Published in final edited form as:

Neurol Clin. 2010 February ; 28(1): 61–73. doi:10.1016/j.ncl.2009.09.004.

Neurological Manifestations of Systemic Lupus Erythematosus in Children and Adults

Eyal Muscal, M.D.¹ and Robin L. Brey, M.D.²

¹ Assistant Professor of Pediatrics, Division of Pediatric Rheumatology, Baylor College of Medicine

² Professor of Neurology, University of Texas Health Science Center at San Antonio

Keywords

Collagen Vascular Disease; Systemic Lupus Erythematosus; Neurologic Disease; Autoantibodies

Introduction

Among the Collagen Vascular Diseases neurological manifestations have been most commonly recognized and well-studied in Systemic Lupus Erythematosus (SLE, lupus). Neurological manifestations are less prevalent in other systemic inflammatory and autoimmune disorders. Rheumatoid Arthritis (RA) in adults, an erosive and potentially deforming inflammatory arthritis has been associated with peripheral neuropathy, brain stem and spinal cord compression due to mass effect from pannus formation in the vertebral joints, and stroke caused by premature atherosclerotic vascular disease. Sjogren's Syndrome, characterized by dry eyes and dry mouth, has been associated with hemispheric and spinal cord lesions that can mimic the clinical and neuroradiographic features of multiple sclerosis.. Scleroderma, characterized by skin hardening and fibrosis, may lead to peripheral neuropathy and trigeminal neuralgia in its systemic form (systemic sclerosis). This review will focus on the clinical presentation, pathophysiology, and treatment strategies of neuropsychiatric lupus (NPSLE) in children and adults.

SLE affects multiple organ systems in women nine times more frequently than men. The prevalence is approximately 130/100,000 in the United States, with African Americans, Hispanics and Asians more frequently affected than Non-Hispanic Whites (1). The nervous system is commonly affected in both children and adults with SLE (2–7), is also associated with a worse prognosis and more cumulative damage in children (4) and adults (5,8). Neuropsychiatric lupus (NPSLE) manifestations can occur in the absence of either serologic activity or other systemic disease manifestations (4). The American College of Rheumatology (ACR) established case definitions for 19 central and peripheral nervous system syndromes listed in Table 1 (9). Some of these are rarely seen in patients with SLE, and all occur in diseases other than SLE. Studies attempting to link NPSLE manifestations to underlying SLE-specific pathophysiological processes are ongoing.

Corresponding author for proof and reprints: Robin L. Brey, M.D., Professor and Chair, Department of Neurology, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, Mail Code #7883, San Antonio, TX 78229-3900, 210-567-4621, 210-567-1948 (fax), brey@uthscsa.edu.

Co-Author: Eyal Muscal, M.D., Assistant Professor, Texas Children's Hospital/Baylor College of Medicine, Division of Rheumatology, 6621 Fannin St. MC 3-2290, Houston, TX 77030, 832-824-3835, emuscal@bcm.tmc.edu

Systemic Lupus Erythematosus

Clinical Manifestations

Prevalence of NPSLE Manifestations in Adults and Children—In adults, approximately 28%–40% of NPSLE manifestations develop before or around the time of the diagnosis of SLE (5). Estimates of the prevalence of NPSLE have ranged from 14% to over 80% in adults (2,5,10–12) and 22%–95% in children (4,6,7,13,14). A retrospective study of NPSLE in 185 Chinese children over a 20 year period found that 11% had NPSLE manifestations at the time of diagnosis and an additional 16% developed them within one year. The mortality rate in this study was 45% in children with NPSLE and 17.4% in those without these manifestations (7). A more recent prospective study of 256 pediatric SLE patients from Toronto followed for approximately 4 years confirmed the morbidity and cumulative organ damage associated with NPSLE manifestations, however, in this study only 6 patients (2.3%) died during the follow-up period (14). The ethnic distribution of the children in this study was not given, and in adults, African American, Hispanic and Asian SLE patients have a higher SLE-related disease morbidity, possibly contributing to the discrepant findings.

NPSLE in Adults—It is important to note that the ACR case definitions do not include the term “lupus cerebritis”, which unfortunately continues to be misused in SLE patients with central nervous system symptoms rather than more specific diagnostic terms (9). Studies in adults using the ACR case definitions collectively have detected the presence of 14–17 of the 19 NPSLE syndromes and reported a fairly consistent prevalence of the following syndromes: total spectrum of headache (39%–61%), seizures (8%–18%), cerebrovascular disease (2%–8%), psychosis (3%–5%), cranial neuropathy (1.5%–2.1%) and movement disorder (1%). Interestingly, the range in the prevalence of mood disorders and cognitive dysfunction is much wider, with studies using systematic assessment of cognitive and psychiatric function finding a higher prevalence (2,5,10,15,16) than studies that only evaluated patients using sensitive instruments if “clinically indicated” (5). These studies testing cognitive function in every patient using sensitive psychiatric and neuropsychological instruments found the prevalence of the total spectrum of mood disorders to be between 69% to 74% and the total range of cognitive disorders to be between 75% to 80%. In contrast, the study which did not do standardized psychiatric or cognitive assessments found that only 12.4% had mood disorder and 5.4% had evidence of cognitive dysfunction (5). The number of patients reported with moderate to severe cognitive dysfunction in most studies is 25–40%, suggesting that the failure to test all patients in that study may have underestimated clinically important cognitive dysfunction.

While the frequency of NPSLE in this large inception cohort study was 28% (158 of 572 patients), lower than other studies, the occurrence of neuropsychiatric events was associated with reduced quality of life and increased organ damage, irrespective of whether the particular event was judged to be SLE-related or not (5). Whether or not this association strengthens or becomes more specific with time is currently being investigated, as more patients are being recruited and followed. Some additional information has been recently published by this group on short-term outcomes of NPSLE events on their inception cohort (17). The maximum time of observation for determining short-term outcomes was 21 months (from up to 6 months prior to SLE diagnosis and up to 15 months after SLE diagnosis). Outcome were determined using a physician generated Likert score: death [1], much worse [2], worse [3], no change [4], improved [5], much improved [6], and resolved [7]. Thus far, 271 (33.5%) of 890 patients had at least 1 NPSLE event and 90 had 2 or more events that included 15 different NPSLE syndromes (see Table 1 for a complete list of the ACR NPSLE case definitions). The authors found that 16.5% to 33.9% of them (depending on which manifestation was being considered) were attributable directly to SLE and the remainder were due to other concomitantly existing

conditions. Short-term outcomes for patients with a neurological event attributed to SLE were better than for those with an event not attributed to SLE. These data highlight an important clinical issue in caring for SLE patients with NPSLE manifestations; the ability to definitively attribute the neurological manifestations appropriately is of paramount importance for both diagnosis and treatment decisions.

A study from Hong Kong examined the direct and indirect costs of SLE in adults to determine the relationship between NPSLE and disease costs (12). The overall prevalence of NPSLE in this cohort was 27%, with the most common manifestations being seizures and stroke. Patients with NPSLE in this study incurred twice the total disease-related costs than those without NPSLE manifestations, strengthening the need to find better treatment strategies to limit NPSLE-related disease activity and cumulative organ damage.

NPSLE in Children—There have been few comprehensive studies detailing NPSLE features and prevalence rates in children and adolescents. A reliance on adult data to understand NPSLE in childhood-onset lupus may ignore potential immunological and brain structural differences between adults and children with the disease (18). Neurological involvement appears to be more severe in children who may accrue permanent organ damage at higher rates than adults (19–21). In an older prospective study of NPSLE in children, nervous system manifestations were more common over a 6-year study period than glomerulonephritis (95% versus 55%, $p \leq 0.0001$) (6). The most prevalent NPSLE syndromes in this longitudinal study included: headaches in 72 % of children, mood disorder in 57%, cognitive dysfunction in 55%, seizure disorder in 51%, acute confusional disorder in 35%, peripheral nervous system impairment in 15%, psychosis in 12%, and stroke in 12%. The more recent prospective study of 256 children with SLE already mentioned confirmed the contribution of both glomerulonephritis and nervous system manifestations in SLE-related morbidity over time (14). A literature review of NPSLE in pediatric patients, with some contribution from the author's own clinical experience, concluded that long-term outcomes for pediatric patients with NPSLE was excellent, and confirmed Hiraki and colleagues' finding of a high overall survival (97%) (13). However, in this study, patients who presented with seizures or stroke and had a high cumulative disease activity rate or frequent central nervous system flares were at higher risk for long-term nervous system damage. A study from Belgium comparing pediatric and adult SLE patients found that pediatric patients had more frequent renal disease and encephalopathy than adults (22).

A retrospective study of NPSLE in children in the San Francisco area also found that NPSLE manifestations were common, occurred early in the course of the disease and were not necessarily associated with disease activity outside the nervous system (4). This was the first study to systematically assess the link between aPL and NPSLE manifestations in children. Although the presence of antiphospholipid antibodies was seen in 70% of children in this study (as compared to approximately 25–30% in adult SLE patients), the association of these antibodies with NPSLE was weak with the exception of cerebrovascular disease. The authors suggest that there may be a different underlying pathophysiologic mechanism for non-cerebrovascular NPSLE manifestations in children as compared with adults, however, cognitive dysfunction, a manifestation that has been strongly linked to aPL in adults, was not systematically studied in these pediatric patients. This may have lead to an underestimation of the importance of aPL overall in relation to NPSLE manifestations in children.

There are sparse data on neurocognitive impairment in children with SLE. Unlike adults with lupus, there is no validated clinical or research neuropsychological testing battery for children with the disease. The few studies that have assessed neurocognitive status in children with SLE did not investigate for concurrent structural brain abnormalities. Mini-Mental Status Examination testing (MMSE), known for its low sensitivity outside of dementia, showed a 55% prevalence rate of neurocognitive deficits in a total of 75 children (6). In a 1990 study,

21 pediatric lupus patients had lower complex problem solving scores when compared to 11 patients with juvenile arthritis (23). A recent study reported neurocognitive impairment in 59% (16 of 27) of children without previously diagnosed NPSLE (24). The true prevalence rate and impact of neurocognitive impairment on academic performance and health-related quality of life status of children with lupus is still unknown.

More work is certainly needed in both pediatric and adult SLE populations to better understand the underlying pathophysiology of NPSLE manifestations and the similarities and differences between children and adults that may be important in treatment considerations.

Pathophysiology and Pathogenesis

The pathogenic etiologies of NPSLE manifestations are likely to be multifactorial and may involve autoantibody production, microangiopathy, intrathecal production of proinflammatory cytokines and premature atherosclerosis (25). Cellular and parenchymal changes in lupus murine models include neuronal cytotoxicity and atrophy of dendritic spines (26). Cerebral spinal fluid from lupus-prone mice and adult patients with NPSLE reduce the viability of proliferating neural cells lines (27). Postmortem histopathologic studies reveal a wide range of brain abnormalities caused by multifocal microinfarcts, cortical atrophy, gross infarcts, hemorrhage, ischemic demyelination and patchy multiple-sclerosis-like demyelination in people with SLE (28). A microvasculopathy which was formerly attributed to deposition of immune complexes but now is suspected to arise from activation of complement, appears to be the most common microscopic brain findings in SLE (29). Consistent with these small vessel changes, SPECT and MR spectroscopy studies suggest that both cerebral atrophy and cognitive dysfunction in SLE patients may be related to chronic diffuse cerebral ischemia. However, all of these are non-specific findings as patients without overt NPSLE manifestations also show these changes (25) and the brain can be pathologically normal in a patient with NPSLE manifestations (28). This neuropathological information along with brain imaging data discussed below strongly suggest that SLE may lead to abnormal neurophysiological changes that are not necessarily accompanied by neuroanatomical abnormalities.

It is becoming clearer that the integrity of the blood-brain-barrier is very important in SLE-related neuropathology (30). Processes leading to brain dysfunction in SLE probably involve abnormal endothelial-white blood cell interactions that allow proteins or cells access to the central nervous system (CNS). As will be discussed further below, this may be a mechanism whereby autoantibody-mediated CNS effects can occur. Vascular endothelial cells can be stimulated by proinflammatory cytokines or autoantibodies that up-regulate the expression of adhesion proteins on their surface facilitating lymphocyte entry into the central nervous system (31). Soluble serum levels of ICAM-1 increase with systemic disease activity in patients with SLE, for example and normalize with remission (32), strengthening the hypothesis that activated endothelial cells and a lack of integrity of the blood-brain-barrier might be an important requisite for disease activity in the brain (33). Blood-brain-barrier damage has also been suggested to be a risk factor for corticosteroid-induced psychiatric disorders in SLE (34).

A variety of autoantibodies have been implicated in NPSLE manifestations, but the evidence for most is not consistent in all studies. Antiphospholipid antibodies (aPL), one of the most frequently studied, are a heterogeneous group of autoantibodies linked to thrombosis, recurrent fetal loss and a variety of neurological manifestations in patients with and without SLE. The European Working Party on SLE studied the morbidity and mortality in patients with SLE over a 10-year period in a cohort of 1,000 patients (35). This is the best study of the risk of thrombotic events and aPL antibodies in people with SLE. At the beginning of this study, there were 204 (20.4%) patients with aCL IgG, 108 (10.8%) patients with aCL IgM and 94 (9.4%) patients with lupus anticoagulant (LA). Thromboses were the most common cause of death in the last

5 years of follow-up and were always associated with APS. The most common thrombotic events in these patients were strokes (11.8%), followed by myocardial infarction (7.4%) and pulmonary embolism (5.9%). This suggests an important role for aPL and recurrent thrombosis in patients with SLE.

aPL elevations have also been associated with several different patterns of cognitive dysfunction in patients with SLE, depending on the study. Verbal memory deficits, decreased psychomotor speed, and decreased cognitive efficiency/productivity have all been significantly correlated to elevated aPL levels in adult patients.

Three longitudinal studies have evaluated the relationship between serially obtained aPL levels and cognitive dysfunction in SLE patients (3,36,37). All studies demonstrated that cognitive dysfunction was significantly associated with persistently positive aPL. Menon and colleagues (37) reported that SLE patients with persistently elevated IgG aCL levels over a period of two to three years performed significantly worse than SLE patients with occasionally elevated or never elevated titers on a variety of neuropsychological tests. These results were not observed with anti-DNA antibody titers or C3 (complement) levels. Attention and concentration, as well as psychomotor speed, were the domains most affected. Hanly and colleagues (36) followed 51 female SLE patients over a five year period and found that persistent aCL IgG elevations were associated with decreased psychomotor speed, while persistent aCL IgA elevations were correlated with problems with executive functioning and reasoning abilities. They also found no association between cognitive deficits and anti-DNA antibodies. Interestingly, no cross-sectional relationship between cognitive dysfunction and aPL was found in this same population. Our group prospectively studied the relationship between aCL and anti- β 2-glycoprotein 1 antibodies in 123 SLE patients over 3 years (3). Factors significantly associated with cognitive decline were persistently positive aPL levels, prednisone use, diabetes, higher depression scores and less education.

Anti-glutamate receptor antibodies may also play a role in cognitive dysfunction and psychiatric disease in patients with SLE. Diamond and colleagues first demonstrated that a subset of lupus anti-DNA antibodies cross-reacts with the NR2 glutamate receptor in patients with SLE (38). This group showed that the NR2 receptor is recognized by both murine and human anti-DNA antibodies and that these antibodies mediate apoptotic cell death of neurons *in vitro* and *in vivo*. The relationship between anti-glutamate receptor antibodies and NPSLE manifestations in humans with SLE has been conflicting. Most studies report that these antibodies are seen in 25–30% of patients with SLE (39–41). Some studies find no cross-sectional relationship between anti-glutamate receptor antibodies and any clinical manifestations or cognitive dysfunction specifically (41,42). Others have reported an association between anti-glutamate receptor antibodies and both cognitive dysfunction and depression (40) or depression but not cognitive dysfunction (42). A study by Kowal and colleagues in an animal model suggests that anti-glutamate receptor antibodies are associated with cognitive dysfunction and hippocampal apoptosis only in the presence of blood-brain-barrier disruption (43). It is possible that the magnitude and degree of blood-brain-barrier dysfunction in concert with the type and level of autoantibodies in human patients with SLE may be the determining factor regarding their pathogenicity in the brain.

Associations between autoantibodies, blood-brain-barrier integrity and childhood NPSLE are not well understood. Lupus-related immune and vascular mechanisms may have different effects on children and adolescents due to impairment of normal developmental milestones. Gray and white matter damage may have more serious effects on patients where myelination in frontal structures is still ongoing (44–46).

Laboratory Evaluation

There is no single diagnostic test that is sensitive and specific for SLE-related neuropsychiatric manifestations. The assessment of individual patients is based on clinical neurologic and rheumatologic evaluation, immunoserologic testing, brain imaging, and psychiatric and neuropsychological assessment. These examinations are used to support or refute the clinical diagnostic impression, exclude alternative explanations, and form the basis for prospective monitoring of clinical evolution and response to treatment interventions. An important consideration in the diagnostic approach to a patient with possible NPSLE manifestations is whether the particular clinical syndrome is due to SLE-mediated organ dysfunction, a secondary phenomenon related to infection, medication side-effects or metabolic abnormalities (e.g. uremia), or is due to an unrelated condition. It cannot be stressed strongly enough that infection is a major cause of central nervous system syndromes in hospitalized SLE patients (47). Thus, it is always important to suspect infection in patients with SLE and central nervous system manifestations.

Brain Imaging

Appenzeller and colleagues have demonstrated a reduction in cerebral and corpus callosum volumes in adult SLE patients that are associated with disease duration and cognitive impairment and other central nervous system manifestations, but not total corticosteroid dose or the presence of aPL (48). Focal neurological and neuropsychological symptoms of SLE-related stroke correlate with structural MRI abnormalities. Using structural MRI, the majority (40% to 80%) of abnormalities in NPSLE are small focal lesions concentrating in periventricular and subcortical white matter (49). Cortical atrophy, ventricular dilation, diffuse white matter and gross infarctions are also common. MRI reveals multiple discrete white matter lesions in periventricular, cortical/subcortical junction, and frontal lobe more commonly in patients with past NPSLE manifestations, than in SLE patients without history of NPSLE (49,50). Disease duration, total corticosteroid dose, and a greater number of central nervous system manifestations, including isolated cognitive impairment, have been associated with hippocampal atrophy in patients with SLE (51). A progression of hippocampal atrophy was associated with total corticosteroids dose and the number of NPSLE events in this study. These results complement the results using passive anti-glutamate receptor antibody infusion in mice with a disrupted blood-brain-barrier, in whom hippocampal apoptosis was seen (43). Brain MRI abnormalities were recently reported by our group in a consecutive cohort of 97 adult SLE patients enrolled within 9 months of diagnosis (52). Brain atrophy was seen in 18% and focal lesions in 8% of patients. This suggests that the brain may be affected early in the course of SLE, even before the diagnosis of SLE is made, and while perhaps worsened by high cumulative corticosteroid dose and NPSLE events, is not dependent for their development.

Visually analysed FDG-PET consistently reveals abnormalities in prefrontal, parietal (inferior and superior), parieto-occipital, posterior temporal, and occipital gray and white matter regions in active and quiescent NPSLE. Prefrontal, anterior cingulate and inferior parietal white matter abnormalities have been seen during acute NPSLE but not during quiescent NPSLE. The metabolic disturbances in parieto-occipital (peritrigonal) white matter remain an intriguing finding. Approximately 60% to 80% of active NPSLE patients consistently show bilateral parieto-occipital white matter FDG-PET hypometabolism in the context of normal conventional MRI and no other PET abnormalities (48).

Magnetic Resonance Spectroscopy (MRS) has revealed neurometabolic abnormalities even in white and gray matter that appears normal on conventional MRI (53). Such abnormalities are thought to reflect neuronal injury or loss and demyelination and have been found during active as well as quiescent periods of NPSLE manifestations (54). Kazora and Colleagues found a correlation between changes in cerebral white matter by MRS and cognitive impairment in

SLE patients, even in the absence of overt NPSLE symptoms (53). Small cross-sectional adult studies revealed white matter changes on diffusion tensor imaging (DTI, an MRI tool that assesses white matter microstructure) in patients with NPSLE and normal conventional MRIs. Lupus patients had findings suggestive of abnormal white matter integrity in frontal tracts, corpus callosal areas, and thalamus in these studies (55,56). Measures of cerebral atrophy also correlated with markers of axonal and myelin loss on MRS and magnetization transfer imaging (MTI) in adult patients (57). Data from DTI, MTI and quantitative volumetric studies suggests that some of these newer imaging techniques may have promise as surrogates for CNS damage and could be used as biomarkers in treatment trials.

There have been few prospective neuroimaging studies in children with SLE. Small prospective pediatric studies show cerebral atrophy and white matter lesions on traditional MRI, as has been seen in adult patients. Single photon emission computer tomography (SPECT) brain abnormalities have been seen in pediatric SLE patients, however, a correlation between NPSLE manifestations and SPECT findings were not clearly evident (58); however, the number of children studied was low (N=7) and the neurologic manifestations were multiple or diffuse whereas the SPECT abnormalities demonstrated focal hypoperfusion defects. Another study examined 24 children with SLE and 20 controls using anatomic brain MRI and MRS (59). Seventy-five percent of the SLE patients had clinically evident NPSLE manifestations and 46% had abnormal anatomic brain MRI scans (three in children without NPSLE manifestations). Four children had N-acetylaspartate/Creatine (NAA/Cr) ratios that were significantly lower than the controls. Three children with relapses showed a correlation between the disease course and abnormal NAA/CR ratios. Thus, MRS may be useful in monitoring the disease course and efficacy of pharmacologic treatment in children.

Treatment

The management of patients with NPSLE includes symptomatic and immunosuppressive therapies, but evidence for the efficacy of the treatment modalities commonly used is largely limited to uncontrolled clinical trials and anecdotal experience (60). The key to treatment is to first establish the correct diagnosis by carefully following the guidelines set forth for the diagnosis of NPSLE syndromes in the ACR 1999 Case Definitions (9). It is also important to remember that for many NPSLE syndromes, symptomatic treatment may also be needed in addition to immuno-modulatory therapy. Currently in the United States as many as 90% of SLE patients are treated with corticosteroids. While this is the only FDA-approved drug for the treatment of SLE, evidence suggests that in addition to the well known side effects of hyperlipidemia, diabetes, hypertension and osteopenia, corticosteroids also contribute to long-term morbidity in patients with SLE. Hydroxychloroquine is also commonly used to treat mild disease and appears to be safe to continue during pregnancy. Psychotropic medications (i.e. anti-depressants and atypical antipsychotics) may have an important adjunctive role in SLE patients with affective or psychotic disorder manifestations. Non-pharmacologic approaches are also important in SLE patients with psychiatric disorders and cognitive dysfunction. Haupt and colleagues demonstrated the ability to improve coping using a novel psychological group intervention (61). Patients receiving this intervention showed a significant and sustained improvement on a number of symptoms, such as depression, anxiety and overall mental burden. The control group, consisting of individuals placed on a waiting list, showed no such improvement.

Cyclophosphamide given as monthly intravenous (500–1000 mg/m²) doses for a six month induction period followed by quarterly maintenance doses for a period of two years is a cytotoxic immunosuppressive treatment option with documented therapeutic benefits in the management of severe NPSLE manifestations unresponsive to other treatment modalities (nephritis and CNS manifestations) (62). A small randomized controlled clinical trial

comparing long-term use of cyclophosphamide and methylprednisolone reported better overall therapeutic control of SLE-related neurological manifestations (refractory seizures, peripheral and cranial neuropathy, and optic neuritis) with monthly intravenous cyclophosphamide (63), with a similar incidence of new infections.

High-dose cyclophosphamide (200 mg/m²), with or without autologous hematopoietic stem cell transplantation has shown remarkable therapeutic benefits in cases of severe, life-threatening SLE with neuropsychiatric manifestations (and other organ involvement) that had been unresponsive to other treatment. The high dose cyclophosphamide destroys lymphocytes but not bone marrow stem cells, thus allowing the immune system to be reconstituted with naïve cellular elements. All studies of therapeutic modality have been open label and a controlled trial is currently being planned. In the 14 patients studied without stem cell rescue, about 40% of patients have had a durable remission (reviewed in 62). Burt and colleagues have recently reported an open-label study of 50 treatment-refractory SLE patients treated with high-dose cyclophosphamide and stem cell rescue (64). Intention-to-treat mortality was 2%. With a mean follow-up of 29 months, overall 5-year survival was 84% and the probability of a 5-year disease-free survival was 50%. Secondary analysis demonstrated stabilization of renal function and significant improvement in the SLE Disease Activity score, ANA, anti-ds DNA, complement and carbon monoxide lung diffusion capacity adjusted for hemoglobin. While this represents significant benefit for SLE patients with severe and otherwise refractory disease, it is clearly not a cure for SLE. Fortunately, other drugs, currently in clinical trials, show great promise with potentially fewer side effects. Mycophenolate mofetil has been demonstrated to have a significantly higher complete response rate over intravenous cyclophosphamide in renal lupus and two open label trials of rituximab also suggest benefit (reviewed in 62).

There have been no published NPSLE treatment trials in pediatric populations. It is unclear whether children may warrant earlier and more aggressive therapies to preclude long-term neurological sequelae.

Conclusion

NPSLE manifestations are common in both children and adults and a significant source of morbidity and mortality. The adoption of the NPSLE case definitions by the American College of Rheumatology has led to major advances in our ability to study nervous system manifestation of SLE and to identify homogeneous groups of patients from multiple studies for comparison purposes. The integrity of the blood-brain-barrier appears to be very important in preventing some brain pathology associated with SLE. It is possible that some of the autoantibodies that have been associated with NPSLE manifestations actually require a disrupted blood-brain-barrier to exert their effect. Gaining a better understanding of this process should be a concerted focus of future research. Brain imaging is a powerful tool that can be used to better understand both structural and functional changes in patients with SLE. It is possible that some of the newer brain imaging modalities will prove useful as biomarkers for SLE-related nervous system damage and also for following treatment response.

References

1. Danchenko N, Satia JA, Anthony MS. Epidemiology of systemic lupus erythematosus: A comparison of worldwide disease burden. *Lupus* 2006;15:308–318. [PubMed: 16761508]
2. Brey RL, Holliday SL, Saklad AR, et al. Neuropsychiatric syndromes in lupus: Prevalence using standardized definitions. *Neurology* 2002;58:1214–1220. [PubMed: 11971089]
3. McLaurin EY, Holliday SL, Williams P, et al. Predictors of cognitive dysfunction in patients with systemic lupus erythematosus. *Neurology* 2005;64:297–303. [PubMed: 15668428]

4. Harel L, Sandborg C, Lee T, et al. Neuropsychiatric manifestations in pediatric systemic lupus erythematosus and association with antiphospholipid antibodies. *J Rheumatol* 2006;33:1873–1877. [PubMed: 16845706]
5. Hanly JG, Urowitz MB, Sanchez-Guerrero J, et al. Neuropsychiatric events at the time of diagnosis of systemic lupus erythematosus: An international inception cohort study. *Arthritis Rheum* 2007;56:265–273. [PubMed: 17195230]
6. Sibbitt WL Jr, Brandt JR, Johnson CR, et al. The incidence and prevalence of neuropsychiatric syndromes in pediatric onset systemic lupus erythematosus. *J Rheumatol* 2002;29:1536–1542. [PubMed: 12136916]
7. Yu HH, Lee JH, Wang LC, Yang YH, Chiang BL. Neuropsychiatric manifestations in pediatric systemic lupus erythematosus: A 20-year study. *Lupus* 2006;15:651–657. [PubMed: 17120591]
8. Bernatsky S, Clarke A, Gladman DD, et al. Mortality related to cerebrovascular disease in systemic lupus erythematosus. *Lupus* 2006;15:835–839. [PubMed: 17211987]
9. The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. *Arthritis Rheum* 1999;42:599–608. [PubMed: 10211873]
10. Ainiola H, Loukkola J, Peltola J, et al. The prevalence of neuropsychiatric syndromes in systemic lupus erythematosus. *Neurology* 2001;57:496–500. [PubMed: 11502919]
11. Mikdashi J, Handwerker B. Predictors of neuropsychiatric damage in systemic lupus erythematosus: Data from the maryland lupus cohort. *Rheumatology* 2004;43:1555–1560. [PubMed: 15342927]
12. Zhu TY, Tam A-S, Lee VWY, et al. Systemic lupus erythematosus with neuropsychiatric manifestations incurs high disease costs: a cost-of-illness study in Hong Kong. *Rheumatology* 2009;48:564–568. [PubMed: 19269959]
13. Benseler SM, Silverman ED. Neuropsychiatric involvement in pediatric systemic lupus erythematosus. *Lupus* 2007;16:564–571. [PubMed: 17711889]
14. Hiraki LT, Benseler SM, Tyrrell PN, et al. Clinical and laboratory characteristics and long-term outcomes of pediatric systemic lupus erythematosus: a longitudinal study. *J Pediatr* 2008;152:550–556. [PubMed: 18346514]
15. Petri M, Naqibuddin M, Carson KA, et al. Cognitive function in a systemic lupus erythematosus inception cohort. *J Rheumatol* 2008;35(9):1776–81. [PubMed: 18634154]
16. Costallat L, Bertolo M, Appenzeller S. The american college of rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes: Analysis of 527 patients. *Lupus* 2001;10:S32.
17. Hanly JG, Urowitz MB, Sanchez-Guerrero J, et al. Short-term outcome of neuropsychiatric events in systemic lupus erythematosus upon enrollment into an international inception cohort study. *Arthritis Rheum* 2008;59:721–729. [PubMed: 18438902]
18. Carreno L, Lopez-Longo FJ, Monteagudo I, et al. Immunological and clinical differences between juvenile and adult onset of systemic lupus erythematosus. *Lupus* 1999;8(4):287–92. [PubMed: 10413207]
19. Brunner HI, Silverman ED, To T, et al. Risk factors for damage in childhood-onset systemic lupus erythematosus: cumulative disease activity and medication use predict disease damage. *Arthritis Rheum* 2002;46(2):436–44. [PubMed: 11840446]
20. Brunner HI, Gladman DD, Ibanez D, et al. Difference in disease features between childhood-onset and adult-onset systemic lupus erythematosus. *Arthritis Rheum* 2008;58(2):556–62. [PubMed: 18240232]
21. Tucker LB, Uribe AG, Fernandez M, et al. Adolescent onset of lupus results in more aggressive disease and worse outcomes: results of a nested matched case-control study within LUMINA, a multiethnic US cohort (LUMINA LVII). *Lupus* 2008;17(4):314–22. [PubMed: 18413413]
22. Hoffman IEA, Lauwerys BR, DeKeyser F, et al. Juvenile-onset systemic lupus erythematosus: different clinical and serological pattern than adult-onset systemic lupus erythematosus. *Ann Rheum Dis* 2009;68:412–415. [PubMed: 18930995]
23. Papero PH, Bluestein HG, White P, et al. Neuropsychologic deficits and antineuronal antibodies in pediatric systemic lupus erythematosus. *Clin Exp Rheumatol* 1990;8(4):417–24. [PubMed: 2397630]
24. Brunner HI, Ruth NM, German A, et al. Initial validation of the Pediatric Automated Neuropsychological Assessment Metrics for childhood-onset systemic lupus erythematosus. *Arthritis Rheum* 2007;57(7):1174–82. [PubMed: 17907235]

25. Hanly JG. Neuropsychiatric lupus. *Curr Rheumatol Rep* 2001;3:205–212. [PubMed: 11352789]
26. Sakic B, Kolb B, Whishaw IQ, et al. Immunosuppression prevents neuronal atrophy in lupus-prone mice: evidence for brain damage induced by autoimmune disease? *J Neuroimmunol* 2000;111(1–2): 93–101. [PubMed: 11063826]
27. Sakic B, Kirkham DL, Ballok DA, et al. Proliferating brain cells are a target of neurotoxic CSF in systemic autoimmune disease. *J Neuroimmunol* 2005;169(1–2):68–85. [PubMed: 16198428]
28. Hanly JG, Walsh NM, Sangalang V. Brain pathology in systemic lupus erythematosus. *J Rheumatol* 1992;19:732–741. [PubMed: 1613703]
29. Belmont HM, Abramson SB, Lie JT. Pathology and pathogenesis of vascular injury in systemic lupus erythematosus. interactions of inflammatory cells and activated endothelium. *Arthritis Rheum* 1996;39:9–22. [PubMed: 8546744]
30. Abbott NJ, Mendonca LL, Dolman DE. The blood-brain barrier in systemic lupus erythematosus. *Lupus* 2003;12:908–915. [PubMed: 14714910]
31. Zaccagni H, Fried J, Cornell J, et al. Soluble adhesion molecule levels, neuropsychiatric lupus and lupus-related damage. *Frontiers in Bioscience* 2004;9:1654–1659. [PubMed: 14977576]
32. Spronk PE, Bootsma H, Huitema MG, et al. Levels of soluble VCAM-1, soluble ICAM-1, and soluble E-selectin during disease exacerbations in patients with systemic lupus erythematosus (SLE); a long term prospective study. *Clin Exp Immunol* 1994;97:439–444. [PubMed: 7521807]
33. Ainiala H, Hietaharju A, Dastidar P, et al. Increased serum metalloproteinase 9 levels in systemic lupus erythematosus patients with neuropsychiatric manifestations and brain magnetic resonance imaging abnormalities. *Arthritis Rheum* 2004;50:858–865. [PubMed: 15022328]
34. Nishimura K, Harigai M, Omori M, et al. Blood-brain barrier damage as a risk factor for corticosteroid-induced psychiatric disorders in systemic lupus erythematosus. *Psychoneuroendocrinology* 2008;33:395–403. [PubMed: 18261856]
35. Cervera R, Khamashta MA, Font J, et al. Morbidity and mortality in Systemic Lupus Erythematosus during a 10-year period: a comparison of early and late manifestations in a cohort of 1,000 patients. *Medicine* 2003;82:299–308. [PubMed: 14530779]
36. Hanly JG, Hong C, Smith S, Fisk JD. A prospective analysis of cognitive function and anticardiolipin antibodies in systemic lupus erythematosus. *Arthritis Rheum* 1999;42(4):728–734. [PubMed: 10211887]
37. Menon S, Jameson-Shortall E, Newman Hall-Craggs SP, et al. A longitudinal study of anticardiolipin antibody levels and cognitive functioning in systemic lupus erythematosus. *Arthritis Rheum* 1999;42(4):735–741. [PubMed: 10211888]
38. DeGiorgio LA, Konstantinov KN, Lee SC, et al. A subset of lupus anti-DNA antibodies cross-reacts with the NR2 glutamate receptor in systemic lupus erythematosus. [see comment]. *Nat Med* 2001;7:1189–1193. [PubMed: 11689882]
39. Husebye ES, Stoeper ZM, Dayan M, et al. Autoantibodies to a NR2A peptide of the glutamate/NMDA receptor in sera of patients with systemic lupus erythematosus. *Ann Rheum Dis* 2005;64:1210–1213. [PubMed: 15708887]
40. Omdal R, Brokstad K, Waterloo K, et al. Neuropsychiatric disturbances in SLE are associated with antibodies against NMDA receptors. *Eur J Neurol* 2005;12:392–398. [PubMed: 15804272]
41. Harrison M, Ravdin L, Volpe B, et al. Anti-NR2 antibody does not identify cognitive impairment in a general SLE population. *Arthritis Rheum* 2004;50:S596.
42. Lapteva L, Nowak M, Yarboro CH, et al. Anti-N-methyl-D-aspartate receptor antibodies, cognitive dysfunction, and depression in systemic lupus erythematosus. *Arthritis Rheum* 2006;54:2505–2514. [PubMed: 16868971]
43. Kowal C, Degiorgio LA, Lee JY, et al. Human lupus autoantibodies against NMDA receptors mediate cognitive impairment. *Proc Natl Acad Sci U S A* 2006;103:19854–19859. [PubMed: 17170137]
44. Klingberg T, Vaidya CJ, et al. Myelination and organization of the frontal white matter in children: a diffusion tensor MRI study. *Neuroreport* 1999;10(13):2817–21. [PubMed: 10511446]
45. Nagy Z, Westerberg H, Klingberg T. Maturation of white matter is associated with the development of cognitive functions during childhood. *J Cogn Neurosci* 2004;16(7):1227–33. [PubMed: 15453975]
46. Filley CM. The behavioral neurology of cerebral white matter. *Neurology* 1998;50(6):1535–40. [PubMed: 9633691]

47. Futrell N, Schultz LR, Millikan C. Central nervous system disease in patients with systemic lupus erythematosus. *Neurology* 1992;42:1649–1657. [PubMed: 1513450]
48. Appenzeller S, Rondina JM, Li LM, et al. Cerebral and corpus callosum atrophy in systemic lupus erythematosus. *Arthritis Rheum* 2005;52(9):2783–9. [PubMed: 16142703]
49. Sibbitt WL Jr, Sibbitt RR, Brooks WM. Neuroimaging in neuropsychiatric systemic lupus erythematosus. *Arthritis Rheum* 1999;42:2026–2038. [PubMed: 10524673]
50. Abreu MR, Jakosky A, Folgerini M, et al. Neuropsychiatric systemic lupus erythematosus: Correlation of brain MR imaging, CT, and SPECT. *Clin Imaging* 2005;29:215–221. [PubMed: 15855069]
51. Appenzeller S, Carnevalle AD, Li LM, et al. Hippocampal atrophy in systemic lupus erythematosus. *Ann Rheum Dis* 2006;65:1585–1589. [PubMed: 16439436]
52. Petri M, Naqibuddin M, Carson KA, et al. Brain magnetic resonance imaging in newly diagnosed systemic lupus erythematosus. *J Rheumatol* 2008;35(12):2348–54. [PubMed: 18793003]
53. Kozora E, Arciniegas DB, Filley CM, et al. Cognition, MRS neurometabolites, and MRI volumetrics in non-neuropsychiatric systemic lupus erythematosus: preliminary data. *Cognitive & Behavioral Neurology* 2005;18(3):159–62. [PubMed: 16175019]
54. Chinn RJ, Wilkinson ID, Hall-Craggs MA, et al. Magnetic resonance imaging of the brain and cerebral proton spectroscopy in patients with systemic lupus erythematosus. *Arthritis Rheum* 1997;40:36–46. [PubMed: 9008598]
55. Zhang L, Harrison M, Heier LA, et al. Diffusion changes in patients with systemic lupus erythematosus. *Magn Reson Imaging* 2007;25(3):399–405. [PubMed: 17371731]
56. Hughes M, Sundgren PC, Fan X, et al. Diffusion tensor imaging in patients with acute onset of neuropsychiatric systemic lupus erythematosus: a prospective study of apparent diffusion coefficient, fractional anisotropy values, and eigenvalues in different regions of the brain. *Acta Radiol* 2007;48(2):213–22. [PubMed: 17354144]
57. Bosma GP, Steens SC, Petropoulos H, et al. Multisequence magnetic resonance imaging study of neuropsychiatric systemic lupus erythematosus. *Arthritis Rheum* 2004;50(10):3195–202. [PubMed: 15476212]
58. Falcini F, De Cristofaro MT, Ermini M, et al. Regional cerebral blood flow in juvenile systemic lupus erythematosus: a prospective SPECT study. Single photon emission computed tomography. *J Rheumatol* 1998;25(3):583–8. [PubMed: 9517785]
59. Mortilla M, Ermini M, Nistri M, et al. Brain study using magnetic resonance imaging and proton MR spectroscopy in pediatric onset systemic lupus erythematosus. *Clin Exp Rheumatol* 2003;21(1):129–35. [PubMed: 12673905]
60. O'Neill SG, Schrieber L. Immunotherapy of systemic lupus erythematosus. *Autoimmunity Reviews* 2005;4:395–402.
61. Haupt M, Millen S, Janner M, et al. Improvement of coping abilities in patients with systemic lupus erythematosus: A prospective study. *Ann Rheum Dis* 2005;64:1618–1623. [PubMed: 15829575]
62. Petri M, Brodsky R. High-dose cyclophosphamide and stem cell transplantation for refractory systemic lupus erythematosus. *JAMA* 2006;295:559–560. [PubMed: 16449623]
63. Barile-Fabris L, Ariza-Andraca R, Olguin-Ortega L, et al. Controlled clinical trial of IV cyclophosphamide versus IV methylprednisolone in severe neurological manifestations in systemic lupus erythematosus. *Ann Rheumatic Dis* 2005;64(4):620–5.
64. Burt RK, Traynor A, Statkute L, et al. Nonmyeloablative hematopoietic stem cell transplantation for systemic lupus erythematosus. *JAMA* 2006;295:527–535. [PubMed: 16449618]

Table 1**Neuropsychiatric Syndromes Associated With SLE**

NPSLE ASSOCIATED WITH CENTRAL NERVOUS SYSTEM

- Aseptic Meningitis
- Cerebrovascular disease
 - Stroke
 - Transient Ischemic Attack
 - Cerebral Venous Sinus Thrombosis
- Cognitive Disorders
 - Delirium (Acute confusional state)
 - Dementia
 - Mild Cognitive Impairment
- Demyelinating syndromes
- Headaches
 - Tension Headaches
 - Migraine Headaches
- Movement disorders (Chorea)
- Psychiatric Disorders
 - Psychosis
 - Mood Disorders
 - Anxiety Disorder
- Seizure Disorders
- Transverse Myelopathy

NPSLE ASSOCIATED WITH PERIPHERAL NERVOUS SYSTEM

- Autonomic Neuropathy
- Myasthenia Gravis
- Peripheral neuropathy
- Sensorineural Hearing Loss
 - Sudden Onset
 - Progressive

 Cranial neuropathy