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Stratification of Primary Sjögren's Syndrome into Clinical Phenotypes and Pathobiological Endotypes

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BACKGROUND

Stratified medicine promises to revolutionise the treatment of complex immune-mediated inflammatory diseases (IMID). Current approaches focusing on identifying biological endotypes have met with mixed success. Using primary Sjögren's Syndrome (pSS) as a model of IMID, we use patient reported symptoms to identify pSS phenotypes and use these to identify underlying endotypes with distinct pathobiology.

METHODS

Phenotypes were identified using hierarchical cluster analysis of patient reported outcomes from a UK cohort (n=608). Models of phenotypic group membership were constructed using multiple logistic regression. Two independent cohorts from France and Norway (n=396) were used to validate biological differences. Differences in gene expression between groups was characterized using partial least squares discriminant analysis.

RESULTS

We identified four phenotypic groups – Low Symptom Burden (**LSB**), High Symptom Burden (**HSB**), Dryness Dominant with Fatigue (**DDF**) and Pain Dominant with Fatigue (**PDF**). In addition to differences quality of life (TTO $p<0{\cdot}001$, EQ-5D VAS $p<0{\cdot}001$), there are significant differences in clinical and laboratory measurements between these groups (IgG $p<0{\cdot}001$, lymphocytes $p<0.001$, ESR $p=0{\cdot}003$, IL-17 $p=0{\cdot}017$, TNF-α $p=0{\cdot}013$). Similar differences in clinical values were observed in two independent cohorts from France (n=334) and Norway (n=62). Longitudinal data from the French cohort showed that group membership was relatively stable during a five year follow-up period. Discriminant analysis of whole blood transcriptomics (discovery cohort: n=186; validation cohort: n=119) permitted the accurate prediction of patient phenotypes. Network reconstruction of the gene expression data revealed distinct gene networks that were differentially expressed within the four phenotypes.

DISCUSSION and CONCLUSION

We have identified four pSS clinical phenotypes characterized by distinct patterns in patient reported outcomes and differences in biology underpinned by differences in gene expression. Our data illustrate real potential for stratified medicine in complex chronic diseases like pSS, with important implications for clinical management, trial design, therapeutic development and potential health gains. This work has important implications for stratified medicine in pSS and other IMIDs.