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

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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 antibodyassociated 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.

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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 neuro-immunology 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 (antimicrosomal 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 underexplored.

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.

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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

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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 receptorbinding 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 prevaccination, 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.

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