



Review

A meta-analysis of serum and cerebrospinal fluid autoantibodies in neuropsychiatric systemic lupus erythematosus



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ABSTRACT

Neuropsychiatric systemic lupus erythematosus (NPSLE) is one of the most devastating presentations of SLE and comprises of psychiatric, central and peripheral neurological signs and symptoms. Previous studies suggest the possible associations between various autoantibodies (Abs) and NPSLE. The magnitudes of such association varied between studies. We performed a meta-analysis to pool data on serum and cerebrospinal fluid (CSF) levels and positivity of Abs in blood and cerebrospinal fluid in patients with NPSLE and SLE.

A systematic literature search was conducted to identify studies that fulfilled inclusion criteria. A random-effects model was used to calculate overall combined odd ratio (OR) and mean levels with its corresponding 95% confidence interval to evaluate the relationship between individual Abs and NPSLE patients relative to SLE patients. Forty-one studies met the inclusion criteria and were used in this analysis. There was a significantly greater proportion of NPSLE patients who demonstrated positivity for serum anti-cardiolipin (aCL) Abs (OR = 1.63, $p = 0.016$), lupus anticoagulants (LA) Abs (OR = 1.91 $p = 0.01$), anti-phospholipid (APL) Abs (OR = 2.08, $p = 0.001$), anti-ribosomal P Abs (OR = 2.29, $p < 0.001$), anti-neuronal Abs (OR = 9.50, $p < 0.001$) as compared to SLE patients. In NPSLE patients, there was a significant increased prevalence of positive titres for CSF anti-neuronal Abs (OR = 36.84, $p = 0.001$) as compared to SLE patients. Among the 19 neuropsychiatric syndromes, the positivity of these serum autoantibodies were found specifically significantly associated with the manifestations of mood disorder, psychosis, cerebrovascular disease, seizure disorders, acute confusional state, cognitive dysfunction, headache, movement disorder, demyelinating syndrome and polyneuropathy, with ORs ranging from 1.84 to 4.73. Meta-regression identified proportion of women as significant moderator for the heterogeneity of aCL ($p = 0.004$) and anti-neuronal Abs ($p = 0.0007$); mean age for the heterogeneity of aCL ($p = 0.042$) and LA ($p = 0.020$) Abs, mean duration of illness for the heterogeneity of aCL Abs ($p = 0.035$), and mean SLEDAI scores for the heterogeneity of anti-ribosomal P Abs ($p = 0.014$).

NPSLE patients are more likely to have elevated serum levels of aCL, LA, APL, anti-ribosomal P Abs and anti-neuronal Abs compared with SLE patients. Further research is required to evaluate the accuracy of using the above antibodies as an adjunct diagnostic tool in NPSLE.

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1. Introduction

1.1. Autoantibodies and SLE

Individual autoantibodies (Abs) play important roles in the pathogenesis of SLE [1,2]; Abs reflect disease activity and are associated with specific manifestations [3]. The key pathogenic processes of NPSLE lie in the interaction between Abs and neuronal antigens, phospholipid proteins and ribosomes [4]. Abs play a key role in the pathogenesis of neuropsychiatric disorders, such as autism, paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS) and Sydenham's chorea [5]. Approximately one hundred Abs have been identified in SLE patients [6], but it remains unknown which Abs play an important role in NPSLE. Previous studies have demonstrated that serum Abs are able to damage neurological tissues by altering vascular function [7], crossing the blood brain barrier (BBB) and combining with antigens in brain tissues to form immune complexes [8–10]. In the brain, auto-reactive T-cells induce the activation of antigen presenting astrocytes and microglia [9]. Other pathogenic processes, such as the deposition of immune complexes onto the BBB, further increase the permeability of Abs [10]. Furthermore, CNS-reactive Abs are often present in the serum of SLE patients [11]. In addition to passive transfer, active intrathecal production of Abs has been identified in NPSLE patients [12]. Of all Abs, anticardiolipin, antiganglioside and antilactocerebroside Abs have demonstrated important predictive roles for NPSLE [13]. Greenwood et al. [1] and Hanly [10] have recommended measurements of anti-neuronal, APL and anti-ribosomal-P Abs as part of the diagnostic investigations for NPSLE. The clinical significance of other Abs in NPSLE are under investigation [14], and further research is required to assess the clinical usefulness of Ab measurement in NPSLE patients [11]. Table 1 summarises the NP symptoms and pathogenic processes associated with various Abs in NPSLE.

1.2. Autoantibodies and NPSLE

Controversies regarding the pathogenic roles of individual Abs in NPSLE have been a topic of debate in the medical literature; however, not all brain reactive Abs are associated with NP symptoms [15]. The elevated titres of anti-ribosomal P Abs have been associated with depression and psychosis [16,17], but other studies have refuted this association [18–20]. Although anti-ribosomal P Abs have been recommended as a marker for NPSLE because of their high specificity [21], a meta-analysis concluded that anti-ribosomal P Abs have a limited diagnostic role in NPSLE [22]. For APL Abs, aCL Abs have been associated with cognitive impairments [23], but other studies have failed to confirm this association [24]. The elevated titres of anti-NR2 Abs have been associated with depression and impairments in short term memory and

learning [25], but other studies have refuted this association [26,27]. The relationship between anti-NR2 Abs and NPSLE remains controversial [17]. Hanly and Harrison [4] did not find that the measurement of anti-neuronal Abs resulted in greater diagnostic specificity of NPSLE. One systematic review indicated that psychiatric morbidity, such as cognitive impairment, depression and psychosis, was associated with brain specific and systemic Abs [17]. This systematic review did not use statistical techniques to combine the data but concluded that aCL Abs were the most commonly found Abs in NPSLE. This finding requires further confirmation. Another systematic review concluded that anti-endothelial cell, anti-N-methyl-D-aspartate (NMDA), APL, anti-ribosomal P, anti-neuronal, and anti-glial fibrillary acid protein Abs were elevated in NPSLE [24]. Li et al. [28] classified Abs into three clusters (Cluster 1: anti-DsDNA; Cluster 2: anti-Sm, anti-RNP, aPL; and Cluster 3: anti-Ro, anti-La) and determined NP involvement did not differ between the 3 clusters. These contradicting views require a meta-analysis to assess the association between Abs and NPSLE. By combining different studies to generate a pooled effect size, a meta-analysis can increase the power to detect differences in the presence or absence of Abs in NPSLE and SLE patients [29]. Heterogeneity may arise, and previous research findings have identified the sources of heterogeneity, including age, ethnicity [24], clinical status [30] and gender [31].

1.3. Aim of this study

The primary aim of this meta-analysis was to assess the presence of individual Abs in the CSF and serum of NPSLE patients as well as the manifestations of the 19 specific neuropsychiatric syndromes of the 1999 American College of Rheumatology (ACR) criteria [32]. We hypothesized that there would be no differences in the proportion or absolute levels in Ab titres between the NPSLE and SLE patients.

2. Methods

2.1. Search strategy

Studies of Abs in SLE and NPSLE were systemically searched in the following databases from inception to February 2014: Pubmed, Embase, BIOSIS, and Science Direct. The search terms used were “autoantibodies”, “anti-phospholipid antibodies”, “anti-ribosomal P antibodies”, “anti-neuronal antibodies”, “anti-glial fibrillary acidic protein antibodies”, “anti-endothelial cell antibodies”, “anti-N-methyl-D-aspartate antibodies (NMDA)”, “anti-nuclear antibodies (ANA)”, “anti-phosphatidylserine antibodies”, “anti-Ro/SSA antibodies”, “anti-La/SSB antibodies”, “anti-ganglioside antibodies”, “anticardiolipin antibodies”, “lymphocytotoxic antibodies”, “anti-dsDNA antibodies”, “anti-beta 2 glycoprotein antibodies”, “anti-Smith beta

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