REVIEW

RJME
Romanian Journal of Morphology & Embryology
http://www.rjme.ro/

Neuroinflammation in systemic lupus erythematosus – a review

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Abstract

Neuroinflammation is a complex process that contributes to the pathogenesis of both immune mediated and neurodegenerative pathologies. Systemic lupus erythematosus (SLE) is the prototype of connective tissue diseases that can present the complete spectrum of neurological and psychiatric dysfunctions. The precise etiological diagnosis of neuropsychiatric systemic lupus erythematosus (NPSLE) is rather difficult to be established and it is still controversial the exact timing of neuropsychiatric (NPS) events: either central nervous system (CNS) is the initial target of autoimmune abnormalities, either NPS symptoms are a part of multisystem involvement. Ischemic and inflammatory mechanisms have an important input on NPSLE pathogenesis. Neuroinflammation, consequent to blood–brain barrier (BBB) damage, local and systemic production of autoantibodies, determine neuronal injury and apoptosis, further responsible for diffuse cerebral events, mostly cognitive dysfunction and psychotic disorder. Moreover, SLE complications or therapy complications can interfere and contribute to complex clinical manifestations that can be present in SLE patients. Understanding the role of each pathogenic way can provide not only an early diagnosis, but a more accurate therapeutic approach of these patients.

Keywords: neuroinflammation, systemic lupus erythematosus, blood–brain barrier, autoantibodies, cytokines.

Introduction

Neuroinflammation is a complex process that contributes to the pathogenesis of different immune-mediated pathologies, as neuropsychiatric involvement present in systemic lupus erythematosus (NPSLE) [1], process that is regulated both by mechanisms at central level and by immune cells [2].

Systemic lupus erythematosus (SLE) is a chronic inflammatory disease, with multifactorial etiology, that induces an abnormal immune response, multisystem involvement and significantly influences the prognosis. SLE is the prototype of connective tissue diseases that can present the complete spectrum of neurological and psychiatric dysfunctions [3]. According to *American College of Rheumatology* (ACR) Classification, proposed initially in 1999 and revised in 2001, neuropsychiatric (NPS) syndromes in SLE patients include 19 entities, central or peripheral, the first ones, focal or diffuse, representing most of the cases, with a percentage of 93% [4].

The precise etiological diagnosis of NPSLE is rather difficult to be established and it is still controversial the exact timing of NPS events: either central nervous system (CNS) is the initial target of autoimmune abnormalities, either NPS symptoms are a part of multisystem involvement. Each of the pathogenic pathways depend of different factors, such as individual variability, that constitute trigger of autoimmune events and neuroinflammation and microvascular changes, responsible of focal or diffuse symptoms, characteristic to neurolupus [5]. As most of rheumatic autoimmune disease, this pathology benefits of modern imaging methods that enable an early diagnosis and proper therapeutic approach [6–19].

Ischemic and inflammatory mechanisms have an important input on NPSLE pathogenesis and associate disruption of the blood–brain barrier (BBB) and pro-inflammatory cytokines secretion [20]. Neuroinflammation, consequent to BBB damage, local and systemic production of autoantibodies, determine neuronal injury and apoptosis, further responsible for diffuse cerebral events, mostly cognitive dysfunction and psychotic disorder [3].

We aimed to describe the main neuronal inflammatory factors (specific and systemic antibodies, cytokines, chemokines and BBB dysfunction) involved in the pathogenesis of NPSLE, considering their impact on specific events, in order to further determine them as biomarkers for identifying possible future CNS events

and to use them as therapeutic targets, improve patients' prognosis and quality of life.

Specific antibodies

Anti-N-methyl-D-aspartate (NMDA) receptor antibodies

N-methyl-D-aspartate receptors (NMDAR), NR2/GluN2A and NR2/GluN2B, are physiologically present on neurons and exhibit major neurological functions [21].

Anti-NMDAR antibodies are anti-double-stranded deoxyribonucleic acid (anti-dsDNA) antibodies that interact with glutamate, widely distributed in the brain, in glutamate synapses, mostly in amygdala and hippocampus, structures that control cognitive functions, as memory and emotional reactions, and induce neuronal apoptosis and degeneration of survival neurons in murine models [22]. They are found in a substantial number of SLE patients, with or without NPS involvement, and the reported percentages vary between studies, generally from 14% to 35%, with one study published by Levite reporting a percentage of 81% for patients with diffuse NPSLE and 44% for patients with focal NPSLE [23].

The pathogenic input of subtype 2 (NR2/GluN2) was proven by several studies, both *in vivo*, and *in vitro*, exclusively in the presence of an altered BBB. It has also been suggested that the neuronal effects are directly related to dose, as their low concentrations alter synaptic functions and high concentrations produce neuronal damage [24–26].

A controversial topic is represented by how anti-NR2 antibodies arrive centrally: either they are produced locally, intrathecal, either they pass through damaged BBB. Moreover, it was mentioned that they stimulate their own transport acting as agonist/co-agonist for NMDA receptors. It was proven their ability to bind to endothelial cells and stimulate the expression of vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1), as the production of pro-inflammatory cytokines, interleukin (IL)-6 and IL-8, which consequently produces local inflammation, an altered BBB permeability and antibodies passage [27].

Several studies tried to establish an association between them and different NPS manifestations. A recent meta-analysis, that included 17 studies, with over 2000 SLE patients, reported that the prevalence of serum anti-NR2A/B antibodies was higher compared to controls, and also higher in patients with NPS syndromes, not specifically associated with one type, data suggesting that circulating anti-NR2A/B antibodies has only a diagnostic value for NPS in SLE subjects, but cannot distinguish a specific one [28]. On the other hand, the reports of various other clinical studies sustained that their presence in cerebrospinal fluid (CFS) is associated with diffuse NPS manifestations [29–31]. Unlike other antibodies, such as anti-ribosomal P protein (anti-RP) or anti-cardiolipin antibodies (aCL), these antibodies are able to individualize patients with CNS manifestations from patients with peripheral neurological symptoms or without NPS involvement [28].

Other specific antibodies associated with NPSLE are represented by *anti-microtubule-associated protein 2* (MAP2) ones, a cellular protein found almost exclusively in neurons, in up to 17% of NPSLE patients, strongly associated to seizures, chorea, psychosis, headache and sensory neuropathy [32].

Anti-glial fibrillary acidic protein (GFAP), protein essential for cellular structure and BBB integrity, located in astrocytes, have a significant positive predictive value for major organic disturbances; another reported conclusion regarding them is that their CSF titer diminishes consequent to Cyclophosphamide treatment, observation that can be used to monitor therapy [33].

Anti-neurofilament antibodies were also found increased in NPSLE patients. *Anti-ganglioside antibodies*, major membrane components that modulate intercellular signaling, are not specific for SLE, but have a positive predictive value for NPS symptoms; their CSF titer has been proven to be associated to depression, migraine and depression [34].

Systemic antibodies

Anti-endothelial cells antibodies (AECA)

AECA is a group of different antibodies that react with various endothelial cell antigens, associated with NPS symptoms (especially depression and psychosis), nephritis and vasculitis in SLE patients. They have been found in 15–80% of SLE patients, and in up to 65% of the ones with psychosis [35]. AECA determine cytokine and chemokine synthesis, stimulate the expression of adhesion molecules and increase BBB permeability. A particular subtype, anti-Ned5, guanosine triphosphatase (GTP-ase) located in cytoskeleton, with role in cytokine synthesis, are specifically involved in NPS events. Studies that used DNA screening in endothelial cells from patients NPSLE showed that an important endothelial antigen, directly inter-related with NPS events, is represented by C region of Ned5; apparently, Ned5 is redistributed on cell surface during apoptosis, event that consequently determines immunogenicity and autoantibody production. Anti-Nedd5 antibodies are statistically significantly reported in psychiatric manifestations in SLE patients, which may suggest the hypothesis that these autoantibodies may play a key role in their occurrence. It is still unclear if these antibodies have a direct cytotoxic function or they are a consequence of NPS events [25, 36].

Anti-ribosomal P antibodies

It has been stated that the presence of these antibodies is strongly associated with NPSLE; they are present in up to 46% of SLE patients and target epitops located on three phosphorylated proteins (P0, P1, P2) found in the 60S subunit of ribosomes [37, 38]. They are highly specific for SLE, with increased serum titers during disease activity, particularly associated with renal, hepatic and NPS manifestations; among the last, psychosis and depression are the most frequent [26, 39, 40]. Their increased CSF titer is a more accurate marker compared to seric one, and was reported to be inter-related with lupus psychosis. A meta-analysis that included 14 studies, with over 1500 subjects, showed no specific association between anti-RP antibodies and certain phenotype of clinical manifestations [41].

However, several experimental studies that tried to associated their presence with a certain type of clinical pattern, proved that they induce a fast and sustained raise of calcium influx and, therefore, apoptosis for neurons that express surface P antigen, located mostly in areas responsible for memory, cognitive function and emotional reactions [42].

Anti-poly [adenosine diphosphate (ADP)–ribose] polymerase-1 and -2 antibodies (anti-PARP-1 and -2) have been associated with a protective role against renal and NPS involvement in SLE patients, being involved in DNA recovery process, mostly type 1. Several experimental studies showed that an increased expression of anti-PARP-1 antibodies is seen in hippocampus, one of the target zones for glucocorticoids that can be atrophic in NPSLE patients. The conclusion that anti-PARP-1 antibodies seric levels are decreased in NPSLE patients confirms that they cross an altered BBB and deposit as immune complexes during flares [43].

Anti-phospholipid antibodies (aPL), present in up to 45% of NPSLE patients, both in serum and CSF, are overall related with NPS events, certainly associated to focal CNS events, but controversial regarding their relationship with diffuse neurological manifestations, and mainly cognitive impairment [44]. Anti-beta$_2$ glycoprotein I (β_2GPI) antibodies were mostly found associated with focal events, consecutive to non-inflammatory microangiopathy, but needs further investigations [45]. aCL antibodies have both direct neuronal inhibitory effect, as well as direct promoter of thrombosis, and are found with increased CSF levels in patients with headache, psychotic events and cognitive impairment [46]. Lupus anticoagulant (LAC) is associated with a 2–3 times fold risk of cognitive dysfunction, mark of subcortical damage, consecutive to thrombosis and vasculopathy. In adult NPSLE patients, aCL have been found to be associated with an overall incidence of events more often than LAC [47].

Other associated antibodies are *anti-histone*, especially H1 and H3, found in up to 50% of NPSLE cases [48]; *anti-Smith (Sm) antibodies* were also associated to NPS events and nephritis [49]. Regarding *anti-Ro antibodies*, they are controversial in NPSLE patients, but some reported their association to suicide attempt. Another report found CSF presence of *anti-topoisomerase*, enzyme with role in glycolysis and energetic metabolism, as immune complexes [50]. A study published by Sato *et al.* concluded that *anti-U1 ribonucleoprotein (RNP) complex antibodies* may be a more specific marker for NPSLE, compared to anti-P or anti-NR2 antibodies [51].

Blood–brain barrier

BBB, constituted by polarized endothelial cells, connected by tight junctions, separates the circulatory system from the brain [27, 52]. This specialized system prevents the entry of different soluble molecules and regulates the uptake and efflux of substances from/to systemic circulation, maintaining a proper microenvironment for neuronal signaling [53, 54]. Besides serving as a barrier, endothelial cells are responsible also for regulating the immune response, in their basal state secreting transforming growth factor beta (TGFβ) and soluble cellular adhesion molecules [27, 52, 53].

BBB dysfunction has been shown to be associated with several pathologies, including neurodegenerative diseases and NPSLE. Diagnosing BBB disruption is limited since there are no imaging methods that can show directly the lesion, and contrast agents typically cannot cross it; the most used biomarker for evaluating BBB integrity is represented by CSF/serum albumin quotient, completed by imaging studies, such as magnetic resonance imaging (MRI). Recent experimental studies suggested that peripheral molecules may reach the brain *via* blood–CSF barrier, rather than BBB, proves that request additional studies and refining NPSLE pathogeny [52, 55–57].

There have been proposed two main mechanisms responsible for BBB disruption: immune-mediated endothelial cells activation, with cytokines and chemokines secretion, and ischemia of cerebral vessels [38]. Inflammatory pathway attributes a key role to complement system, in altering BBB integrity, especially through complement C5a/C5aR. C5a was found to induce apoptosis in endothelial cells *in vitro*, presumably through C5aR1 receptor, whose *transcript* is found to be abundant in microglia [58]. Immune complexes induce the production of pro-inflammatory cytokines and cellular adhesion molecules, by endothelial cells, *via* nuclear factor-*kappa* B (NF-κB) signaling. A report published by Jacob *et al.*, that studied how C5a/cluster of differentiation 88 (CD88) signaling alters BBB integrity in lupus through NF-κB, found increased NF-κB translocation. Decreased *zona occludens* levels and increased expression of MAP levels, all of them increasing the permeability of BBB [59]. The conclusions of several reports showed that an increased systemic signaling, determined by cytokines and complement, is the key inductor for CNS endothelial cells' apoptosis, with BBB damage and leaky, with a particular role of tumor necrosis factor (TNF)-like weak inducer of apoptosis (TWEAK)/fibroblast growth factor-inducible 14 (Fn14) pathway [58].

Cytokines and chemokines

An important pathogenic pathway in NPSLE is provided by pro-inflammatory cytokines and chemokines, molecules with major role in immune response. Autoantibodies, hallmark of SLE, interact with correspondent cellular antigens, promote cellular signaling and consequent pro-inflammatory molecules production and neurotransmitter release. All these processes modify physiological immune regulatory mechanisms, determine local inflammation and tissue damage, with BBE disruption [60].

Several cytokines and chemokines were reported to be increased in CSF of NPSLE patients, some of them correlated with disease activity (IL-6, IL-10) or specific clinical patterns [60, 61].

Of the many cytokines proven to be present in CSF, such as IL-4, IL-6, IL-8, IL-10, TNF-α, interferon (IFN)-α and IFN-γ, monocyte chemoattractant protein-1 (MCP-1)/CC-motif chemokine ligand 2 (CCL2), IFN-γ-inducible protein-10 (IP-10)/C–X–C motif chemokine ligand (CXCL) 10 and fractalkine/CXCL1, IL-6 has the strongest positive correlation with NPS syndromes and the level of neuronal degradation product, even in the absence of BBB disruption [62, 63]. Recent reports proved that IL-6 is increased in CSF of NPSLE patients, associated especially with acute confusional state or psychosis; a multicenter retrospective study, that included 45 subjects with lupus psychiatric manifestations, showed a significant sensitivity (87.5%) and specificity (92.3%) for IL-6 in diagnosis of lupus psychosis [64]. Another report, published by Fragoso-Loyo *et al.*, that aimed to determine the cytokine and chemokine expression in CSF from NPSLE patients, concluded that NPS manifestations are associated with IL-6 and chemokines, but not with T-helper (Th) 1/Th2 cytokines [61, 65]. A recent study, that included 52 SLE

patients, showed that IL-6, IL-8, IP-10, MCP-1 and granulocyte-colony stimulating factor (G-CSF) are found with significant high values only in CSF of patients, evidence that suggest that their production might be in the CNS [66].

There are also evidence showing that CSF MCP-1/ CCL2 and IP-10/CXCL10 levels are higher in NPSLE patients; C–X–C motif chemokine receptor 3 (CXCR3), the receptor of IP-10/CXCL10, is expressed mostly on Th1 cells, whereas CCR2 is expressed not only on activated T-cells, but also on basophils, monocytes and dendritic cells, and CXCR3 and CCR2 signaling contribute to NPSLE pathogenesis, through effector T-cells, such as Th1, Th2 and Th17 cells [67–69].

Another molecule with a major role in neuroinflammation is represented by TWEAK, which mediates the activation of inflammation, angiogenesis, cellular proliferation and apoptosis, through activation of its receptor – Fn14, a member of TNF receptor superfamily [70]. In CNS, TWEAK targets astrocytes, endothelial cells and neurons. Fn14 is expressed in cerebral endothelial cells and astrocytes, while TWEAK only in astrocytes. Several experimental studies, that proposed to analyze how TWEAK induces BBB disruption, found that it determines increased secretion of ICAM-1, CCL2, IL-6 and IL-8, by endothelial cells and increased expression of matrix metalloproteinase-9 (MMP-9) that decreased occludin expression and increased BBB permeability [70–72].

Several experimental studies have proven that increased levels of TWEAK are present in the cortex of NPSLE mice and a more frequent presence of cognitive impairment and anhedonia, compared to Fn14 deficient mice; it was also observed that the last group had more integrity of BBB and a decreased brain expression of CC-motif chemokine ligand 5 (CCL5)/regulated on activation, normal T-cell expressed and secreted (RANTES) and other proinflammatory mediators [71, 73, 74].

Elevated levels of the TNF family ligands B-cell activating factor belonging to the TNF family (BAAF) and A proliferation-inducing ligand (APRIL), essential for B-cell survival and function, have been found in patients with SLE. An important report concluded that BAAF CSF levels were 200-fold higher compared to controls and APRIL levels more than 20-fold higher, and APRIL CSF levels were significantly increased in NPSLE patients, compared to non-NPSLE patients; they have also found that CSF APRIL levels were correlated with BAAF, but not IL-6 [75–78].

Although a large number of studies have been performed in order to establish the precise role of cytokines and chemokines in pathophysiology of NPSLE, further molecular studies are required in order to prove their accurate role, and to be used as therapeutic targets for these patients. Corroborating clinical, laboratory and imaging techniques, the diagnosis can be accurate and a proper therapeutic approach can be established, in order to improve patients' prognosis and quality of life [6–20].

Conclusions

NPSLE pathogenesis is complex, not completely elucidated and includes an association of vascular mechanisms, especially aPL input, with a direct consequence represented by focal events, with neuroinflammatory pathway, initiated by BBB damage, direct action of cytokines and chemokines intervention and antibody neurotoxicity, that produces diffuse symptoms. Moreover, SLE complications or therapy complications can interfere and contribute to complex clinical manifestations that can be present in SLE patients. Understanding the role of each pathogenic way can provide not only an early diagnosis, but a more accurate therapeutic approach of these patients.

Conflict of interests

The authors declare that they have no conflict of interests.

Authors' contribution

Andreea Lili Bărbulescu and Raluca Elena Sandu equally contributed to the manuscript.

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Received: March 30, 2019 *Accepted: November 8, 2019*