Chapter 6

Perfusion MRI in Neuro-Psychiatric Systemic Lupus Erythemathosus

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ABSTRACT

Purpose

Multiple pathogenic mechanisms can underlie systemic lupus erythematosus (SLE) patients developing neuropsychiatric (NP) symptoms. Our aim was to use perfusion weighted MR to quantify any perfusion abnormalities and to determine their contribution to neuropsychiatric involvement in SLE.

Methods

We applied dynamic susceptibility contrast (DSC) perfusion MRI in 15 active NPSLE, 26 inactive NPSLE patients and 11 control subjects. Cerebral blood flow (CBF), cerebral blood volume (CBV) and mean transit time (MTT) maps were reconstructed and regions of interest were compared between groups. In addition, the effect of SLE criteria, NPSLE syndromes, immunological coagulation disorder and medication on CBF, CBV and MTT was investigated.

Results

No significant differences were found between the groups in CBF, CBV and MTT. No significant influence of SLE criteria or NPSLE syndromes on CBF, CBV or MTT was found. No significant influence of anti-cardiolipin antibodies, lupus anti-coagulant, the presence of anti-phospholipid syndrome (APS) or medication on CBF, CBV or MTT was found.

Conclusion

Our findings suggest CBF, CBV and MTT in the white and the gray matter in SLE patients is not significantly different from healthy controls or between patients with an without specific symptoms and with or without immunological disorder involving coagulation.

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease caused by auto-antibodies acting against cellular components and DNA fragments of the patient. These auto-antibodies cause injury to multiple organs in SLE. In up to 95 percent of SLE patients the central nervous system is affected. (1) These patients develop neuro-psychiatric (NP) symptoms and are classified as NPSLE patients. Ischemia and auto-antibody mediated neuronal loss have both been implicated as pathogenic mechanisms leading to NP symptoms in SLE. (2-4) Ischemia has been suggested to be the result of endothelial damage, caused by anti-endothelial antibodies, or generalized vasculopathy, caused by increased circulating inflammatory mediators. (5,6) Another well-known cause of ischemia in SLE is the presence of anti-cardiolipin antibodies that result in hypercoagulability by binding to anti-thrombotic substances in the blood. (7) It is still unknown how medication and the pathological pathways mentioned above influence the clinical status of the NPSLE patient and in what way they contribute to neuropsychiatric symptoms.

Studies of brain perfusion in SLE patients with neuropsychiatric symptoms have produced ambiguous results. Patchy hypoperfusion has been implicated in the past as a possible cause of NP symptoms in SLE. On the one hand, previous investigators suggested patchy or random focal hypoperfusion, using single photon emission computed tomography (SPECT) in NPSLE patients. (8) A recent study with SPECT suggested that the gray matter in SLE patients was relatively hypoperfused compared to healthy controls. (9) On the other hand, Emmi and coworkers reported perfusion abnormalities in patients with severe, mild and without neuropsychiatric symptoms and concluded that the role of CBF abnormalities remained unclear. Furthermore they found no association with anticardiolipin antibodies. (10) In another SPECT study Nossent and colleagues reported CBF abnormalities in 75% of their patients. However, they found no correlation with overall disease activity or serological disease parameters and poor correlation with the expert neuropsychiatric diagnosis. (11) So far, no significant associations or correlations between (regional) CBF and neuropsychiatric involvement have been reported. (8,10-15) To our knowledge, no perfusion weighted MR studies are available in NPSLE patients so far.

The aim of the present study was to assess whether MR perfusion abnormalities can be observed in NPSLE and whether such defects contribute to neuropsychiatric involvement in SLE. To determine the presence and influence of global or focal hypoperfusion, we measured the CBF, CBV and MTT of white matter and gray matter in controls, active and inactive NPSLE patients. In addition, we correlated our perfusion findings with SLE criteria and anti-cardiolipin antibody status.

METHODS

Subjects

We applied dynamic susceptibility contrast (DSC) perfusion MRI in 15 NPSLE patients with active disease, 26 with inactive disease and 11 control subjects. Controls were recruited from subjects who underwent gadolinium enhanced MRI because of routine follow-up of small acoustic nerve tumors. Control subjects did not have any further abnormalities on MRI. Special care was taken to exclude patients with secondary causes of NP symptoms, like medication, metabolic derangement or infection. Patient characteristics are shown in table 1. Of the 15 patients with lupus anticoagulant (LAC) one or both anticardiolipin antibodies (AcL IgM and/or AcL IgG) were present in 13.

Table 1. Patient characteristics.

	Active NPSLE	*Inactive NPSLE*	*Controls*
N	*15*	*26*	*11*
Mean age (SD)	*40.1 (13.8)*	*36.4 (11.8)*	*50.9 (11.8)*
Male/female	*1/14*	*0/26*	*6/5*
SLE duration (SD)	*8.0 (7.6)*	*10.0 (9.1)*	-
NPLSE duration (SD)	*1.7 (2.8)*	*5.4(6.2)*	-
LAC	*6 (na:1)*	*9 (na:3)*	-
AcL IgG	*10 (na:1)*	*15 (na:2)*	-
AcL IgM	*7 (na:1)*	*13 (na:2)*	-
APS	*5*	*5*	-
Prednisone	*4*	*15*	-
Methylprednisone	*6*	*7*	-
Marcoumar	*5*	*6*	-
Cyclophosphamide	*2*	*7*	-
Imuran	*2*	*8*	-
Ascal	*1*	*5*	-
None of the medication above	*3*	*2*	-

LAC= lupus anticoagulant; AcL = anticardiolipin antibodies; na: =not available in n number of patients

MRI

All MRI scans were carried out on a Philips Gyroscan Intera ACS-NT 1.5T MR scanner (Philips Medical Systems, Best, The Netherlands). Axial proton-density (TR/TE 2500/30 ms), T2-weighted (TR/TE 2500/120 ms), and fluid-attenuated inversion recovery (FLAIR; TR/TI/TE 8000 msec/2000 msec/120 m) images were acquired with the following parameters: field of view (FOV) 220 mm, matrix 256 x 256, and 22 6mm slices with 0.6-mm slice gap.

Perfusion weighted MRI

Bolus-tracking perfusion MRI was performed by means of gradient echo imaging (9 slices of 6 mm thickness, FOV 250 mm, scan matrix 89x55, segmented EPI (5 shots), TR

400 ms, TE 30 ms, flip angle 90 degrees, 25 ml of Gd-DTPA was injected at 5 ml/sec and this injection of contrast agent was followed by a saline chaser of 15 ml at 5 ml/s). Scans were processed on an off-line workstation using oscillation index regularized singular value decomposition (SVD). (16,17) The arterial input function (AIF) was manually determined on the basis of early arrival time and small width of the bolus passage curve, after which CBF, CBV and MTT maps were reconstructed. (18-20)

ROIs of the cortical gray and the white matter as well as the thalamus on both sides were manually drawn on anatomical scans, the perfusion scans before the arrival of contrast. Typical ROIs in the white matter were semi-circular in shape in the white matter of the centrum semiovale, taking care to avoid areas were large vessles could be included (average number of white matter ROIs: 4 range 2-6, average size 971.3 mm^2 range 731-1301 mm^2). Typical ROIs in the cortical gray matter were banana shaped and special care was taken to obtain a margin at the sides to minimize influence of atrophy (average number of gray matter ROIs: 4 range 2-6, average size 489,3 mm^2 , range 265-803). In addition special care was taken to exclude the sinus sagitalis superior. The ROIs in the thalamus were circular in shape and a typical margin of 5 mm was preserved in order not to include any surrounding brain tissue (average number of thalamus ROIs: 2 range 2-4, average size 128,7 mm^2, range 111-196 mm^2). An example of typical ROI placement is given in figure 1. These ROIs were automatically transferred to the CBF, CBV and MTT maps and the mean pixel intensity was determined for each ROI. Subsequently, the ROIs of the thalamus were combined to

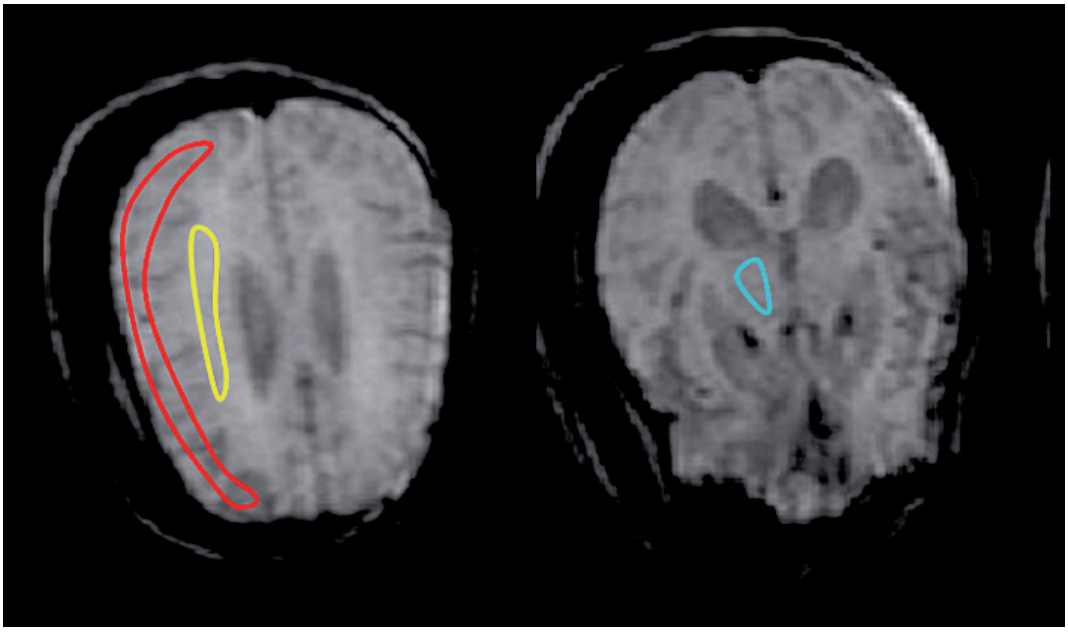

Figure 1. Example of typical ROI placement in the thalamus (blue line), white (yellow line) and gray matter (red line). Special care was taken not to include any surrounding brain tissue, large vessles or atrophy. These ROIs were automatically transferred to the CBF, CBV and MTT maps and the mean pixel intensity was determined for each ROI.

form one region, this was also done for the white and gray matter. Since only the shape and not the amplitude of the AIF could be measured, the CBF and CBV were normalized for each patient with respect to the CBF of white matter (set at 24 ml/100ml/min). (21)

Statistical analysis

All results were corrected for multiple testing using post-hoc Bonferroni analysis. First, to study the influence of age and gender, we performed a linear regression for age and a binary logistic regression for gender and the perfusion parameters.

Second, one-way ANOVA and post-hoc Bonferroni analysis were used to test for significant differences in CBF, CBV and MTT between control subjects, active and inactive NPSLE patients. Third, one-way ANOVA and posthoc Bonferroni analysis were used to test for significant differences in perfusion parameters between patients with a certain 1997 revised American College of Rheumatology SLE criterion (except for neurological involvement, present in all patients), i.e. malar rash (n=12), discoid rash (n=17), photosensitivity (n=13), oral ulcers (n=12), arthritis (n=33), serositis (n=21), renal disorder (n=17), hematologic disorder (n=23), immunologic disorder (n=39), antinuclear antibody (n=39) and those without the criterion. Fourth, one-way ANOVA and posthoc Bonferroni was used to test for significant differences in perfusion parameters between active or inactive patients groups with a NP syndrome present in 10 or more SLE patients, i.e. cerebrovascular disease (n=12), headache (n=10), seizures (n=10), cognitive dysfunction (n=11). Fifth, one-way ANOVA and posthoc Bonferroni was used to test for significant differences in perfusion parameters between patients groups with anti-cardiolipin antibodies, the lupus anti-coagulant LAC and the presence of APS. Finally, one-way ANOVA and posthoc Bonferroni was used to test for significant differences between patients groups with prednisone, methylprednisone, marcoumar, cyclophophamide, imuran or ascal.

RESULTS

Using the linear regression analysis, no influence of age was found on the perfusion parameters CBF, CBV or MTT. Using the binary logistic regression no influence of gender was found on the perfusion parameters.

Table 2 shows the mean values of the perfusion parameters of the controls, the active and the inactive NPSLE patients. No significant differences were found between the groups. Although not significant, there was a trend for a higher CBF in the gray matter of NSPLE patients and higher CBV in patients with NPSLE especially in the active group. Remarkably the MTT was lower in the patients with NP symptoms in the past.

Table 2. Perfusion parameters in controls and NPSLE patients.

	Active NPSLE (n=15)	Inactive NPSLE (n=26)	Controls (n=11)
CBF GM ml/ 100ml/min	50.2 (6.1)	50.2 (6.7)	46.9 (3.6)
CBV GM ml/100ml	4.94 (0.58)	4.71 (0.72)	4.60 (0.53)
MTT GM seconds	5.99 (0.34)	5.71 (0.37)	5.97 (0.50)
CBV WM ml/ 100ml/min	2.54 (0.13)	2.40 (0.16)	2.55 (0.27)
MTT WM ml/100ml	6.47 (0.37)	6.10 (0.42)	6.50 (0.68)

Mean (SD). All group means were tested for significance using ANOVA with post-hoc Bonferroni correction. No significant differences were found.

Table 3 shows the mean values of the perfusion parameters in patient groups positive for a SLE criterion. None of the SLE criteria showed significantly different perfusion parameters from the healthy controls and the NPSLE group without this criterion.

Table 4 shows the mean values of the perfusion parameters in controls and patient groups with NPSLE syndromes present in 10 or more patients. None of the NPSLE syndromes showed significantly different perfusion parameters from the healthy controls and the group without this syndrome.

Table 5 shows the mean values of the perfusion parameters in controls and patient groups with anti-cardiolipin antibodies, the lupus anti-coagulant LAC and the presence of APS. None of these groups showed any significant difference from the healthy control group or the group without the antibodies or syndrome.

Finally, the ANOVA with post-hoc Bonferroni correction of the groups of patients with medication did not reveal any significant influence of any of the medications used. Typical examples of CBF maps in all three groups are shown in figure 1. The previously reported patchy areas of hypoperfusion could not visually be replicated in our study.

DISCUSSION

To our knowledge, this is the first quantitative perfusion study in NPSLE patients. The most important finding of this study is that we did not find any signs of focal or global abnormalities in the perfusion parameters. In patients with global or focal infarcts the MTT is typically prolonged, whereas the CBF is reduced (hypoperfusion), sometimes accompanied by increased CBV (vasodilatation) or decreased CBV (microvascular collapse). Comparing NPSLE patients with control subjects none of these typical perfusion abnormalities were observed. Furthermore, no significant differences were found when

Table 3. Perfusion parameters in controls and patient groups positive for a SLE criterion

	Controls (n=11)	*Malar rash (n=12)*	*Discoid Rash (n=17)*	*Photosensitivity (n=13)*	*Oral ulcers (n=12)*	*Arthritis (n=33)*	*Serositis (n=21)*	*Renal disorder (n=17)*	*Hemato-logical disorder (n=23)*	*Immuno-logical disorder (n=39)*	*Anti-nuclear antibody (n=39)*
CBF GM ml/100ml/min	46.9 (3.6)	52.2 (7.0)	51.2 (7.0)	52.3 (7.3)	51.8 (7..0)	49.7 (6.7)	52.1 (6.7)	52.5 (7.3)	51.5 (6.8)	50.0 (6.4)	50.1 (6.5)
CBV GM ml/100ml	4.60 (0.53)	4.93 (0.60)	4.95 (0.73)	4.84 (0.74)	4.91 (0.57)	4.76 (0.69)	5.01 (0.67)	5.02 (0.68)	4.97 (0.66)	4.78 (0.68)	4.78 (0.67)
MTT GM Seconds	5.97 (0.50)	5.78 (0.35)	5.90 (0.44)	5.65 (0.36)	5.79 (0.42)	5.84 (0.41)	5.85 (0.41)	5.81 (0.35)	5.87 (0.39)	5.82 (0.38)	5.81 (0.36)
CBV WM ml/100ml/min	2.55 (0.27)	2.49 (0.12)	2.48 (0.15)	2.42 (0.14)	2.40 (0.14)	2.46 (0.17)	2.50 (0.18)	2.45 (0.13)	2.49 (0.16)	2.46 (0.17)	2.46 (0.16)
MTT WM Seconds	6.50 (0.68)	6.32 (0.29)	6.30 (0.39)	6.14 (0.39)	6.11 (0.37)	6.26 (0.47)	6.34 (0.48)	6.21 (0.34)	6.33 (0.43)	6.25 (0.44)	6.24 (0.44)

Mean (SD). All group means were tested for significance using ANOVA with post-hoc Bonferroni correction. No significant differences were found.

Table 4. Perfusion parameters in controls and patient groups with NPSLE syndromes present in 10 or more patients

	Controls (n=11)	Cerebrovas-cular disease (n=12)	Headache (n=10)	Seizures (n=10)	Cognitive dysfunction (n=11)
CBF GM ml/100ml/min	46.9 (3.6)	50.3 (7.4)	48.9 (7.5)	50.2 (4.2)	51.4 (7.4)
CBV GM ml/100ml	4.60 (0.53)	4.79 (0.61)	4.74 (0.90)	4.79 (0.61)	4.83 (0.80)
MTT GM seconds	5.97 (0.50)	5.81 (0.30)	5.83 (0.36)	5.79 (0.46)	5.71 (0.38)
CBV WM ml/100ml/min	2.55 (0.27)	2.45 (0.13)	2.47 (0.13)	2.41 (0.18)	2.47 (0.19)
MTT WM seconds	6.50 (0.68)	6.23 (0.30)	6.23 (0.29)	6.10 (0.50)	6.29 (0.50)

Mean (SD). All group means were tested for significance using ANOVA with post-hoc Bonferroni correction. No significant differences were found.

Table 5. Perfusion parameters in controls and patient groups with anti-cardiolipin antibodies

	Controls (n=11)	IgM (n=20)	IgG (n=25)	LAC (n=15)	APS (n=10)
CBF GM ml/100ml/min	46.9 (3.6)	50.6 (7.0)	50.8 (6.1)	51.2 (7.3)	51.2 (7.0)
CBV GM ml/100ml	4.60 (0.53)	4.76 (0.71)	4.87 (0.61)	4.77 (0.60)	4.81 (0.57)
MTT GM seconds	5.97 (0.50)	5.71 (0.39)	5.84 (0.36)	5.69 (0.33)	5.75 (0.41)
CBV WM ml/100ml/min	2.55 (0.27)	2.42 (0.18)	2.45 (0.14)	2.42 (0.19)	2.43 (0.14)
MTT WM seconds	6.50 (0.68)	6.16 (0.47)	6.23 (0.37)	6.18 (0.50)	6.19 (0.36)

Mean (SD). All group means were tested for significance using ANOVA with post-hoc Bonferroni correction. IgG and IgM was not determined in 3 of the 41 patients and LAC was not determined in 4 patients. No significant differences were found.

comparing patients with a specific SLE criterion to the controls. In addition, patients with anti-cardiolipin antibodies did not show different perfusion parameters compared to the healthy controls. Finally, in the analysis of the different NP syndromes present in more than ten patients no significant differences were found.

Our data do not provide evidence for widespread ischemia as a cause of neuropsychiatric symptoms. Patchy hypoperfusion has been implicated in the past as a possible cause of NP symptoms in SLE using SPECT. Emmi and coworkers reported CBF abnormalities in patients with severe, mild and without neuropsychiatric symptoms and concluded that the role of CBF abnormalities remained unclear. Furthermore they found no association with anticardiolipin antibodies. (10) In another SPECT study Nossent and colleagues

reported CBF abnormalities in 75% of their patients. However, they found no correlation with overall disease activity or serological disease parameters and poor correlation with the expert neuropsychiatric diagnosis. (11) In line with the studies mentioned above, we found no influence on the perfusion values of the SLE criteria, the neuropsychiatric syndromes, anticardiolipin antibodies or medication.

So far, no significant associations or correlations between (regional) CBF and neuropsychiatric involvement have been reported. (8,10-15) Rubbert et al. reported that they did not find any association between clinical SLE manifestations and found no relation between CBF observations and neuropsychiatric symptoms. (13) Waterloo and coworkers performed a battery of neuropsychological tests in SLE patients but failed to find any association with CBF. (14) Other SPECT studies also did not find any significant differences in perfusion parameters between SLE patients with and without NP symptoms. (12,15)

A limitation of the studies mentioned above is the fact that the analyses of SPECT data have been limited to qualitative, i.e. visual inspection to CBF maps. A recent voxel-based SPECT study found no difference in perfusion parameters between healthy controls and SLE patients with inactive NP involvement. However the authors found a global hypoperfusion in active NPSLE patients compared to healthy controls, which was mainly located in the cortical gray matter. Still, due to the relative nature of the underlying SPECT data, the interpretation of these analyses remains problematical. (9) Furthermore, partial volumeing effects, inherent to the relatively low spatial resolution of SPECT compared to perfusion weighted MR, cause incorrectly low perfusion values in atrophied areas, i.e. the gray matter. This is particularly the case in voxel based analyses. In perfusion weighted MR this effect is smaller due to the higher spatial resolution.

A limitation of the current study is the use of a scan protocol that has a relatively low temporal resolution and some inherent sensitivity to T1-effects. This could lead to the underestimation of normal CBF and overestimation of MTT. However, these aspects would influence both patient and control groups equally and will therefore have limited influence on the inter-group comparisons. Furthermore, due the slice thickness used in DSC perfusion MRI small defects can be missed. In addition, the patient groups with the same neuropsychiatric syndrome are still relatively small. Perfusion MR studies in a larger number of patients with a certain syndrome or in a certain brain structure or region might reveal an influence of perfusion abnormalities in certain NP syndromes. Finally, since the data are normalized to the values of the white matter, absolute quantitative data cannot be given. . The fact that the CBF and CBV values have been calibrated to normal white matter implies the assumption that perfusion in the contralateral white matter is normal. This assumption could be erroneous in SLE patients with diffuse neuropsychiatric symptoms, like cognitive dysfunction or headache. Future studies should include the

use of a partial volume corrected AIF, which would elude the necessity of normalization with respect to white matter CBF. (23)

In conclusion, our findings suggest that hypoperfusion is not involved in the etiology of NP symptoms of active SLE patients. The origin of the perfusion changes in patients with longstanding inactive disease needs to be studied further.

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