Cerebral and Cerebellar Volume Loss in Children and Adolescents with Systemic Lupus Erythematosus: A Review of Clinically Acquired Brain Magnetic Resonance Imaging

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ABSTRACT. ***Objective.*** Cerebral atrophy is a prominent feature in adults with systemic lupus erythematosus (SLE). We assessed cerebral and cerebellar volume loss on clinically acquired brain magnetic resonance imaging (MRI) scans of children and adolescents with SLE.

Methods. We abstracted information on disease course for patients who underwent clinical brain MRI during the period 2002-2008. We completed qualitative assessments of volume loss and measured corpus callosum thickness and ventricular enlargement for patients with lupus and controls.

Results. Forty-nine children underwent brain MRI during the review period due to clinical indications. The lupus cohort was predominantly female and ethnically diverse. Mean age at imaging was 15.3 ± 2.6 years and mean disease duration was 30.6 ± 33.3 months. Findings suggestive of cerebral and cerebellar volume loss were seen respectively in 89.8% and 91.8% of lupus patients. Cerebral volume loss was moderate or severe in 26.5% of children. Cerebellar volume loss was moderate in 20.4% of these patients. Linear measurement means reflected corpus callosum thinning and ventricular enlargement in lupus patients. Volume loss was observed in newly diagnosed patients prior to corticosteroid use. Disease duration and corticosteroid use did not predict the severity of volume loss. There were statistically significant differences in linear imaging measurements comparing lupus patients to 14 similar-age controls.

Conclusion. Regional volume loss was observed in most adolescents with lupus undergoing clinical brain MRI scans. As in other pediatric conditions with inflammatory or vascular etiologies, these findings may be reflecting disease-associated neuronal loss and not solely the effects of corticosteroid. (J Rheumatol First Release June 1 2010; doi:10.3899/jrheum.090983)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS
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Systemic lupus erythematosus (SLE) is an autoimmune disorder that affects 5,000–15,000 American children[1,2]. The disorder is characterized by systemic inflammation and autoantibody production and may lead to significant morbidities during childhood. Early in the disease course children develop neuropsychiatric manifestations (NPSLE) at higher frequencies than adult patients[3]. Lupus-related neurological insults during childhood may affect cognition, academic performance, interpersonal relationships, and functional outcomes in young adulthood. These effects may be due to gray and white matter damage and disruption of normal myelination patterns throughout childhood and adolescence[4,5]. Damage to developing brain structures in children with SLE may be more detrimental than similar insults in adult patients[3].

Anatomic neuroimaging often reveals nonspecific gray and white matter abnormalities in adult patients. Subcortical and periventricular white matter lesions indicative of small infarcts or edema are commonly observed in the magnetic resonance imaging (MRI) scans of adults with SLE[6]. Larger infarctions, cortical atrophy, and diffuse white matter lesions are frequently seen in patients with a history of NPSLE.

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Quantitative volumetric measures of cerebral and corpus callosum atrophy in adult patients correlate with disease duration, history of NPSLE, and cognitive impairment[7]. In addition, associations between cumulative corticosteroid dosing and hippocampal or cerebral atrophy are seen in adults with SLE[8,9]. In a recent study of adult patients with newly diagnosed SLE, cerebral atrophy was found in 18% of patients and was unrelated to higher corticosteroid dosing[10]. Observed cerebral volume losses in these studies may be a result of disease associated axonal/myelin loss. Although cerebellar changes are associated with neurocognitive deficits in other inflammatory and ischemic disorders, there are minimal data on cerebellar involvement in patients with SLE[11,12]. Yet determinations of regional brain volume loss are not objectively or routinely assessed in the neuroimaging evaluations of patients with lupus. Newer MRI modalities that measure metabolic, perfusion, and diffusion abnormalities may eclipse conventional neuroimaging as surrogate measures of lupus-induced brain histopathological changes[6]. As in other neuroinflammatory disorders, newer neuroimaging methods may allow earlier identification of structural abnormalities in normal-appearing gray and white matter.

Although developing brain structures may be more sensitive to damage there is a paucity of prospective studies utilizing neuroimaging methods in childhood-onset SLE. There have been no published pediatric lupus MRI studies utilizing quantitative volumetric analyses. Small prospective studies and retrospective reviews of conventional structural brain imaging [computed tomography (CT) and MRI] describe prominent rates of cerebral atrophy and white matter lesions in pediatric lupus patients[13,14]. Pediatric lupus studies have not described the clinical or research criteria used to define volume loss or atrophy of their patients. Linear measures of corpus callosum thickness and ventricular size have been utilized in adult multiple sclerosis, schizophrenia, and pediatric disability research studies[15-18]. Linear measures (1-D and 2-D) appear to be reliable and correlate with quantitative 3-D volume assessments in adults with multiple sclerosis[15,19]. Similar measures have not been described in pediatric SLE studies. Volumetric assessments have been incorporated in studies of children with sickle-cell disease, diabetes mellitus (type I), cancer, and traumatic brain injury[20-23]. Evidence of regional brain volume losses that are independent of corticosteroid usage are described in these pediatric populations.

We assessed cerebral and cerebellar volume loss in clinically acquired brain MRI scans of children and adolescents with lupus. We hypothesized that evidence of volume loss would be observed in children with NPSLE even prior to corticosteroid exposure. We hoped to generate structural hypotheses for future neuroimaging research in patients with childhood-onset SLE.

MATERIALS AND METHODS

Patient demographic and clinical data. We identified all brain MRI acquired for clinical indications at a tertiary care pediatric hospital during the period January 2002 to February 2008 (Texas Children's Hospital, Houston, TX, USA). Children and adolescents with SLE treated at the pediatric rheumatology center of this institution are drawn from ethnically diverse urban and rural communities of metropolitan Houston, western Louisiana, and central and southeast Texas. Patient MRI were identified through multiple search strategies. A clinical radiology database was searched for brain MRI with documentation of Lupus or NPSLE terms in diagnosis or impression fields. The electronic medical records of SLE patients treated during the review period were searched for completed brain MRI. All patients met 4 or more American College of Rheumatology (ACR) 1997 revised classification criteria for SLE prior to 18 years of age to be included[24]. Local institutional review board approval was obtained for data review and collection.

Patient ethnicity and race were determined by parent report. Age at diagnosis and disease duration from first lupus-attributable symptom was obtained from rheumatology office visit or inpatient consultation. Oral prednisone dosing was recorded at time of MRI evaluation. We ascertained immunosuppressive and vasculopathy medication use (aspirin, low molecular weight heparin, and pentoxifylline) at time of imaging. Pentoxifylline, a xanthine derivative, is commonly used in our clinic for patients with features of lupus or antiphospholipid antibody syndrome-associated vasculopathy (i.e., Raynaud's phenomenon, livedo reticularis). The medication increases red blood cell deformability, reduces blood viscosity, decreases platelet aggregation, and partially inhibits synthesis of tumor necrosis factor-α. Information was abstracted on biopsy-proven nephritis and nervous system involvement since diagnosis (documentation of NPSLE at any point between diagnosis and the acquisition of the brain MRI). Active nephritis was determined by presence of proteinuria (> 2+ on random urine dipstick or > 0.5 g on 24-hour collection) or abnormal urinary sediment. Nervous system manifestations at time of imaging were classified according to the ACR case definitions for NPSLE[25]. We documented previous cyclophosphamide administration for nephritis or NPSLE.

We calculated SLE Disease Activity Index (SELENA SLEDAI) scores from the rheumatology visit or inpatient consultation prompting imaging[26,27]. We abstracted complement activation (C3, C4) and C-reactive protein (CRP) values at imaging (both as mg/dl). Lupus-specific autoantibody titers preceding imaging evaluation were documented. Double-stranded DNA (dsDNA) antibody testing was performed by commercial laboratories using either *Crithidia luciliae* or enzyme linked immunosorbent assays (a titer of 1:80 was considered elevated). Antiphospholipid antibody (aPL) testing was performed by laboratories utilizing $ß_2$-glycoprotein-I-dependent ELISA. Testing and interpretation of lupus anticoagulants (LAC) was performed according to International Society for Thrombosis and Hemostasis guidelines[28]. Antiribosomal-P testing was performed by multiple commercial laboratories with ELISA kits utilizing synthetic C-22 terminus proteins[29]. Antineuronal antibody testing was performed by a commercial laboratory with SK-N-SH neuroblastoma cell membrane extract as its ELISA antigen[30].

MRI acquisition and assessment of volume loss. Clinical MRI were all acquired on a 1.5 Tesla scanner (Philips Healthcare, Best, The Netherlands) at Texas Children's Hospital during a typical complete brain examination with 5-mm slice thickness. Scans included sagittal T1-weighted (5/5.5 mm), axial T2-weighted (5/6 mm), axial T1-weighted (5/6 mm), axial fluid-attenuated inversion-recovery (FLAIR) (5/5 mm), and axial diffusion-weighted imaging sequences. A senior pediatric neuroradiologist (JVH) read all previously acquired clinical scans for this study using a standardized scoring sheet. The neuroradiologist was blinded to patients' clinical status, organ involvement, vasculopathy risk factors, and initial clinical interpretation. The blinded assessments of MRI were performed for this study often years after the initial clinical interpretation and did not affect the management of any patient.

Criteria for qualitative cerebral volume loss included sulcal widening and ventricular or cistern prominence. Criteria for qualitative cerebellar volume loss included prominence of the cerebellar folia (in particular those of the median sulci). These criteria have been utilized in other pediatric imaging studies in our institution[31]. Linear measures of corpus callosum thickness and ventricular enlargement were obtained on all MRI scans with Philips Archive

iSite software and a distance tool (PACS, Best, The Netherlands). Thickness at the junction of the genu and anterior body of the corpus callosum on a midline sagittal T1-weighted sequence was recorded. Normative means for this measurement are > 4 mm after 8 months of age (when the corpus callosum assumes adult appearance on sagittal images)[32]. Based on clinical experience, a value < 6 mm indicates thinning and a value < 5 mm frankly abnormal by late childhood and early adolescence. Corpus callosum thinning may reflect loss of deep white matter tissue as it is the single largest white matter fasciculus joining left and right cerebral hemispheres. An assessment of ventricular enlargement was based on measurement of the widest portion of the third ventricle and calculation of an Evans ratio/index (ratio of maximum width of the bifrontal horns divided by the maximum distance between the inner table of the skull at the same level). These values were measured from an axial T1-weighted sequence or axial FLAIR (if T1-weighted image was not available)[17]. Normative third ventricle width measurements range between 3 and 4 mm (lower in females) according to a MRI review of healthy 19-year-olds[33]. Widening of the third ventricle may indicate loss of both white and deep gray matter. A mean Evans ratio of 0.26 was observed in a small cohort of healthy adults and a value > 0.30 was indicative of ventricular enlargement[15,17]. Corpus callosum thickness and maximum third ventricle width measurements were reported in mm. It is recognized that these linear measures using PACS electronic distance tools are prone to observer error and may be inaccurate by up to 1 voxel (potential for a 1 mm difference).

Blinded assessment of volume loss in similar-age controls. We identified children with normal clinical brain MRI acquired at our institution using similar 5 mm slice protocols (acquired January 2002 to November 2009). These controls were selected to approximate the age and sex of lupus patients in this study. Inclusion criteria for control MRI included (1) normal clinical scan with no focal parenchymal abnormality; (2) subject had no diagnosis of underlying inflammatory, developmental, or neurodegenerative condition; and (3) subject had no history of corticosteroid use. Control MRI were read by the same senior neuroradiologist (JVH) using an identical protocol.

Statistical analysis. Descriptive statistics were calculated for demographic, clinical, and neuroimaging variables and reported as means and standard deviations (SD) or proportions (%). Differences of clinical and imaging mean values between newly diagnosed (corticosteroid-naive) children and those with a chronic disease course were assessed by an unequal variance Student t test. A one-way analysis of variance (ANOVA) was used to assess differences of lupus patients' linear imaging measures (corpus callosum thickness, third ventricle width, and Evans ratio) based on disease duration (new onset and steroid-naive, less than 3 years, and more than 3 years of disease duration). An equal variance Student t test was utilized to assess differences in linear imaging values based on clinical factors (nephritis status, aPL or LAC positivity, and history of severe NPSLE). Differences in ordinal variables were assessed with Fisher exact tests. The ability of disease duration to predict the severity of a qualitative determination of volume loss (none/mild or moderate/severe loss) was assessed with univariable logistic regression. Associations between disease duration, prednisone dosing, SELENA SLEDAI scores, and linear imaging measures (outcome measures) were assessed with univariable Pearson correlation coefficients. Differences in linear measure means between lupus patients and controls were assessed using an unequal variance Student t test.

The validity of statistical test assumptions was verified by quantitative and graphical approaches. Statistical tests were considered significant at $\alpha < 0.05$. All p values were 2-sided and not adjusted for multiple testing due to the exploratory nature of these analyses. 95% confidence intervals were reported where applicable. Analyses were performed using NCSS v. 2004 (NCSS, LLC, Kaysville, UT, USA).

RESULTS

Demographic and clinical characteristics. Forty-nine children and adolescents with SLE completed clinical brain MRI during the period January 2002 to February 2008. A majority of brain MRI were acquired due to severe disease presentations and neurological manifestations that often required emergency evaluation and inpatient admission. The most common clinical indications for imaging were acute confusional state (18.3%), seizure disorder (18.3%), mood disorder (14.3%), and psychosis (14.3%; Table 1). The lupus patients had a mean age of 15.3 ± 2.6 years with a mean disease duration of 30.6 ± 33.3 months (95% CI 23.5, 44.5). Patients undergoing clinical MRI were predominantly African American and Hispanic females (Table 2). All but 4 of the patients were imaged due to concern about an NPSLE manifestation. These 4 subjects underwent MRI as part of endocrine evaluations of short stature or pituitary dysfunction. Nine patients (18.3%) had previously completed at least 6 months of cyclophosphamide therapy. The severity of disease in this cohort was reflected by elevated mean SELENA SLEDAI scores, abnormal mean CRP values, depressed mean complement levels, and active nephritis and hypertension at time of neuroimaging (Table 2).

Fourteen of the children with lupus had a brain MRI at the time of their initial disease presentation and were corticosteroid-naive. Children imaged at their initial presentation were younger than those with a longer disease course [mean difference 1.4 yrs (95% CI –0.1 to –2.6 yrs, p = 0.03)]. SELENA SLEDAI, C4, and CRP values were similar between groups. Lower C3 values in the newly diagnosed patients were not statistically significant [mean difference 27.3 mg/dl (95% CI –55.7 to 1.0 mg/dl, p = 0.06)] and indeed low values in both groups indicated immune complex deposition.

Neuroimaging findings: MRI of patients with lupus. Findings suggestive of cerebral and cerebellar volume loss were designated in all but a few patients (Table 3). Blinded assessments of cerebral volume loss were concordant on every occasion when volume loss was described on the initial clinical observation. We designated cerebral volume loss on 13 occasions (11 mild, 2 moderate) when there was no documentation of volume loss on the initial clinical observation. Sulcal widening was the most common finding in children designated to have cerebral volume loss. Cerebral volume loss was deter-

Table 1. Clinical indications for brain MRI acquisition.

Indication	n (%)*
Acute confusional state	9 (18.3)
Seizures	9 (18.3)
Mood disorders	7 (14.3)
Psychosis	7 (14.3)
Migraine headaches	6 (12.2)
Cerebrovascular disease	4 (8.2)
Peripheral neuropathy	2 (4.1)
Other**	10 (20.4)

* 5 children had more than one indication for brain MRI. ** Other indications included 5 children with tremors, 4 with assessment of pituitary anatomy, and 1 with papilledema. Children with tremors were imaged due to concern of a lupus-associated movement disorder.

Table 2. Demographic and clinical characteristics of patients with lupus.

Characteristic	Mean (SD) or n (%)
Age at imaging, yrs	15.3 (2.6)
Female	41 (83.7)
Race/ethnicity	
African American	23 (46.9)
Hispanic	17 (34.7)
Caucasian	5 (10.2)
Asian	3 (6.1)
Native American	1 (2.0)
Mean disease duration, mo	30.6 (33.3)
History of nephritis	23 (46.9)
Proliferative (III/IV)	15 (65.2)
Current hypertension	14 (28.6)
Active nephritis	29 (59.2)
Previous NPSLE	11 (22.4)
Current medication	
Hydroxychloroquine	35 (71.4)
Prednisone dose, mg	29.6 (18.1)
Methotrexate	5 (10.2)
Mycophenolate mofetil	3 (6.1)
ASA	17 (34.7)
Pentoxifylline	17 (34.7)
Cyclophosphamide (current)	5 (10.2)
Past exposure	9 (18.3)
C3, mg/dl*	78.3 (42.5)
C4, mg/dl*	12.8 (9.4)
ds-DNA antibody-positive	23 (46.9)
LAC-positive	10 (20.4)
aPL-positive	22 (44.9)
aCL-positive	15 (30.6)
Antiribosomal P antibody-positive, n = 18	6 (33.3)
Antineuronal antibody-positive, n = 15	9 (60.0)
SLEDAI scores**	12.9 (9.4)

* C3 normal range 86–182 mg/dl; C4 normal range 17–51 mg/dl. ** SELENA SLEDAI scores were not calculated for 11 patients due to insufficient documentation of clinical data in electronic medical record. NPSLE: neuropsychiatric lupus; LAC: lupus anticoagulant; aPL: antiphospholipid; aCL: anticardiolipin.

mined to be moderate or severe in 26.5% of children, while moderate cerebellar volume loss was designated in 20.4% of patients (Figures 1-3). Mean values for third ventricle width (5.7 ± 1.9 mm) and Evans ratio (0.31 ± 0.03) indicated ventricular enlargement and volume loss. Fifty-five percent (27/49) of children had corpus callosum values < 6 mm and indicative of thinning (Figure 4). Twenty-five (51%) patients had evidence of white matter lesions on MRI scans. White matter lesions were most often located in subcortical frontal regions (11/25, 44%). Rates of qualitative cerebral or cerebellar volume loss were not greater in patients with white matter lesions. Linear measurement mean values were similar when comparing lupus patients with and those without white matter lesions.

There were no statistically significant differences in qualitative volume loss rates or linear measurement means comparing patients according to LAC status, aPL positivity, previous severe NPSLE manifestations (psychosis, stroke, acute confusional state), or current nephritis (data not shown). There were statistically significant differences in corpus callosum thickness and Evans ratios when analyzing according to previous biopsy-proven nephritis. Children with previous nephritis had a thicker corpus callosum measurement [mean difference 0.7 mm (95% CI 0.08 to 1.4 mm); p = 0.03]. Children with a history of nephritis had lower mean Evans ratios [mean difference 0.02 (95% CI 0.01 to 0.04); p = 0.01]. Disease duration did not predict the severity of qualitative cerebral or cerebellar volume loss assessments (odds ratio 1.0, p = 0.1). Disease duration (months of disease, continuous variable) was not correlated with any of the linear imaging measures (r values –0.04 to 0.15, p > 0.2).

Table 3. MRI findings suggestive of volume loss. Data are no. (%) or mean (SD).

Factor	Lupus Patients, n = 49	Controls, n = 14
Cerebral volume loss		
None	4 (8.2)	14 (100)
Mild	32 (65.3)	—
Moderate	12 (24.5)	—
Severe	1 (2.0)	—
Sulcal widening	41 (83.7)	—
Ventricular dilation	25 (51.0)	—
Cistern prominence	24 (49.0)	—
Cerebellar volume loss		
None	5 (10.2)	12 (85.7)
Mild	34 (69.4)	2 (14.3)
Moderate	10 (20.4)	—
Linear measures*		
Corpus callosum, mm	6.3 (1.2)	7.2 (0.7)
Thickness < 6 mm (%)	21 (42.9)	1 (7.1)
< 5 mm (%)	6 (12.2)	—
3rd ventricle width, mm	5.7 (1.9)	2.9 (0.5)
Evans ratio	0.31 (0.03)	0.29 (0.02)
Ratio > 0.30 (%)	32 (65.3)	4 (28.5)

* Mean differences in linear measures were all statistically significant at p < 0.01.

Linear measurement means were similar comparing new-onset to chronic lupus groups. Mean Evans ratios were > 0.30 in both groups. Rates of moderate or severe volume loss were most prominent in patients with disease duration > 3 years [cerebral volume loss 7/16 (43.8%) and cerebellar volume loss 6/16 (37.5%)]. Differences in Evans ratios, third ventricle width, and mean values of corpus callosum thickness were not statistically significant when stratified by disease duration [newly diagnosed (n = 14), patients with < 3 years of disease (n = 19), and those with > 3 years of disease (n = 16)].

Neuroimaging findings. Comparison of qualitative assessments and linear measures to similar-age controls. The clinical MRI of 14 children (all females) without apparent underlying inflammatory or neurodegenerative disorders were identified and read. The mean age of these children was 14.4 ± 2.3 years and this not statistically different from the lupus cohort (95% CI mean difference of –2.4 to 0.5 yrs, p = 0.2). Eleven (78.6%) of these healthy controls were imaged due to chronic or recurrent headaches. Other indications included persistent emesis (n = 1), short stature (1), and regional pain syndrome

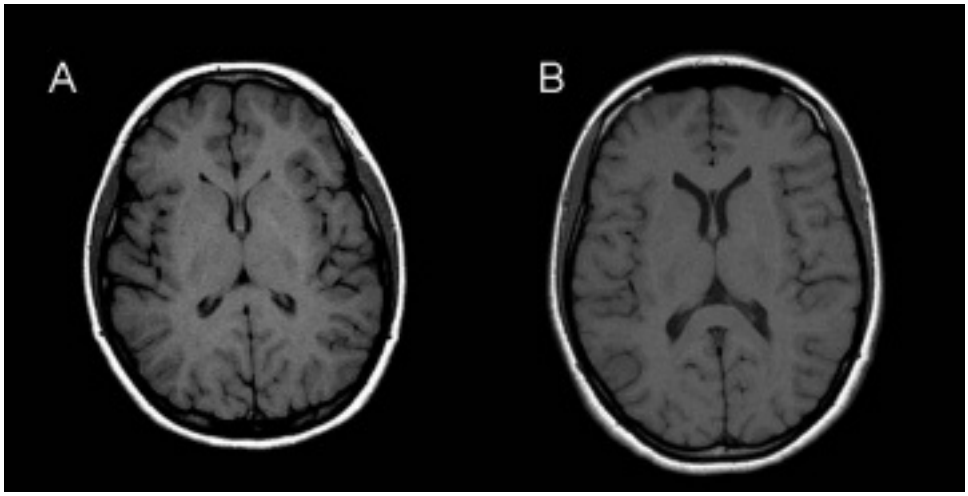

Figure 1. Qualitative features of mild cerebral volume loss. A. Axial T1-weighted image through the plane of the basal ganglia showing normal sulci, third ventricle, and supratentorial ventricular system in a 15.5-year-old girl with new-onset SLE and seizures. B. Slight prominence to the supratentorial ventricular system. Mild increase in size of lateral ventricles, cerebral sulci preserved in a 17-year-old girl with new-onset SLE and behavior changes.

(1). There was no evidence of cerebral volume loss on any control MRI (Table 3). Two (14.2%) of these children were designated as having mild cerebellar volume loss. Five additional children had prominence of the cerebellar median sulcus without a formal designation of volume loss. All mean differences of linear measurements between children with lupus and controls were statistically significant (corpus callosum values greater and third ventricle width and Evans ratio values lower in control patients). Corpus callosum mean difference was 0.9 mm (95% CI 0.3, 1.3 mm, p = 0.001), third ventricle width mean difference –2.8 mm (95% CI –3.3, –2.1 mm, p < 0.001), and Evans ratio mean difference –0.02 (95% CI –0.08, –0.008, p = 0.002).

DISCUSSION

We report imaging findings of SLE patients completing clinical brain MRI during a 6-year period at a large pediatric institution with an ethnically diverse SLE clinic. Evidence of cerebral and cerebellar volume losses was visualized in most of the brain MRI of pediatric patients with NPSLE manifestations. These findings were often observed within the first 4 years of disease presentation. Cerebral and cerebellar volume loss was also visualized in newly diagnosed patients with neurologic manifestations prior to corticosteroid exposure. These imaging changes may reflect sequelae of active NPSLE and not just physiologic corticosteroid effects. Qualitative assessments and quantitative linear measures were similar, comparing children and adolescents imaged at their initial presentation to those with a chronic disease course. Additionally, hyperintense lesions were often visualized in white matter structures. Surprisingly, children with a history of nephritis had thicker mean corpus callosum measurements and lower mean Evans ratios. Less prominent volume loss in patients with previous nephritis may be related to more aggressive control of systemic inflammation or vasculopathy. It is unclear if these statistically significant differences are clinically meaningful. Linear measurement means suggestive of corpus callosum thinning and ventricular enlargement in the lupus cohort were statistically significant compared to similar-age control MRI values.

Our findings of volume loss early in the disease course of pediatric patients are similar to those described in adult SLE cohorts. Volume loss in adult patients (within the first 5 years) is described by 2 studies utilizing both conventional MRI measurements and quantitative volumetrics[7,10]. As in our retrospective study, corticosteroid use was not a significant predictor of atrophy findings in these 2 prospective adult studies. Evidence of cerebral atrophy has been reported in small pediatric SLE studies using CT and MRI. A prospective study reported that 11/24 (46%) children with SLE (mean age 15.4 ± 4.4 yrs) had abnormal MRI findings. Cortical atrophy was described in 12.5% of these children, corpus callosum atrophy in 8.3%[13]. Volumetric assessments of SLE patients in these studies were not compared to those of healthy controls. In a 20-year retrospective review of pediatric NPSLE manifestations (mean age of patients 13.0 ± 3.0 yrs), abnormal MRI were seen in 37 of 40 children (92.5%). Cortical atrophy was described in 35% of these scans[34]. Similar findings were reported in reviews of CT scans in children with SLE. A retrospective review of Chinese and Malaysian children with lupus reported that 13/16 (81.3%) patients had abnormal CT findings during active NPSLE episodes. The most common abnormality reported was cerebral atrophy, which was found on 62.5% of scans (10/16)[35]. Another retrospective study of children with NPSLE found that 6/8 (75%) had abnormal CT scans, with cortical atrophy being the most common finding[36].

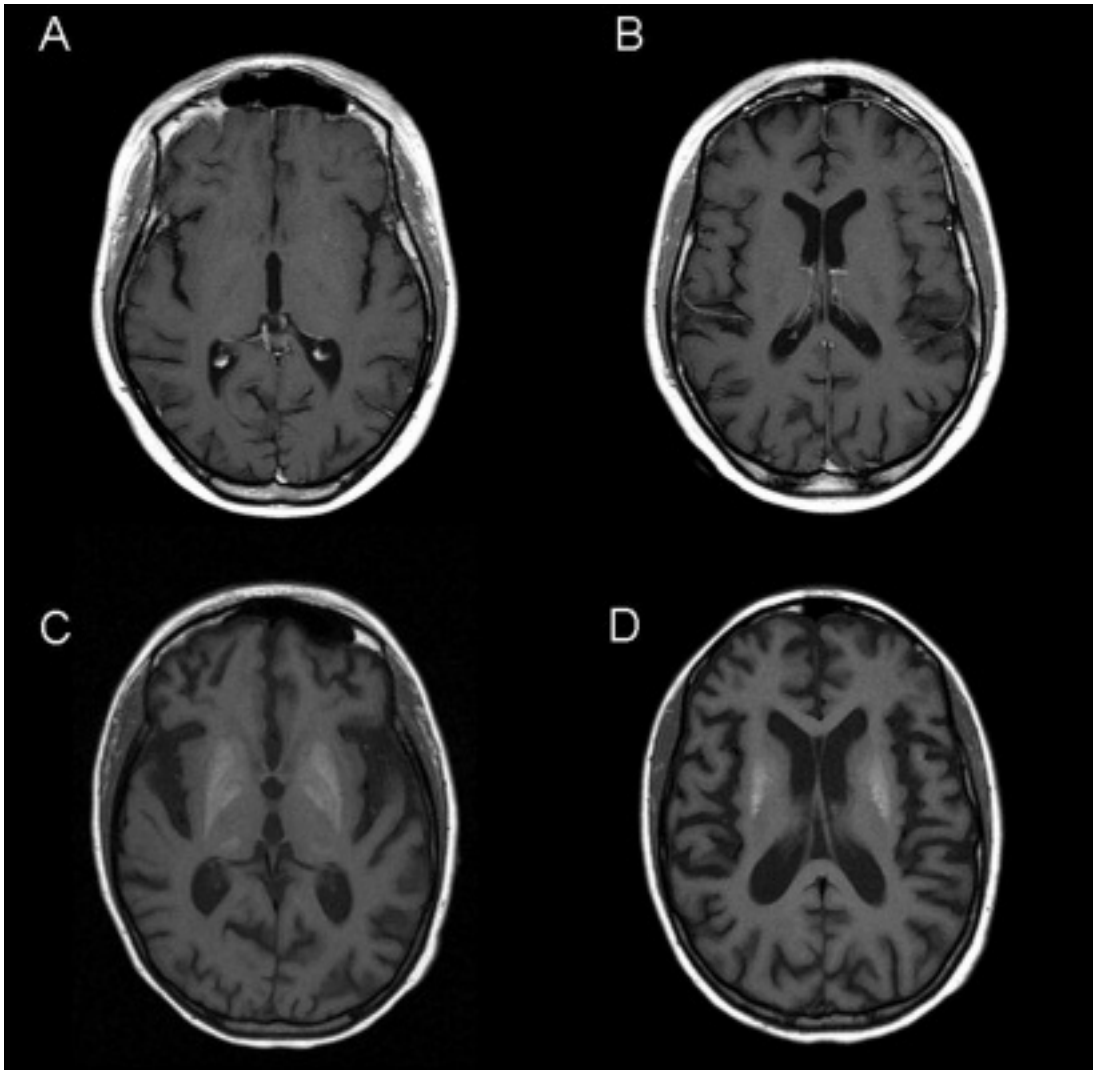

Figure 2. Qualitative assessment of moderate and severe cerebral volume loss. A. Axial T1-weighted image showing moderate dilatation of the third ventricle and cerebral sulci in a 14-year-old girl with protracted lupus disease course and presentation of acute confusional state and psychosis. B. Moderate dilatation of the supratentorial ventricular system in the same patient. C. Severe widening of the cerebral sulci and dilatation of third ventricle in a 20-year-old woman with protracted disease, multiple episodes of NPSLE, and recent lower extremity weakness. Note T1 bright signal in deep gray nuclei. D. Gross dilatation of bodies of lateral ventricles in association with widening of cerebral sulci in the same patient.

There were no descriptions of actual measurements or the qualitative criteria with which radiologists characterized atrophy in any of these studies, and none described the appearance of cerebellar structures.

While our study represents one of the larger pediatric lupus neuroimaging cohorts, it has several limitations. Since pediatric SLE patients without neurologic manifestations do not obtain brain MRI during the course of standard care, we cannot compare our findings to those of patients without NPSLE. We are thus unable to determine if structural changes such as mild volume loss or borderline corpus callosum thinning in children with SLE may be related to developmental or demographic factors unrelated to systemic inflammation or ischemia. Our assessments of volume changes are based on qualitative criteria and crude linear measures and not quantitative volumetrics (morphometrics). Due to the potential imprecision of these linear measures and complexity of predictor variables we have not reported multivariable modeling of volume loss factors. We have also not reported cumulative lifetime corticosteroid dosing due to concerns about unreliable ascertainment of intravenous methylprednisolone dosing since initial diagnosis.

Due to the paucity of pediatric SLE neuroimaging data, limitations notwithstanding, our study provides important information that may enhance clinical care and research of children with SLE. Linear MRI measures of children and adolescents with SLE (corpus callosum thickness, third ventricle width, and Evans ratio) differed from those of young adults

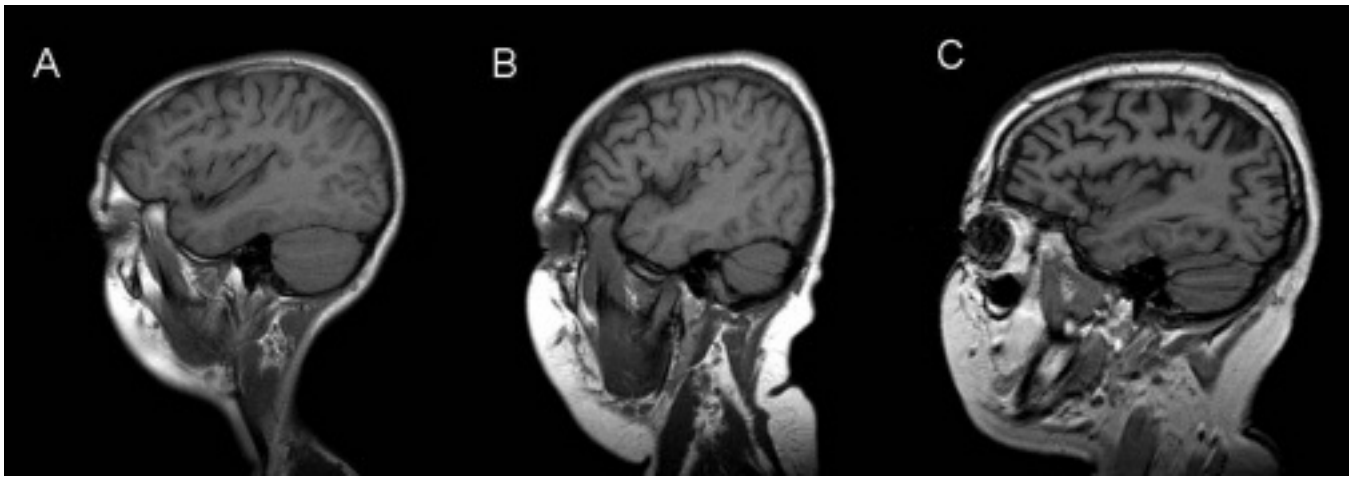

Figure 3. Features of cerebellar volume loss. A. T1-weighted parasagittal image (off midline) showing normal appearance of the cerebellum in a 17-year-old girl with new-onset SLE and seizures. B. Mild prominence of the median sulci in a 19-year-old male with protracted disease and recent transient ischemic attack. C. Moderate widening of the cerebellar folia in a 14-year-old girl with protracted disease course and recent acute confusional state and psychosis. Both B and C show progressive widening of cerebral sulci.

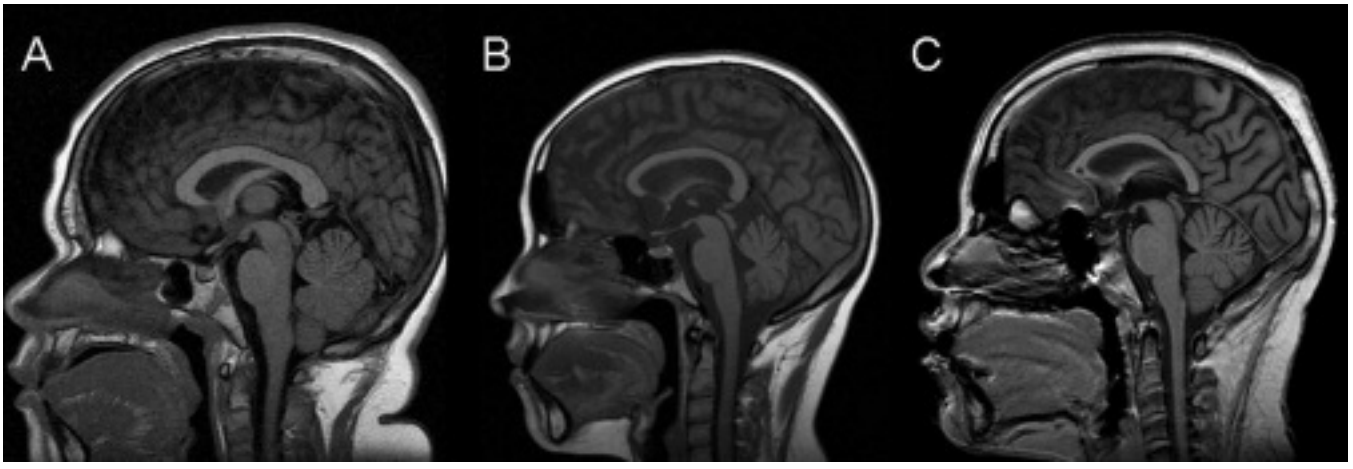

Figure 4. Assessment of corpus callosum thickness. A. Sagittal T1-weighted image showing intact corpus callosum appearance with a thickness of 7.5 mm at the level of the junction of the anterior body and genu in a 19-year-old male with protracted disease and recent transient ischemic attack. B. Uniform thinning of the corpus callosum with a thickness of 5.0 mm at the same location in a 20-year-old female with protracted disease, multiple episodes of NPSLE, and recent lower extremity weakness. C. Uniform thinning of the corpus callosum with a thickness of 4.2 mm at the same location in a 14-year-old girl with protracted disease course and acute confusional state and psychosis. Note T1 focal hypointense lesion in genu.

described in the literature and a similar-age control group. That corticosteroid use was not associated with structural brain abnormalities in children with SLE is an important finding. Together with less prominent volume loss in children treated aggressively for nephritis, this suggests that qualitative and linear measures may be utilized to assess disease effects on brain structures. Evidence of volume losses indicates active disease in other neuroinflammatory disorders and often leads to earlier neurocognitive evaluations and repeat MRI assessments. Similar algorithms may be appropriate for children with lupus and findings of volume loss. Progression of volume loss in a pediatric lupus patient may be an additional tool to assess disease activity and response to clinical interventions. As in other neuroinflammatory disorders, structural imaging changes observed in children with lupus are not strictly reflections of chronic corticosteroid use. The use of accepted linear imaging measures and qualitative volume loss criteria may provide clinicians and researchers with "markers" to compare clinical MRI data in larger retrospective reviews, neuroimaging data repositories, and clinical trials. It remains unclear how to utilize qualitative and linear volume loss assessments in children with lupus who do not have other structural imaging abnormalities related to stroke or vasculitis.

Prospective MRI studies utilizing precise quantitative volumetrics are needed to clearly assess the effects of disease factors on cerebral and cerebellar volume loss. Morphometric studies are necessary to assess associations between structural changes and neurocognitive outcomes in children and adoles-

cents with SLE. Morphometry of the cerebellum, basal ganglia, and thalamus may complement measurements of cerebral and white matter volumes in children with SLE. Precise volumetric tools may allow assessment of NPSLE disease progression and response to therapy in future studies. Such studies may lead to the standardization of clinical and research neuroimaging protocols for pediatric patients with lupus.

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