Published in final edited form as:

Nat Clin Pract Rheumatol. 2009 February ; 5(2): 106–114. doi:10.1038/ncprheum0988.

Neurocognitive Impairment in Children and Adolescents with SLE

DM Levy¹, SP Ardoin², and LE Schanberg²

¹Morgan Stanley Children's Hospital of New York-Presbyterian, Columbia University Medical Center

²Department of Pediatrics, Duke University Medical Center

Summary

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease in which neuropsychiatric manifestations are a common cause of significant morbidity. The American College of Rheumatology (ACR) has identified 19 distinct neuropsychiatric syndromes of SLE although the 1982 ACR classification criteria for SLE recognize only two: seizures and psychosis.

¹ Neurocognitive impairment (NCI) is one of the most common and clinically challenging of all SLE manifestations, however, its pathophysiology remains poorly understood. This review examines the epidemiology and pathophysiology, as well as diagnostic and therapeutic approaches to cognitive impairment in children and adolescents with SLE.

Keywords

SLE; pediatric; cognitive impairment; cognitive dysfunction

Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease in which neuropsychiatric manifestations are a common cause of significant morbidity. Cognitive impairment is frequent with as many as 59% of children and adolescents with SLE developing impairment,^{2,3,4} similar to prevalence rates in adult SLE populations.^{5,6} Differences in study design, variability in measures of cognitive function and definitions of impairment, lack of appropriate control groups, and the absence of large-scale prospective studies in pediatric SLE preclude precise estimates of the incidence of neurocognitive impairment. However, it is clear that a significant proportion of children and adults with SLE suffer from cognitive difficulties.

Available data do not suggest that demographic factors such as race and ethnicity are predictive of cognitive impairment in SLE. Cognitive impairment can occur in the apparent absence of SLE disease activity or other manifestations of neuropsychiatric SLE.⁷ While comorbid affective disorders may play a role in cognitive complaints, most studies of adults with SLE have not found a significant association between cognitive impairment and current symptoms of depression or anxiety.^{8,9,10} Corticosteroids are known for their potential to cause psychiatric side-effects, and studies of adults with SLE show mixed results concerning the relationship between steroids and cognitive impairment, although most studies suggest no significant relationship.^{7,11,12,13} Several studies of adults with SLE suggest a

relationship between circulating antiphospholipid antibodies (aPLs) and the presence or extent of cognitive impairment in SLE. However, pediatric studies have not consistently replicated these findings, showing instead associations between aPLs and chorea or focal ischemic events.^{14,15}

Patterns of Cognitive Impairment

No consistent pattern of cognitive impairment has emerged in assessment of adults with SLE, and the degree of impairment can range from mild or subclinical findings to severe dementia. Abnormalities in processing speed, verbal memory, working memory, visuospatial learning, and attention are often reported.^{16,10,17,18} The few available data concerning patterns of cognitive impairment in pediatric SLE suggest issues with complex problem solving, working memory, verbal memory attention and visuomotor integration.^{19,4,20} The significant diversity in cognitive problems identified in SLE likely reflects the heterogeneous underlying pathophysiology of NPSLE.

Cognitive development in healthy children and adolescents

Cognitive development is complex in healthy individuals, and children and adolescents with SLE are at particular risk for perturbations of this process. The number of neurons and synapses in the human brain peaks at age two years. Despite the pruning of existing neurons which occurs over the first two years of life, brain mass continues to grow. Continued brain growth represents an increase in glial cells and proliferation of existing cells; by age five years neuronal development is nearly complete.²¹

In contrast, myelination is a longer, slower process, continuing well into the second or third decade. The extent of myelination correlates with maturation of motivation, attitudes, executive function and frontal lobe functions, all of which are necessary for adult behavior.²² Therefore, cognitive development is not complete until late adolescence or early adulthood.²³ Mature adult performance becomes evident between 14 and 19 years of age for the domains of processing speed, voluntary control of inappropriate behavior, and working memory.²⁴

The critical cognitive maturation period from late childhood through adolescence and into young adulthood coincides with the pediatric age spike for SLE onset and may also reflect a period of exceptional vulnerability of the CNS.²⁵ As a result, children and adolescents are at particular risk for delays and impairments in cognitive development, especially processing speed, response inhibition and working memory.²⁴

Pathogenesis

While the exact mechanisms underlying the pathogenesis of cognitive impairment in SLE remain unknown, autoantibodies and cytokines likely play key roles in mediating CNS damage via thrombosis, vasculopathy, inflammation, and neuronal cell death. Autopsy studies in NPSLE are small and few, but often show bland small vessel vasculopathy and a surprising absence of inflammatory changes. The generalizability of these neuropathologic studies is limited by their bias toward more severe cases and lack of temporal relationship to clinical events.^{26,27}

Several autoantibodies are linked with cognitive impairment and other neuropsychiatric manifestations of SLE (see Table 1). Among these, those most commonly associated with cognitive impairment in SLE include anti-neuronal antibodies, aPLs, lymphotoxic antibodies, and anti-NR2 receptor antibodies. Anti-neuronal antibodies in the serum and CSF have been implicated in NPSLE; however, studies have not specifically focused on

cognitive impairment and results have been mixed.^{28,29} Small studies have suggested a link between lymphotoxic antibodies and cognitive impairment in adults with SLE.³⁰ Anti-ribosomal P antibodies are linked to NPSLE, most commonly to affective disorders and psychosis, although several studies have not found an association and clinical utility remains questionable.³¹⁻³² Of interest, however, are murine models in which intraventricular injection of anti-ribosomal P antibodies induces depressive behavior with histologic staining of the antibody in limbic structures.³³

As mentioned previously, several studies link the presence of aPLs to NPSLE and specifically to cognitive impairment. In the central nervous system, aPL may promote microthrombi and non-inflammatory vasculopathy, resulting in ischemic damage.^{14,34} However, many adults and children with SLE have circulating antibodies without evidence of cognitive impairment or other manifestations of NPSLE, and it is not clear whether anticoagulation has a role in prevention or treatment of cognitive impairment in SLE.

Recent attention has focused upon anti-NR2 receptor antibodies, a class of anti-double stranded DNA antibodies which cross reacts with the neuronal N-methyl-D-aspartate (NMDA) receptor, NR2. In a murine model, these antibodies induce non-inflammatory, excitatory neuronal damage but require a breach in the blood-brain barrier to exert their effect.^{35,36} Results of studies of adults and children have yielded mixed results with the strongest correlations present when NR2 antibodies are detected in the CSF.³⁶⁻³⁸ The conflicting results may reflect that most studies assess NR-2 antibodies only in the peripheral blood making it impossible to discern whether the requisite breach in the blood-brain barrier has occurred.

In addition to circulating autoantibodies, intrathecal expression of cytokines and chemokines likely impacts the development of NPSLE and cognitive impairment. Among the potential mediators of neuronal damage and disease are interleukin 6 (IL-6), IL-8, CCL5 (RANTES), CX3CL1 (fractalkine), monocyte chemoattractant protein-1 (MCP-1), and CXCL9 (MIG).^{39,40}

Diagnosing cognitive impairment in pediatric SLE

The diagnosis of NCI in pediatric SLE remains a clinical one, relying upon a comprehensive history, physical examination and formal neuropsychological testing. Other potentially reversible factors may influence cognitive function including seizures, psychiatric disorders, learning disorders, medications, illicit drug use, infection, metabolic derangement, pain, sleep deprivation, psychosocial stressors and structural brain abnormalities. A detailed school history can provide a clue to the presence of NCI. Given the challenge in detecting cognitive abnormalities, formal neuropsychological assessment is warranted whenever cognitive decline is suspected, and some argue that all children with SLE should undergo formal neurocognitive assessment at diagnosis to establish a baseline level of cognitive function. Clinical assessment by a psychologist to identify mood and attention disorders is also recommended.

Assessment of cognition in the constraints of a clinic visit is challenging and has not been extensively studied in children and adolescents with SLE. Self, teacher and parent reports of cognitive difficulties can be helpful but are unreliable in establishing a diagnosis. The 21 item Cognitive Symptoms Inventory Questionnaire has been used in adults with SLE, but its role in assessing NCI remains unclear and it has not been validated in children or adolescents with SLE.⁴¹ The Mini Mental Status Exam (MMSE) can be used in children 4 years and older but has not been studied as a screening tool for NCI in SLE.⁴²

A wide array of instruments is available for formal neurocognitive testing, however no standardized battery has yet been validated for the pediatric SLE population. The inherent

changes due to age and development make neurocognitive testing in children and adolescents harder to administer effectively and interpret appropriately. An adult-oriented battery proposed by the ACR may be appropriate for older adolescents (Table 1), but this battery includes instruments known to be inappropriate for use in younger children. As a result members of an ad hoc working group of the Childhood Arthritis and Research Alliance (CARRA) SLE subcommittee recently proposed a standardized core set of neuropsychological tests for assessment of pediatric cognitive function based on their experience, a literature search and consensus.⁴³ The CARRA Neuropsychological Assessment Core Set has not yet been validated, but the selected instruments assess the major cognitive domains including attention, visual and verbal memory, visuomotor skills, and psychomotor speed. For cognitive testing in both adults and children, general consensus is that a score two standard deviations below the mean on at least one of the five key cognitive domains represents cognitive impairment.⁴⁴

While a full battery of neuropsychological testing provides comprehensive and useful information, it takes several hours, is expensive, and may not be covered by insurance. In addition, neurocognitive testing in children and adolescents may be difficult to assess because of developmental variability, a lack of appropriate controls, and limited information about premorbid functioning. Limitations of all neurocognitive testing approaches include language and cultural factors and the potential for score inflation via “learning effects” after repetitive testing. Children and adolescents also tend to have shorter attention spans and be more prone to fatigue than their adult counterparts, negatively influencing lengthy testing batteries and threatening the validity of test results. The CARRA core set seeks to address many of these issues by including instruments selected for the broadest age range of pediatric subjects (9–18 years) with attention to reducing language barriers, minimizing learning effects and limiting completion time to 2–3 hours.

While not yet validated on a large scale in pediatric SLE, computer-administered neurocognitive assessment is a promising tool. Most commonly used is the Automated Neuropsychological Assessment Metrics, a computerized battery developed by the US military in the 1980's. The ANAM instrument does not require pre-existing computer skills, has been validated extensively in healthy adults and clinical populations in both English and Spanish, is sensitive to change, and can be completed in 20 to 45 minutes.^{45,46} ANAM has been used and validated in adults with SLE, showing results comparable to traditional neuropsychological batteries.^{47,48} The Pediatric Automated Neuropsychological Assessment Metrics (Ped-ANAM) has been used in children with SLE 10 years and older but has not been tested in comparison to standard paper batteries.⁴ While this tool offers a more time and cost efficient alternative in pediatric SLE, it requires further study before it can be recommended as a clinical tool.

Neuroimaging

Neuroimaging can be a useful part of the initial assessment when cognitive impairment or other NPSLE manifestations are suspected clinically in children and adolescents with SLE. While routine computerized tomography (CT) and magnetic resonance imaging (MRI) are the most commonly used modalities to assess for structural and functional abnormalities, other potentially useful techniques include functional MRI, positron emission spectroscopy (PET), single photon emission computerized tomography (SPECT), and magnetization transfer imaging (MTI).

CT imaging of the brain is most useful in emergency settings to exclude cerebral hemorrhage, large infarct or mass, but rarely has a role in the assessment of cognitive impairment. However, conventional MRI sequences of the brain, including spin-echo T2

weighted imaging and fluid attenuated inversion recovery (FLAIR) technique are widely used.

The majority of research studies assess MRI in NPSLE patients as a whole, rather than specifically focusing on cognitive impairment. In these heterogeneous populations, diffuse cerebral atrophy, small cortical infarcts, and nonspecific foci of increased signal in grey and white matter on T2 weighted images are frequently identified, although their clinical significance is often unclear.^{49,50} Similar findings are also often present in SLE patients without neuropsychiatric manifestations and also in other systemic illnesses.⁵¹ In one small study of adults with SLE, individuals with cognitive impairment had more cerebral atrophy and larger T2 weighted lesions compared to SLE patients with normal cognitive abilities.⁵² However, other studies have not found significant associations between specific MRI findings and cognitive function in SLE.⁵³ No published studies have formally addressed conventional MRI findings and cognitive function in children and adolescents. Diffusion weighted imaging (DWI) and diffusion tensor imaging (DTI) detect motion of water molecules through neural tissue. Although not yet studied extensively, these modalities may allow very detailed assessment of white matter and integrity in assessment of NCI.

CT and MR angiography play little role in the assessment of cognitive impairment in SLE. Vasculopathy, if present, involves small vessels not detectable by these modalities. If a vasculopathy is strongly suspected, conventional arteriography may be the best option; however, arteriography may also fail to detect changes in the smallest vessels. Positron emission tomography (PET) scanning measures cerebral blood flow, glucose uptake and oxygen consumption in the brain. In the setting of SLE, PET often identifies areas of hypometabolism, most often in the parietal or frontal lobes. However, these findings are not specific for cognitive impairment and can be seen in SLE without NPSLE.^{54,55} Single photon emission computerized tomography (SPECT) also measures cerebral blood flow. SPECT scans are often abnormal in NPSLE but correlations with cognitive impairment have been inconsistent.^{56,57} Given their high sensitivity and unclear specificity, PET and SPECT modalities require further study and results should be interpreted cautiously.

Promising imaging modalities include proton magnetic resonance spectroscopy (MRS), a noninvasive technique that measures biochemical metabolites in the brain. Preliminary studies in NPSLE suggest that decreased levels of N-acetyl aspartate, a neuronal marker, and increased choline/creatine ratio (marker of glial and neuron transport system) correlate with cognitive abnormalities in adult SLE.^{58,59} Magnetization transfer imaging (MTI) is another MRI technique that quantifies alterations in properties of water protons and other magnetic nuclei as they change physical state or chemical configuration. Although studied most extensively in multiple sclerosis, abnormalities in MTI have correlated with active NPSLE and SLE-related cognitive impairment.⁶⁰⁻⁶³ To date, neither MRS nor MTI have been studied in children or adolescents with SLE.

Functional MRI (fMRI) allows the assessment of brain activation patterns in response to specific cognitive tasks. In both adults and children with SLE, small studies have demonstrated abnormal fMRI, suggesting that further study is warranted.⁶⁴

Laboratory assessment

Laboratory evaluation of SLE-related cognitive impairment is most useful in excluding alternate causes such as infections, medication or illicit drug toxicity, metabolic derangement and endocrinopathy. No single laboratory test is diagnostic of cognitive impairment or confirms that SLE is responsible for cognitive problems. As NCI can occur with or without systemic disease activity, typical markers of SLE activity may or may not be useful. While anti-neuronal and anti-NR2 receptor antibodies have enjoyed recent

enthusiasm, neither yet has a clear role in diagnosing or monitoring cognitive impairment in SLE. As several studies suggest increased prevalence of anticardiolipin or other antiphospholipid antibodies in patients with cognitive impairment, these antibodies may be assessed; however, there is no clear evidence that intervening with aspirin or other anticoagulation improves cognitive outcomes. CSF analysis is necessary to exclude infection and assess for generalized CNS inflammation. The presence of oligoclonal bands in the CSF suggests intrathecal immunoglobulin production consistent with active CNS SLE. While CSF and serum blood tests may be useful in following individual patients, there are no current guidelines for their use in adults and children with SLE with suspected cognitive impairment.

Treatment of cognitive impairment in SLE

Little is known about the optimal treatment of cognitive impairment in patients with SLE of any age. Immunosuppression is often entertained, particularly if there is evidence of CNS inflammation. The role of anticoagulation with warfarin, heparin, or aspirin remains unclear. A randomized, placebo-controlled study of memantine (a NMDA receptor antagonist) in adults with SLE showed no improvements in cognitive function in the memantine-treated group at 12 weeks. A major limitation of this study is that subjects were not required to have anti-NR2 receptor antibodies. Psychological support and educational interventions to maximize memory and function can play important roles for children and families.⁶⁵

Future Directions

Despite the fact that cognitive impairment is a common complication of SLE, surprisingly little is known about its epidemiology, pathogenesis and treatment. Data from ongoing longitudinal observational studies of neurocognitive function in pediatric SLE will provide improved epidemiological data on which to formulate and evaluate the multitude of remaining questions. Studies are underway to address the lack of consensus on pediatric-specific neurocognitive outcome measures in order to advance research in this area. Through CARRA, studies include validation of the (CARRA) Neuropsychological Assessment Core Set and larger-scale assessment and validation of the PedANAM for pediatric SLE. The development of sophisticated neuroimaging that can assess microanatomy and function, coupled with better understanding of the precise roles of autoantibodies and cytokines in pathogenesis will allow for improved detection of disease. Imaging studies will include assess MTI, and further evaluate fMRI in this population, and serum NR-2 antibodies will be correlated with CSF antibody profiles in the search for a useful marker of disease. Ultimately, evaluating targeted therapies for children and adolescents with SLE-related cognitive impairment will be necessary.

REVIEW CRITERIA

Published full-text, English-language articles for inclusion in this Review were identified from a search in April 2008 of the PubMed database. Search terms included: “systemic lupus erythematosus”, “pediatric” and “childhood” cross-referenced with “neurocognitive” and “neuropsychiatric”. Separate searches of “neuroimaging”, “pathogenesis” and “antibodies” cross-referenced with the previous searches were also performed. Emphasis was placed on discussing findings from prospective studies of children and adolescents although retrospective and adult studies were also reviewed. Studies were cited on the basis of relevance and date.

KEY POINTS

- Neurocognitive Impairment (NCI) is an important and prevalent cause of morbidity in Pediatric Lupus; deficits in processing speed, memory and concentration are often observed
- Cytokines and autoantibodies including antiphospholipid antibodies and NR2 (a glutamate receptor antibody) likely play a important role in the pathogenesis of NCI
- The diagnosis of NCI requires administration of an extensive neuropsychological testing battery, although limited studies suggest that computerized testing may be valuable for both NCI diagnosis and monitoring
- Studies to validate both a pediatric lupus neuropsychological testing battery and the computerized battery are being planned
- Several neuroimaging modalities appear promising for NCI, and further investigation into the utility of MTI, MRS and fMRI is warranted

Acknowledgments

Disclosures: This publication was made possible by Grant Number 5K23AR53202 from National Institutes of Arthritis and Musculoskeletal and Skin Diseases (Dr. Levy).

Author Bios

DM Levy is an Assistant Professor in the division of Rheumatology at the Morgan Stanley Children's Hospital of New York-Presbyterian, Columbia University Medical Center.

SP Ardoin is a Clinical Associate at Duke University Medical Center in the divisions of Adult and Pediatric Rheumatology.

LE Schanberg is co-Chief and Associate Professor in the division of Pediatric Rheumatology at Duke University Medical Center.

References

1. The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. *Arthritis Rheum* 1999;42:599–608. [PubMed: 10211873]
2. Sibbitt WL Jr. et al. The incidence and prevalence of neuropsychiatric syndromes in pediatric onset systemic lupus erythematosus. *J Rheumatol* 2002;29:1536–42. [PubMed: 12136916]
3. Hiraki LT, et al. Clinical and laboratory characteristics and long-term outcome of pediatric systemic lupus erythematosus: a longitudinal study. *J Pediatr* 2008;152:550–6. [PubMed: 18346514]
4. Brunner HI, et al. Initial validation of the Pediatric Automated Neuropsychological Assessment Metrics for childhood-onset systemic lupus erythematosus. *Arthritis Rheum* 2007;57:1174–82. [PubMed: 17907235]
5. Mikdashi JA, et al. Proposed response criteria for neurocognitive impairment in systemic lupus erythematosus clinical trials. *Lupus* 2007;16:418–25. [PubMed: 17664232]
6. Ainiala H, Loukkola J, Peltola J, Korpela M, Hietaharju A. The prevalence of neuropsychiatric syndromes in systemic lupus erythematosus. *Neurology* 2001;57:496–500. [PubMed: 11502919]
7. Glanz BI, et al. Pattern of neuropsychologic dysfunction in inactive systemic lupus erythematosus. *Neuropsychiatry Neuropsychol Behav Neurol* 1997;10:232–8. [PubMed: 9359119]

8. Denburg SD, Carbotte RM, Denburg JA. Cognitive impairment in systemic lupus erythematosus: a neuropsychological study of individual and group deficits. *J Clin Exp Neuropsychol* 1987;9:323–39. [PubMed: 3597726]
9. Kozora E, Thompson LL, West SG, Kotzin BL. Analysis of cognitive and psychological deficits in systemic lupus erythematosus patients without overt central nervous system disease. *Arthritis Rheum* 1996;39:2035–45. [PubMed: 8961909]
10. Shucard JL, et al. Working memory and processing speed deficits in systemic lupus erythematosus as measured by the paced auditory serial addition test. *J Int Neuropsychol Soc* 2004;10:35–45. [PubMed: 14751005]
11. Ginsburg KS, et al. A controlled study of the prevalence of cognitive dysfunction in randomly selected patients with systemic lupus erythematosus. *Arthritis Rheum* 1992;35:776–82. [PubMed: 1622416]
12. Hanly JG, et al. Cognitive impairment in patients with systemic lupus erythematosus. *J Rheumatol* 1992;19:562–7. [PubMed: 1593578]
13. McLaurin EY, Holliday SL, Williams P, Brey RL. Predictors of cognitive dysfunction in patients with systemic lupus erythematosus. *Neurology* 2005;64:297–303. [PubMed: 15668428]
14. Harel L, Sandborg C, Lee T, von Scheven E. Neuropsychiatric manifestations in pediatric systemic lupus erythematosus and association with antiphospholipid antibodies. *J Rheumatol* 2006;33:1873–7. [PubMed: 16845706]
15. Avcin T, Benseler SM, Tyrrell PN, Cucnik S, Silverman ED. A followup study of antiphospholipid antibodies and associated neuropsychiatric manifestations in 137 children with systemic lupus erythematosus. *Arthritis Rheum* 2008;59:206–13. [PubMed: 18240179]
16. Emori A, et al. Cognitive dysfunction in systemic lupus erythematosus. *Psychiatry Clin Neurosci* 2005;59:584–9. [PubMed: 16194262]
17. Benedict RH, Shucard JL, Zivadinov R, Shucard DW. Neuropsychological impairment in systemic lupus erythematosus: a comparison with multiple sclerosis. *Neuropsychol Rev* 2008;18:149–66. [PubMed: 18521755]
18. Carbotte RM, Denburg SD, Denburg JA. Cognitive deficit associated with rheumatic diseases: neuropsychological perspectives. *Arthritis Rheum* 1995;38:1363–74. [PubMed: 7575686]
19. Wyckoff PM, Miller LC, Tucker LB, Schaller JG. Neuropsychological assessment of children and adolescents with systemic lupus erythematosus. *Lupus* 1995;4:217–20. [PubMed: 7655493]
20. Ardoin SP, W.R. Anthony K, Bonner M, Schanberg LE. Retrospective analysis of neurocognitive testing in children and adolescents with SLE. *Arthritis Rheum.* in press.
21. Filley CM. White matter and behavioral neurology. *Ann N Y Acad Sci* 2005;1064:162–83. [PubMed: 16394155]
22. Filley CM. The behavioral neurology of cerebral white matter. *Neurology* 1998;50:1535–40. [PubMed: 9633691]
23. Luna B, Sweeney JA. Studies of brain and cognitive maturation through childhood and adolescence: a strategy for testing neurodevelopmental hypotheses. *Schizophr Bull* 2001;27:443–55. [PubMed: 11596846]
24. Luna B, Garver KE, Urban TA, Lazar NA, Sweeney JA. Maturation of cognitive processes from late childhood to adulthood. *Child Dev* 2004;75:1357–72. [PubMed: 15369519]
25. Korkman M, Kemp SL, Kirk U. Effects of age on neurocognitive measures of children ages 5 to 12: a cross-sectional study on 800 children from the United States. *Dev Neuropsychol* 2001;20:331–54. [PubMed: 11827092]
26. Devinsky O, Petito CK, Alonso DR. Clinical and neuropathological findings in systemic lupus erythematosus: the role of vasculitis, heart emboli, and thrombotic thrombocytopenic purpura. *Ann Neurol* 1988;23:380–4. [PubMed: 3382174]
27. Ellis SG, Verity MA. Central nervous system involvement in systemic lupus erythematosus: a review of neuropathologic findings in 57 cases, 1955–1977. *Semin Arthritis Rheum* 1979;8:212–21. [PubMed: 424765]
28. Kang EH, et al. Flow cytometric assessment of anti-neuronal antibodies in central nervous system involvement of systemic lupus erythematosus and other autoimmune diseases. *Lupus* 2008;17:21–5. [PubMed: 18089679]

29. Papero PH, Bluestein HG, White P, Lipnick RN. Neuropsychologic deficits and antineuronal antibodies in pediatric systemic lupus erythematosus. *Clin Exp Rheumatol* 1990;8:417–24. [PubMed: 2397630]
30. Zandman-Goddard G, Chapman J, Shoenfeld Y. Autoantibodies involved in neuropsychiatric SLE and antiphospholipid syndrome. *Semin Arthritis Rheum* 2007;36:297–315. [PubMed: 17258299]
31. Benseler SM, Silverman ED. Neuropsychiatric involvement in pediatric systemic lupus erythematosus. *Lupus* 2007;16:564–71. [PubMed: 17711889]
32. Toubi E, Shoenfeld Y. Clinical and biological aspects of anti-P-ribosomal protein autoantibodies. *Autoimmun Rev* 2007;6:119–25. [PubMed: 17289545]
33. Katzav A, et al. Induction of autoimmune depression in mice by anti-ribosomal P antibodies via the limbic system. *Arthritis Rheum* 2007;56:938–48. [PubMed: 17328071]
34. Hanly JG, Hong C, Smith S, Fisk JD. A prospective analysis of cognitive function and anticardiolipin antibodies in systemic lupus erythematosus. *Arthritis Rheum* 1999;42:728–34. [PubMed: 10211887]
35. DeGiorgio LA, et al. A subset of lupus anti-DNA antibodies cross-reacts with the NR2 glutamate receptor in systemic lupus erythematosus. *Nat Med* 2001;7:1189–93. [PubMed: 11689882]
36. Kowal C, et al. Cognition and immunity; antibody impairs memory. *Immunity* 2004;21:179–88. [PubMed: 15308099]
37. Yoshio T, Onda K, Nara H, Minota S. Association of IgG anti-NR2 glutamate receptor antibodies in cerebrospinal fluid with neuropsychiatric systemic lupus erythematosus. *Arthritis Rheum* 2006;54:675–8. [PubMed: 16447246]
38. Levy D. Anti-NR-2 antibodies are prevalent in childhood-onset SLE (cSLE), but do not predict neurocognitive dysfunction. *Arthritis Rheum* 2007;55:S143.
39. Iikuni N, et al. Raised monocyte chemotactic protein-1 (MCP-1)/CCL2 in cerebrospinal fluid of patients with neuropsychiatric lupus. *Ann Rheum Dis* 2006;65:253–6. [PubMed: 16410530]
40. Fragosio-Loyo H, et al. Interleukin-6 and chemokines in the neuropsychiatric manifestations of systemic lupus erythematosus. *Arthritis Rheum* 2007;56:1242–50. [PubMed: 17393453]
41. Hanly JG, Fisk JD, McCurdy G, Fougere L, Douglas JA. Neuropsychiatric syndromes in patients with systemic lupus erythematosus and rheumatoid arthritis. *J Rheumatol* 2005;32:1459–6. [PubMed: 16078320]
42. Ouvrier RA, Goldsmith RF, Ouvrier S, Williams IC. The value of the Mini-Mental State Examination in childhood: a preliminary study. *J Child Neurol* 1993;8:145–8. [PubMed: 8505476]
43. Brunner H, Z.F. Levy D, et al. Standardizing the Neuropsychological Evaluation of Children with Systemic Lupus Erythematosus. *Lupus* 2008;17:467.
44. Levy D. Neurocognitive function in childhood-onset systemic lupus erythematosus. *Arthritis Rheum* 2007;56:S368.
45. Reeves DL, Winter KP, Bleiberg J, Kane RL. ANAM genogram: historical perspectives, description, and current endeavors. *Arch Clin Neuropsychol* 2007;22(Suppl 1):S15–37. [PubMed: 17276030]
46. Kane RL, Roebuck-Spencer T, Short P, Kabat M, Wilken J. Identifying and monitoring cognitive deficits in clinical populations using Automated Neuropsychological Assessment Metrics (ANAM) tests. *Arch Clin Neuropsychol* 2007;22(Suppl 1):S115–26. [PubMed: 17101258]
47. Roebuck-Spencer TM, et al. Use of computerized assessment to predict neuropsychological functioning and emotional distress in patients with systemic lupus erythematosus. *Arthritis Rheum* 2006;55:434–41. [PubMed: 16739211]
48. Holliday SL, et al. Validating a computerized neuropsychological test battery for mixed ethnic lupus patients. *Lupus* 2003;12:697–703. [PubMed: 14514133]
49. Sibbitt WL Jr, Sibbitt RR, Brooks WM. Neuroimaging in neuropsychiatric systemic lupus erythematosus. *Arthritis Rheum* 1999;42:2026–38. [PubMed: 10524673]
50. Jennings JE, Sundgren PC, Attwood J, McCune J, Maly P. Value of MRI of the brain in patients with systemic lupus erythematosus and neurologic disturbance. *Neuroradiology* 2004;46:15–21. [PubMed: 14648006]

51. Gonzalez-Crespo MR, et al. Magnetic resonance imaging of the brain in systemic lupus erythematosus. *Br J Rheumatol* 1995;34:1055–60. [PubMed: 8542207]
52. Ainiala H, et al. Cerebral MRI abnormalities and their association with neuropsychiatric manifestations in SLE: a population-based study. *Scand J Rheumatol* 2005;34:376–82. [PubMed: 16234185]
53. Kozora E, et al. Magnetic resonance imaging abnormalities and cognitive deficits in systemic lupus erythematosus patients without overt central nervous system disease. *Arthritis Rheum* 1998;41:41–7. [PubMed: 9433868]
54. Kao CH, et al. The role of FDG-PET, HMPAO-SPET and MRI in the detection of brain involvement in patients with systemic lupus erythematosus. *Eur J Nucl Med* 1999;26:129–34. [PubMed: 9933346]
55. Weiner SM, et al. Diagnosis and monitoring of central nervous system involvement in systemic lupus erythematosus: value of F-18 fluorodeoxyglucose PET. *Ann Rheum Dis* 2000;59:377–85. [PubMed: 10784521]
56. Sabbadini MG, et al. Central nervous system involvement in systemic lupus erythematosus patients without overt neuropsychiatric manifestations. *Lupus* 1999;8:11–9. [PubMed: 10025594]
57. Waterloo K, et al. Neuropsychological dysfunction in systemic lupus erythematosus is not associated with changes in cerebral blood flow. *J Neurol* 2001;248:595–602. [PubMed: 11518002]
58. Kozora E, et al. Cognition, MRS neurometabolites, and MRI volumetrics in non-neuropsychiatric systemic lupus erythematosus: preliminary data. *Cogn Behav Neurol* 2005;18:159–62. [PubMed: 16175019]
59. Brooks WM, Jung RE, Ford CC, Greinel EJ, Sibbitt WL Jr. Relationship between neurometabolite derangement and neurocognitive dysfunction in systemic lupus erythematosus. *J Rheumatol* 1999;26:81–5. [PubMed: 9918245]
60. Bosma GP, et al. Detection of cerebral involvement in patients with active neuropsychiatric systemic lupus erythematosus by the use of volumetric magnetization transfer imaging. *Arthritis Rheum* 2000;43:2428–36. [PubMed: 11083265]
61. Rovaris M, et al. Brain involvement in systemic immune mediated diseases: magnetic resonance and magnetisation transfer imaging study. *J Neurol Neurosurg Psychiatry* 2000;68:170–7. [PubMed: 10644783]
62. Emmer BJ, et al. Detection of change in CNS involvement in neuropsychiatric SLE: a magnetization transfer study. *J Magn Reson Imaging* 2006;24:812–6. [PubMed: 16941632]
63. Emmer BJ, et al. Correlation of magnetization transfer ratio histogram parameters with neuropsychiatric systemic lupus erythematosus criteria and proton magnetic resonance spectroscopy: association of magnetization transfer ratio peak height with neuronal and cognitive dysfunction. *Arthritis Rheum* 2008;58:1451–7. [PubMed: 18438847]
64. DiFrancesco MW, et al. Functional magnetic resonance imaging assessment of cognitive function in childhood-onset systemic lupus erythematosus: a pilot study. *Arthritis Rheum* 2007;56:4151–63. [PubMed: 18050246]
65. Harrison MJ, et al. Results of intervention for lupus patients with self-perceived cognitive difficulties. *Neurology* 2005;65:1325–7. [PubMed: 16247073]

Table 1**Autoantibodies Associated with Cognitive Impairment and Other Neuropsychiatric Manifestations of SLE**

Autoantibodies Associated with Cognitive Impairment in SLE

Anti-neuronal antibodies
Anti-phospholipid antibodies
Anti-NR2 receptor antibody
Lymphocytotoxic antibody

Autoantibodies Associated with Other NPSLE Manifestations

Anti-ribosomal P antibody
Anti-neurofilament antibody
Anti-endothelial cell antibody
Anti-Ro antibody
Anti-Smith antibody

Reference: Zandman-Goddard G, et al. Autoantibodies Involved in Neuropsychiatric SLE and Antiphospholipid Syndrome. *Semin Arthritis Rheum* 2007;36:297–315.

Table 2

One-Hour Neuropsychological Battery Proposed by the ACR to Assess Cognitive Function in Adults with SLE*

Name of Measure
National Adult Reading Test **
Digit Symbol Substitution Test
Trail Making Test, parts A and B
Stroop Color and Word Test
California Verbal Learning Test
Rey Osterrieth Complex Figure Test with delayed recall
WAIS III letter numbering sequencing **
Controlled oral word association test
Animal Naming
Finger tapping
Definitions
Neurocognitive impairment = score in one or more of the five key cognitive domains that 2 standard deviations below the mean
Neurocognitive decline = score on one or more of the five key cognitive domains that is 1.5 to 1.9 standard deviations below the mean. ⁵
* From the Ad Hoc Committee on Lupus Response Criteria: Cognition Subcommittee. <i>Lupus</i> 2007; 16: 418–425.
** Not recommended for children and adolescents

Table 3 Proposed CARRA Neuropsychological Assessment Core Set for Children and Adolescents with SLE⁴³

Core pSLE Battery		
Name of Measure	Duration	Cognitive Domain
Wechsler Abbreviated Scales of Intelligence (WASI) 2 - subtest version (Vocabulary, Matrix Reasoning)	30 min	General intelligence
Wechsler Intelligence Scale for Children (WISC)-IV Coding, Symbol Search	10 min	Psychomotor speed
WISC-IV Digit Span and Letter-Number Sequencing	20 min	Verbal working memory
Conners' CPT-II	15 min	Attention, processing speed
Woodcock-Johnson-III Achievement subtests: Letter-word Identification, Reading Fluency, Calculations, Math Fluency	30 min	Academic skills mastery
Wide Range Assessment of Memory and Learning (WRAML-2); Screening subtests (Story Memory, Verbal Learning, Picture Memory Design Memory)	30 min	Verbal and visual memory and learning
Stroop Color and Word Test	5 min	Attention, cognitive flexibility, response inhibition
Additional Tests to be done for Comprehensive Neurocognitive Assessment		
Delis-Kaplan Executive Function System Verbal & Design Fluency subtests	10 min	Speed/executive functioning
Grooved Pegboard	5 min	Manual dexterity/speed