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 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.

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

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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.

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

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