Rheumatologie Investigator Meeting 06.09.21

FV 002

Genetic forms of juvenile-onset SLE in the UK

Amandine Charras[1]; Sam Haldenby[2]; Eve Smith[1]; Michael Beresford[1]; Christian Hedrich[3]

[1]Institute of Life Course and Medical Sciences, University of Liverpool, Liverpool, UK., Department of Women›s & Children›s Health, Liverpool, United Kingdom; [2]Institute of Infection, Veterinary & Ecological Sciences, University of Liverpool, Liverpool, UK., Centre for Genomic Research, Liverpool, United Kingdom; [3]University of Liverpool & Department of Rheumatology, Alder Hey Children's NHS Foundation Trust, Department of Women's and Children's Health, Institute of Life Course and Medical Sciences, Liverpool, United Kingdom

Objectives: Juvenile-onset systemic lupus erythematosus (jSLE) affects 15-20% of lupus patients. When compared to adult-onset SLE, it is characterized by increased organ involvement and damage, and higher need for immunosuppressive treatment. Clinical heterogeneity between ethnicities, age groups and individual patients suggest variable pathophysiology. This study aimed at the definition of patient sub-cohorts with "genetic" vs. "classical" SLE to allow individualized care.

Methods: Applying target enrichment and new generation sequencing, jSLE patients (N=348) from the UK JSLE Cohort Study were screened for disease-causing mutations. Findings were integrated with demographic and clinical data, including SLEDAI, pBILAG organ domain and SLICC damage scores.

Results: Approximately 5.5% of jSLE patients carried disease-causing mutations, primarily affecting nucleic acid sensing and metabolism (68%), immune complex clearance (11%), their combination (11%), immune cell (5%) and NFκB signalling (5%). When compared to "classical" SLE, "genetic SLE" patients were younger, and exhibited less organ involvement and damage (neuropsychiatric, haematological, gastrointestinal). Notably, neuropsychiatric involvement developed over time. When compared to the remaining cohort, "genetic SLE" associated with anti-dsDNA antibody positivity at diagnosis, and reduced ANA, anti-LA and anti-Sm antibody positivity at last visit.

Conclusions: Genetic disease accounts for ≥5.5% of jSLE cases and associates with young age at onset, and distinct clinical features. As less commonly present after treatment induction, in "genetic SLE", autoantibody positivity may be a secondary result of tissue damage and explain reduced immune complex-mediated renal and haematological involvement. Routine sequencing will allow for patient stratification, risk assessment, and target-directed treatment with reduced toxicity and increased efficacy.