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Biomarkers for Childhood-Onset Systemic Lupus Erythematosus

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Abstract

Childhood-onset systemic lupus erythematosus (cSLE) is a systemic autoimmune disease characterized by the presence of autoantibodies. cSLE often affects multiple organs in the body and is known to have a poorer prognosis than adult-onset disease (Azevedo et al. 2014). Current laboratory tests are clearly insufficient for identifying and monitoring the disease. Recent studies have yielded novel biomarkers for cSLE which can be used for monitoring disease activity and response to treatment. The most encouraging biomarkers will be discussed herein and include cell-bound complement activation products, some genomic profiles, and urinary proteins such as neutrophil gelatinase-associated lipocalin, monocyte chemoattractant protein-1, and others. Previous studies suggested that a combination of the novel biomarkers might help to enhance sensitivity and specificity for early diagnosis, disease monitoring, and prediction of cSLE flares.

Keywords

Childhood-onset systemic lupus erythematosus; cSLE; SLE; Biomarker; Kidney disease; Urinary biomarkers; Cardiovascular disease; CNS lupus

Introduction

Systemic lupus erythematosus (SLE) is a multisystemic chronic autoimmune disease that is characterized by autoantibody production directed against nuclear antigens. There is a diversity of autoantibodies of which those against nuclear antigens typically predominate immune complex formation and deposition, endothelial cell and complement activation, and leucocyte emigration and activation [1•]. SLE is more common among females, and although the etiology of SLE is not fully understood, numerous lines of evidence suggest that genetic, hormonal, and environmental factors are involved in the pathogenesis of SLE [1•].

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Childhood-onset SLE (cSLE) is defined as SLE onset prior to age 18 years of age [2]. Compared to SLE in adults, cSLE is accompanied by more severe multiorgan involvement [2]. The current laboratory tests such as urinalysis, quantitative proteinuria, complete blood count, ESR, C-reactive protein, antidouble-stranded DNA antibodies, and the complement components C3 and C4 are clearly insufficient for identifying or monitoring the disease activity. Treatment of cSLE, particularly renal involvement with cSLE, continues to lack support from large randomized clinical trials. Instead, medication regimens for cSLE are deduced from studies in adult SLE and pediatric solid-organ transplants or are based on consensus reached by associations of health care providers. Until recently, progress in the treatment of cSLE has been severely hampered by the absence of biomarkers to support medical decision making. In this review, we focus on peer-reviewed studies on biomarkers for cSLE published since 2010. A summary of the biomarkers discussed here are presented in Table 1.

What Is a Good Biomarker?

The National Institutes of Health Biomarkers Working Group has defined a biological marker (short biomarker) as “a characteristic that can be objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention” [3, 4•]. Biomarkers may be laboratory tests, imaging, or other physiological tests, such as body temperature. Biomarkers are essential for the implementation of personalized medicine. Characteristics of high-quality biomarkers are as follows: [1••] they should be noninvasive, easily measured, and economical and produce rapid results; [2] they should be from readily available sources, such as blood or urine; [3] they should have a high sensitivity, allowing early detection, and no overlap in values between diseased patients and healthy controls; [4•] they should have a high specificity, being greatly upregulated (or downregulated) specifically in the diseased samples and unaffected by comorbid conditions; [5] their levels should vary rapidly in response to treatment; [6] their levels should aid in risk stratification and possess prognostic value in terms of real outcomes; and [7] they should be biologically plausible and provide insight into the underlying disease mechanism [5–7].

Commonly, receiver operating characteristic (ROC) curves are used to assess the quality of a biomarker [6]. The ROC curve is derived from a binary classification test and measures the sensitivities and specificities of a biomarker, depending on cutoff levels of the biomarker considered. The area under the ROC curve (AUC_{ROC}) is a statistic to assess the overall accuracy of a biomarker. An AUC_{ROC} of 1.0 represents a perfect biomarker, whereas an AUC_{ROC} of 0.5 identifies a biomarker that does not perform better than the flip of a coin. AUC_{ROC} of 0.75 or greater is generally considered a good biomarker, while an AUC_{ROC} of 0.90 is considered an excellent biomarker [5]. It must be noted that a biomarker is best judged by assessing the AUC_{ROC} and levels of sensitivity and specificity that can be achieved using various biomarker threshold values. Correlation analysis alone does not suffice to assess the quality of biomarkers [8]. Given the diversity of SLE phenotypes, most likely combinations of biomarkers are needed to accurately describe the presence of a certain organ involvement with SLE or changes in SLE disease states.

Biomarkers for Lupus Nephritis

Among the main determinants of poor prognosis in cSLE is renal involvement. Lupus nephritis (LN) continues to result in significant morbidity and mortality [9, 10]. The severity of LN is categorized as per the International Society for Nephrology/Renal Pathology Society (ISN/RPS) classification [11, 12]. Owing its heterogeneity and unpredictable clinical course, the therapeutic management of LN remains a major clinical challenge. The pathogenesis of LN is still incompletely understood, and there is a lack of markers that accurately predict LN flares, response to treatment, renal prognosis, and development of end-stage renal disease (ESRD). It is well known that early treatment improves the prognosis of LN, and there is a strong association between delayed diagnosis and higher incidence of ESRD. Although LN flares can often be treated successfully by aggressive immunosuppression, the associated side effects and toxicity may be unacceptably high [9, 10]. Current treatments could be used more effectively and potentially with less toxicity, if LN activity, flare severity, response to treatment, and prognosis were predicted accurately [13].

Given its importance for long-term patient outcomes, LN biomarkers have been an intense field of research. The most readily available sources of biomarkers are urine and blood. The arrival of new technologies over the last few decades has led to a blast in the identification of innovative biomarkers for many disease conditions. Summarized in the following sections are LN biomarkers that have shown moderate to good sensitivity and specificity in LN activity and its changes. Notably, these biomarkers are often more closely related to LN when measured in the urine rather than in the blood of patients with LN.

Monocyte Chemoattractant Protein-1/CCL2

Monocyte chemoattractant protein-1 (MCP-1) is a leukocyte chemotactic protein involved in the mediation of inflammation and renal injury in LN [14]. Several cross-sectional studies have verified that urine MCP-1 levels are concurrently higher in patients with active LN than with inactive LN [15–17]. The AUC_{ROC} of MCP-1 for distinguishing active LN from inactive LN or extrarenal SLE flares is 0.76 [18•]. Urine MCP-1 holds promise in helping to distinguish certain classes of LN. Urine MCP-1 levels are significantly higher with ISN/RPS classes III and IV than with other classes of LN ($P<0.01$) [19]. Both children and adults with class IV LN have the highest glomerular expression of MCP-1 in the tissues [20].

Neutrophil Gelatinase-Associated Lipocalin

Neutrophil gelatinase-associated lipocalin (NGAL) is expressed in several cell types, including neutrophils, specific epithelia, and renal tubular cells. NGAL is markedly upregulated in the distal tubules in response to many types of kidney injury. Cross-sectional studies investigated NGAL as a biomarker for LN in pediatric patients [21] and adults [22–24]. In children, elevated urine NGAL levels had a high sensitivity and specificity for active biopsy-proven LN (AUC_{ROC} 0.94). In adults, the specificity was still high (91 %), but sensitivity was lower (50 %) for LN [21]. More recent longitudinal studies in the pediatric population have shown that urine NGAL are significantly higher in SLE patients than those

with juvenile idiopathic arthritis or healthy controls, unrelated to physiologic factors such as height, weight, and age [25]. Levels of urine NGAL, but not plasma NGAL, correlated well with clinical measures of LN activity [25, 26]. Urine NGAL rose 3 to 6 months before clinically diagnosed LN flare, demonstrating value in predicting flares. Similar to MCP-1, urine NGAL is not specific to LN and thus must be used in a context-specific setting.

Urine Protein Signature

Transferrin, orosomucoid (or α -1 acid glycoprotein [AGP]), ceruloplasmin (CP), and lipocalin-type prostaglandin D synthase (L-PDGS or b-trace protein) are all part of a LN urine protein signature that was discovered and then subsequently validated by Suzuki and colleagues [27]. These four proteins were found to be significantly higher in patients with active LN than in those with nonrenal SLE or JIA controls. Urine L-PDGS, AGP, and transferrin all increased as early as 3 months before renal flare.

Colony-Stimulating Factor 1

Colony-stimulating factor 1 (CSF 1) is expressed in the renal tubular epithelial cells (TECs) and is involved in cell development, survival, proliferation, and activation [28]. Earlier studies showed that CSF 1 is highly expressed in the kidneys of animal models of LN [23]. In a longitudinal study of over 60 adults with LN, both CSF 1 in the urine and serum were elevated at the time of the initial LN diagnosis and with LN flares; levels decreased upon achieving remission of LN. Notably, rises in serum or urine CSF-1 preceded recurrences of LN as measured before clinical evidence of glomerular dysfunction and conventional serologic methods by 54 days [29•].

MicroRNA

MicroRNAs (miRNAs) are a novel class of endogenous, noncoding small RNAs of approximately 19–25 nucleotides in length. They regulate gene expression at the post-transcriptional level by targeting specific miRNAs for degradation or suppressing mRNA translation. Recent studies demonstrated that miRNAs can be detected in the circulation and may serve as potential biomarkers of various diseases as miRNA levels vary with the degree of inflammatory activity. Wang et al. [30] reported that miR-126 is overexpressed in the blood of the adult SLE patients compared to normal controls. In contrast, miR-125a-3p, miR-155, and miR-146a trended lower in SLE patients. The same group investigated urinary miRNA in 40 adult SLE patients and showed that urinary miR-200a, miR-200c, miR-141, miR-429, and miR-192 levels were all lower in LN patients than those of controls. However, none of these miRNA when measured in the urine correlated with clinical parameters of LN activity [30].

Type 1 Interferon

Increased expression of type 1 interferon (IFN) regulated genes; in other words, an IFN signature is present in blood and tissue cells from patients with SLE and other autoimmune diseases [31•, 32]. There have been recent reports of using IFN signature as a biomarker for SLE activity. However, the IFN signature in the blood remained stable and failed to change

with SLE activity [33]. Conversely, IFN-induced chemokines have been reported to change with SLE activity, but further research is needed to assess their value as biomarkers for predicting the course of SLE and cSLE [34].

Cell Adhesion Molecules

The cellular adhesion molecules, vascular cell adhesion molecule-1 (VCAM-1) and E-selectin, are expressed exclusively on the surface of endothelial cells. VCAM-1 and E-selectin facilitate leucocyte endothelial cell interactions. These molecules are shed into the circulation, acting as markers of endothelial activation and dysfunction [35•]. In a cohort of 178 SLE patients, Skeoch et al. reported that blood E-selectin was increased in SLE patients compared to age-matched controls (median [IQR] of E-selectin 10.5 [6.85, 13.9] vs. 7.86 [5.39, 10.4] ng/ml; $P<0.001$). In regression models, E-selectin was also associated with overall SLE damage scored by using the Systemic Lupus International Collaborating Clinics (SLICC) Damage Index (slope [95 % confidence interval] 0.27 [0.029, 0.511]) [35•]. Based on the above, E-selection may be a biomarker for overall SLE damage. However, presentation of an AUC_{ROC} is needed to better judge the usefulness of E-selectin to serve as a biomarker for SLE damage.

Complement Components

Traditional complement components C3 and C4 are measured in routine practice to follow cSLE disease activity in general and LN activity in particular. Despite their use, they are not good LN biomarkers especially after correcting for extrarenal disease activity [27]. Recent studies suggest that complement split products may be better biomarkers of LN activity than total C3 and C4. Batal et al. prospectively evaluated 15 adult LN patients and measured complement component C4d on the circulating erythrocyte (E-C4d) and its deposition in kidney biopsies. Compared to controls which were 239 SLE patients and 13 patients with other chronic kidney diseases besides LN, circulating E-C4d levels were higher in LN patients ($P=0.002$). Additionally, E-C4d concentrations correlated with the National Institutes of Health (NIH) activity index scores in the kidney biopsy ($r=0.55$, $P=0.04$). These findings suggest a potential role of C4d as a biomarker for LN [36] but warrant study to confirm its role as a superior biomarker of LN.

Urine Protein Biomarker Panel for LN

Brunner et al. measured select urinary biomarkers for 76 patients with LN within 2 months of biopsy-proven active LN. A combination of MCP-1, AGP, and CP levels plus protein/creatinine ratio was found to be very good in predicting LN activity (AUC_{ROC} of 0.85). NGAL, together with creatinine clearance plus MCP-1, was shown to be an excellent diagnostic test for LN chronicity with an AUC_{ROC} of 0.83 [37•]. In a secondary analysis of data from a randomized, open-label multinational, multicenter clinical trial, Maria Dall'era et al. set out to identify biomarkers that when measured at diagnosis with active proliferative LN could serve as early predictors of renal response to mycophenolate mofetil or intravenous cyclophosphamide [38]. Normalization of C3, C4, or both by week 8 was strongly predictive of achieving remission of LN at week 24 (odds ratio [OR] of 2.5, 2.6,

and 2.9, respectively, $P<0.05$). Similarly, a reduction in proteinuria by at least 25 % by week 8 was predictive of LN response at week 24 (OR=3.2, $P<0.05$). In contrast, a reduction in antidouble-stranded DNA titers by week 8 was not predictive of renal response. These results are likely applicable to renal involvement with cSLE, given that this study included 370 patients and 15 % were less than 20 years of age.

Biomarkers for Neuropsychiatric Lupus

Among others, neuropsychiatric systemic lupus erythematosus (NPSLE) can result in impairment of cognitive ability [39]. Indeed, cognitive ability is often considered a measure of overall brain function and health. Currently, formal neuropsychological testing is used to estimate cognitive ability of cSLE patients.

A proposed mechanism leading to NPSLE is neuronal damage caused by exposure of the brain tissues to circulating autoantibodies due to breakdown of the blood-brain barrier [40]. A number of autoantibodies have been associated with the presence of NPSLE, including anti-*N*-methyl-D-aspartate (NMDA) receptor antibodies and antiribosomal P and antiphospholipid antibodies [41–44]. Although elevated levels of these antibodies have been detected in serum and cerebrospinal fluid with NPSLE, a direct association between their concentration and neuropsychiatric disease status remains elusive as their impact likely depends strongly on the current and past condition of the blood-brain barrier. In a study of 1047 recently diagnosed SLE patients followed over a mean of 3.6 years, antiribosomal P antibodies were associated with an increased risk of lupus psychosis (hazard ratio 3.92, 95 % confidence interval [CI] 1.23 to 12.5, $P=0.02$) [45]; hence, it might be a biomarker of NPSLE-associated psychosis.

Mostafa et al. prospectively studied serum antiganglioside M1 antibodies in NPSLE [46]. These antibodies were measured serially in the serum of 30 cSLE patients without clinical evidence of NPSLE. During an average follow-up of 12 months, 12 cSLE patients developed new NPSLE manifestations, with 83.3 % of them testing positive for serum antiganglioside M1 antibodies. There was a significant positive association between antiganglioside titer seropositivity and the level of cognitive dysfunction (OR=36, 95 % CI 4.3–302.8, $P<0.001$).

Recent years have seen the advent of neuroimaging, especially magnetic resonance imaging (MRI), as a promising tool to delineate imaging biomarker for NPSLE. Conventional structural brain MRI often fails to identify matching pathology [47–49]. More recently, advanced functional magnetic resonance imaging using blood oxygenation level-dependent contrast to measure brain activation allowed the demonstration of changes in activation of functional brain networks which were related to cognitive ability with NPSLE [50] (see Fig. 1). Furthermore, using structural magnetic resonance imaging, there was volumetric loss in the gray matter morphology in children with cSLE compared to healthy children, especially when decreased cognitive ability was present (Fig. 2) [52•]

Biomarkers of Cardiovascular Risks

Since the early 1970s, patients with SLE have been known to be at increased risk for premature atherosclerosis [45]. There are only few studies examining the cardiovascular risk

of children with cSLE. However, there is recent evidence that adipokine cytokines like leptin, adiponectin, and ghrelin may be important in the development of atherosclerosis in otherwise healthy individuals and in disease states like SLE. Low serum adiponectin and elevated leptin concentrations have been proposed as biomarkers of atherosclerosis risk in patients with metabolic syndrome and renal disease [53, 54]. Marjon et al. examined the value of adipokines to serve as potential biomarkers for cardiovascular risk in cSLE. Among 35 cSLE patients, about one in three children had abnormally elevated leptin levels. In children with cSLE, serum adiponectin concentrations were significantly positively associated with prednisone dosage in both male and female patients but not with disease activity ($r=0.655$; $P=0.0017$) [55]. Further studies are needed to determine which degree of serum adiponectin elevation is reflective of a clinically relevant cardiovascular risk increase with cSLE.

Conclusions

Biomarker research has yielded several promising biomarker candidates to help monitor critical organ involvement with cSLE. Especially if combined, these biomarkers appear superior to the current tools available to rheumatologists to monitor cSLE and its course. We anticipate that in the upcoming decade, some of these biomarkers will reach the patient's bedside, thereby facilitating and improving the management of cSLE.

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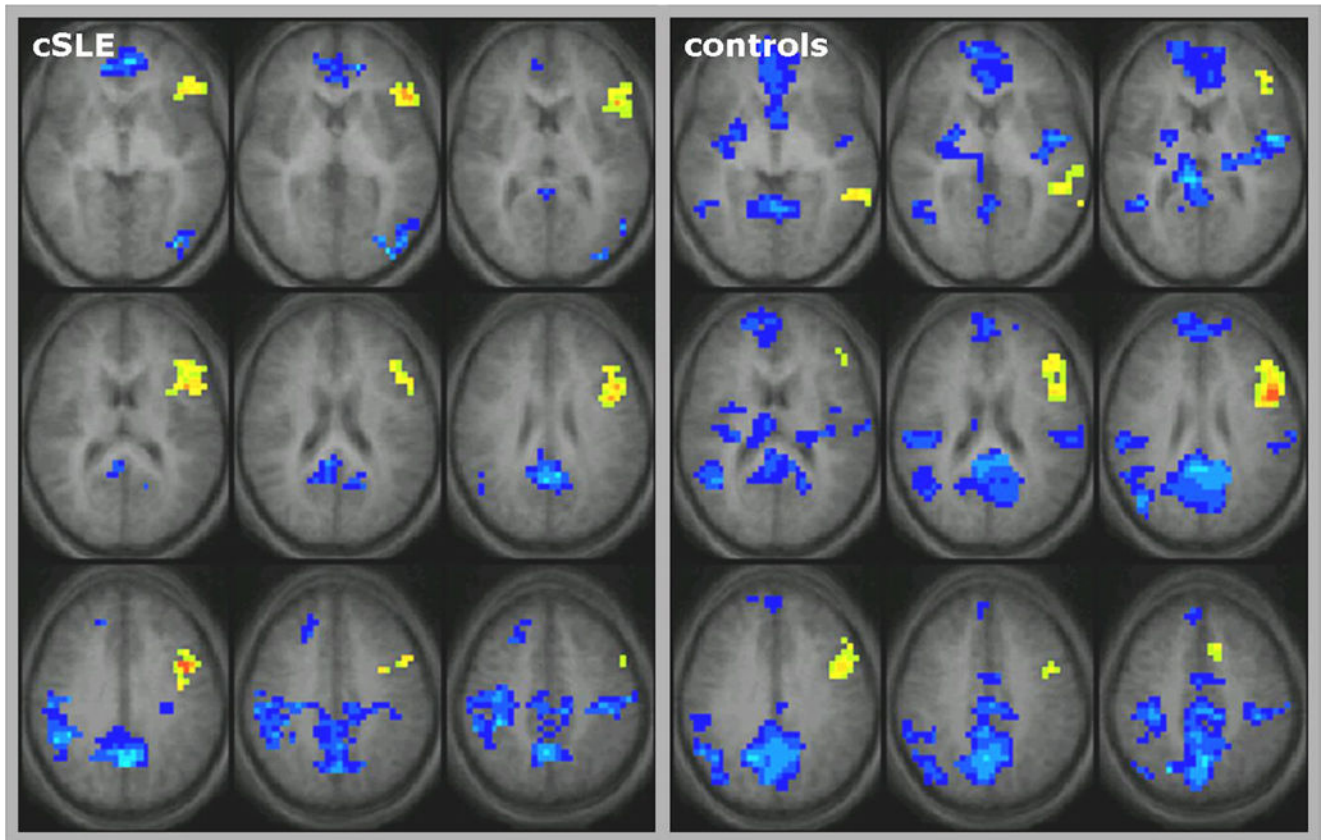


Fig. 1.

Functional MRI (fMRI) images for assessing the effects of childhood-onset SLE on brain activation patterns when testing attention using a continuous performance paradigm. Differences in activation (*yellow*) and suppression (*blue*) patterns in children with SLE and healthy controls. In SLE, larger brain areas need to be activated for performing an fMRI task and fewer are suppressed [51]

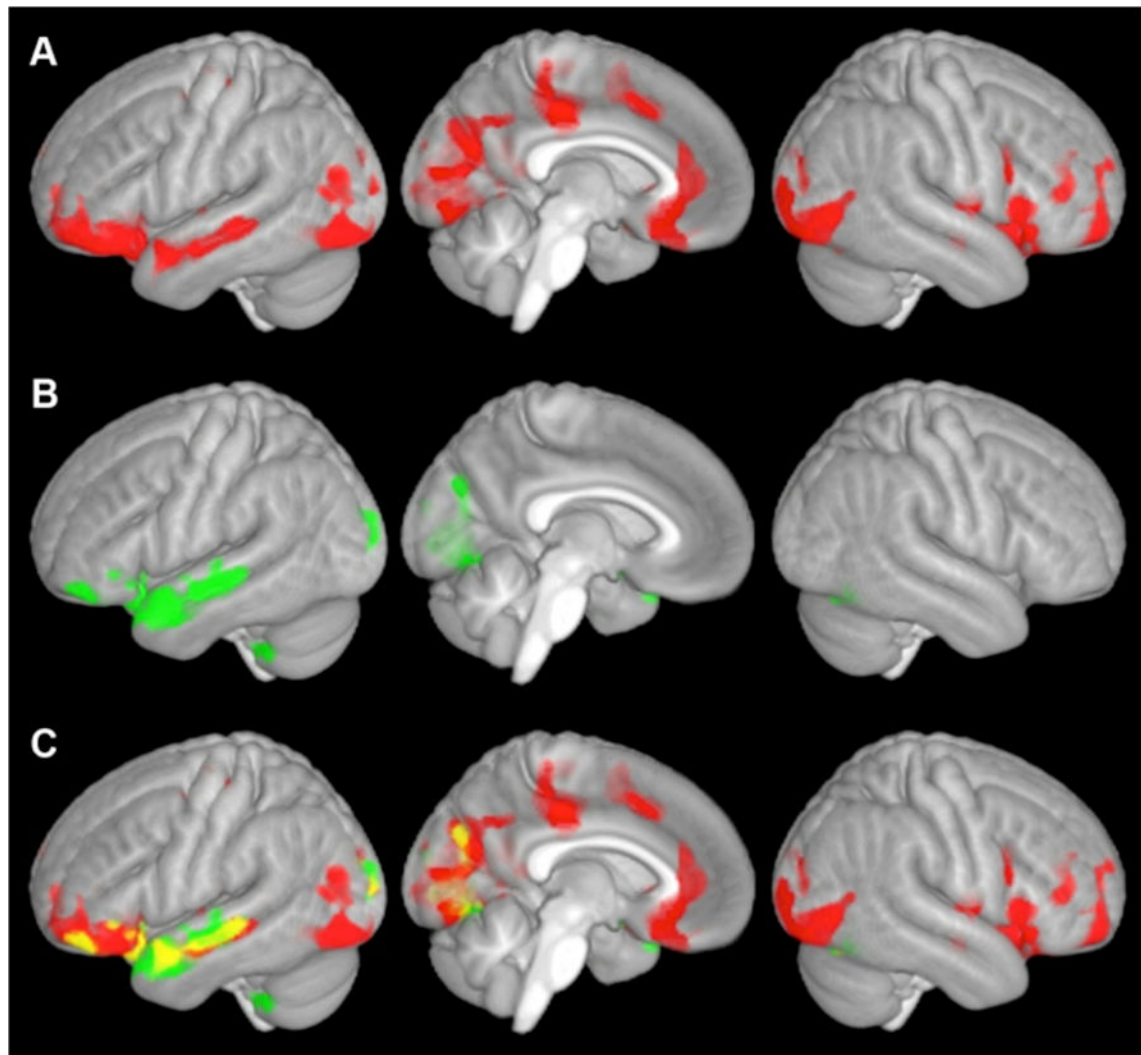


Fig. 2.

Decreases in gray matter in patients cSLE with neurocognitive deficit versus controls and patients with childhood-onset SLE with normal cognition. *Red*, *green*, and *yellow* designate differences in gray matter volume that were statistically significant at $P < 0.05$ after correction for multiple comparisons across the entire brain. Sagittal surface three-dimensional views of (a) regions with decreased gray matter in patients with neurocognitive deficit versus controls (*red*), (b) regions with decreased gray matter in patients with neurocognitive deficit versus patients with normal cognition (*green*), and (c) overlap (*yellow*) between the comparisons shown in a and b. Compared to the controls and patients with cSLE with normal cognition, the patients with cSLE with neurocognitive deficit showed extensive areas of decreased gray matter in the limbic cortex (orbitofrontal and cingulate), inferior frontal, temporal, and visual association cortex

Table 1

Summary of biomarkers studied in cSLE

Biomarker	Organ/system	Comments
NGAL (urine)	Lupus nephritis	High sensitivity for renal injury, may predict renal injury 3–6 months prior to clinical parameters
MCP-1 (urine)	Lupus nephritis	High sensitivity for renal injury, potential in distinguishing different classes of lupus nephritis
Urine protein signature	Lupus nephritis	Moderate sensitivity, may predict renal flares 3 months prior to clinical parameters
Colony-stimulating factor 1 (serum and urine)	Lupus nephritis	New biomarker. Correlated with LN disease activity and response to treatment. May predict LN flare about 2 months prior
Urinary miRNAs	Lupus nephritis	Moderate correlation with LN disease activity. More studies are needed
Interferon (IFN) signature	Lupus nephritis	No correlation with disease activity when measured in the blood. However, IFN-induced chemokines had some correlation
Antiribosomal P	CNS lupus	Elevation causes increased risk of lupus psychosis
Antiganglioside M1	CNS lupus	Potential for prediction of a neuropsychiatric manifestation in lupus. Moderate correlation with ganglioside seropositivity and the level of cognitive dysfunction
Advanced brain MRI (functional MRI)	CNS lupus	Potential for diagnosis or prediction of cognitive dysfunction in lupus
Adiponectin	CVS lupus	Low serum levels may be a risk factor for premature atherosclerosis