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This study aimed to characterise both neuronal autoantibodies and levels of interferon α, two proposed causative agents in neuropsychiatric systemic lupus erythematosus (NPSLE). Cerebrospinal fluid (CSF) and plasma from 35 patients with systemic lupus erythematosus (SLE; 15 with NPSLE) showed no antibodies against natively expressed N-methyl-D-aspartate receptors (NMDARs), or the surface of live hippocampal neurons. By comparison to controls (n = 104), patients with SLE had antibodies that bound to a peptide representing the extracellular domain of NMDARs ($p < 0.0001$), however, binding was retained against both rearranged peptides and no peptide (r = 0.85 and r = 0.79, respectively, $p < 0.0001$). In summary, neuronal-surface reactive antibodies were not detected in NPSLE. Further, while interferon α levels were higher in SLE ($p < 0.0001$), they lacked specificity for NPSLE. Our findings mandate a search for novel biomarkers in this condition.

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Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease associated with antibodies against native DNA. A subset of patients have neuropsychiatric SLE (NPSLE), a disabling clinical syndrome with widely varied features, including headache, seizures, stroke, and psychosis.[1,2] This clinical heterogeneity means accurate biomarkers are required to better define NPSLE.

Human autoantibodies are one proposed biomarker. This field began with characterisation of a double-stranded DNA (dsDNA) reactive mouse monoclonal antibody (R4A). Upon transfer to mice, R4A led to glomerular deposition, a key feature of SLE pathology. Importantly, a peptide phage display library revealed R4A bound a consensus pentapeptide sequence (D/E-W-D/E-Y-S/G, DWEYS for short) present within the extracellular domain of the NR2A and NR2B subunits of the N-methyl-D-aspartate receptor (NMDAR), and induced neuronal death in mice.[3,4] In addition, DWEYS-reactive B cell receptors isolated from patients with SLE, including the G11 recombinant monoclonal antibody, were reported to bind NMDARs.[5] These observations led to the proposal of NMDAR-directed autoantibodies as pathogenic agents in NPSLE.

Yet, human autoantibodies against NR2A/B subunit peptides have been disputed as a clinically useful test for NPSLE.[6–8] A recent meta-analysis of ~3,000 subjects observed these serum autoantibodies in more patients with SLE and Sjögren's syndrome versus controls, but with only a modest increase within the NPSLE subset.[8] Very few studies presented parallel data from cerebrospinal fluid (CSF).

An independent literature describes a clinically distinctive form of encephalitis, with prominent neuropsychiatric features, which is consistently associated with serum and CSF autoantibodies against the native extracellular domain of the NMDAR NR1 subunit.[9,10] These patients, with NMDAR-antibody encephalitis, very rarely have coexistent SLE despite often being young women.[9,10] Their NR1-reactive autoantibodies also bind the surface of live hippocampal neurons but not NR1-derived

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peptides, consistent with selectivity for native epitope confirmations.[9–11] Similarly, preferential binding to native, conformational surface proteins is a feature of other pathogenic neurological antibodies, directed against leucine-rich glioma inactivated 1 (LGI1), contactin-associated protein-like 2 (CASPR2) and aquaporin-4 (AQP4).[12,13]

Herein, we show that immunoglobulin G (IgG) from the sera and CSF of patients with NPSLE neither react with surface-expressed native neuronal epitopes, nor show specificity toward peptides representing NMDARs. Our data support a fundamental need to redirect the search for biomarkers in human NPSLE, away from causative autoantibodies.

Patients and Methods

Patient Selection and Involvement

Paired plasma and CSF samples were frozen from 35 consecutive patients who met American College of Rheumatology (ACR) criteria for SLE, in a tertiary neuroinflammation clinic (Karolinska University Hospital, Sweden). Clinical and laboratory features were extracted retrospectively from case notes. Control plasma and CSFs were from healthy controls (HCs; n = 36), with additional plasmas from central nervous system (CNS)-autoimmunity disease controls (DCs; n = 68: multiple sclerosis (n = 32) plus LGI1/CASPR2- (n = 13), AQP4- (n = 12), and NMDAR- (n = 11) antibody mediated diseases). Study procedures and sample testing were ethically approved (Stockholm: 2009/2107-31/2; and Oxford: REC16/YH/0013). All assays were performed blinded to clinical details.

Autoantibody and Interferon α (IFNα) Measurements

As previously described,[10,14] plasma (1:20 dilution) and CSF (1:2 dilution) underwent live cell based assays (CBAs) to detect autoantibodies against the extracellular domains of conformationally active NMDARs. In addition, plasma (1:200) and CSF (1:2) were incubated with live cultured rodent hippocampal neurons after around day 18 in vitro. The DWEYS enzyme-linked immunosorbent assay (ELISA) followed a published protocol,[4] coating plates with either 20 μg/mL of DWEYSVWLSN ("DWEYS"), a decapeptide with 2 substitutions (KWRYSVWLSN; with positively charged amino acids replacing negative ones), a randomly scrambled DWEYS decapeptide (SDYVWLNESW), or no peptide. Plasma (1:500), CSF (1:1), and the humanized DWEYS monoclonal antibody (G11, kind gift from Prof. Diamond, USA) were incubated for 1 hour prior to washing and incubation with anti-human/mouse horseradish peroxidase (HRP; 1:2,000 dilution, DAKO) followed by TMB (Bethyl) to develop the reaction. IFNα quantification utilized single molecule array (SIMOA) technology, as previously reported.[15]

Results

Patient and CSF Characteristics

At the time of assessment and sampling, the median patient age was 47 years (range = 18–77), 34 of 35 patients (97%) were female, and 32 of 34 patients (94%) were receiving immunotherapies. Twenty-three of 35 patients had active SLE and 15 had active NPSLE, with multiple neurological features (Fig 1A).

CSFs revealed raised IgG in 11 of 35 patients (31%, normal range < 45 mg/L), with accompanying raised IgG index in just one, and pleocytosis in 5 of 35 patients (14%, normal range < 5 cells/μL). In addition, 12 of 35 patients (34%) showed a raised albumin quotient (normal range < 7.1), consistent with blood–brain barrier dysfunction. No differences in these parameters were observed between subjects with and without NPSLE.

Absent Binding of Patient Plasma/CSF IgGs to the Extracellular Domains of Either Expressed NMDARs or Live Neuronal Cultures

Using live CBAs, surface expression of NR1/2 subunits was confirmed with commercial antibodies and the serum/CSF IgGs from patients with NMDAR-antibody encephalitis (Fig 1B, C).[9,10] However, the 35 SLE serum/CSF samples, HC sera, and the G11 monoclonal antibody neither bound to the extracellular domains of mammalian cell expressed NR1/2A or NR1/2B heteromers nor to the array of native surface proteins expressed on live rodent primary hippocampal cultures (see Fig 1B). This contrasted strikingly with the strong punctate somatic and dendritic binding observed with plasma/CSF IgGs from patients with encephalitis, including those with NMDAR- and CASPR2-antibodies (Fig 1D).[9,12]

Autoantibody Binding to NMDAR-Derived Peptides Is Not Peptide-Specific

Next, the original detection of DWEYS antibodies was revisited. On DWEYS-coated ELISA plates, the anti-DWEYS G11 monoclonal bound clearly and an isotype control (B1) consistently showed optical densities (ODs) < 0.3, both as predicted (Fig 2A). Statistically significant differences were observed between patients with SLE versus both HCs ($p = 0.03$) and DCs ($p = 0.009$). However, using a conservative cutoff, plasma IgG from 8 of 35 patients with SLE, 2 of 36 HCs, and 1 of 68 DC showed DWEYS reactivity (see Fig 2A), and only 3 of 35 SLE samples, including 1 without active NPSLE, were clearly above all HCs/DCs (see Fig 2A). This represented

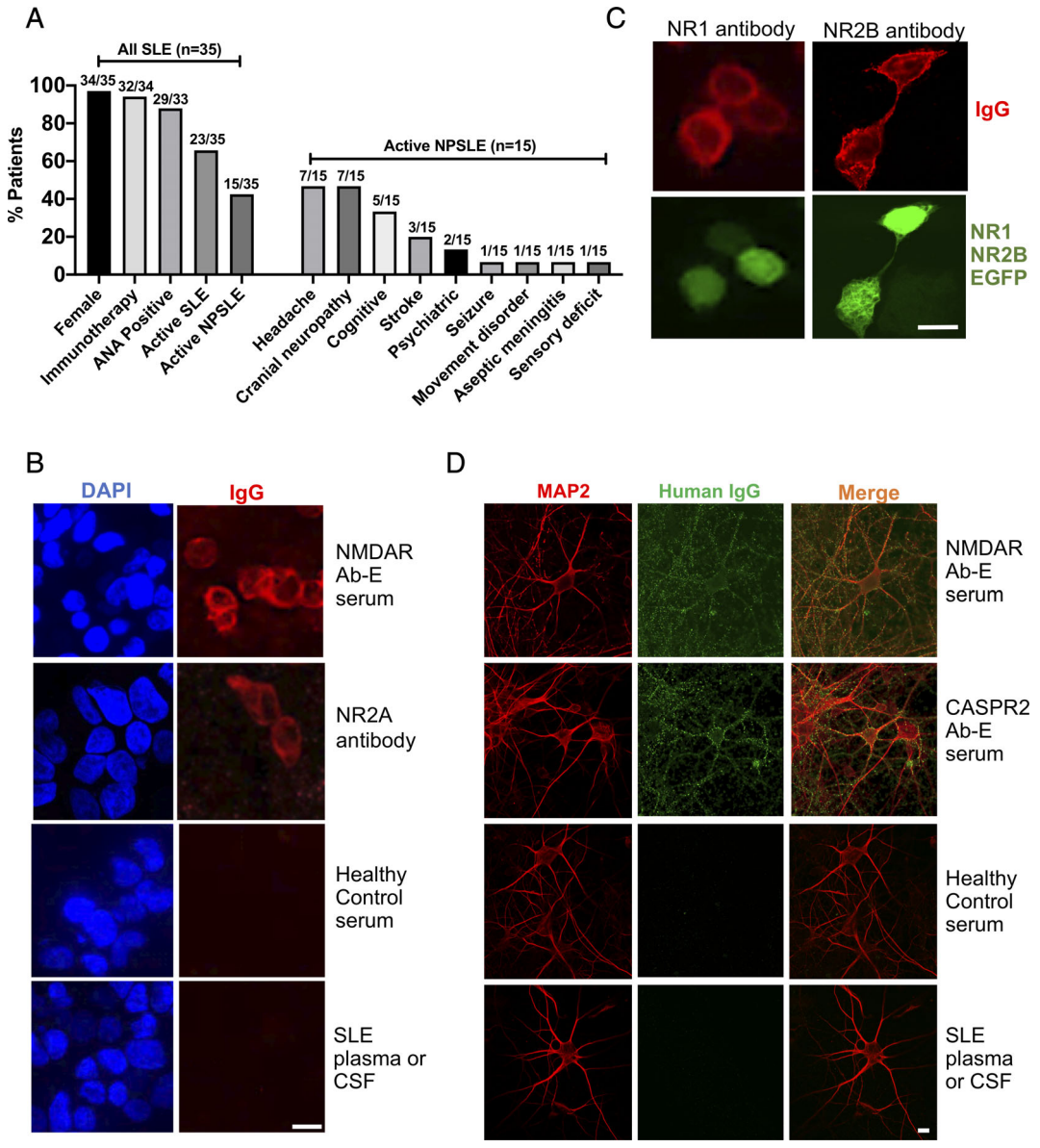

FIGURE 1: **Clinical features and immunoglobulin G (IgG) binding to conformational neuronal surface epitopes from plasma and cerebrospinal fluid (CSF) of patients with neuropsychiatric systemic lupus erythematosus (NPSLE).** (A) Clinical features of 35 patients with systemic lupus erythematosus (SLE), including 15 with active NPSLE, at the time of sampling. Thirty-two of 34 patients (94%) were on immunotherapies, including prednisolone (71%), hydroxychloroquine (41%), belimumab (6%), and rituximab (3%). ANA = anti-nuclear antibody. (B) Live cell-based assays using HEK293T cells with surface expressed N-methyl D-aspartate receptors (NMDARs) as NR1-NR2A or NR1-NR2B heteromers (nuclei highlighted with DAPI, 4′,6-diamidino-2-phenylindole). The first row shows that NMDAR-antibody encephalitis (NMDAR-Ab-E) patient (n = 11) serum IgGs bind to NR1-NR2A heteromers (and to NR1-NR2B heteromers/NR1 homomers; similar binding was observed using NMDAR-antibody patient CSFs; data not shown). In the second row, a commercial antibody directed against the extracellular domain of the NR2A-subunit (red) binds to HEK293T cells, which express NR1-NR2A heteromers. Serum from healthy controls (n = 36), plasma and CSFs from patients with SLE (n = 35 of each) show no binding and no binding was observed with the G11 antibody (data not shown, lower panel representative). Throughout, IgG binding was visualized with an anti-human 568-Alexa Fluor antibody (1:750 dilution, A-21090). (C) Commercial antibodies against the extracellular domains of NR1 (Alomone, AGC-001), NR2A (Alomone, AGC-002), and NR2B (kind gift from Prof. Stephenson, London) subunits bound to the surface of live HEK293T cells co-transfected with EGFP plus NR1 and NR2A/NR2B subunits. (D) Hippocampal neuron somae and dendrites are stained with a commercial antibody against microtubule associated protein 2 (MAP2, *red*). Live neurons in culture are robustly bound by IgGs with sera (top two panels) or CSF (data not shown) from patients with NMDAR-antibody encephalitis (n = 11) and CASPR2-antibody encephalitis (n = 5; CASPR2-Ab-E). However, no binding was detected using plasma/CSFs from 35 patients with SLE and 36 sera from healthy controls. All scale bars = 10 μm.

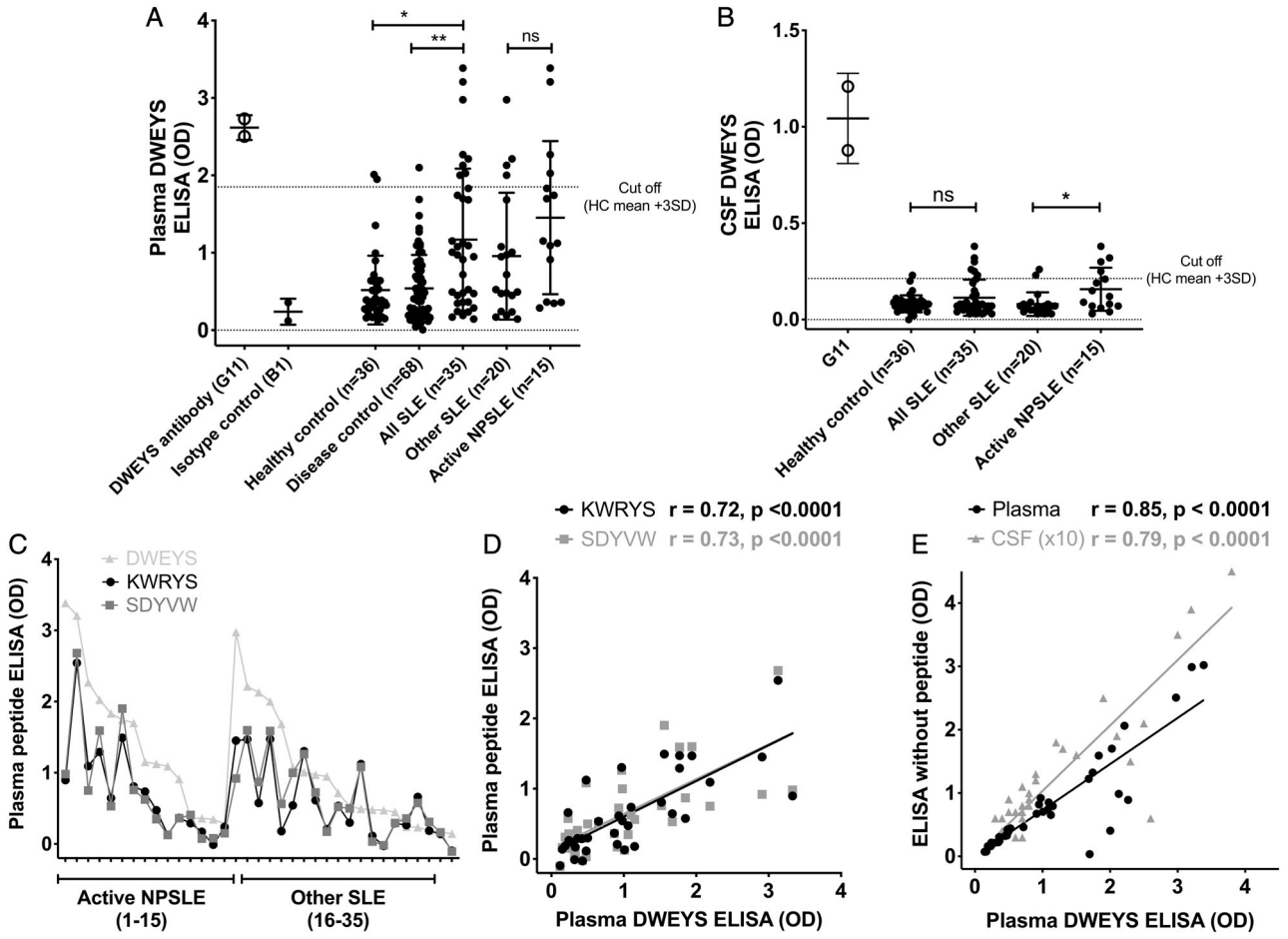

FIGURE 2: Plasma and cerebrospinal fluid (CSF) reactivities against DWEYS and related peptides. (A) Optical density (OD) results from the DWEYS ELISA, using G11 (humanized anti-DWEYS antibody), an isotype control (B1), and plasma from disease controls (n = 68), healthy controls (n = 36), and patients with SLE (n = 35), including those with active neuropsychiatric systemic lupus erythematosus (NPSLE). Significant differences (Kruskal Wallis test with post hoc Dunn's correction) were observed between patients with SLE and healthy controls (p = 0.03*) and disease controls (p = 0.009), but not between active NPSLE and other cases of SLE (ns). Cutoff for positivity (*dotted line*) represents the mean plus 3 standard deviations of healthy control values. (B) From CSF, the DWEYS ELISA results showed no difference between healthy controls and patients with SLE, and modest difference within a comparison of patients with active NPSLE versus other SLE (p = 0.021, Mann–Whitney U test without correction for multiple comparisons). (C, D) ELISA findings across all 35 patients with SLE paralleled each other when using the DWEYS peptide, a scrambled peptide (SDYVWLNESW; Spearman's r 0.72, p < 0.0001) and a peptide with two positive amino acid substitutions (KWRYSVWLSN; Spearman's r 0.73, p < 0.0001). E. In both plasma (*black*) and CSF (*grey*, data multiplied 10 fold), the ODs were highly correlated when performed in the presence versus absence of DWEYS peptide (Spearman's rank r = 0.85 and 0.79, respectively, both < 0.0001).**

~23% sensitivity and ~97% specificity for the detection of SLE, and did not distinguish the NPSLE cases. Similarly, CSF DWEYS reactivity did not discriminate between SLE and HCs, with a modest difference between active NPSLE and other SLE cases (p = 0.021, Mann–Whitney U test; Fig 2B). Overall, the DWEYS IgG ELISA showed very limited specificity for NPSLE but cohort-based differences revealed higher levels in SLE versus HC/DC plasmas.

Next, this antigenic specificity was interrogated. Individual plasma samples showed very similar IgG binding to the DWEYS peptide and to both the scrambled peptide "SDYVW" (r = 0.73, p < 0.0001) and a substituted peptide "KWRYS" (r = 0.72, p < 0.0001; Fig 2C, D). Furthermore, the DWEYS-IgG reactivity from both plasma and CSF correlated closely with binding to the uncoated ELISA plate (r = 0.85, p < 0.0001 and r = 0.79, p < 0.0001, respectively; Fig 2E).

IFNα Levels Better Distinguish SLE from Controls, but Not from NPSLE

Finally, plasma IFNα levels were investigated as IFNα is associated with SLE, the development of neurological autoantibody-mediated complications in SLE, and is directly a neurotoxic cytokine.[15–17] Plasma IFNα levels were ~100-fold higher in patients with SLE compared

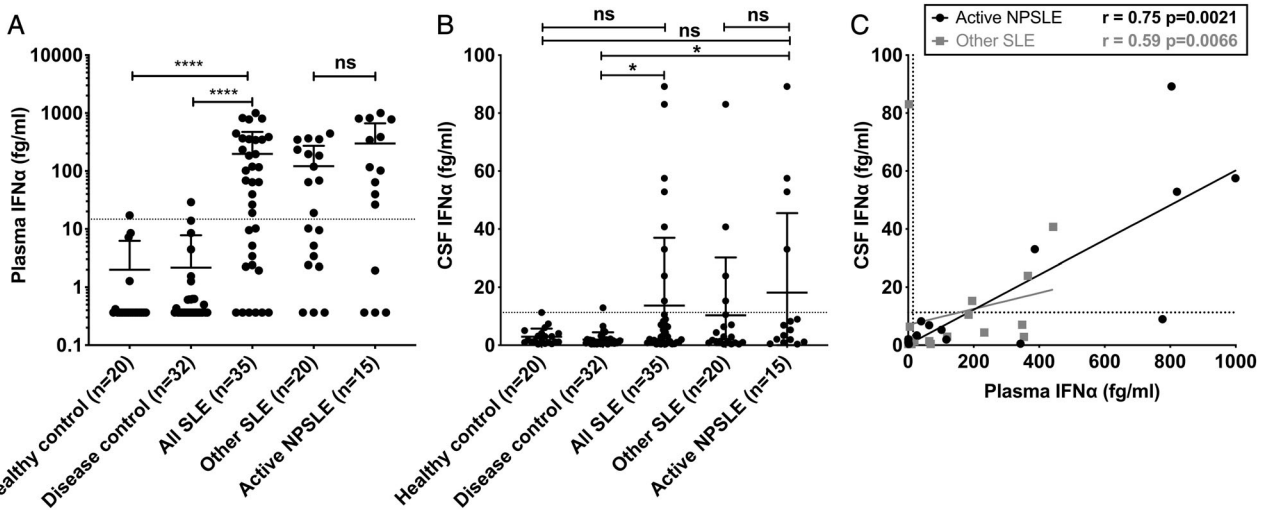

FIGURE 3: Interferon alpha (IFNα) levels in neuropsychiatric systemic lupus erythematosus (NPSLE). (A) Plasma IFNα levels differentiate patients with systemic lupus erythematosus (SLE) from healthy controls (n = 20) and from disease controls (n = 32; both $p < 0.0001$**, Kruskal Wallis with post hoc Dunn's). There were no differences between patients with SLE with active NPSLE versus those without ($p = 0.39$). Comparisons of active NPSLE and other SLE versus both healthy controls or disease controls all $p < 0.01$ (data not charted). (B) Cerebrospinal fluid (CSF) IFNα does not differentiate between SLE and healthy controls but does patients with SLE and disease controls ($p = 0.02$, Kruskal Wallis with post hoc Dunn's). There was no difference between active NPSLE versus other SLE. IFNα levels in active NPSLE versus disease controls are significantly different ($p = 0.03$) but not by comparison to healthy controls. (C) Overall, plasma and CSF IFNα levels correlate closely (Spearman's r = 0.68, $p < 0.0001$) in both active NPSLE (r = 0.75, $p = 0.002$) and inactive NPSLE (r = 0.59, $p = 0.007$).**

with HCs/DCs (both $p < 0.0001$; Fig 3A), with fewer striking differences in CSF (Fig 3B). Consistent with their close correlations (Fig 3C), IFNα levels in neither fluid distinguished active NPSLE from other SLE cases (see Fig 3A, B). Using the mean plus 3 standard deviations of HC data as a cutoff for IFNα 'positivity', 22 of 35 (63%) patients with SLE, 1 of 36 (3%) HCs, and 1 of 68 (1%) DCs were positive in plasma, while 8 of 35 (23%) patients with SLE and 1 of 36 (1%) DCs in CSF (sensitivities and specificities of ~63 and ~97% in plasma, and ~23 and ~99% in CSF).

Discussion

Our results show the absence of auto-antibodies directed against conformationally active neuronal surface targets, in both the plasma and CSF of patients with NPSLE. Furthermore, although SLE samples reacted more strongly with the DWEYS peptide, this binding was adequately accounted for by reactivity directly to the ELISA plate, suggesting a lack of antigenic specificity. The use of suitable antigen controls is therefore key in NPSLE studies, and may account for conflicting results in previous human reports. Taken together, our data suggest that autoantibodies have very limited clinical value in the definition or diagnosis of NPSLE and should prompt a search for novel biomarkers. IFNα is one such plausible candidate.[15,16] However, whereas IFNα levels performed slightly better in distinguishing patients with SLE from controls, they were also not enriched in the NPSLE subset.

In routine neurology practice, autoantibodies that bind to the surface of membrane proteins, such as the NMDAR, typically associate closely with a highly distinctive clinical phenotype.[9,10,12] These autoantibodies preferentially react with conformationally active, natively expressed forms of the whole antigen: this fundamental feature confers their pathogenic potential.[9–13] However, in patients with SLE/NPSLE, we could not detect autoantibodies that react with the natural range of surface epitopes presented on cultured hippocampal neurons or, more specifically, the extracellular domain of native NMDARs in patients with SLE or NPSLE,[18] despite proven adequate surface expression.

Several observations question the clinical and pathogenic relevance of DWEYS-peptide reactive antibodies.[7,8,19] First, the DWEYS motif exists in multiple other human proteins, such as caeruloplasmin. Next, binding of a monoclonal antibody to a small peptide, without reacting with the full-length, conformational protein, is unlikely to mediate target-specific functional effects *in vivo*. Third, from our data, DWEYS-reactive IgGs showed similar binding to scrambled and no peptide conditions. Hence, these antibodies do not specifically bind

DWEYS. Rather, the physiochemical properties of naturally occurring self-reactive antibodies, which are well described in SLE, are likely to account for their promiscuous binding characteristics.[20]

Limitations of this study include a modest cohort size and no examination of native glial or vascular reactivities, where the latter in particular may account for complement deposition observed in NPSLE brain tissue.[21] In addition, we studied only one cytokine and used rodent hippocampal neurons, which in culture may not express key surface antigens for human NPSLE. Nevertheless, our use of simliar, parallel assays has been successful previously in the detection of > 10 other likely pathogenic neurological autoantibodies.[12,13] Also, we test a sizeable set of CSFs and use rigorous control peptides, which accurately assess autoantibody specificity.

Our observations suggest that the brain disease associated with SLE is likely to have pathological drivers other than neuronal surface autoantibodies. Future studies might take broader "omics" approaches to assessing this clinically important manifestation of SLE, investigate innate immune components in greater detail, and identify reliable biomarkers for diagnosis, monitoring, and to better understand the primary pathology.

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Author Contributions

J.V., F.P., P.W., and S.R.I. contributed to the conception and design of the study. J.V., M.A., E.G., A.B., M.Z., V.B., D.D., D.H., F.P., P.W., and S.R.I. contributed to the acquisition and analysis of data. J.V., E.G., A.B., D.D., D.H., P.W., and S.R.I. contributed to drafting the text and preparing the figures.

Potential Conflicts of Interest

The authors declared no conflict of interest.

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