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Biomarkers for CNS involvement in pediatric lupus

Tamar B Rubinstein[1,*], **Chaim Putterman**[2], and **Beatrice Goilav**[3]

[1]Department of Pediatrics, Division of Rheumatology, The Children's Hospital at Montefiore, Albert Einstein College of Medicine, 3415 Bainbridge Avenue, Bronx, NY 10467, USA

[2]Department of Medicine, Division of Rheumatology, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, NY 10461, USA

[3]Department of Pediatrics, Division of Nephrology, The Children's Hospital at Montefiore, Albert Einstein College of Medicine, 3415 Bainbridge Avenue, Bronx, NY 10467, USA

Abstract

CNS disease, or central neuropsychiatric lupus erythematosus (cNPSLE), occurs frequently in pediatric lupus, leading to significant morbidity and poor long-term outcomes. Diagnosing cNPSLE is especially difficult in pediatrics; many current diagnostic tools are invasive and/or costly, and there are no current accepted screening mechanisms. The most complicated aspect of diagnosis is differentiating primary disease from other etiologies; research to discover new biomarkers is attempting to address this dilemma. With many mechanisms involved in the pathogenesis of cNPSLE, biomarker profiles across several modalities (molecular, psychometric and neuroimaging) will need to be used. For the care of children with lupus, the challenge will be to develop biomarkers that are accessible by noninvasive measures and reliable in a pediatric population.

Keywords

biomarkers; CNS; neuropsychiatric; pediatric; systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by multi-organ damage caused in part by antibodies directed against self antigens. Pediatric lupus affects 3.3–8.8 per 100,000 children [1,2], and 20% of lupus patients are diagnosed in childhood [3]. Racial and ethnic differences in prevalence are well described in lupus, and are even more striking in childhood lupus than in adults [4]. African–American, Asian and Hispanic children have a threefold higher incidence of developing lupus than white children [1,5–7]. While one of the most significant contributions to mortality of lupus in children, as

[*]Author for correspondence: Tel.: +1 718 696 2604, Fax: +1 718 944 0463, trubinst@montefiore.org.

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in adults, is renal disease, an equal if not greater contributor to morbidity and decreased quality of life is neuropsychiatric systemic lupus erythematosus (NPSLE), specifically CNS disease (central neuropsychiatric systemic lupus erythematosus [cNPSLE]) [8,9].

Estimates of the proportion of pediatric lupus patients affected by cNSPLE vary depending on definitions, detection methods and populations, and range from 43–95% [10,11]. CNS lupus may be both more prevalent and more severe in children, and may have greater consequences in young patients whose brains are still developing [5,12,13].

Within the many specific organ diseases of lupus, cNPSLE remains a most challenging diagnosis to make. This is because of the wide variety of phenotypes included in this disease and the fact that cNPSLE is often a diagnosis of exclusion in a lupus patient, in whom a complex interaction of many different etiologies and mechanisms can result in CNS disease. Several diagnostic tools are used, but there is no established gold standard to rule-in or rule-out the disease as a whole [14,15]. Furthermore, diagnostic tools used to examine the CNS for disease may be costly, time burdensome and invasive. Diagnosis of cNPSLE often requires imaging that may be difficult to perform or interpret in children, lengthy testing by expert neuropsychologists and invasive procedures to obtain biospecimens from the CNS [12,16]. These procedures may be particularly objectionable in children, for whom there are higher standards for what are considered acceptable risks and burdens in medical testing. Because of this, the diagnosis of CNS disease in lupus may be delayed or missed.

Because of these challenges, there has been an effort to discover more accessible biomarkers for cNPSLE, the impact of which would arguably be greater in pediatrics. Biomarkers appropriate for the use in pediatric lupus patients suspected of cNPSLE would facilitate diagnosis, enable practitioners to follow patients over time and to monitor their progression and remission of disease, and permit researchers to evaluate new interventions and treatments. Moreover, the discovery of new biomarkers may lead to a deeper understanding of the pathogenesis of this disease and in doing so may indicate new therapeutic targets.

In general, there is a paucity of biomarker studies in pediatrics; often biomarkers discovered in adult populations are then extrapolated to pediatric patients [17]. The same is true in biomarker research in lupus. Thus, many of the biomarkers discussed here have had limited pediatric studies. To assess the validity and applicability of biomarkers in a pediatric population, one must consider whether the pathogenesis of the disease is the same as in adults, whether there are age, weight or developmental variations, and whether obtaining the biomarkers is feasible in a child.

The pathogenesis of cNPSLE is thought to be similar in adult and pediatric lupus patients [18]; however, age and developmental differences and the modalities required to obtain these measures are exceedingly important to consider in approaching a child suspected of cNPSLE. In this review, we aim to cover the advances of a nascent field in biomarker research in cNPSLE and their applicability to the care of pediatric patients.

Classification of disease

The American College of Rheumatology classifies NPSLE as a disease with 19 possible different manifestations, including those of the peripheral nervous system and the CNS [19]. The majority of NPSLE (>90%) consists of CNS disease or cNPSLE [20]. Within CNS disease there are varying pathologies and phenotypes, and these have been largely characterized as either focal or diffuse disease, referring to examination and imaging findings, indicating a specific region of the CNS that is affected versus disease that is not easily anatomically defined [15] (Table 1).

Pediatric cNPSLE can present years after the initial diagnosis [10] and may not correlate with other forms of disease activity [10,21]. While focal disease is usually evident on examination and neuroimaging [16], diffuse disease, most commonly manifesting as mood disorder and cognitive dysfunction, is often present with neither [22,23]. Thus, this form of cNPSLE can be the most difficult to diagnose, and there are few established tools to determine whether disease is attributable to lupus versus other etiologies [12]. Diffuse manifestations of disease, being most elusive to practitioners, have been the focus of efforts in developing and improving diagnostic biomarkers and will be the focus of our discussion of cNPSLE.

Pathogenesis of disease

The pathogenesis of cNPSLE is quite variable and much of the disease remains obscure and poorly understood. Early case series revealed that most SLE patients who present with CNS symptomatology have normal brain histology [24]. The cases where postmortem neuropathology is seen indicate a vascular pathology: thrombotic events, microinfarcts, vasculitis and perivascular inflammation [25]. Besides vascular insults, both thrombotic and inflammatory, the pathogenesis of cNPSLE is thought to be immune mediated by either autoantibodies that gain access to the CNS or inflammatory cytokines, but most likely by both working in concert [14].

However, a significant portion of CNS disease in lupus patients, especially diffuse disease, is likely not due to the primary pathophysiology of lupus, but to downstream effects of chronic damage or etiologies circumstantially related to lupus, for example, medication effects [14]. Many of these are common and well described, such as reactive depression secondary to chronic illness and steroid psychosis, but are still difficult to differentiate from primary disease.

Lastly, CNS disease in lupus patients may be due to other diseases unrelated to lupus, such as infection or primary psychiatric or neurologic disease. One recent large prospective study found that 30% or fewer neuropsychiatric events in adult lupus patients were primarily attributable to lupus [20]. In the case of primary psychiatric and neurologic diseases, many rheumatologists will try to differentiate these from lupus etiologies in part by timing, where manifestations that long precede the diagnosis of lupus are not attributed to lupus [8,14]. In pediatrics, this becomes much more difficult. Patients are young, and there may not be as much time between the onset of symptoms from a primary psychiatric or neurologic disease and lupus.

In general, CNS disease in lupus patients with etiologies not directly due to lupus is differentiated from cNPSLE [14]. In fact, in a recent consensus statement by the European League Against Rheumatism, recommendations were made to exclude patients from the NPSLE classification system with some of these commonly occurring diffuse neuropsychological manifestations (headache, mood disorder, anxiety and mild cognitive dysfunction) because of the significant proportion of these which are thought not to be primary cNPSLE, and because differentiating them from cNPSLE with the current diagnostic tools is so challenging [26]. Nevertheless, in pediatric rheumatology there is still great concern surrounding these manifestations and particular attention has been paid recently to the problem of cognitive dysfunction [16]. Because differentiating disease that is immune mediated versus disease from other etiologies is paramount to decisions on appropriate treatment of CNS lupus, diffuse disease has been a focus in efforts to develop and improve diagnostic biomarkers.

Established biomarkers of disease

Cerebrospinal fluid, neuropsychometric evaluations & imaging biomarkers

Cerebrospinal fluid (CSF) analysis for inflammatory markers has long been established as part of the standard laboratory examination for cNPSLE. These biomarkers include: white blood cell count, protein, oligoclonal bands and the IgG/albumin CSF index (a measure of proportionate immunoglobulin in CSF compared with serum). However, most evidence indicates that these markers neither alone nor together are particularly sensitive or specific for cNPSLE in adults or children [10,23,27–29].

Traditional neuropsychological testing by an expert neuropsychologist is another well-established measure for assessing cognitive dysfunction in lupus and other diseases. Though current literature supports patterns in cognitive impairment that are suggestive of cNPSLE, namely impairments involving executive function, memory, attention and visual-spatial processing [30,31], this is still not a means of specifically identifying the disease and differentiating it from other etiologies. Because traditional neuropsychological tests are costly, time burdensome and difficult to obtain and repeat, shorter batteries have been proposed by expert panels in adults [32] and children [33]; however, in the case of the pediatric population, they have not yet been validated.

MRI is the most utilized neuroimaging modality in the diagnosis of pediatric cNPSLE. In contrast to focal cNPSLE (e.g., cerebrovascular disease) which often correlates with abnormalities on neuroimaging, findings in diffuse cNPSLE are often normal. When abnormalities are present, the most common lesions associated with cNPSLE are periventricular and subcortical high intensity white matter changes seen on T2-weighted images, followed by cerebral atrophy and small cortical infarcts [16]. EEG is also commonly used as an adjunct diagnostic tool. While EEGs frequently exhibit a generalized slowing pattern in patients with cNPSLE [27], some studies have shown that it is relatively insensitive when there is no seizure disorder [34]. Like so many of the other aforementioned markers, abnormalities seen in cNPSLE in this modality are nonspecific and EEGs are not easily obtained in an outpatient rheumatology clinic visit.

Blood biomarkers

Biomarkers obtained from blood draws are far easier to obtain and less costly than CSF biomarkers or neuroimaging. Unfortunately, very few serum biomarkers have proven reliable markers for disease, but some are used frequently in conjunction with the markers above, to help aid in the diagnosis of cNPSLE in suspected patients.

Lupus disease surveillance markers—Though cNPSLE does not always follow lupus disease activity, high disease activity markers are generally thought to increase the index of suspicion for neuropsychiatric symptoms having an etiology primary to lupus [14]. Accordingly, standard disease activity laboratory tests are obtained in the examination of both adult and pediatric patients with cNPSLE. These include complete blood counts, complement levels and anti-dsDNA antibodies. Evidence for the individual importance of each of these is mixed in both adults [35–39] and children [10,40].

Anti-ribosomal Pantibodies—Antibodies with avidity to ribosomal phosphoproteins, or anti-ribosomal P antibodies, were originally described in 1986 in lupus patients [41] and in a case series shortly thereafter were reported to occur in almost all 20 patients with lupus psychosis, including several adolescents [42]. While most studies report that anti-ribosomal P antibodies occur in about 10–20% of adult lupus patients [43], their prevalence in pediatric lupus is 20–42% [44–46]. Researchers discovered that injecting anti-ribosomal P antibodies into the ventricles of mice induced depressive behavior [47]; however, human clinical studies of the utility of anti-ribosomal P to reliably indicate diffuse cNPSLE have had varying results [43,48]. In studies in both pediatric and adult patients, a robust association seems to be specific for lupus psychosis, but not other forms of the disease [46,49].

Experimental biomarkers

Neuropsychometric biomarkers

Because the established neuropsychometric markers for diffuse cNPSLE require the expertise of a neuropsychologist and lengthy comprehensive testing to determine the presence of neurocognitive disease and affective disorders, efforts have been made to develop shorter screening tools for practitioners to use in the clinic setting (Table 2).

Some short cognitive screening tools already in use in evaluating adult lupus patients, are the Mini Mental Status Exam (MMSE) [50,51] and the Montreal Cognitive Assessment [52,53]. The MMSE, a widely used test in clinical medicine that can be administered to children [54], has been used in some studies of pediatric cNPSLE [11], as well as in practice [16]. However, MMSE is not a validated instrument in pediatric lupus and concern has been raised over its use in lupus in general, due to its poor sensitivity for mild cognitive dysfunction and for subtle disability in executive function [55]. While the Montreal Cognitive Assessment is a more sensitive tool [56], it was designed to screen for dementia in older adults and has not been validated in a pediatric population [57].

In adults with SLE, studies are mixed in regards to the utility of short self administered screening questionnaires of neuropsychiatric symptoms as alternatives for formal neuropsychological testing [58,59]. In children, the one study that investigated a cognitive

symptom questionnaire showed it was unable to detect disease [60]. In adults, symptom questionnaires have proven more useful as markers for NPSLE, with reported high sensitivity for the presence of disease, but only modest specificity [61]. For depression and anxiety, there are several validated and established screens that may be self administered and can be used in children or adolescents, including the Children's Depression Inventory [62], the Patient Health Questionnaire-9 for depression [63], the Screen for Child Anxiety Related Disorders [64] and the Generalized Anxiety Disorder 7-item scale for anxiety [65]. While these have been recommended for the use in lupus patients [66,67] and some have been used in research in pediatric lupus [68], none have been specifically validated for pediatric cNPSLE.

Over the past two decades, several different automated computerized cognitive tests have been developed, studied and marketed as screening tools for cognitive impairment that are cost effective, brief and easy to administer compared with traditional neuropsychological testing. Initially developed to screen for disease in patients suffering from traumatic brain injury, the application of these tests has recently been adopted for patients, including children and adolescents, with other neuropsychiatric diseases, such as cNPSLE [69,70].

In the case of pediatric lupus, the only validated computerized cognitive tool to date is the pediatric version of the Automated Neuropsychological Assessment Metrics [71]. Recently, this test has been validated in a larger cohort and composite scores for facilitating clinical use developed [72]. Further testing is needed to determine how the Pediatric Automated Neuropsychologic Assessment Metrics performs longitudinally as a measure of disease progression or remission in pediatric cNPSLE.

Advanced neuroimaging biomarkers

Neuroimaging techniques recently studied as potential markers for cNPSLE have tried to improve upon the sensitivity of conventional MRI, although none of these have been extensively studied in pediatrics. Advanced MR technologies that have been investigated include magnetic resonance spectroscopy, magnetization transfer imaging and functional MRI (fMRI). These studies are more sensitive to subtle neuronal injury and demyelination that would otherwise appear normal on conventional MRI [18]. One small study of magnetic resonance spectroscopy in pediatric lupus patients found that it correlated well with changes in neuropsychiatric symptoms over time [73]. fMRI studies in adults and pediatric lupus patients indicate differences in lupus patients and healthy controls [74], and initial pediatric studies have also indicated differences in lupus patients with and without cognitive dysfunction, indicating the possible utility of fMRI as a marker for cNPSLE [75]. While fMRI is a noninvasive modality with little to no risk, it is practically difficult to obtain in children, who have to comply with instructions and stay still throughout the procedure [76].

There is also emerging research in nuclear medicine imaging modalities for cNPSLE that reflect functional changes in the brain. Single-photon emission computer tomography (SPECT) is a modality that measures cerebral blood flow and regional metabolism in the brain. Studies in pediatric patients have shown abnormalities in cNPSLE [77] but changes in clinical status over time did not match SPECT findings [78], nor was SPECT specific for diffuse cNPSLE [79]. In considering SPECT as a potential marker in children, its

informative value must be weighed against the risk of radiation exposure to the developing brain, especially if SPECT is to be obtained repeatedly [80]. Studies with fluorodeoxyglucose-positron emission tomography have shown hypometabolism in parieto-occipital and frontal white matter associated with cNPSLE in adults [18]. However, there are limited data in pediatric cNPSLE, and these findings, which are considered nonspecific, may not ultimately help differentiate cNPSLE from other etiologies of neuropsychiatric disease.

Cerebrospinal fluid biomarkers

Antineuronal antibodies—One of the first groups of autoantibodies investigated in cNPSLE was antineuronal antibodies, specifically IgG that bound to neuroblastoma cell lines. These antibodies have been linked to other neurodegenerative diseases, most notably paraneoplastic syndromes [81]. Early adult studies showed a strong association with diffuse forms of cNPSLE in both CSF [82] and serum [83]. Subsequent studies determining their clinical utility to detect cNPSLE have, however, been mixed; some studies report that serum antineuronal antibodies in adults with lupus are neither sensitive nor specific [84,85], making them poor biomarkers in either the detection of disease or in confirming that disease is primary cNPSLE. In the few studies in pediatrics, there are also mixed findings in regards to an association between cNPSLE and serum antineuronal antibodies [86–88], but little data concerning CSF antibodies. In general, it appears that CSF antineuronal antibodies have improved sensitivity and specificity compared with serum antibodies and there may be little utility in these as a marker from peripheral blood [82,89]. Furthermore, antineuronal antibodies react with a broad range of neuronal antigens, and research is being done to determine more specific serologies that may be potential markers for cNSPLE.

Anti-NR2 antibodies—One of the most promising experimental biomarkers for a neuronal component is a particular anti-dsDNA antibody that crossreacts to the NR2 subunit of a neuronal glutamate receptor, the NMDA receptor. These were first implicated in lupus when immunization with a peptide sequence derived from the glutamate receptor was found to elicit anti-dsDNA antibodies [90]. Later, these anti-dsDNA antibodies were identified as anti-NR2 antibodies [91]. Anti-NR2 antibodies in the CSF were found to be highly associated with cNPSLE, but less reliably in serum [92]. Studies looking specifically at the ability for this antibody to reflect cognitive dysfunction, depression and other forms of diffuse cNPSLE have been mixed [92,93], including studies in pediatric patients that showed no association with cognitive dysfunction [94]. Interestingly, in murine studies, breakdown of the blood–brain barrier by various modalities led to differential access of NR2 antibodies to CNS tissue and different phenotypic disease [95], lending to a hypothesis that the effects of these antibodies may be modulated by the original insult to the blood–brain barrier. Other antibodies to different subunits of the NMDA receptor have not been associated with CNS lupus, but only with other autoimmune encephalopathies [96].

Cytokines—Because cytokines are inherently present in inflammatory disease, and CNS disease is no exception, these have been investigated as markers of cNPSLE. Patterns of CSF cytokine expression in cNPSLE, include elevated levels of TGF-β, IFN-α, and IL-1, -8 and -17 [97]. However, the strongest data exist for IL-6, and in one study this cytokine was

found to be both a sensitive and specific biomarker to differentiate lupus psychosis from other etiologies of psychosis in adult lupus patients [98].

Serum biomarkers

Antiphospholipid antibodies—In lupus patients, antiphospholipid antibodies (APLAs) have long been associated with an increased risk of thromboembolic events [49] and their presence is a well-established biomarker for focal cNPSLE (cerebrovascular disease and chorea) [26]. In pediatric lupus there is also evidence that antiphospholipid antibodies are associated with focal cNPSLE [99,100], but which specific antibodies are most important remains unclear [99–101].

Antiphospholipid antibodies have been implicated in not only hypercoagulable neuropathology, but also in inflammatory and immune-mediated neuropathology. APLAs are thought to induce adhesion of leukocytes to small vessel walls and help activate complement [102]. In addition, it has been hypothesized that through activation of endothelial cells and micro-infarcts from small vessel thrombi, APLAs may lead to defects in the blood–brain barrier, and thus cause further susceptibility of the CNS to inflammatory mediators. APLAs have also been shown to interact directly with neuronal tissue, and in experimental models to have neuromodulatory and neurotoxic effects [103].

Interestingly, like anti-ribosomal P, APLAs are more prevalent in pediatric lupus [104]. While some studies have found associations with cNPSLE in children [99], diffuse disease specifically has not been examined in pediatric cohorts. Although there is literature describing associations of antiphospholipid antibodies and cognitive dysfunction in adults with lupus [84,105–108], there is not yet evidence of this association in pediatric lupus.

Potential biomarkers

In the search for better biomarkers for cNPSLE, several new potential biomarkers have emerged both from epidemiologic studies of already identified lupus autoantibodies and, more recently, from research that has been driven by new discoveries in disease mechanisms (Table 2). This includes translational research, in which findings from experimental mouse models of cNPSLE have informed hypotheses for potential markers, from those indicating blood–brain barrier dysfunction, to immunomodulatory molecules, such as autoantibodies and chemokines that lead to neuronal injury.

Antibodies to neuronal components

Autoantibodies to specific neuronal proteins have been hypothesized as potential markers for cNPSLE. Among them are anti-GFAP, antibodies to an intermediate filament predominantly found in neurons and known to be important for maintenance of the blood–brain barrier and anti-MAP2, antibodies specific to the neuronal cytoskeleton. Serum antibodies to GFAP and MAP2 have been investigated and were associated with cNPSLE in adults in singular studies [109,110].

Antiendothelial cell antibodies

The association of autoantibodies against neuronal proteins with cNPSLE implicates dysfunction of the blood–brain barrier in cNPSLE, as 'leaky' blood–brain barriers allow the adaptive immune system access to an otherwise immune-privileged site. Endothelial cells are integral players in the blood–brain barrier, which is mostly built from interactions between endothelial cells and astrocyte processes, connected via tight junctions and epithelial cells of the choroid plexus and arachnoid [111]. The importance of the blood–brain barrier in the development of cNPSLE in experimental mouse models has led scientists to search for markers of its components and reflective of its integrity. There is emerging research into antiendothelial cell antibodies as mediators of injury to the blood–brain barrier and potential markers for cNPSLE. So far, antiendothelial cell antibodies have been associated with cNPSLE manifestations of affective disorders and psychosis in adults [35]. In pediatrics, these antibodies have been associated with Kawasaki disease [112], but there are no studies yet in cNPSLE.

Chemokines—Several chemokines thought to be important in inflammatory pathways that might lead to NPSLE have been investigated, such as RANTES (or CCL5) and MCP-1, which have both been observed in increased levels in the CSF of adult patients with NPSLE [97]. Recently implicated in the pathogenesis of cNPSLE in experimental murine models is TNF-associated weak inducer of apopotosis, or TWEAK. These studies suggest that TWEAK can induce increased blood–brain barrier permeability and incite diffuse CNS manifestations [113,114]. A preliminary study in adult patients showed an association between CSF TWEAK levels and cNPSLE [115]. All these markers, though intriguing, are limited in utility as screening biomarkers because they require obtaining CSF.

Markers & mediators of neuronal injury—Research into markers of neuronal injury has highlighted potential biomarkers for disease monitoring that may indicate in patients with known cNPSLE when disease is ongoing or progressive versus remitting. Among these are GFAP measured in the CSF as a marker of astrocyte injury. GFAP was found to persist in adult lupus patients with progressive cognitive dysfunction and CSF signs of inflammatory disease, and subsequently improve in patients treated with immunosuppressive therapy [116].

There are other potential markers of neuronal injury that may be seen in serum rather than CSF. MMP9 is a zinc metalloproteinase important in the degradation of the extracellular matrix and lymphocyte migration, which has been hypothesized to be a direct mediator of neuronal injury and to increase the permeability of the blood–brain barrier in NPSLE [117]. Elevated levels of MMP-9 in serum have been described in adult NPSLE patients [118].

Markers of blood–brain barrier dysfunction—Research into the pathogenesis of cNPSLE using murine models of lupus and autoimmune CNS disease has revealed that defects in the blood–brain barrier may be a prerequisite for the exposure of otherwise protected brain parenchymal tissue to the circulating autoantibodies that are the hallmark of disease in lupus [15,36,114,119]. Hence, markers of blood–brain barrier dysfunction may be useful for identifying cNPSLE, especially early disease where interventions may have the

most impact. While the most established markers for blood–brain barrier permeability are found in the CSF (ratio of albumin in CSF/serum or IgG index), there are a few serum markers that have emerged from research in traumatic brain injury. These include some of the neuron-specific markers discussed earlier that also function as markers of injury (namely GFAP) [120].

Levels of serum S100B, a calcium binding protein on astrocytes, are associated with both neuronal damage and increased permeability of the blood–brain barrier [121,122]. Specific interest has developed in the role of S100B in inflammatory CNS diseases with the discovery of associations between increases in S100B and NF-κB induction, leading to neuronal production and secretion of IL-6, in addition to an increased IFN-γ response and activation of microglia similar to that described in some neurodegenerative and inflammatory brain diseases [123]. In initial studies in adults with lupus, serum S100B levels were elevated in patients with NPSLE [51,124] and in particular diffuse cNPSLE [125]. A recent study investigated differences in patients with cNPSLE, peripheral NPSLE, lupus patients without neuropsychiatric disease and patients with other forms of CNS disease. While no difference was established between groups, several groups contained fewer than five patients and >10% of the patients with cNPSLE had outlying high levels of S100B [126], so further studies may be warranted. The first pilot study in children that assessed S100B looked specifically at cognitive dysfunction and found that, though the marker was not independently associated with cognitive dysfunction, it was informative in a multivariate model with other putative serum biomarkers [127]. Of particular importance in pediatric lupus, S100B levels appear to be age and BMI dependent [128,129].

Conclusion & future perspective

Because of the devastating nature of cNPSLE, its consequences in children and the paucity of established diagnostic tools, this area is in desperate need for accessible, cost and time-efficient biomarkers. Markers of disease that will prove of greatest clinical utility must be easily obtained so they can be measured regularly to screen for, diagnose and monitor disease in a manner that is reliable and acceptable to both pediatric patients and their families.

As disease pathogenesis has yet to be fully understood, research into novel biomarkers will be informed by new discoveries in disease pathways. The variability in disease phenotypes between patients points to a diversity in mechanisms. Because of this, there will likely not be one biomarker that will emerge as sensitive and specific for cNPSLE as a whole. Biomarker profiles across multiple modalities will be necessary, not only to help diagnose disease, but to enable prediction of pediatric cNPSLE outcomes. These modalities will include neuropsychometric and imaging techniques, in addition to molecular markers measured from serum or other biospecimens. Brief psychometric screens that are appropriate for children and adolescents and specific for cNPSLE patterns of disease pathology will need to be developed and rigorously tested in ethnically, socially and developmentally diverse populations. More comprehensive research in pediatric lupus is needed in advanced neuroimaging techniques to develop norms for pediatric lupus and to define indicators of cNPSLE pathology.

Lessons should be learned, not only from adult lupus, but from other neuropsychiatric diseases in pediatrics that may share some similar disease pathways. Several potential biomarkers currently being studied are obtained noninvasively, which is especially important in the management of pediatric patients. Further studies are certainly necessary to test modalities in children to ensure both validity and feasibility in this population.

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Executive summary

Neuropsychiatric systemic lupus erythematosus classification

- Nineteen manifestations by American College of Rheumatology case definition consisting of:
  - Central neuropsychiatric system lupus erythematosus (cNPSLE; seen in >90%) and peripheral neuropsychiatric lupus erythematosus;
  - cNPSLE consists of focal disease (e.g., cerebrovascular disease, chorea) and diffuse disease (e.g., psychosis, affective disorders, cognitive dysfunction);
  - Challenging diagnoses with limited established tools that are either sensitive or specific, especially in the case of diffuse cNPSLE.

cNPSLE in pediatric lupus

- Likely more common and more severe than in adults with lupus.
- Variable pathogenesis for the disease, similar to lupus in adults.
- Particularly important and difficult in pediatrics to differentiate between primary cNPSLE and other primary neuropsychiatric diseases that may manifest in close temporal approximation.

Established biomarkers for cNPSLE

- Diffuse disease diagnosis aided by cerebrospinal fluid (CSF) analysis for markers of inflammation, traditional neuropsychological assessment, neuroimaging (MRI and EEG) and anti-ribosomal P antibodies (specifically in patients with psychosis).

Experimental biomarkers for diffuse cNPSLE

- Neuropsychological biomarkers:
- Computerized cognitive screens and screens for affective disorder symptoms will likely have utility in pediatric lupus.
- Neuroimaging biomarkers:
  - Advanced MRI technologies and nuclear medicine techniques have promise for greater sensitivity, but need to be studied in pediatric lupus patients.
- CSF biomarkers:
  - CSF antineuronal antibodies and cytokines as nonspecific markers of cNPSLE;
  - CSF antibodies to the NR2 subunit of the N-methyl-D-aspartate neuronal receptors, a specific subtype of antidouble stranded DNA

antibodies, are highly associated with cNPSLE, but less as a serum biomarker.

- Serum biomarkers:
- Antiphospholipid antibodies associated with cNPSLE in a pediatric study and with cognitive dysfunction in adult studies.

Potential biomarkers for diffuse cNPSLE

- Informed by new research in potential pathogenic pathways for disease.
- Autoantibodies to neuronal antigens may be implicated in pathogenesis of disease.
- Chemokines, markers of neuronal injury and markers of blood–brain barrier disruption may indicate disease progression, remission and/or therapeutic response.

Future perspective

- Development and testing of brief psychometric screens appropriate for pediatric patients and specific to lupus.
- Comprehensive study of advanced neuroimaging techniques as well as practical point-of-care modalities to develop norms for pediatric lupus and identify abnormalities that indicate cNPSLE.
- Development of accessible serum biomarkers so specimens can be obtained for screening purposes and disease follow-up in a manner that is acceptable to patients and families.
- Synthesis of biomarker profiles across several modalities to help diagnose specific forms of cNPSLE.

Table 1

American College of Rheumatology classification for neuropsychiatric systemic lupus erythematosus.

pNPSLE	**cNPSLE**	
	Focal cNPSLE	**Diffuse cNPSLE**
Autonomic disorder	Aseptic meningitis	Acute confusional state
Cranial neuropathy	Cerebrovascular disease	Anxiety
Mononeuropathy	Demyelinating syndromes	Cognitive dysfunction
Myasthenia gravis	Movement disorder/chorea	Headache
Plexopathy	Myelopathy	Mood disorder
Polyneuropathy	Seizures	Psychosis
Acute inflammatory demyelinating polyradiculopathy		

The 19 manifestations that comprise the 1999 American College of Rheumatology neuropsychiatric systemic lupus.

cNPSLE: Central NPSLE; NPSLE: Neuropsychiatric systemic lupus erythematosus; pNPSLE: Peripheral NPSLE.

Data taken from [15,18].

Table 2

Experimental and potential biomarkers for diffuse central neuropsychiatric systemic lupus erythematosus.

Biomarker	Modality	Manifestations	Strengths	Weaknesses		Ref.
MMSE	Psychometric	Cognitive dysfunction	Some use in pediatrics; easy to administer	Insensitive to mild cognitive impairment		[11,53,54,58]
PedANAM			Preliminarily validated in pediatric lupus	Requires computer and software		[71,72]
fMRI	Neuroimaging	Cognitive dysfunction in pediatrics	Increased sensitivity, indicates impairment in neuronal networks; noninvasive	Expensive, difficult to administer to children		[74–76]
SPECT		cNPSLE	May be more sensitive functional imaging than fMRI	Expensive, radiation exposure, contradictory studies in pediatrics, nonspecific in most adult studies		[77–80]
Antineuronal	Cerebrospinal fluid	Cognitive dysfunction in pediatrics; cNPSLE in adults	Strong evidence for association in adults	Not lupus specific	Requires lumbar puncture to obtain	[81–89]
Anti-NR2		cNPSLE, cognitive dysfunction, depression	Strong evidence for association in adults, supportive evidence from experimental mouse models	Studies in pediatrics show no association with cognition		[91–96]
Anti-GFAP/anti-MAP2		cNPSLE	May indicate progressive disease versus resolving disease	No studies in pediatrics		[109,110]
TWEAK/RANTES/MCP-1		cNPSLE	TWEAK may be an early disease marker for cNPSLE	Limited preliminary studies		[97,113–115]
Antiphospholipid	Serum	cNPSLE in pediatrics; cognitive dysfunction in adults	Established lupus biomarker for focal cNSPLE	To confirm positivity should be measured twice 12 weeks apart		[26,49,84,99–101,104–108]
Antiendothelial cell		Mood disorder, psychosis	May precede disease and identify patients at risk	No studies in pediatrics		[39]
S100B		cNPSLE	May precede disease and identify patients at risk	Contradictory studies, little data in pediatric cNPSLE		[54,129–132]

Selected experimental and potential biomarkers for cNPSLE and their strengths and weaknesses in terms of their utility in the management of pediatric lupus patients.

cNPSLE: Central neuropsychiatric systemic lupus erythematosus; fMRI: Functional MRI; GFAP: Glial fibrillary acidic protein; MAP2: Microtubule-associated protein 2; MMSE: Mini Mental Status Exam; PedANAM: Pediatric Automated Neuropsychologic Assessment Metrics; TWEAK: TNF-associated weak inducer of apoptosis.