A Potential Synergistic Role of AIRE and HLA in Neurological autoimmunity

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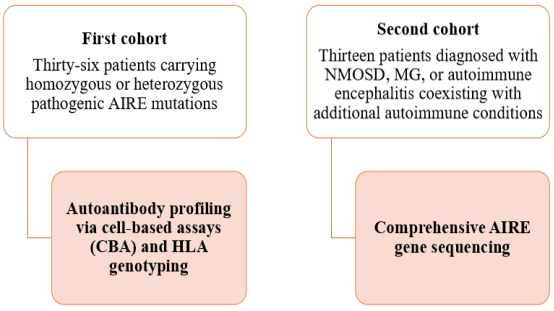
Background:

Neuromyelitis optica spectrum disorder (NMOSD), myasthenia gravis (MG), and neuromyotonia are autoimmune disorders associated with autoantibodies against AQP4, AChR, and CASPR2. While peripheral tolerance defects are well-described, the role of central tolerance, regulated by AIRE-expressing medullary thymic epithelial cells (mTECs), remains unclear.
Patients with AIRE mutations (e.g. in APS-1) show a breakdown of central tolerance.
However the role of AIRE mutations in incidence of neurological autoimmunity remains to be established.

Objective:

To investigate the role of AIRE mutations and HLA polymorphisms in neurological autoimmunity by:
•Assessing the prevalence of AQP4, AChR, and CASPR2 autoantibodies in AIRE-mutated patients
•Identifying AIRE mutations in patients with neurological autoimmune diseases and systemic autoimmune comorbidities
•Evaluating HLA haplotype interactions with AIRE mutations

Methods:



Gender	Autoimmune phenotype	Sierological profile
Female	NMOSD, MCTD	AQP4-Abs, ANA positivity
Female	NMOSD, MG, SLE	AQP4-Abs, AChR-Abs, ANA positivity
Female	NMOSD, MG	AQP4-Abs, AChR-Abs, ANA positivity
Female	MG, SLE, Graves' disease	AChR-Abs, ANA positivity
Male	MG, DM1, Sjogren's syndrome, UCTD	AChR-Abs, ANA positivity
Female	MG, Rheumatoid arthritis	AChR-Abs, FR
Female	SPS, vitiligo, DM1, autoimmune thyroiditis	GAD-Abs
Female	MG, SLE, Sjogren's syndrome, autoimmune thyroiditis	AChR-Abs, ANA, dsDNA-Abs
Female	MG, SLE, autoimmune thyroiditis	AChR-Abs, ANA, dsDNA-Abs
Female	LEMS, SLE	ANA positivity, RNP-Abs, Sm-Abs, dsDNA-Abs,
Male	MG, acquired neuromyotonia	AChR-Abs, CASPR2-Abs
Female	dSNMG, chronic candidiasis	IFNω-Abs
Female	MG, NMOSD, acquired neuromyotonia, SLE,	AChR-Abs, AQP4-Abs, CASPR2-Abs, dsDNA-Abs

Fig. 1: Autoimmune phenotype and sierological profile of patients in the secondo cohort

Results:

Thirty-six patients with confirmed AIRE mutations underwent CBA testing for autoantibodies against AChR, AQP4, and CASPR2. Among these, five patients exhibited low-titer CASPR2-specific antibodies. Additionally, AIRE sequencing in twelve patients with neurological autoimmune disorders and systemic autoimmune comorbidities identified the same AIRE mutation (W78R) in two patients, while the same sequencing in other ten individuals resulted negative. One patient with this mutation sequentially developed acquired neuromyotonia, systemic lupus erythematosus, and subsequently both AQP4-positive NMOSD and AChR-positive MG. The other patient presented with seronegative MG and was positive only for interferon omega (IFNω)-IgG.

Key Findings

5/36 AIRE-mutated patients (first cohort) resulted positive for CASPR2 antibodies
2/13 patients (see Fig. 3 below for clinical history) with neurological and systemic autoimmunity (second cohort) carried the same AIRE mutation (W78R)

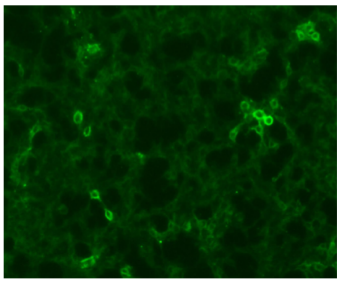
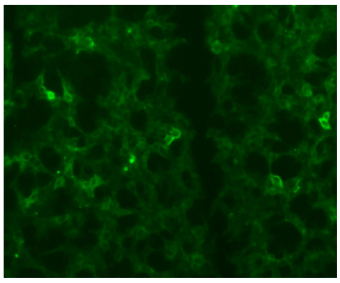


Fig. 2: fixed CBA, positivity for CASPR2-Abs in two patients of the first cohort



CLINICAL PICTURE	**Seropositive Myasthenia gravis with AChR-IgG** **Onset of MG**: 2023 **Other autoimmune conditions**: • Acquired neuromyotonia (2012) • Systemic lupus erythematosus (2021) • NMOSD (2023)	**Seronegative Myasthenia gravis** **Onset of MG**: 1998 **Other relevant conditions**: • Mucosal candidiasis • Undifferentiated colitis • Erythema nodosum • Malignant perivascular ephiteloid cell tumor (PEComa)
AUTOANTIBODY PROFILING	AChR-Abs CASPR2-Abs LGI1-Abs AQP4-Abs dsDNA-Abs *retrospective testing of 2021 and 2023 serum samples	**Seronegative** for AChR, MuSK, LRP4, AQP4, CASPR2, LGI1 and other antibodies IFNω-Abs
GENETIC TESTING	**HLA haplotype**: A26/A66; B08/B13; C06/C07; DR3/DR5; DQ02/DQ07	**HLA haplotype**: A01/A11, B35/B51, C0/C14, DR11/DR16; DQ03/05

Fig. 3: Clinical history in two patients with neurological autoimmunity and AIRE mutation (W78R)

Conclusion:

These preliminary findings support a potential key role of AIRE mutations in neurological autoimmune pathogenesis and highlight the need for further investigation into the interplay between AIRE defects and genetic susceptibility conferred by specific HLA haplotypes.