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Autoantibodies involved in neuropsychiatric manifestations associated with Systemic Lupus Erythematosus: a systematic review

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Abstract:

Background: Neuropsychiatric SLE (NPSLE) is one of the most important manifestations of SLE, and includes a variety of clinical manifestations, classified by the American College of Rheumatology in 19 different neuropsychiatric syndromes. To date, more than 116 antibodies have been reported in SLE and at least 20 of them, including 11 brain-specific and 9 systemic antibodies, have been controversially associated with NPSLE.

Objectives: To systematically review the available evidence, in order to define the association between the above antibodies and NPSLE as a whole and with the 19 neuropsychiatric syndromes associated with SLE, by strictly applying the American College Rheumatology case definitions.

Methods: Medline-reports published between 1999 and 2013 investigating the association between antibodies and NPSLE were included. Whenever possible, associations between antibodies and both NPSLE as a whole and with the 19 syndromes were analysed.

Results: This systematic review is based on available data from more than 8000 patients and controls from 42 studies analyzing antibodies and NPSLE. Nineteen studies analysed the role of antiphospholipid antibodies (aPL), 11 focused on anti-ribosomal-P protein antibodies and 5 on anti-N-Methyl-D-Aspartate receptor antibodies. Two studies analysed, respectively, antibodies to aquaporin-4 and VH4-34 encoded antibodies.

Conclusion: Given the multitude of clinical manifestations related to NPSLE, a single biomarker failed to be reliably associated with all neuropsychiatric events.

Our findings provide evidence that aPL, mainly the Lupus Anticoagulant, and anti- ribosomal P antibodies are significantly associated with specific manifestations of neuropsychiatric disease attributed to SLE, namely cerebrovascular events and psychosis, respectively.

INTRODUCTION:

Systemic lupus erythematosus (SLE) is a model autoimmune disease affecting multiple organ systems including the skin, joints, kidneys, and nervous system.

Neuropsychiatric SLE (NPSLE) is one of the most important manifestations of SLE, and it includes a variety of focal or diffuse, central or peripheral, psychiatric, isolated, complex, simultaneous and/or sequential symptoms and signs, representing both active and inactive disease states. Central nervous system disease predominates and may take the form of either diffuse (e.g. psychosis or depression) or focal disease (e.g. stroke or transverse myelitis) [1-5].

In 1999, the American College of Rheumatology (ACR) proposed a standard nomenclature with case definitions for 19 neuropsychiatric syndromes associated with SLE [6]. The ACR case definitions have provided a much needed and currently widely used platform for the classification of neuropsychiatric events in SLE. Yet, the detection of autoantibodies in serum or cerebrospinal fluid has not been included as a diagnostic marker within the classification. To date, more than 116 antibodies have been reported in SLE[7] and at least 20 of them, including 11 brain-specific and 9 systemic antibodies, have been associated with NPSLE [8].

Available studies on the significance of different autoantibodies in NPSLE have shown controversial results[9]. Therefore, the value of testing for these antibodies as markers of NPSLE remains to be determined and the strength of the association of with 19 neuropsychiatric syndromes associated with SLE is still to be established.

To contribute to this issue, we carried out a systematic review of the literature. We sought to identify all antibodies reported as potentially related to NPSLE in order to define their association with both NPSLE as a whole and with the 19 neuropsychiatric syndromes associated with SLE, by strictly applying the ACR case definitions.

Patients, materials, and methods

Data Sources and Searches

Articles were identified by a computer-assisted search of the literature. The search strategy was applied to Ovid MEDLINE (R) In Process & other non-indexed citations and Ovid MEDLINE from 1999 through 2013. The grey literature was searched by applying a similar strategy to Google Scholar[R], PubMed[R] and the Proquest Dissertation & Theses databases. Additional references were identified from manual review of the reference lists of included articles.

A schematic representation of the search strategy, key words and subject terms used in the search is given in Figure 1. This approach has been previously reported and validated [10, 11]. We conducted the search utilizing the following commonly used keywords: 'neuropsychiatric' and 'lupus' or 'CNS' and 'lupus,' combined with 'American College of Rheumatology' or 'ACR.' The obtained articles were combined with a search utilizing the 'autoantibodies' or 'autoantibody' as keywords. A follow-up of the relevant bibliography in articles was also undertaken to identify additional relevant articles.

Study Selection

Potential studies identified with the above search strategy were exported to an electronic reference management software program (RefWorks v.2.0). Duplicate studies were identified and removed using the filter functions “exact duplicates” and “close duplicates.” Two independent reviewers (SS, MLB) reviewed all potential studies. Eligibility was first determined by review of the title and abstract and then by full article review. Disagreements were resolved by consensus; if consensus could not be achieved, a third party (GS) would provide an assessment of eligibility. As the data on eligibility were dichotomous (eligible: yes / no), inter-rater agreement at both the title and abstract review and the full article review stages was determined by calculation of Cohen’s kappa coefficient [12].

The patient population and laboratory methods were systematically examined.

In details, case reports, review articles, and papers not dealing with SLE patients were excluded and were not further reviewed. In case an abstract was considered potentially relevant, the article was reviewed in full-text and assessed for relevance by applying a checklist of inclusion and exclusion criteria.

Included were studies investigating NP syndromes in patients with definite systemic lupus erythematosus (SLE) (i.e. each patient fulfilling at least 4 ACR criteria for SLE), strictly applying the 1999 ACR case definitions, and having a sample size of at least 20 patients exploring the clinical association with one or more autoantibodies potentially related to NPSLE.

Excluded were studies that did not relate to the 19 NPSLE syndromes, studies that presented duplicate data, or irrelevant studies that were not identified in the initial review of abstracts (e.g. case reports or review articles).

Data Extraction and Quality Assessment

For each relevant study, we identified and recorded the total number of SLE patients, the number of patients having NPSLE, the number of neuropsychiatric syndromes (each patient could have more than 1 neuropsychiatric syndrome during the course of the disease), the study design and characteristics of patients, including age group (adult or pediatric). We also recorded the cumulative prevalence of each of the 19 NPSLE syndromes in each cohort, as well as the prevalence of the autoantibodies tested. When possible, we extracted the exact numbers of syndromes and patients resulting positive for autoantibodies testing as reported in the articles. When not available we calculated them from proportions provided in the manuscript.

Statistical analysis

Odds ratio with 95% CI (OR [95%CI]) for each autoantibody in NPSLE was recorded or, if not available, calculated for each study, whenever possible, by means of contingency tables. In case-control and cross-sectional studies, contingency tables were used to compare the proportion of each tested autoantibody in patients with and without NPSLE. In prospective studies, contingency tables were established as previously reported[10, 11]: (1) if SLE was the enrolment criterion, the OR [95%CI] was calculated by comparing the proportion of each tested autoantibody in patients who did or did not develop NPSLE during follow-up; (2) if NPSLE was the enrolment criterion, the OR [95%CI] was calculated by comparing the

proportion of each tested autoantibody in patients with or without recurrent NPSLE during follow-up; and (3) if positivity for each tested autoantibody was the enrolment criterion, the OR [95%CI] was calculated by comparing the rates of thrombosis during follow-up of patients grouped according to different antibody types and titers.

Risk of Bias Assessment

One reviewer (SS) assessed the risk of bias of individual studies using the Newcastle-Ottawa Scale (NOS) for cohort studies, and the NOS for case control studies. The NOS is a scoring tool used to assess quality of evidence and risk of bias for non-randomized studies included in meta-analyses[13]. The overall quality of evidence was determined using GRADE criterion and summarized using GRADE profiler [14].

Results

Literature search strategy and articles retrieved

Forty-two articles were retrieved. Nineteen studies [15-33] analysed the role of antiphospholipid antibodies (aPL), eleven[16, 20, 25-27, 34-39] focused on anti-ribosomal P protein antibodies and 5 on anti-N-Methyl-D-Aspartate (NMDA) receptor antibodies[18, 19, 25, 40, 41]. Two studies, respectively, analysed antibodies to aquaporin-4[42] and VH4-34 encoded antibodies[43]. Nine studies[44-52] studies were excluded because it was not possible to extract the exact numbers of syndromes and/or patients resulting positive for autoantibodies tested or because they were not relevant for the purpose of this review.. Four studies[53-56] were also excluded as they focused on other biomarkers than autoantibodies.

Three further publications[57-59] were obtained from review of the reference lists of included articles.

Overall, all studies included gave information on 8000 patients. While most of the studies were of a retrospective design, 4 studies, contributing with 2447 patients were prospective [27, 31, 36, 60].

SLE was the enrolment criteria in all the studies.

The lack of objective documentation of temporal sequence between measurement of the autoantibody and the time of the events, and the absence of a control group greatly reduced the level of evidence. Ten studies[15, 18, 20-22, 25-27, 31, 35] performed multivariate analysis using logistic regression.

Antiphosholipid antibodies (aPL)

Most aPL, in particular, anticardiolipin (aCL) and lupus anticoagulant (LAC), have been the most widely investigated autoantibodies in NPSLE. There is abundant research on their association with focal manifestations such as stroke, seizures, epilepsy, and migraine headaches, and diffuse neurological manifestations including cognitive impairment. We retrieved nineteen studies [15-33] dealing with the role of aPL in NP manifestations in SLE (Table 1). While some of the studies dealt directly with possible association of aPL with NPSLE in general, others focused on specific manifestations within the 19 neuropsychiatric syndromes associated with SLE.

A strong correlation between aPL and the overall frequency of neuropsychiatric manifestations was reported in many studies[15, 17, 22, 24, 31], but refuted in others[19, 28-30].

In pediatric SLE, elevated titers of aCL and LAC have been reported and associated with NP manifestations[23, 24], especially with cerebrovascular involvement[23]. One study[29] could not confirm this association.

In adult SLE patients, aCL have been found to be associated with an overall NPSLE involvement more often than LA[17, 20, 24, 31, 33]. However, when investigating cerebrovascular disease (CVD), predominantly stroke[16, 18, 20, 23, 25, 26, 33], the LAC has been proved to be the most strongly associated aPL[16, 25, 26]. aPL have also been found associated with seizures[20, 21, 61].

A recent prospective study including 1047 SLE patients refuted the association between aPL and seizures[27], but confirmed LA as a biomarker for increased risk of intracranial thrombosis in a previous study from the same cohort[26]. Of note, neuropsychiatric damage is prevalent in Chinese patients with SLE and seems to be independently associated with aPL[22].

One study on SLE patients without overt NPLSE, used the Wechsler Adult Intelligence Scale (WAIS) for auditive backspan showing and association between aCL and cognitive impairment[32].

While most studies have demonstrated an association between aCL and/or LA and NPSLE, the role of anti-β2 glycoprotein I (anti-β2GPI) needs further investigation, as only five[16, 25, 26, 30, 62] studies[16, 25, 26, 30, 61], all failing to show a significant association with any of the 19 neuropsychiatric syndromes associated with SLE, are available in the literature. Overall, these studies show that while they can be frequently found in patients with NPSLE, aPL, especially LA, are strongly associated with cerebrovascular disease.

Anti-ribosomal P protein antibodies (anti-RP)

Considerable data show that anti-RP antibodies are present in 6 to 46% of subjects with SLE[63]. These antibodies recognize 3 specific ribosomal proteins termed P0, P1, and P2, which carry molecular weights of 35, 19, and 17 kd, respectively [64-66]. One of the major points of interest of anti-RP derives from their high specificity for SLE[64-66]. Elevated titers of anti-RP are mainly detected in SLE patients during active disease and may be associated with particular clinical manifestations including NPSLE[8]. Eleven studies were identified in which anti-RP antibodies and NPSLE were reported[16, 20, 25-27, 34-39]. One further publication[58] was obtained from review of the reference lists of included articles. All data are summarised in Table 2. All the available studies refuted the association between anti-RP antibodies and NPSLE manifestations as a whole[13, 17, 22-24, 31-35,39].

In contrast, the association between anti-RP and psychosis, originally described by Bonfa and coworkers in two patients with active lupus psychosis[67], was largely confirmed in subsequent studies. Four studies[2, 22, 25, 31] including 1710 patients confirmed the association between elevated titers of anti-RP antibodies and psychosis. Moreover, data from the largest multicenter prospective study in the field conducted by members of the Systemic Lupus International Collaborating Clinics (SLICC) [68], provides evidence that anti-RP are significantly associated with psychosis attributed to SLE[26].

In contrast, an international meta-analysis combining standardized data from 1,537 lupus patients from 14 research centres refuted the association between anti-RP and any manifestation of NPSLE[39]. This meta-analysis aimed at evaluating the diagnostic accuracy of anti-RP for NPSLE as a whole as well as for psychosis, mood disorder or both, and for other

diffuse manifestations. The reported sensitivity and specificity estimates for the diagnosis of NPSLE were 26% [95% CI 15–42%] and 80% [95% CI 74–85%], respectively. For psychosis, mood disorder or both, the sensitivity and specificity were 27% [95% CI 14–47%] and 80% [95% CI 74–85%], respectively. For other diffuse manifestations, the sensitivity was 24% [95% CI 12– 42%] and the specificity 80% [95% CI 73–85%]. These results were supported by published studies. While the sensitivity for psychosis and/or mood disorder was slightly improved, it was still suboptimal (42% [95% CI 30–53%]). The specificity remained similar to that from published data (81% [95% CI 76–85%])[39].

In summary, anti-RP testing does not discriminate between patients with NPLSE manifestations (diffuse or focal) from those without. In view of the contradictory reports, the issue of an association of these antibodies with NPSLE as a whole remains still contentious. Conversely, patients with psychotic manifestations are reported to have higher titers of anti-RP and testing for these antibodies can help to differentiate these patients from those with other thrombotic and/or inflammatory manifestations.

Anti-N-Methyl-D-Aspartate (NMDA) Receptor antibodies

The NMDA receptors NR2a and NR2b that bind the neurotransmitter glutamate are present on neuronal cells throughout the brain and play a role in many neurological functions including memory and learning[8]. Studies in animal models of SLE have shown that a subset of anti-double-stranded (ds) DNA antibodies cross-react with the extracellular, ligand-binding domain of NR2 receptors, thereby suggesting a plausible biological role for these autoantibodies in the pathogenesis of NPSLE[69].

We found 5 studies assessing NMDA antibodies in SLE patients[18, 19, 25, 40, 41], all failing to show an association with clinically overt NPSLE.

Three further publications were obtained from review of the reference lists of included articles[57-59]. While one of those[59] showed and association between serum anti-NR2 antibodies and depressive mood (but not with cognitive dysfunction), Fragoso-Loyo et al. reported no association[58].

More recently, Gono et co-workers analysing a cohort of 107 SLE patients, found that NPSLE was the most significant independent variable associated with anti-NR2A antibody positivity, as estimated by multiple linear regression analysis[57].

Taken together, data show that anti-NR2 antibodies can occur in up to 30% of patients with SLE[28]. Nevertheless, they are infrequent in the antibodiesence of detectable anti-dsDNA antibodies and their presence in the circulation is not associated with any of the 19 neuropsychiatric syndromes associated with SLE .

Other Antibodies

Other two studies, one analysing the antibodies to aquaporin-4[42, 57] and the other VH4-34 encoded antibodies[43] were retrieved. Zavada et al[42] investigated the seroprevalence and specificity of anti-aquaporin 4 antibodies (also known as AQP4-antibodies or NMO-IgG) in patients with NPSLE. Out of 76 SLE patients, 50 met the ACR case definitions of NPSLE. Out of these 50, anti-aquaporin 4 antibodies were positive in only one case. This patient suffered from transverse myelitis, ranging over two vertebral segments on spinal MRI. None of the 75 NPSLE without transverse myelitis was found to be seropositive for anti-aquaporin 4 antibodies.

Bath et al[43] carried on a study to determine the clinical significance of elevated serum levels of VH4-34 encoded IgM and IgG antibodies with respect to the clinical characteristics of SLE. The self-specificities of VH4-34 encoded antibodies include red blood cells, B lymphocytes, and autoantigens such as single stranded DNA and cardiolipin. The authors reported that while IgG VH4-34 was positive in all patients with the most severe SLE manifestations, such as NPSLE, their IgM isotype was lacking, suggesting that isotype switching of VH4-34 encoded antibodies or loss of VH4-34 IgM encoded antibodies may influence the progression of disease in SLE.

Conclusion

We have systematically reviewed the usefulness of measuring selected antibodies potentially associated with NPSLE. To the best our knowledge, this is the first study to compile the body of data in the field strictly using the 1999 ACR case definitions.

As expected, given the multitude of clinical manifestations related to NPSLE, it was very unlikely that a single biomarker could reliably be associated with all neuropsychiatric events. Our findings provide evidence that aPL, mainly LA, and anti-RP antibodies are significantly associated with specific manifestations of neuropsychiatric disease attributed to SLE, namely cerebro-vascular events and psychosis, respectively.

It is also true that our study has some limitations, as this approach was influenced by significant between-study heterogeneity. We addressed heterogeneity by strictly applying ACR case definition as inclusion criteria. We acknowledge that by using this approach some studies only focusing on specific neuropsychiatric manifestations but not referring to the ACR case definition were left out of the analysis, leading to possible underestimation of

some associations between NPSLE manifestations and selected antibodies. Therefore, as per any review, caution in interpreting or generalizing the findings is mandatory.

Finally, time frame between clinical presentation and autoantibody testing was not available for most of the included studies, limiting the possibility to perform any further sub-analysis.

In conclusion, the diagnosis of NPSLE has still to be determined primarily by clinical assessment. The use of antibodies testing can help to confirm a suspected diagnosis in selected clinical settings. The use of a large panel of antibodies as screening for NPSLE is not supported by the currently available evidence.

Table 1: aPL and NPSLE: main characteristics of 19 articles on 6239 patients

Article	Year	Number of patient	study design	enrolment criteria	tested aPL	associated clinical manifestation
Mok et al.	2001	518	retrospective	SLE	LA, aCL	LA and aCL associated with NPSLE manifestations, in particular with CVD
Brey et al.	2002	128	longitudinal study	SLE	LA, aCL, aβGPI	anti-beta2-GP1 levels with angina and a history of either arterial or venous thrombosis; LA with a history of stroke
Afeltra et al.	2003	61	cross-sectional	SLE	LA, aCL, anti-phosphatidylserine, anti-phosphatidylinositol, and anti-phosphatidic acid, aβGPI	aCL associated with NPSLE manifestations
Sanna et al.	2003	323	retrospective	SLE	LA, aCL	CVD, headache, and seizures
Houman at al.	2004	100	retrospective	SLE	LA, aCL	no association
Mikdashi et al.	2004	130	longitudinal	SLE	LA, aCL	aCL with seizures and CVD
Mikdashi et al.	2005	195	longitudinal study	SLE	LA, aCL	aCL with seizures and epylepsy LA with seizures
Mok et al.	2005	282	retrospective	newly SLE diagnosed patients	aPL	aPL with NP damage.
Harel et al.	2006	106	retrospective	pediatric and adolescent SLE	LA, aCL,	CVD
Yu et al.	2006	185	retrospective	children with SLE	aPL	aCL with NPSLE group
Hanly et al.	2008	412	retrospective	SLE	LA, aCL, aβGPI)	LA and CVD
Kamen et a.l	2008	184	cohort-study	SLE	LA, aCL	no association
Singh at al.	2009	53	retrospective	children with SLE	LA, aCL	no association
Hanly J et al.	2011	1047	prospective	SLE	LA, aCL, aβGPI	LA and intracranial thrombosis
Koroka et al.	2011	84	retrospective	SLE subjects without overt NPSLE	LA, aCL, aβGPI	no association
Borowoy et al.	2012	1253	prospective	SLE	LA, aCL	aPL increased in the NPSLE group
Hanly J et al.	2012	1047	prospective	SLE	LA, aCL, aβGPI	no association with seizures
Peretti et al.	2012	31	cross-sectional	SLE subjects without overt NPSLE	aCL	aCL with impairment in auditive backspan
Zirkzee et al.	2012	100	prospective	SLE	LA, aCL	aCL with ischemic NPSLE

Table 2: Anti-RP and NPSLE: main characteristics of 12 articles on 4905 patients

Article	Year	Number of patients	Study design	Associated clinical manifestation
Gerli et al.	2002	149	prospective	no association
Brey et al.	2002	128	longitudinal study	no association
Mikdashi et al.	2004	130	longitudinal study	no association
Yoshio et al.	2005	70	cross-sectional	no association
Karassa et al.	2006	1537	Meta-analysis	no association
Abdel-Nasser et al.	2008	32	cross-sectional	mood disorder, borderline association with Psychosis
Hanly et al.	2008	412	retrospective	psychosis
Fragoso-Loyo et al.	2008	47	Longitudinal Study	no association
Briani et al.	2009	219	retrospective	psychosis, mononeuropathy multiplex*
Jarpa et al.	2011	87	cross-sectional	no association
Hanly et al.	2011	1047	prospective	psychosis
Hanly et al.	2012	1047	prospective	no association with seizures

* not confirmed after further analysis

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LEGEND

Figure 1: Literature search strategy on the association between NPSLE and autoantibodies.

Table 1: aPL and NPSLE: main characteristics of 19 articles on 6239 patients

Table 2: Anti-RP and NPSLE: main characteristics of 12 articles on 4905 patients