Review

Biomarkers in Neuropsychiatric Systemic Lupus Erythematosus: A Systematic Literature Review of the Last Decade

Julius Lindblom 1, Chandra Mohan 2 and Ioannis Parodis 1,3,*

1 Division of Rheumatology, Department of Medicine Solna, Karolinska Institute and Karolinska University Hospital, 17176 Stockholm, Sweden; julius.lindblom@ki.se
2 Department Biomedical Engineering, University of Houston, Houston, TX 77204, USA; cmohan@central.uh.edu
3 Department of Rheumatology, Faculty of Medicine and Health, Örebro University, 70182 Örebro, Sweden
* Correspondence: ioannis.parodis@ki.se; Tel.: +46-722321322

Abstract: Nervous system involvement in patients with SLE, termed neuropsychiatric SLE (NPSLE), constitutes a diagnostic challenge, and its management is still poorly optimised. This review summarises recent insights over the past decade in laboratory biomarkers of diagnosis, monitoring, and prognosis of NPSLE. An initial systematic search in the Medline and Web of Science was conducted to guide the selection of articles. Emerging diagnostic biomarkers in NPSLE that displayed satisfactory ability to discriminate between NPSLE and controls include serum interleukin (IL)-6, microRNA (miR)-23a, miR-155, and cerebrospinal fluid (CSF) α-Klotho. CSF lipocalin-2, macrophage colony-stimulating factor (M-CSF), and immunoglobulin (Ig)M also displayed such ability in two ethnically diverse cohorts. Serum interferon (IFN)-α and neuron specific enolase (NSE) were recently reported to moderately correlate with disease activity in patients with active NPSLE. CSF IL-8, IL-13, and granulocyte colony-stimulating factor (G-CSF) exhibited excellent sensitivity, yet poorer specificity, as predictors of response to therapy in patients with NPSLE. The overall lack of validation studies across multiple and diverse cohorts necessitates further and well-concerted investigations. Nevertheless, we propound CSF lipocalin 2 among molecules that hold promise as reliable diagnostic biomarkers in NPSLE.

Keywords: systemic lupus erythematosus; neuropsychiatric systemic lupus erythematosus; biomarkers; diagnosis; monitoring; prognosis

1. Introduction

Involvement of the central and peripheral nervous systems is a common but poorly understood manifestation of systemic lupus erythematosus (SLE), termed neuropsychiatric SLE (NPSLE). Although studies have reported varying prevalence estimates [1], largely depending on the level of stringency in definitions, NPSLE affects at least 20% of patients with SLE within the first years of the disease course [2]. Similar to other organ manifestations in SLE, NPSLE is highly heterogeneous and is commonly stratified into 19 different neuropsychiatric syndromes according to the 1999 American College of Rheumatology (ACR) NPSLE classification, including 12 central nervous system (CNS) and 7 peripheral nervous system (PNS) manifestations [3]. The CNS manifestations can be further subdivided into focal neurological deficits and diffuse psychiatric or neuropsychological syndromes, as shown in Table 1 [3]. It remains a challenge to distinguish these diverse clinical features from neuropsychiatric events unrelated to SLE. The state of the art in diagnostics relies on multidisciplinary approaches and expert-based attribution of the neuropsychiatric symptoms to SLE upon exclusion of other causes, following an extensive diagnostic workup that includes laboratory assessment and neuroimaging [4]. The management of NPSLE is poorly optimised due to the lack of high-level evidence in the literature and comprises, to a large extent, symptomatic strategies rather than specific treatment of the underlying
causes [5–8]. The purpose of this review was to summarise recent insights in laboratory biomarkers of diagnosis, monitoring, and prognosis of NPSLE, based on literature over the past decade. Among the biomarkers reviewed, CSF lipocalin 2 holds promise as a reliable diagnostic biomarker in NPSLE. Overall, NPSLE appears scarcely researched, and the vast majority of biomarker investigations lack validation across multiple and diverse cohorts.

Table 1. Neuropsychiatric syndromes according to the 1999 ACR NPSLE classification [3].

| CNS | PNS |
|-----|-----|
| **Diffuse** | **Focal** |
| Acute confusional state | Aseptic meningitis | Acute inflammatory demyelinating polyradiculoneuropathy |
| Anxiety disorders | Cerebrovascular disease | Autonomic disorder |
| Cognitive dysfunction | Demyelinating syndromes | Mononeuropathy (single/multiplex) |
| Mood disorders | Headache | Myasthenia gravis |
| Psychosis | Movement disorder | Cranial neuropathy |
| Seizure disorders | Myelopathy | Plexopathy |

| CNS | PNS |
|-----|-----|
| Seizure disorders | Polyneuropathy |

Adapted from “The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes.” Arthritis Rheum. 1999;42(4):599–608. Copyright 1999 by the American College of Rheumatology. Adapted with permission. ACR: American College of Rheumatology; CNS: central nervous system; PNS: peripheral nervous system; NPSLE: neuropsychiatric systemic lupus erythematosus.

2. Methods

An initial systematic search for relevant articles was performed as described in the online Supplementary Material (Figure S1; Tables S1 and S2), including a Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 flow diagram (Figure S1) [9]. In short, a search of the Medline and Web of Science for laboratory biomarker studies in English language comprising adult patients with NPSLE published between 1 January 2012 and 14 January 2022 was conducted. The search strategy and terms are detailed in the online Supplementary Material (Tables S1 and S2). Animal studies were beyond the scope of this review. The risk of bias (RoB) in the included studies was assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Analytical Cross-Sectional Studies, the JBI Critical Appraisal Checklist for Systematic Reviews and Research Syntheses, and the JBI Critical Appraisal Checklist for Cohort Studies [10], as appropriate.

2.1. Diagnostic Biomarkers

Recent literature reporting diagnostic biomarkers in NPSLE is summarised in Table 2. Serum anti-β2-glycoprotein I (β2GPI) antibodies of immunoglobulin (Ig)G and/or IgM isotypes displayed an odds ratio (OR) of 2.5 (95% confidence interval [CI]: 1.2–5.2) for distinguishing NPSLE from non-neuropsychiatric SLE in a large Italian cohort of SLE patients [11]. However, earlier studies failed to show such an association [12–14]. Nevertheless, in a study of focal NPSLE by Hawro et al. [15], serum anti-β2GPI IgM yielded an OR of 5.6 (95% CI: 1.2–26.9) for ischemic stroke and anti-β2GPI IgG yielded an OR of 11.3 (95% CI: 2.0–63.0) for seizures in a smaller cohort of SLE patients. A similar albeit weaker (OR: 6.5; 95% CI: 1.3–31.9) association was found for serum anti-cardiolipin (aCL) IgA and seizures [15]. These results are in line with previous reports of a link between anti-phospholipid (aPL) antibodies and neuropsychiatric manifestations of SLE, including cerebrovascular disease and seizures, supporting the role of vascular pathogenetic mechanisms in a substantial fraction of NPSLE patients [16–19]. Furthermore, the association between serum anti-ribosomal P antibodies and NPSLE (OR: 2.0; 95% CI: 1.2–3.4) was recently corroborated [20,21] and reported to be even stronger for diffuse involvement e.g., psychosis (OR: 3.1; 95% CI: 1.9–4.9) in a meta-analysis by Choi et al. [20]. Interestingly,
anti-ribosomal P antibodies purified from patients with NPSLE were shown to induce apoptosis in hippocampal neurons and impair memory in mice [22].

Emerging diagnostic protein and cytokine biomarkers in NPSLE that have displayed satisfactory ability to discriminate between NPSLE and non-neuropsychiatric SLE include serum interleukin (IL)-6 (area under the curve [AUC]: 0.89; p-value not available) [23], high-mobility group box protein 1 (HMGB1; AUC: 0.84; p < 0.05) [24] and cerebrospinal fluid (CSF) α-Klotho (AUC: 0.94; p < 0.001) [25], as detailed in Table 2. IL-6 serves an important function in stimulating activated B cells to secrete Ig and is known to be elevated in the CSF of NPSLE patients [26,27]. HMGB1 is a DNA-binding protein exerting various effects on immune cells but also on neuronal cells [28]. As HMGB1 has been reported as a marker of SLE disease activity [29] and an HMGB1 antagonist was shown to decrease seizure recurrence in mice [30], HMGB1 may constitute a target for future drug development in NPSLE. Interestingly, the single-pass transmembrane protein α-Klotho has been reported to have anti-inflammatory properties as well as regulate age-related cognitive decline, and reduced α-Klotho levels have been associated with myelin degradation [31–33]. CSF lipocalin-2, macrophage colony-stimulating factor (M-CSF), and IgM displayed good ability to distinguish patients with NPSLE from healthy individuals and/or patients with other neurological diseases in two separate cohorts of Canadian and Chinese patients (AUC: 0.80–0.85; p < 0.001 for all, AUC: 0.71–0.91; p < 0.05 for all, and AUC: 0.78–0.95; p < 0.01 for all, respectively) [34–36]. Lipocalin 2 is an acute-phase glycoprotein that is secreted by neurons among multiple cell types during cellular stress [37,38]. M-CSF expressing T helper (T_h) cells were recently reported to be elevated in CSF from patients with MS, a neurological disease that resembles NPSLE in terms of certain neuroinflammatory attributes, while CSF IgG index was associated with inflammatory activity in magnetic resonance imaging (MRI) of the brain in MS patients [39,40].

Using a novel proteomic approach to investigate immune complex (IC)-associated antigens in CSF in patients with NPSLE, Aibara et al. [41] discovered several proteins with excellent specificity, yet overall poor sensitivity for distinguishing NPSLE patients from healthy controls (Table 2). Among those, occurrence of CSF suprabasin isoform 1 precursor displayed the best diagnostic properties, with a specificity of 100% but a sensitivity of 35% [41]. These results prompted further investigation by Ichinose et al. [42], who reported that CSF anti-suprabasin antibodies could distinguish patients with NPSLE from patients with non-neuropsychiatric SLE, multiple sclerosis (MS), and normal pressure hydrocephalus (NPH) in a Japanese cohort (N = 103), with a specificity of 92% and a sensitivity of 42% using an antibody index (A.I.) cut-off of 1.0. Results from the same study lent support for a pathogenetic role of anti-suprabasin antibodies through alterations of senescence and autophagy pathways in astrocytes [42].

A common single nucleotide polymorphism (SNP) i.e., rs11797 of the three prime repair exonuclease 1 (TREX1) gene was reported to be more frequent in patients with NPSLE than in patients without any non-neuropsychiatric manifestations with an OR of 6.4 (95% CI: 1.7–26.2) [43]. Similarly, an earlier study found rs11797 to discriminate between SLE patients with focal involvement i.e., seizures and healthy controls (OR: 1.7; 95% CI: 1.2–2.4) [44]. Mutations in the TREX1 gene have been linked to several diseases, including SLE and Aicardi-Goutières syndrome (AGS), a rare neurological condition that is characterized by its onset in early childhood and bears some clinical resemblance with SLE [45]. Emerging epigenetic biomarkers in NPSLE that have displayed satisfactory ability to discriminate between NPSLE and controls (healthy individuals or other neurological diseases) include microRNA (miR)-23a (AUC: 0.95–0.98; p < 0.001 for all) [46] and miR-155 (AUC: 0.76–0.92; p < 0.05 for all) [46]. MicroRNAs (miRNAs) are short single-stranded RNA molecules that regulate gene expression through degradation of messenger RNAs [47] and have been indicated to have a role in disease mechanisms of SLE in recent epigenetic research [48,49].
Table 2. Performance of selected diagnostic biomarkers in NPSLE.

| Biomarker               | Sample          | Feature            | Comparator                        | Metrics                          | References                                      |
|-------------------------|-----------------|--------------------|-----------------------------------|----------------------------------|------------------------------------------------|
| Anti-ribosomal P (+)    | Serum/plasma    | Unspecified        | Non-NP SLE                         | AUC: 0.57; OR: 2.0–3.3           | Huang et al., 2020 [24]; Zhang et al., 2021 [21] |
|                         |                 |                    | Unspecified; Diffuse              | Pooled OR: 1.6–3.1               | Choi et al., 2020 [20]                          |
| Anti-Sm (+)             | Serum/plasma    | Focal; Unspecified | Non-seizure SLE; Non-NP SLE, MS, NMO and VM | OR: 1.0–3.3                      | Mikdashi et al., 2005 [17]; Ushigusa et al., 2016 [25] |
| aCLs * (+)              | Serum/plasma    | Unspecified; Focal | Non-NP SLE; Non-seizure SLE       | OR: 1.9–7.3                      | Govoni et al., 2012 [11]; Karassa et al., 2000 [18]; Hawro et al., 2015 [15]; Mikdashi et al., 2005 [17] |
| Anti-β2GP1 * (+)        | Serum/plasma    | Unspecified; Focal | Non-NP SLE; Non-CVD SLE; Non-headache SLE; Non-seizure SLE | OR: 2.5–11.3                     | Govoni et al., 2012 [11]; Hawro et al., 2015 [15] |
| Anti-GAPDH (levels)     | Serum/plasma    | Unspecified        | N/A                               | ρ = 0.57                         | Sun et al., 2019 [50]                           |
| Anti-GABAR † (+)        | Serum/plasma    | Unspecified        | Non-NP SLE                         | OR: 4.6–5.5                      | Tsuchiya et al., 2014 [51]                      |
| Anti-vimentin † (<40.5 NFI) | Serum/plasma   | Unspecified        | Non-NP SLE                         | Sens.: 88%; Spec.: 66%; AUC: 0.81; OR: 13.5 | van der Meulen et al., 2017 [52]               |
| Anti-heparan sulphate † (>205 NFI) | Serum/plasma | Unspecified        | Non-NP SLE                         | Sens.: 65%; Spec.: 70%; AUC: 0.72; OR: 4.5 |
| Anti-nucleoporin 62 † (<26.5 NFI) | Serum/plasma | Unspecified        | Non-NP SLE                         | Sens.: 81%; Spec.: 55%; AUC: 0.72; OR: 4.5 |
| Anti-prothrombin † (<32.5 NFI) | Serum/plasma | Unspecified        | Non-NP SLE                         | Sens.: 65%; Spec.: 65%; AUC: 0.69; OR: 3.6 |
| Anti-glycoprotein 2 † (<34.5 NFI) | Serum/plasma | Unspecified        | Non-NP SLE                         | Sens.: 68%; Spec.: 65%; AUC: 0.68; OR: 4.0 |
| Anti-cardiolipin † (>0.5 NFI) | Serum/plasma | Unspecified        | Non-NP SLE                         | Sens.: 45%; Spec.: 87%; AUC: 0.66; OR: 5.3 |
| Anti-histone H2A † (>189.0 NFI) | Serum/plasma | Unspecified        | Non-NP SLE                         | Sens.: 61%; Spec.: 64%; AUC: 0.65; OR: 2.7 |
| Anti-histone H2B † (>146.5 NFI) | Serum/plasma | Unspecified        | Non-NP SLE                         | Sens.: 64%; Spec.: 63%; AUC: 0.65; OR: 2.9 |
| Anti-collagen II † (>4.5 NFI) | Serum/plasma | Unspecified        | Non-NP SLE                         | Sens.: 65%; Spec.: 58%; AUC: 0.65; OR: 2.6 |
| Anti-heparin † (>174.0 NFI) | Serum/plasma | Unspecified        | Non-NP SLE                         | Sens.: 65%; Spec.: 61%; AUC: 0.65; OR: 2.8 |
| Anti-amyloid † (>1.5 NFI) | Serum/plasma    | Unspecified        | Non-NP SLE                         | Sens.: 70%; Spec.: 58%; AUC: 0.65; OR: 3.2 |
Table 2. Cont.

| Biomarker                        | Sample       | Feature | Comparator                      | Metrics               | References                                      |
|---------------------------------|--------------|---------|---------------------------------|-----------------------|------------------------------------------------|
| Anti-suprabasin (A.I. ≥1.0)     | CSF          | Unspecified | Non-NP SLE, MS and NPH         | Sens.: 42%; Spec.: 92%; AUC: 0.78 | Ichinose et al., 2018 [42]                       |
|                                 |              |          |                                 |                       |                                                |
| Proteins/cytokines              |              |         |                                 |                       |                                                |
| C3 (low)                        | Serum/plasma | Unspecified | Non-NP SLE                      | OR: 3.8               | Karassa et al., 2000 [18]                       |
| C3 (levels)                     | Serum/plasma | Unspecified | Non-NP SLE, MS, NMO and VM      | Adj. OR: 1.1          | Ushigusa et al., 2016 [25]                      |
| NfL (↑)                         | Serum/plasma | Unspecified | Non-NP SLE                      | AUC: 0.65             | Engel et al., 2021 [53]                         |
| NSE (levels)                    | Serum/plasma | Unspecified | Non-NP SLE                      | ρ = −0.37             | Hawro et al., 2015 [54]                         |
| HMGB1 (levels)                  | Serum/plasma | Unspecified | Non-NP SLE                      | AUC: 0.84; OR: 1.7    | Huang et al., 2020 [24]                         |
| IL-6 (>74.9 pg/mL; ↑)           | Serum/plasma | Unspecified | Non-NP SLE                      | Sens.: 75%; Spec.: 100%; AUC: 0.89 | Kitagori et al., 2019 [23]                       |
| IL-17 (↑)                       | CSF          |          | Non-NP SLE, MS and NMO          | Sens.: 88%; Spec.: 98%; PPV: 97; NPV: 91 | Ichinose et al., 2015 [55]                       |
| IL-2 (↑)                        | Serum/plasma | Diffuse  | N/A                             | ρ = 0.19–0.32         | Lu et al., 2021 [56]                            |
| Free T3 (levels)                | Serum/plasma |         | Free T4 (levels)                | ρ = 0.28–0.42         |                                                |
| HDL-C (levels)                  | Serum/plasma |          | Free T4 (levels)                | ρ = 0.19–0.32         |                                                |
| IGFBP7 (levels)                 |              |          | Free T4 (levels)                | ρ = 0.05–0.08         |                                                |
| S100B (>0.0218 ng/mL)           | Serum/plasma | Unspecified | Non-NP SLE                      | Sens.: 81%; Spec.: 67%; PPV: 84%; NPV: 62%; AUC: 0.74 | Noris-Garcia et al., 2018 [57]                   |
| IL-15 (↑)                       | CSF          | Unspecified | MS and NMO                     | Sens.: 91%; Spec.: 90%; PPV: 88; NPV: 93 |                                                |
| IL-15 (↑)                       | CSF          | Unspecified | MS and NMO                     | Sens.: 88%; Spec.: 98%; PPV: 97; NPV: 91 |                                                |
| FGF2 (↑)                        |              |          |                                  | Sens.: 88%; Spec.: 95%; PPV: 93; NPV: 91 |                                                |
| IL-8 (↑)                        |              |          |                                  | Sens.: 94%; Spec.: 95%; PPV: 94; NPV: 95 |                                                |
| Osteopontin (>963.4 ng/mL)      | CSF          | Unspecified | Non-NP SLE                      | Sens.: 70%; Spec.: 100%; AUC: 0.88 | Kitagori et al., 2019 [23]                       |
| Lipocalin 2 (↑, ≥122 pg/mL; ≥126 pg/mL; ▼) | CSF          | Unspecified | HC/other neurological diseases | Sens.: 76–94%; Spec.: 80%; PPV: 63–84%; NPV: 88–92%; AUC: 0.80–0.85 | Mike et al., 2019 [35]; Vanarsa et al., 2022 (in print) [34] |
| α-Klotho (<230.2 pg/mL)         | CSF          | Unspecified | Non-NP SLE, MS, NMO and VM      | Sens.: 82%; Spec.: 94%; AUC: 0.94; OR: 0.98 | Ushigusa et al., 2016 [25]                       |
Table 2. Cont.

| Biomarker          | Sample          | Feature                  | Comparator                      | Metrics                             | References                          |
|--------------------|-----------------|--------------------------|---------------------------------|-------------------------------------|-------------------------------------|
| Angiostatin        | CSF              | Unspecified              | HC/other neurological diseases   | Sens.: 88%; Spec.: 44%; PPV: 45%; NPV: 88%; AUC: 0.65 | Vanarsa et al., 2022 (in print) [34] |
| DAN                | CSF              | Unspecified              | HC/other neurological diseases   | Sens.: 76%; Spec.: 63%; PPV: 52%; NPV: 84%; AUC: 0.75 | Vanarsa et al., 2022 (in print) [34] |
| DAN                | CSF              | Unspecified              | HC/other neurological diseases   | Sens.: 67%; Spec.: 85%; PPV: 70%; NPV: 83%; AUC: 0.81 | Vanarsa et al., 2022 (in print) [34] |
| Fibronectin        | CSF              | Unspecified              | HC/other neurological diseases   | Sens.: 52%; Spec.: 85%; PPV: 65%; NPV: 78%; AUC: 0.69 | Vanarsa et al., 2022 (in print) [34] |
| HCC-1              | CSF              | Unspecified              | HC/other neurological diseases   | Sens.: 47–80%; Spec.: 94–100%; PPV: 87–100%; NPV: 62–90%; AUC: 0.71–0.91 | Vanarsa et al., 2022 (in print) [34] |
| M-CSF              | CSF              | Unspecified              | HC/other neurological diseases   | Sens.: 71%; Spec.: 80%; PPV: 65%; NPV: 85%; AUC: 0.78 | Vanarsa et al., 2022 (in print) [34] |
| SERPING1           | CSF              | Unspecified              | HC/other neurological diseases   | Sens.: 70–100%; Spec.: 89–100%; PPV: 83–100%; NPV: 75–100%; AUC: 0.78–0.95 | Vanarsa et al., 2022 (in print) [34] |

IC-associated antigens

| Isoform 7 of nesprin-1 (+) | CSF (IC-associated) | Unspecified | HC | Sens.: 8%; Spec.: 100% | Aibara et al., 2018 [41] |
| Suprabasin isoform 1 precursor (+) | CSF (IC-associated) | Unspecified | HC | Sens.: 35%; Spec.: 100% | Aibara et al., 2018 [41] |
| Calmodulin-like protein 5 (+) | CSF (IC-associated) | Unspecified | HC | Sens.: 12%; Spec.: 92% | Aibara et al., 2018 [41] |
| cDNA FLJ58075, highly similar to ceruloplasmin (+) | CSF (IC-associated) | Unspecified | HC | Sens.: 4%; Spec.: 96% | Aibara et al., 2018 [41] |
| Desmoglein-1 (+) | CSF (IC-associated) | Unspecified | HC | Sens.: 15%; Spec.: 96% | Aibara et al., 2018 [41] |
| INTS4-like protein 2 (+) | CSF (IC-associated) | Unspecified | HC | Sens.: 4%; Spec.: 96% | Aibara et al., 2018 [41] |
| Isoform 1 of α1-antitrypsin (+) | CSF (IC-associated) | Unspecified | HC | Sens.: 4%; Spec.: 96% | Aibara et al., 2018 [41] |
| Isoform 2 of NUMA1 (+) | CSF (IC-associated) | Unspecified | HC | Sens.: 4%; Spec.: 96% | Aibara et al., 2018 [41] |
| Protein piccolo (+) | CSF (IC-associated) | Unspecified | HC | Sens.: 8%; Spec.: 98% | Aibara et al., 2018 [41] |
| Isoform 3 of RICTOR (+) | CSF (IC-associated) | Unspecified | HC | Sens.: 19%; Spec.: 100% | Aibara et al., 2018 [41] |

Genetic/epigenetic markers
| Biomarker | Sample Feature | Comparator | Metrics | References |
|-----------|----------------|------------|---------|------------|
| PD-1 (FC) | Blood (gene expression) | Diffuse | Non-psychosis SLE | $\rho = 0.24$ | Bassiouni et al., 2021 [58] |
| TREX1 (relative frequencies) | Blood (SNPs §) | Unspecified; Focal | Non-NP SLE; HC; Non-neurological SLE | OR: 1.6–44.7 | Fredi et al., 2015 [43]; Namjou et al., 2011 [44] |
| TRPC6 (relative frequencies) | Blood (SNP rs925662) | Unspecified | Non-NP SLE | HR: 0.4–3.3 | Ramirez et al., 2015 [59]; Ramirez et al., 2018 [60] |
| miR-145 | Serum/plasma (expression) | Unspecified | HC; MS; NMO | Sens.: 60–80%; Spec.: 83–100%; PPV: 57–100%; NPV: 77–94%; AUC: 0.76–0.90 | Sharaf-Eldin et al., 2017 [61] |
| miR-223 | Serum/plasma (expression) | Unspecified | HC; MS | Sens.: 90%; Spec.: 87–100%; PPV: 75–100%; NPV: 90–97%; AUC: 0.91–0.99 | Sharaf-Eldin et al., 2017 [61] |
| miR-326 | Serum/plasma (expression) | Unspecified | HC | Sens.: 70%; Spec.: 78%; PPV: 58%; NPV: 86%; AUC: 0.73 | Sharaf-Eldin et al., 2017 [61] |
| SMAD3 | Serum/plasma (expression) | Unspecified | MS | Sens.: 80%; Spec.: 76%; PPV: 47%; NPV: 93%; AUC: 0.82 |
| SP1 (FC > 0.795) | Serum/plasma (expression) | Unspecified | MS | Sens.: 80%–90%; Spec.: 88%–90%; AUC: 0.76–0.92 | Sharaf-Eldin et al., 2020 [46] |
| miR-23a (FC ≥ 0.1; FC ≥ 0.7) | Serum/plasma (expression) | Unspecified | HC; MS | Sens.: 90%–100%; Spec.: 96–100%; AUC: 0.95–0.98 |
| miR-155 (FC ≥ 0.1; FC ≥ 0.7) | Serum/plasma (expression) | Unspecified | HC; NMO; MS | Sens.: 60–90%; Spec.: 88–90%; AUC: 0.76–0.92 | Sharaf-Eldin et al., 2020 [46] |
| miR-572 (FC ≥ 4.5) | Serum/plasma (expression) | Unspecified | HC | Sens.: 90%; Spec.: 68%; AUC: 0.80 |

*aCL*: anti-cardiolipins; *adj.:* adjusted; *A.I.:* antibody index; *ApoA1*: apolipoprotein A1; *ApoE*: apolipoprotein E; *AUC*: area under the curve; *β2-GPI*: β2-glycoprotein 1; *C3*: complement component 3; *cDNA*: circular deoxyribonucleic acid; *CFD*: cerebrospinal fluid; *CVD*: cerebrovascular disease; *FC*: fold change; *FGF2*: fibroblast growth factor 2; *GABAR*: gamma-aminobutyric acid type B receptors; *GAPDH*: glyceraldehyde 3-phosphate dehydrogenase; *HC*: healthy control; *HDL-C*: high-density lipoprotein cholesterol; *HMGB1*: high-mobility group box protein 1; *HR*: hazard ratio; *IC*: immune complex; *IFN*: interferon; *Ig*: immunoglobulin; *IGFBP7*: insulin-like growth factor binding protein 7; *IL*: interleukin; *INT5*: integrator complex subunit 4; *M-CSF*: macrophage colony-stimulating factor; *miR*: microRNA; *NFI*: net fluorescent intensity; *NPH*: normal pressure hydrocephalus; *NP*: neuropsychiatric; *NPSLE*: neuropsychiatric systemic lupus erythematosus; *NS*: neuron specific enolase; *MS*: multiple sclerosis; *NMO*: neuromyelitis optica; *NPV*: negative predictive value; *NUMA1*: nuclear mitotic apparatus protein 1; *OR*: odds ratio; *PD*: programmed death 1; *PPV*: positive predictive value; *RICTOR*: rapamycin-insensitive companion of mammalian target of rapamycin; *S100B*: S100 calcium-binding protein B; *Sens.*: sensitivity; *SERPING1*: serpin family G member 1; *SLE*: systemic lupus erythematosus; *Sm*: Smith; *SMAD3*: signaling mother against decapentaplegic peptide 3; *SNP*: single nucleotide polymorphism; *SP1*: specificity protein 1; *Spec.*: specificity; *T3*: triiodothyronine; *T4*: thyroxine; *TREX1*: three prime repair exonuclease 1; *TRPC6*: transient receptor potential cation channel, subfamily C, member 6; *VM*: venous malformation; *↑*: elevated. *IgA, IgG and/or IgM isotypes; *†*: anti-GABAR<sub>b1b</sub> and anti-GABAR<sub>b2</sub> antibodies; *‡*: IgG isotype; *§*: rs11797, rs922075, rs6776700, rs6442123, rs2242150, or rs3135945.
2.2. Biomarkers of Disease Activity

Serum interferon (IFN)-α exhibited a trend towards a moderate correlation ($\rho = 0.33; p = 0.05$) with disease activity measured with the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) \cite{62} in patients with NPSLE at the onset of neuropsychiatric manifestations \cite{63}. Type I IFNs are considered key mediators in SLE pathogenesis \cite{64}, with the recent approval of the anti-type I IFN receptor monoclonal anifrolumab \cite{65,66} by the US Food and Drug Administration (FDA) for the treatment of SLE \cite{67}, lending cogent credence to this notion. By contrast, serum neuron-specific enolase (NSE) displayed a negative correlation with disease activity ($\rho = -0.42; p < 0.05$) measured with the Systemic Lupus Activity Measure (SLAM) \cite{68} in patients with active NPSLE \cite{54}. NSE is a glycolytic enzyme that is expressed in neural cells \cite{69}. Peripheral blood levels of NSE have been shown to increase upon acute neuronal injury, whereas reduced levels have been reported in chronic diseases of the CNS, and a negative correlation between plasma NSE and disease progression was reported in patients with MS \cite{70–73}.

Fatigue is a major complaint in patients with SLE and has been linked to SLE disease activity \cite{74}, as well as cognitive impairment in NPSLE \cite{75}. A study by Hopia et al. \cite{76} comprising 28 patients with NPSLE from a Swedish clinical setting showed a positive correlation ($\rho = 0.43; p < 0.05$) between CSF levels of a proliferation-inducing ligand (APRIL) and fatigue measured with the Fatigue Severity Scale (FSS) \cite{77}.

2.3. Biomarkers of Response to Therapy

Ichino et al. \cite{78} recently investigated the performance of selected molecules measured in CSF from patients with NPSLE (N = 28) as predictors of response to conventional immunosuppressive therapy with or without the addition of rituximab, evaluated 1 year after treatment commencement. Several markers displayed excellent sensitivity yet poorer specificity for predicting treatment response, with downregulated IL-8 (sensitivity: 100%; specificity: 50%), IL-13 (sensitivity: 100%; specificity: 50%), and G-CSF (sensitivity: 100%; specificity: 50%) displaying the best overall metrics \cite{78}.

2.4. Prognostic Biomarkers

Data on prognostic biomarkers of long-term outcome in NPSLE were scarce. In a study from the large Hopkins Lupus Cohort by Huang et al. \cite{79} of which 46% of patients were followed up for more than 5 years, a history of anti-Smith (Sm) antibodies (rate ratio [RR]: 1.8; $p = 0.005$), low complement component 3 (C3; RR: 2.0; $p = 0.001$), low C4 (RR: 1.7; $p = 0.006$), and urine dipstick protein 3+ at the most recent visit (RR: 7.4; $p < 0.001$) predicted incidence of seizures upon SLE diagnosis, after adjustment for age. However, only a history of low C3 (RR: 1.8, $p = 0.008$) and urine dipstick protein 3+ (RR: 2.7; $p = 0.004$) remained significant in multivariable analyses \cite{79}. A study by Zhang et al. (21) showed that elevated serum creatinine levels were an independent contributor to premature mortality in patients with NPSLE with an adjusted hazard ratio (HR) of 3.3 (95% CI: 1.1–9.5) in multivariable regression analysis, which however is a finding with no apparent manifestation-specific relevance.

3. Perspective

Although in-depth understanding of the pathogenesis of NPSLE remains poor, technological advances are anticipated to help shed light on this complex SLE manifestation, and investigations of the last decade have contributed useful insights for a more appropriate management of these patients. However, while research has focused on optimisation of diagnostic procedures through the derivation of novel biomarkers, little has been done with regard to surveillance and prognosis of long-term outcomes. Moreover, while several candidate markers have emerged, the study populations have overall been limited and heterogenous, partly owing to the rarity of the different NPSLE syndromes. Most of the studies included in the present review investigated associations with the entire NPSLE spectrum i.e., all items in the 1999 ACR classification \cite{3} together rather than as distinct
groups of NPSLE patients e.g., patients with focal neurological or diffuse psychiatric or neuropsychological manifestations. In this respect, it is worth noting that studies that focused on either focal or diffuse manifestations investigated serum or plasma biomarkers. Since CSF constitutes a source of sampling that is more specific to the CNS, future CSF biomarker survey might be useful towards identification of manifestation-specific mediators and acquisition of further insights into underlying pathogenetic mechanisms. Among emerging diagnostic biomarkers, CSF α-Klotho and serum IL-6, miR-23a and miR-155 exhibited satisfactory ability to discriminate between patients with NPSLE and controls, as did CSF lipocalin-2, M-CSF, and IgM in two ethnically diverse cohorts. Serum IFN-α and NSE were reported to moderately correlate with disease activity in patients with NPSLE, while CSF IL-8, IL-13, and G-CSF exhibited excellent sensitivity, yet poorer specificity, as predictors of response to therapy.

In our assessment of RoB, sources of bias primarily included three bias types i.e., some studies did not describe the subjects and the setting in detail, some did not use standard classification to define NPSLE, and some did not account for confounding factors, as indicated in the online Supplementary Material (Tables S3–S5). The overall lack of validation studies across multiple cohorts necessitates further and well-concerted investigations.

In contrast with more clearly defined neurological conditions e.g., MS, where imaging constitutes an invaluable guide of diagnosis and monitoring, NPSLE still suffers challenges with regard to definite classification, owing to its immense heterogeneity and, partly as a consequence of the latter, inconsistent nomenclature in the literature. Thus, we advocate bolstering the classification of distinct syndromes within the clinical spectrum of NPSLE, with validated candidate biomarkers emerging from detailed molecular characterisation of these distinct clinical phenotypes. We foresee that broad molecular and cellular profiling through next-generation sequencing, cutting-edge proteomic and metabolomic investigations, and data integration with sophisticated bioinformatics that incorporate systems biology will revolutionise the field of NPSLE and pave the way toward person-centred diagnostics, and management and prevention of long-term damage, flares, or even disease occurrence. A prerequisite for research with such premise would be broad multicentre collaborations beyond country or continental borders.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/brainsci12020192/s1, Figure S1: PRISMA 2020 flow diagram for new systematic reviews that included searches of databases and registers only; Table S1. Search in the Medline; Table S2. Search in the Web of Science; Table S3. Risk of bias assessment of cross-sectional studies; Table S4. Risk of bias assessment of meta-analyses; Table S5. Risk of bias assessment of cohort studies.

Author Contributions: Conceptualization, J.L., C.M. and I.P.; methodology, J.L., C.M. and I.P.; investigation, J.L.; writing—original draft preparation, J.L.; writing—review and editing, J.L., C.M. and I.P.; supervision, I.P.; funding acquisition, C.M. and I.P. All authors have read and agreed to the published version of the manuscript.

Funding: C.M. research is supported by NIH R01 AR074096 and the Lupus Research Alliance. I.P. has received grants from the Swedish Rheumatism Association (R-941095), King Gustaf V’s 80-year Foundation (FAI-2020-0741), Professor Nanna Svartz Foundation (2020-00368), Ulla and Roland Gustafsson Foundation (2021–26), Region Stockholm (FoUI-955483), and Karolinska Institutet.

Acknowledgments: We thank the librarians Love Strandberg and Narcisa Hannerz from the Karolinska Institutet library (KIB) for their assistance with the construction of the search strategy.

Conflicts of Interest: J.L. and C.M. declare that they have no conflicts of interest. I.P. has received research funding and/or honoraria from Amgen, AstraZeneca, Aurinia Pharmaceuticals, Elli Lilly and Company, Gilead Sciences, GlaxoSmithKline, Janssen Pharmaceuticals, Novartis, and F. Hoffmann-La Roche AG. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.
References

1. Unterman, A.; Nolte, J.E.; Boaz, M.; Abady, M.; Shoenfeld, Y.; Zandman-Goddard, G. Neuropsychiatric Syndromes in Systemic Lupus Erythematosus: A Meta-Analysis. *Semin. Arthritis Rheum*. 2011, 41, 1–11. [CrossRef] [PubMed]

2. Hanly, J.G.; Urowitz, M.B.; Su, L.; Bae, S.-C.; Gordon, C.; Wallace, D.J.; Clarke, A.; Bernatsky, S.; Isenberg, D.; Rahman, A.; et al. Prospective analysis of neuropsychiatric events in an international disease inception cohort of patients with systemic lupus erythematosus. *Ann. Rheum. Dis.* 2009, 69, 529–535. [CrossRef] [PubMed]

3. The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. *Arthritis Rheum.* 1999, 42, 599–608. [CrossRef]

4. Schwartz, N.; Stock, A.D.; Putterman, C. Neuropsychiatric lupus: New mechanistic insights and future treatment directions. *Nat. Rev. Rheumatol.* 2019, 15, 137–152. [CrossRef]

5. Barilefabris, A.L.; Ariza-Andraca, R.; Olguín-Ortega, L.; Jara, L.J.; Fraga-Mouret, A.; Miranda-Limón, J.M.; De La Mata, J.F.; Clark, A.P.; Vargas, F.S.; Alcocer-Varela, J. Controlled clinical trial of IV cyclophosphamide versus IV methylprednisolone in severe neurological manifestations in systemic lupus erythematosus. *Ann. Rheum. Dis.* 2005, 64, 620–625. [CrossRef] [PubMed]

6. Mok, C.C.; Lau, C.S.; Wong, R.W. Treatment of lupus psychosis with oral cyclophosphamide followed by azathioprine maintenance: An open-label study. *Ann. J. Med.* 2003, 115, 59–62. [CrossRef]

7. Tokunaga, M.; Saito, K.; Kawabata, D.; Imura, Y.; Fujii, T.; Nakayamada, S.; Tsujimura, S.; Nawata, M.; Iwata, S.; Azuma, T.; et al. Efficacy of rituximab (anti-CD20) for refractory systemic lupus erythematosus involving the central nervous system. *Ann. Rheum. Dis.* 2006, 66, 470–475. [CrossRef] [PubMed]

8. Bertsias, G.K.; Ioannidis, J.P.A.; Aringer, M.; Bollen, E.; Bombardieri, S.; Bruce, I.N.; Cervera, R.; Dalakas, M.; Doria, A.; Hanly, J.G.; et al. EULAR recommendations for the management of systemic lupus erythematosus with neuropsychiatric manifestations: Report of a task force of the EULAR standing committee for clinical affairs. *Ann. Rheum. Dis.* 2010, 69, 2074–2082. [CrossRef] [PubMed]

9. Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Brennan, S.E.; et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ* 2021, 372, 71. [CrossRef]

10. JBI Critical Appraisal Tools. Available online: https://jbi.global/critical-appraisal-tools (accessed on 19 January 2022).

11. Govoni, M.; Bombardieri, S.; Bortoluzzi, A.; Caniatti, L.; Casu, C.; Conti, F.; De Vita, S.; Doria, A.; Farina, I.; Ferraccioli, G.; et al. Factors and comorbidities associated with first neuropsychiatric event in systemic lupus erythematosus: Does a risk profile exist? A large multicentre retrospective cross-sectional study on 959 Italian patients. *Rheumatology* 2011, 51, 157–168. [CrossRef]

12. Hanly, J.G.; Urowitz, M.B.; Su, L.; Bae, S.-C.; Gordon, C.; Clarke, A.; Bernatsky, S.; Vasudevan, A.; Isenberg, D.; Rahman, A.; et al. Autoantibodies as biomarkers for the prediction of neuropsychiatric events in systemic lupus erythematosus. *Ann. Rheum. Dis.* 2011, 70, 1726–1732. [CrossRef] [PubMed]

13. Hanly, J.G.; Urowitz, M.B.; Siannis, F.; Farewell, V.; Gordon, C.; Bae, S.-C.; Isenberg, D.; Dooley, M.A.; Clarke, A.; Bernatsky, S.; et al. Autoantibodies and neuropsychiatric events at the time of systemic lupus erythematosus diagnosis: Results from an international inception cohort study. *Arthritis Care Res.* 2008, 58, 843–853. [CrossRef] [PubMed]

14. Hanly, J.G.; Urowitz, M.B.; Su, L.; Gordon, C.; Bae, S.-C.; Sanchez-Guerrero, J.; Romero-Diaz, J.; Wallace, D.J.; Clarke, A.E.; Ginzel, E.; et al. Seizure disorders in systemic lupus erythematosus results from an international, prospective, inception cohort study. *Ann. Rheum. Dis.* 2012, 71, 1502–1509. [CrossRef] [PubMed]

15. Hawro, T.; Bogucki, A.; Krupińska-Kun, M.; Maurer, M.; Woźniacka, A. Intractable Headaches, Ischemic Stroke, and Seizures Are Linked to the Presence of Anti-β2GPI Antibodies in Patients with Systemic Lupus Erythematosus. *PLoS ONE* 2015, 10, e0119911. [CrossRef] [PubMed]

16. Mok, C.C.; Lau, C.S.; Wong, R.W. Neuropsychiatric manifestations and their clinical associations in southern Chinese patients with systemic lupus erythematosus. *J. Rheumatol.* 2001, 28, 766–771.

17. Mikkashi, J.; Krumholz, A.; Handwerger, B. Factors at diagnosis predict subsequent occurrence of seizures in systemic lupus erythematosus. *Neurology* 2005, 64, 2102–2107. [CrossRef]

18. Karassa, F.; Ioannidis, J.; Toulioumi, G.; Boki, K.; Moutsopoulos, H. Risk factors for central nervous system involvement in systemic lupus erythematosus. *QJM: Int. J. Med.* 2000, 93, 169–174. [CrossRef] [PubMed]

19. Leal Rato, M.; Bandeira, M.; Romão, V.C.; Aguier de Sousa, D. Neurologic Manifestations of the Antiphospholipid Syndrome-an Update. *Curr. Neurol. Neurosci. Rep.* 2021, 21, 41. [CrossRef]

20. Choi, M.Y.; Fitz, P.R.D.; Buhrer, K.; Mahler, M.; Fritzler, M.J. A review and meta-analysis of anti-ribosomal P autoantibodies in systemic lupus erythematosus. *Autoimmun. Rev.* 2020, 19, 102463. [CrossRef] [PubMed]

21. Zhang, S.; Li, M.; Zhang, L.; Wang, Z.; Wang, Q.; You, H.; Wang, Y.; Li, M.; Zeng, X. Clinical Features and Outcomes of Neuropsychiatric Systemic Lupus Erythematosus in China. *J. Immunol. Res.* 2021, 2021, 1–10. [CrossRef]

22. Bravo-Zehnder, M.; Toledo, E.; Segovia-Miranda, F.; Serrano, F.; Benito, M.J.; Metz, C.; Retamal, C.; Álvarez, A.; Massardo, L.; Inestrosa, N.C.; et al. Anti-Ribosomal P Protein Autoantibodies from Patients With Neuropsychiatric Lupus Impair Memory in Mice. *Arthritis Rheumatol.* 2015, 67, 204–214. [CrossRef] [PubMed]

23. Kitagori, K.; Yoshifuchi, H.; Oku, T.; Ayaki, T.; Kuzuya, A.; Nakajima, T.; Akizuki, S.; Nakashima, R.; Murakami, K.; Ohmura, K.; et al. Utility of osteopontin in cerebrospinal fluid as a diagnostic marker for neuropsychiatric systemic lupus erythematosus. *Lupus* 2019, 28, 414–422. [CrossRef] [PubMed]
24. Huang, Q.; Shen, S.; Qu, H.; Huang, Y.; Wu, D.; Jiang, H.; Yuan, C. Expression of HMGB1 and TLR4 in neuropsychiatric systemic lupus erythematosus patients with seizure disorders. *Ann. Transl. Med.* 2020, 8, 9. [CrossRef] [PubMed]

25. Ushigusa, T.; Ichinose, K.; Sato, S.; Michitsui, T.; Shimizu, T.; Umeda, M.; Fukui, S.; Nishino, A.; Nakashima, Y.; Koga, T.; et al. Soluble α-klotho is a potential biomarker associated with neuropsychiatric systemic lupus erythematosus. *Clin. Immunol.* 2016, 165, 29–34. [CrossRef] [PubMed]

26. Hirohata, S.; Miyamato, T. Elevated levels of interleukin-6 in cerebrospinal fluid from patients with systemic lupus erythematosus and central nervous system involvement. *Arthritis Rheum.* 1990, 33, 644–649. [CrossRef] [PubMed]

27. Hirano, T.; Yasukawa, K.; Harada, H.; Taga, T.; Watanabe, Y.; Matsuda, T.; Kashiwamura, S.-I.; Nakajima, K.; Koyama, K.; Iwamatsu, A.; et al. Complementary DNA for a novel human interleukin (BSF-2) that induces B lymphocytes to produce immunoglobulin. *Nature* 1986, 324, 73–76. [CrossRef]

28. Harris, H.E.; Andersson, U.; Pisetksy, D.S. HMGB1: A multifunctional alarmin driving autoimmune and inflammatory disease. *Nat. Rev. Rheumatol.* 2012, 8, 195–202. [CrossRef]

29. Li, J.; Xie, H.; Wen, T.; Liu, H.; Zhu, W.; Chen, X. Expression of High Mobility Group Box Chromosomal Protein 1 and Its Modulating Effects on Downstream Cytokines in Systemic Lupus Erythematosus. *J. Rheumatol.* 2010, 37, 766–775. [CrossRef]

30. Maroso, M.; Balosso, S.; Ravizza, T.; Liu, J.; Aronica, E.; Iyer, A.M.; Rossetti, C.; Molteni, M.; Casalgrandi, M.; Manfredi, A.A.; et al. Toll-like receptor 4 and high-mobility group box-1 are involved in icotogenesis and can be targeted to reduce seizures. *Nat. Med.* 2010, 16, 413–419. [CrossRef]

31. Abraham, C.R.; Chen, C.; Cuny, G.D.; Glicksman, A.M.; Zeldich, E. Small-molecule Klotho enhancers as novel treatment of neurodegeneration. *Future Med. Chem.* 2012, 4, 1671–1679. [CrossRef]

32. Shiozaki, M.; Yoshimura, K.; Shibata, M.; Koike, M.; Matsuura, N.; Uchiyama, Y.; Gotow, T. Morphological and biochemical signs of age-related neurodegenerative changes in klotho mutant mice. *Neuroscience* 2008, 152, 924–941. [CrossRef] [PubMed]

33. Liu, F.; Wu, S.; Ren, H.; Gu, J. Klotho suppresses RIG-I-mediated senescence-associated inflammation. *Nat. Cell Biol.* 2011, 13, 254–262. [CrossRef] [PubMed]

34. Vanarsa, K.; Sasidharan, P.; Duran, V.; Gojalaru, S.; Ndhi, M.; Titus, A.S.C.L.S.; Soomro, S.; Puttermann, C.; Greenberg, B.; Mok, C.C.; et al. Comprehensive aptamer-based screen of cerebrospinal fluid from Neuropsychiatric Lupus reveals potential biomarkers that overlap with the choroid plexus transcriptome. *Arthritis Rheumatol.* 2022, in print.

35. Mike, E.V.; Makinde, H.M.; Gulinello, M.; Vanarsa, K.; Herlitz, L.; Gadhvi, G.; Winter, D.R.; Mohan, C.; Hanly, J.G.; Mok, C.; et al. Lipocalin-2 is a pathogenic determinant and biomarker of neuropsychiatric lupus. *J. Autoimmun.* 2019, 96, 59–73. [CrossRef] [PubMed]

36. Lindblom, J.; Mohan, C.; Parodis, I. Diagnostic, predictive and prognostic biomarkers in systemic lupus erythematosus: Current insights. *Curr. Opin. Rheumatol.* 2012, 34, 139–149. [CrossRef]

37. Mucha, M.; Skrzypiec, A.E.; Schiavon, E.; Attwood, B.K.; Kucerova, E.; Pawlak, R. Lipocalin-2 controls neuronal excitability and anxiety by regulating dendritic spine formation and maturation. *Proc. Natl. Acad. Sci. USA* 2011, 108, 18436–18441. [CrossRef]

38. Chakraborty, S.; Kaur, S.; Guha, S.; Batra, S.K. The multifaceted roles of neutrophil gelatinase associated lipocalin (NGAL) in inflammation and cancer. *Biochim. Biophys. Acta BBA Rev. Cancer* 2012, 1826, 129–169. [CrossRef]

39. Klein, A.; Selter, R.C.; Hafelmeier, A.; Berthele, A.; Müller-Myhsok, B.; Pongratz, V.; Gasperi, C.; Zimmer, C.; Mühlau, M.; Hemmer, B. CSF parameters associated with early MRI activity in patients with MS. *Neuro. Neuroimmunol. Neuroinflammation* 2019, 6, e573. [CrossRef]

40. Galli, E.; Hartmann, F.; Schreiner, B.; Ingelfinger, F.; Arvaniti, E.; Diebold, M.; Mrdjen, D.; Van Der Meer, F.; Krieg, C.; Al Nimer, F.; et al. GM-CSF and CXCR4 define a T helper cell signature in multiple sclerosis. *Nat. Med.* 2019, 25, 1290–1300. [CrossRef]

41. Aibara, N.; Ichinose, K.; Baba, M.; Nakajima, H.; Satoh, K.; Atarashi, R.; Kishikawa, N.; Nishida, N.; Kawakami, A.; Kuroda, N.; et al. Proteomic approach to profiling immune complex antigens in cerebrospinal fluid samples from patients with central nervous system autoimmune diseases. *Clin. Chim. Acta* 2018, 484, 26–31. [CrossRef]

42. Ichinose, K.; Ohyama, K.; Furukawa, K.; Higuchi, O.; Mukaino, A.; Satoh, K.; Nakane, S.; Shimizu, T.; Umeda, M.; Fukui, S.; et al. Novel anti-suprabasin antibodies may contribute to the pathogenesis of neuropsychiatric systemic lupus erythematosus. *Clin. Immunol.* 2018, 193, 123–130. [CrossRef] [PubMed]

43. Fredi, M.; Bianchi, M.; Andreoli, L.; Greco, G.; Olivieri, I.; Orsesi, S.; Fazzi, E.; Cereda, C.; Tincani, A. Typing TREX1 gene in patients with systemic lupus erythematosus. *Reumatismo* 2015, 67, 1–7. [CrossRef] [PubMed]

44. Namjou, B.; Kothari, P.H.; Kelly, J.; Glenn, S.B.; Ojwang, O.J.; Adler, A.; Riquelme, M.E.A.; Gallant, C.J.; Boackle, S.A.; Criswell, A.L.; et al. Evaluation of the TREX1 gene in a large multi-ancestral lupus cohort. *Genes Immun.* 2011, 12, 270–279. [CrossRef] [PubMed]

45. Kavanagh, D.; Spitzer, D.; Kothari, P.H.; Shaikh, A.; Liszewski, M.K.; Richards, A.; Atkinson, J.P. New roles for the major human 3′-5′ exonuclease TREX1 in human disease. *Cell Cycle* 2008, 7, 1718–1725. [CrossRef] [PubMed]

46. Sharaf-Eldin, W.; Kishk, N.; Sakr, B.; El-Hariri, H.; Reafet, M.; ElBaghouri, N.; Essawi, M. Potential Value of miR-23a for Discriminating Neuromyelitis Optica Spectrum Disorder from Multiple Sclerosis. *Arch. Iran. Med.* 2020, 23, 673–687. [CrossRef]

47. Wu, L.; Belasco, J.G. Let Me Count the Ways: Mechanisms of Gene Regulation by miRNAs and siRNAs. *Mol. Cell* 2008, 29, 1–7. [CrossRef]
73. Hein Née Maier, K.; Köhler, A.; Diem, R.; Sättler, M.B.; Demmer, I.; Lange, P.; Bähr, M.; Otto, M. Biological markers for axonal degeneration in CSF and blood of patients with the first event indicative for multiple sclerosis. *Neurosci Lett.* 2008, 436, 72–76. [CrossRef] [PubMed]

74. Dey, M.; Parodis, I.; Nikphorou, E. Fatigue in Systemic Lupus Erythematosus and Rheumatoid Arthritis: A Comparison of Mechanisms, Measures and Management. *J. Clin. Med.* 2021, 10, 3566. [CrossRef] [PubMed]

75. Kozora, E.; Ellison, M.C.; West, S. Depression, fatigue, and pain in systemic lupus erythematosus (SLE): Relationship to the American College of Rheumatology SLE neuropsychological battery. *Arthritis Care Res.* 2006, 55, 628–635. [CrossRef] [PubMed]

76. Hopia, L.; Thangarajh, M.; Khademi, M.; Laveskog, A.; Wallstrom, E.; Svenungsson, E.; Andersson, M. Cerebrospinal fluid levels of a proliferation-inducing ligand (APRIL) are increased in patients with neuropsychiatric systemic lupus erythematosus. *Scand. J. Rheumatol.* 2011, 40, 363–372. [CrossRef]

77. Krupp, L.B.; LaRocca, N.G.; Muir-Nash, J.; Steinberg, A.D. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol.* 1989, 46, 1121–1123. [CrossRef]

78. Ichinose, K.; Arima, K.; Umeda, M.; Fukui, S.; Nishino, A.; Nakashima, Y.; Suzuki, T.; Horai, Y.; Koga, T.; Kawashiri, S.-Y.; et al. Predictors of clinical outcomes in patients with neuropsychiatric systemic lupus erythematosus. *Cytokine* 2016, 79, 31–37. [CrossRef]

79. Huang, X.; Magder, L.S.; Petri, M. Predictors of Incident Seizure in Systemic Lupus Erythematosus. *J. Rheumatol.* 2016, 43, 565–575. [CrossRef]