than those with FBDS. Regardless of seizure type, patients with LGI1-Ab-E are at risk for significantly worsening disability despite treatment and seizure freedom.

Disclosure: An immediate family member of Dr. Swetlik has received personal compensation for serving as an employee of Global Blood Therapeutics. An immediate family member of Dr. Swetlik has stock in Global Blood Therapeutics. Dr. Kunchok has received personal compensation in the range of $500-$4,999 for serving on a Scientific Advisory or Data Safety Monitoring board for Genentech. Dr. Kunchok has received personal compensation in the range of $10,000-$49,999 for serving as an Editor, Associate Editor, or Editorial Advisory Board Member for Neurology. Brittany Lapin has received personal compensation for serving as an employee of Cleveland Clinic. Brittany Lapin has received personal compensation in the range of $500-$4,999 for serving as an Editor, Associate Editor, or Editorial Advisory Board Member for Quality of Life Research. Brittany Lapin has received personal compensation in the range of $500-$4,999 for serving as an Editor, Associate Editor, or Editorial Advisory Board Member for Anesthesia and Analgeisa. Ms. Li has nothing to disclose. Dr. Punia has nothing to disclose.

An Observational Study on the Humoral and Cellular Immune Response to SARS-CoV-2 mRNA Vaccination in Multiple Sclerosis and Other Autoimmune Neurological Disorders Treated With Anti-CD20 Therapies

Tyler L. Borko, Sean Selva, Ryan Baxter, Berenice Cabrera-Martinez, Cody Rester, Stefan Sillau, Daniel M. Pastula, Maite Sabalza, Iswariya Venkataraman, Eagappanath Thiruppathi, Jeffrey L. Bennett, Enrique Alvarez, Robert Gross, Anna Shah, Ryan Kammeyer, Timothy L. Vollmer, Ross Kedl, John R. Corboy, Elena Hsieh, Amanda L. Piquet

Objective
To assess adaptive immunity to SARS-CoV-2 in anti-CD20 treated individuals with mRNA vaccination.

Background
Anti-CD20 therapies attenuate humoral responses to vaccines. However, their effect on T cell responses is less clear. We examined B and T cell responses following COVID-19 vaccination in patients receiving anti-CD20 therapy for multiple sclerosis (MS) and other autoimmune inflammatory neurologic diseases (AINDs, e.g., autoimmune encephalitis, stiff person syndrome, etc.).

Design/Methods
MS and AIND patients on anti-CD20 therapies were prospectively enrolled for longitudinal analysis of antibody and T cell responses after a 3rd COVID-19 vaccination. Serum antibodies against the receptor-binding domain of the S1 spike protein (RBD-S1 IgG), neutralizing antibodies, and SARS-CoV-2 CD8 T cell responses, using activation-induced markers (AIM) and INF-γ release assays (EUROIMMUN, Germany), were measured at various time points including pre-vaccination, post initial vaccination series, and 4 and 12 weeks after 3rd dose.

Results
Thirty-four MS and AIND participants are enrolled. Results for these patients (mean age 52 years-old, 79% female, 21 Pfizer, 13 Moderna) demonstrated attenuated RBD IgG antibody responses. However, a robust CD8 T cell response was observed, following a two-dose series, compared to non-immunosuppressed, age-matched vaccinated controls or unvaccinated with severe SARS-CoV-2 infection (p = 0.01). T cell response was sustained long-term (>12 weeks post 3rd dose) in all 11 anti-CD20 patients analyzed thus far. Collections are completed for all participants at 12 weeks and analysis to be completed by 05/15/22. Further analysis includes correlation of the INF- γ release assay compared to RBD-CD8 T cell response detected by AIM assay.

Conclusions
Results suggest that patients treated with anti-CD20 therapy generate a robust CD8 T cell response to SARS-CoV-2 mRNA after three doses but remain with attenuated humoral immune responses. Our observational study will provide important data to guide vaccine management in patients on or anticipating anti-CD20 therapy.

Disclosure: Mr. Borko has nothing to disclose. Sean Selva has nothing to disclose. Mr. Baxter has nothing to disclose. Ms. Cabrera-Martinez has nothing to disclose. Mr. Rester has nothing to disclose. The institution of Stefan Sillau has received research support from Alzheimer's Association. The institution of Stefan Sillau has received research support from Hewitt Family Foundation; State of Colorado. The institution of Stefan Sillau has received research support from PCORI. The institution of Stefan Sillau has received research support from NINR. The institution of Stefan Sillau has received research support from Michael J. Fox Foundation. The institution of Stefan Sillau has received research support from Department of Defense. The institution of Stefan Sillau has received research support from Colorado Department of Public Health and Environment. The institution of Stefan Sillau has received research support from Benign Essential Blepharospasm Research Foundation. Stefan Sillau has a non-compensated relationship as a Statistician with Novartis that is relevant to AAN interests or activities. Stefan Sillau has a non-compensated relationship as a Statistician with Biogen that is relevant to AAN interests or activities. Dr. Pastula has nothing to disclose. Dr. Sabalza has received personal compensation for serving as an employee of EUROIMMUN US. Dr. Venkataraman has received personal compensation for serving as an employee of EUROIMMUN US. Dr. Venkataraman has received intellectual property interests from a discovery or technology relating to health care. Dr. Thiruppathi has nothing to disclose. Dr. Bennett has received personal compensation in the range of $10,000-$49,999 for serving as a Consultant for Horizon Therapeutics. Dr. Bennett has received

Understanding Correlation of Electroclinical Findings With Functional and Neuropsychiatric Outcomes in Patients with LGI1-Encephalitis

Carol Swetlik, Amy Kunchok, Brittany Lapin, et al.

Neurology 2022;99;S51-S52
DOI 10.1212/01.wnl.0000903424.19914.85