patients and controls. Factors associated with sero-reversion of the anti-HPV antibodies were studied by statistical analyses.

Results: 50 SLE patients (age 25.8 ± 3.9 years) and 50 controls (25.8 ± 3.9 years) were vaccinated with Gardasil in 2011. The sero-conversion rates of anti-HPV serotypes 6, 11, 16 and 18 in patients and controls were 82%, 89%, 95%, 76%, and 98%, 98%, 98%, 80%, respectively, at month 12 post-vaccination. Among those subjects who sero-converted and were available for follow-up, persistence of the antibodies to HPV serotypes 6, 11, 16 and 18 at 5 years was present in 24/27 (89%), 26/31 (84%), 32/34 (94%), 24/25 (96%) of the SLE patients and 32/33 (97%), 32/33 (97%), 32/32 (100%) and 23/24 (96%) of the controls, respectively. Moreover, antibody titers to HPV serotypes 6 and 16 at 5 years were significantly lower in SLE patients than controls. Seven (21%) SLE patients had sero-reversion of any one of the four anti-HPV antibodies (6, 11, 16 or 18) at year 5 post-vaccination. Patients who sero-reverted had received a significantly higher cumulative dose of prednisolone (13.0 ± 5.34 vs 4.63 ± 4.59 grams; $p=0.002$), mycophenolate mofetil (1050 ± 1180 vs 238 ± 49.5 grams; $p=0.007$) and tacrolimus (375 ± 580 vs 268 ± 1180 mg; $p=0.03$) during the 5 year follow-up than those with persistence of immunogenicity. These sero-reverted patients had also received a non-significantly higher cumulative dose of cyclophosphamide (1.97 ± 5.22 vs 0.43 ± 2.24 grams; $p=0.27$). In addition, sero-reverted patients had more SLE flares in the 5 year follow-up period compared to those with persistence of immunogenicity (3.14 ± 1.21 vs 1.89 ± 1.28 ; $p=0.03$). Among 64 flares in patients with persistent anti-HPV antibodies and 26 flares in those with sero-reversion, renal flares occurred more frequently in the latter group of patients (16% vs 38%; $p=0.02$).

Conclusions: Immunogenicity of the quadrivalent HPV vaccine was retained in 79% of SLE patients at 5 year post-vaccination. Antibody titers to HPV serotypes 6 and 16 were significantly lower in SLE patients than controls. Patients who had more SLE flares, especially renal flares, and had received higher cumulative doses of glucocorticoids, mycophenolate mofetil and tacrolimus were more likely to have sero-reversion of one or more anti-HPV antibodies. Re-vaccination of these patients should be considered.

Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2018-eular.4332

SAT0422

INDIRECT PATHOGENIC ROLES OF CEREBROSPINAL FLUID ANTI-U1RNP ANTIBODIES IN THE PRESENCE OF ANTI-NR2 ANTIBODIES IN PATIENTS WITH NEUROPSYCHIATRIC SYSTEMIC LUPUS ERYTHEMATOSUS

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Background: Autoantibodies (auto Abs) and inflammatory mediators (IMs) in cerebrospinal fluid (CSF) may be involved in the pathogenesis of neuropsychiatric systemic lupus erythematosus (NPSLE). Previous studies indicated that anti-N-methyl D-aspartate receptor NR2 subunit (NR2) Abs have a pathogenic role in NPSLE by BBB disruption.¹Hirohata S, et al, *Arthritis Res Ther*, 2014² We also reported the association between NPSLE and CSF-anti-U1RNP Abs (Sato, et al, *A and R*, 2010).

Objectives: In the present study, synergistic effects of these auto Abs, their associated IMs, and blood brain barrier (BBB) permeability are determined in NPSLE patients.

Methods: CSF samples were collected from 69 of NPSLE patients at their acute phase and 13 of non-NPSLE control after obtaining the written informed consent. CSF anti-NR2 and anti-U1RNP Abs were determined by ELISA. CSF IL-6, IL-8, and monokine induced by IFN- γ (MIG) were measured by quantitative multiplex cytokine analysis. BBB permeability was evaluated by albumin quotient (Qalb).

Results: 1) CSF IL-6 levels were higher in CSF anti-NR2 Ab +ve (70 ± 178 pg/mL) than in -ve (11 ± 32 , $p=0.02$) patients and in controls (16 ± 40 , $p=0.003$) and positively correlated with anti-NR2 Ab titer ($r=0.42$, $p=0.003$). Anti-U1RNP Ab positivity was not associated with CSF IL6 elevation. 2) CSF IL-8 levels were higher in CSF anti-U1RNP Ab +ve than in -ve (270 ± 862 vs. 52 ± 177 pg/mL, $p=0.04$) patients. Anti-NR2 Ab positivity was not involved in CSF IL8 elevation. 3) CSF MIG levels were more elevated in both CSF anti-NR2 +ve (4483 ± 11845 pg/mL, $p=0.04$) and anti-U1RNP Ab +ve (5519 ± 13504 , $p=0.03$) patients than in controls (115 ± 125). 4) All the patients were divided into 4 groups: CSF anti-NR2 +ve/anti-U1RNP+ve (double positive [DP], $n=9$), anti-NR2 +ve/anti-U1RNP -ve (aNR2, $n=15$), anti-NR2 -ve/anti-U1RNP+ve (aU1RNP, $n=9$), and anti-NR2 -ve/anti-

U1RNP -ve (double negative [DN], $n=36$). In comparison between DP and aNR2 groups, anti-U1RNP Abs had a synergistic effect on CSF IL-6 elevation (150 ± 260 vs. 18 ± 44 pg/mL, $p=0.03$) that is not directly associated with anti-U1RNP Ab positivity. In comparison with aNR2 group, both CSF IL-8 (543 ± 1198 vs. 43 ± 102 pg/mL, $p=0.04$) and MIG ($10104 \pm 17\,748$ vs. 1111 ± 2584 pg/mL, $p=0.03$) levels, which were positively correlated with CSF anti-U1RNP Ab titer, were more elevated in DP group. 5) Qalb was positively correlated with CSF IL-8 ($r=0.51$, $p<0.0001$) and MIG ($r=0.44$, $p=0.0003$), suggesting that CSF anti-U1RNP Ab positivity is involved in the BBB disruption. Actually, Qalb ($\times 10^3$) tended to be higher in DP than in aNR2 group (13 ± 9 vs. 9 ± 8 , $p=0.06$) and CSF anti-NR2 Ab titer appeared to be more elevated in DP than in aNR2 group (81 ± 47 vs. 57 ± 21 , $p=0.06$).

Conclusions: The present study suggested that anti-NR2 and U1RNP Abs have synergistic effects on CSF IL-6 elevation in patients with NPSLE. CSF IL-6 level was associated with anti-NR2 Ab titers, which depend on BBB permeability. CSF anti-U1RNP Ab-mediated IL-8 and MIG elevation may induce BBB disruption followed by anti-NR2 Ab penetration into CSF.

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Acknowledgements: The present study is supported by the Japanese Ministry of Education, Culture, Sports, Science, and Technology.

Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2018-eular.3033

SAT0423

MOLECULAR PROFILES ASSOCIATE WITH CLINICAL DISEASE ACTIVITY AND INFORM PATIENT SUBSETTING IN ADULT SYSTEMIC LUPUS ERYTHEMATOSUS

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Background: Systemic lupus erythematosus (SLE) is characterised by remarkable clinical and pathophysiological diversity, hindering diagnosis, treatment and treatment development. Subsetting of patients based upon clinical presentations alone has not identified homogeneous groups of patients best treated with a directed therapeutic.

Objectives: To cluster SLE patients into more homogeneous subsets with common molecular pathway signatures, and to assess the clinical, therapeutic, and demographic features enriched in each cluster.

Methods: Serial or single plasma, serum and RNA samples ($n=290$) were collected from 198 SLE patients who met ACR classification. Disease activity was assessed by modified SLEDAI-SLEDAI at an average of 17 visits per patient. Transcriptional co-expression signature module scores were calculated from Illumina Beadchip Microarray gene expression data for 29 immune pathway related modules. Plasma soluble mediators ($n=23$) and 12 antinuclear autoantibodies (anti-dsDNA, chromatin, ribosomal P, Sm, Sm, SmRNP, RNP, Ro/SSA, La/SSB, centromere B, Scl-70 and Jo-1) were assessed by multiplex bead-based assay and ELISA. Spearman correlations were used for univariate and multivariate analysis using R. Patients were clustered on module signature scores and soluble mediators using random forest and tSNE.

Results: SLEDAI scores strongly correlated with interferon modules and were modestly correlated with plasmablast and select cell cycle signatures in this adult lupus collection. SLEDAI scores also correlated with soluble levels of IFN α , IL21, IL1 α , IL17A, IP10 and MIG. Random forest defined seven clusters of SLE patients with unique molecular phenotypes based upon gene co-expression module signatures and soluble mediators. Inflammation and interferon (IFN) signatures were elevated in Clusters 1 (moderately) and 4, with decreased T cell signatures in Cluster 4. The other clusters had lower IFN and inflammation signatures, but differed in their monocyte, plasmablast and T cell signatures. Clusters 1 and 4 had the highest SLEDAI scores, with high rates of anti-dsDNA, low complement, proteinuria and hematuria; these features were also prominent in Cluster 3, which lacked the IFN and inflammation signatures. Cluster 6 had the highest plasmablast module score, highest IL1 α levels, and SLEDAI scored rashes, but only moderate IFN and inflammation module scores. Cluster 2 had higher rates of SLEDAI scored alopecia, a slightly elevated inflammation signature, but lower interferon signature and lower soluble mediator levels.