

岩手医科大学
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(博士)

Figure 1

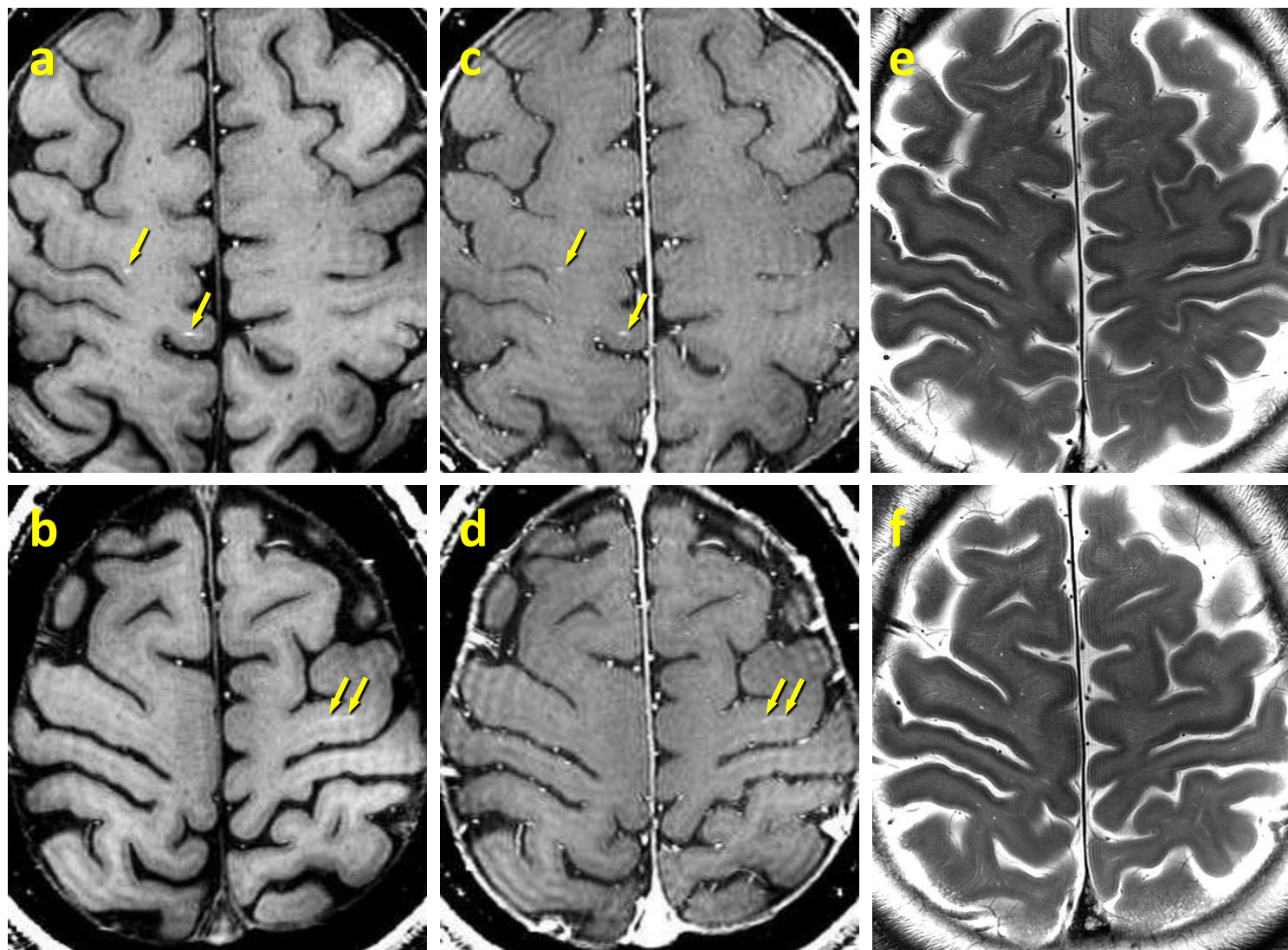
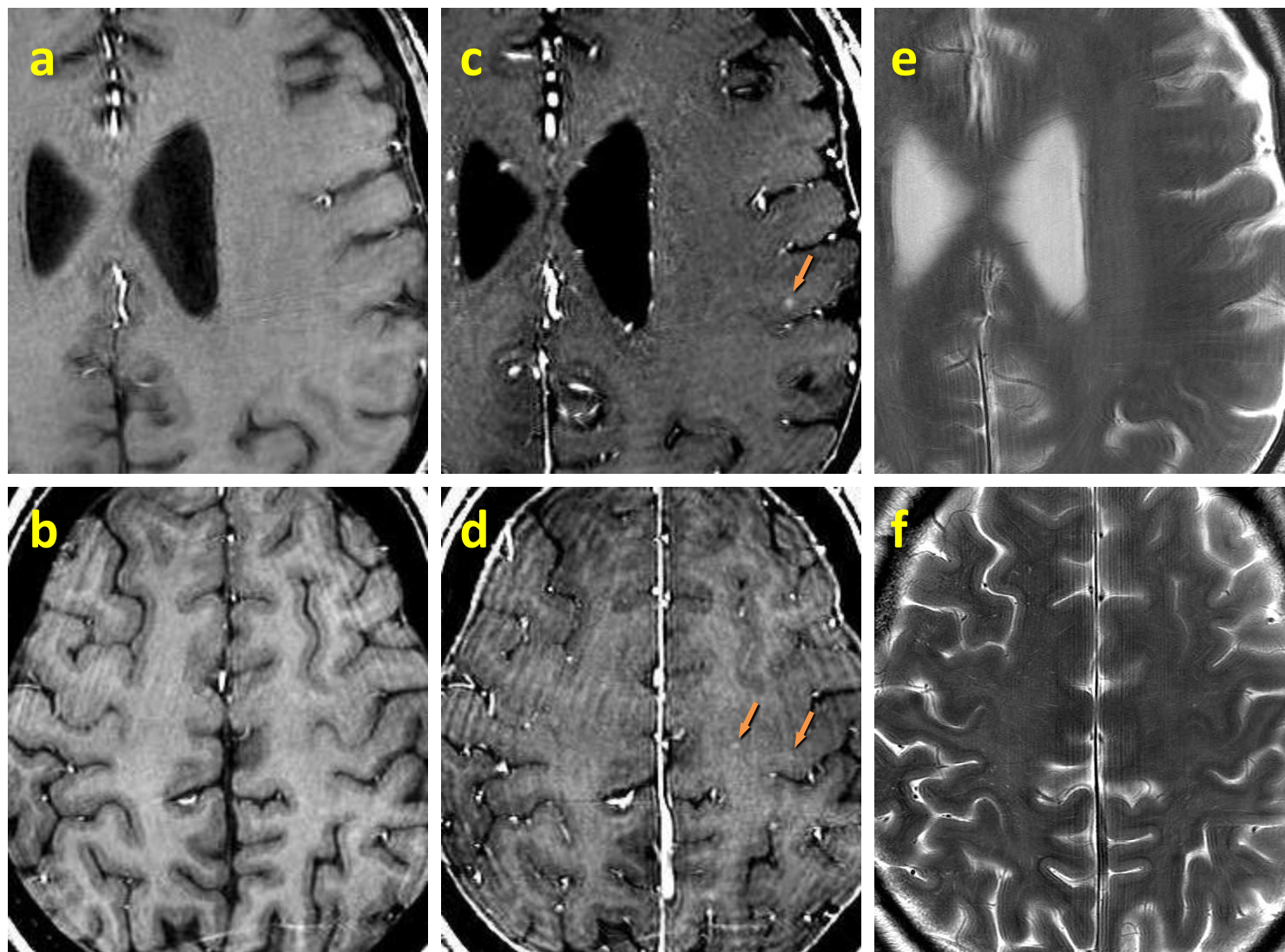


Figure 2



Detection of cerebral microvascular lesions by 7 Tesla MRI in patients with neuropsychiatric systemic lupus erythematosus

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Running title: Detecting NPSLE lesions by 7 Tesla MRI

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Abstract

Background: Neuropsychiatric systemic lupus erythematosus (NPSLE) is speculated to be caused by disturbed microcirculation of the central nervous system. However, characteristic imaging findings of NPSLE have not been established. Hence, we investigated whether high-resolution images using ultrahigh field magnetic resonance imaging (MRI) at 7 Tesla can detect microcerebrovascular lesions in patients with NPSLE, which have never been detected by conventional MRI.

Methods: We prospectively examined 20 patients with SLE, including 5 with NPSLE, using a 7 Tesla MRI scanner. High-resolution 2-dimensional T2-weighted images (T2WIs) and high-resolution 3-dimensional T1-weighted images (T1WIs) before and after the administration of contrast agents were obtained.

Results: On high-resolution T1WIs at 7 Tesla, minute punctate/linear hyper-intense lesions in subcortical and/or cortical areas were found in 4 (80%) NPSLE patients and in 1 (7%) non-NPSLE patient. Furthermore, the

minute punctate enhanced lesions in these areas were only found on contrast-enhanced T1WIs in 3 (60%) NPSLE patients. These findings suggesting microvascular thrombi or inflammation were significantly more frequent in the NPSLE than in the SLE patients without NPSLE ($p=0.001$). In contrast, other imaging findings, laboratory findings, and clinical characteristics were not different between the two groups.

Conclusion: High-resolution T1WIs at 7 Tesla can detect minute findings indicating intracerebral microvascular lesions in patients with NPSLE.

Key words. SLE, NPSLE, 7 Tesla MRI, CNS

Author contribution; O.M. performed the primary data analysis and wrote the manuscript. N.S. contributed to study design and clinical management. M.S. contributed to study design, interpretation of results and writing of manuscript. K.K., Y.N., Y.O., H.K. and Y.N. helped data collection of SLE

patients. K.Y. contributed to discussion of results and writing of manuscript.

Conflict of interest

We declare no conflict of interest.

Introduction

Systemic lupus erythematosus (SLE) is a multisystemic autoimmune disease of unknown etiology. The clinical manifestations of SLE show mucocutaneous, articular, renal, serosal, hematologic and immunologic involvement. Among the manifestations, neuropsychiatric SLE (NPSLE) is one of the most common causes of morbidity and mortality in patients with SLE.

No acceptable methods for diagnosing NPSLE have been established. NPSLE exhibits various symptoms and comprises a wide range of clinical conditions affecting the central, peripheral, or autonomic nervous system, such as cognitive dysfunction, psychosis, depression, and acute confusional state. More focal syndromes also occur, such as stroke, seizures, chorea, and transverse myelitis (3). The etiology of NPSLE is still incompletely understood. In 1999, the American College of Rheumatology (ACR) established the nomenclature and detailed case definitions for 17 NPSLE syndromes, which provide a clear description of the multiple clinical faces

of the disorder (4). Based on this definition, 63~91% of patients exhibited neuropsychiatric symptoms, including those directly and indirectly relating to SLE (1-3).

As NPSLE represents 7~13 % of deaths in patients with SLE, early diagnosis has been thought to be critically important (6). Although laboratory testing with serum and cerebrospinal fluid (CSF) and radiological testing were reported to be beneficial to the diagnosis of NPSLE (7, 8), these methods need further investigation to be established. To elucidate the causes of NPSLE, MRI often provides findings in the central nervous system (CNS) relevant to the symptoms of patients with NPSLE. Therefore, conventional MRI of the brain has been thought to be a useful tool to understand the etiologic processes of NPSLE. To date, several papers have reported various conventional MRI finding in patients with NPSLE **such as cerebral infarction and non-specific periventricular or deep white matter hyperintensity (PVH/DWMH) on T2WI** (9-11).

However, whether MRI findings are related to the symptoms of NPSLE

remains unclear. In fact, although CNS lesions **such as cerebral infarction and focal or diffuse PVH/DWMH** have been found in patients without NPSLE, no CNS findings have been observed in patients with NPSLE (12).

NPSLE cases without MRI finding could potentially be attributed to a low power field of magnetic resonance and low-resolution capacity of conventional MRI. Recently, studies of 7 Tesla MRI for deep brain structures have provided promising results due to an increase in tissue contrast compared with the lower field strength of conventional MRI (13). Therefore, we analyzed the CNS lesions of patients with NPSLE by 7 Tesla MRI in the present study.

Methods

Subjects

We recruited 20 consecutive patients with SLE (age range, 15–54 years [mean age, 35.5 years]; 3 men and 17 women) who were admitted to our hospital from February, 2012 to March, 2013. All patients fulfilled the

1982 revised criteria for the classification of SLE (14). The patients with NPSLE were diagnosed by a board-certified rheumatologist (N.S.) as well as board-certified neurologists and psychiatrists according to the 1999 Case Definitions for NPSLE Syndromes (4). The study protocol was approved by the ethics committee (No.H23-72) and informed written consent was obtained from each patient.

Imaging Protocol

The MRI examination was conducted using a 7-Tesla scanner (Discovery MR950, GE Healthcare, Milwaukee, WI, USA) with a 32-channel head coil. High-resolution axial 2-dimensional (2D) spin-echo T2-weighted images (T2WIs) and high-resolution axial 3-dimensional (3D) spoiled gradient-echo T1-weighted images (T1WIs) before and after the administration of contrast agent (gadopentetate dimeglumine 0.1 mmol/kg, Bayer AG, Leverkusen, Germany) were obtained. The scanning parameters of these images were as follows: T2W images, repetition time (TR) 3000 ms, echo time (TE) 60 ms, field of view (FOV) 200 mm, matrix size 1024

× 512 (pixel size 0.2 × 0.4 mm), slice thickness 4 mm, number of slices 38, and acquisition time, 13 min 48 s; T1W images, TR 12 ms, TE 2.8 ms, flip angle 12°, FOV 200 mm, matrix size 512 × 320 (pixel size 0.4 × 0.6 mm), slice thickness 0.5 mm (after zero-fill interpolation), number of slices 170, and acquisition time, 9 min 35 s.

Image Interpretation and Statistical Analyses

A board-certified senior neuroradiologist (M.S.) who was unaware of the clinical status of the patients visually evaluated the presence of any abnormalities on all images two times, with an intervening two months interval. Differences between the interpretations of the two sessions were resolved by a third interpretation. Differences in the incidence of CNS lesions between the NPSLE patients and the non-NPSLE patients were examined using Fisher's exact test. Differences in the clinical characteristics and laboratory findings between the two groups were also examined using Fisher's exact test or Mann-Whitney's test. *P*-values of less than 0.05 were considered statistically significant.

Results

Among the 20 patients with SLE, 5 (age range, 15–39 years [mean age, 27.0 years]; 1 man and 4 women) were diagnosed with NPSLE. The symptoms of the patients with NPSLE included polyneuropathy (1 patient), acute confusional state (2), psychosis (1), cognitive dysfunction (1), and ischemic stroke (2). The clinical characteristics and laboratory findings of the patients are shown in Table 1. There were no significant differences in the age, sex, the titers of anti-double stranded DNA antibody, anti-Sm antibody, anti-cardiolipin antibody, or lupus anticoagulant between the NPSLE and non-NPSLE groups. The SLEDAI score was significantly higher in the NPSLE group compared with the non-NPSLE group ($p=0.023$). However, this finding was expected because SLEDAI included the scoring of NPSLE symptoms.

All of the patients received MRI examinations and the resulting images were all eligible for further analyses. On the high-resolution T1WIs, minute

punctate and/or linear hyperintense lesions, subcortical/cortical micro-hyperintensities (SCMH), were found in subcortical and/or cortical areas of the cerebral hemisphere, particularly in high convexity areas, in 4 of 5 patients with NP-SLE (80%) and 1 of 15 patients with non-NPSLE (7%) (Table 1, Figure 1). In addition, on the high-resolution T1WIs after the administration of the contrast agent, punctate enhanced lesions, subcortical/cortical micro-enhancement (SCME), were only found in these areas in 3 NPSLE patients (60%), with some lesions showing hyperintensity and others being unclear on the non-enhanced T1WIs (Table 1, Figure 2). These lesions were significantly more frequent in the NPSLE patients compared with the non-NPSLE patients ($p=0.001$, Fisher's exact test). No abnormal signals were found in the corresponding areas on the high-resolution T2WIs. In addition to these lesions, findings indicating old infarct including hemorrhagic infarct were found in 1 NPSLE patient (20%) (thalamus and cerebellum) and 3 non-NPSLE patients (20%) (cerebral deep white matter and basal ganglia). Non-specific **DWMHs** were

found in 1 (20%) NPSLE patient and 4 (27%) non-NPSLE patients. There were no significant differences in the incidence of these lesions between the two groups. No other lesions were found on the images.

Discussion

In the present study, we found SCM_H in 80% of the NPSLE patients using high-resolution T1WIs at 7 Tesla. Furthermore, SCME was found on the contrast-enhanced T1WIs in 60% of NPSLE patients. These findings suggesting microvascular thrombi or inflammation were significantly more frequent in the NPSLE patients than the SLE patients without NPSLE.

SCM_H were thought to indicate microvascular thrombi associated with coagulopathy or inflammation because SCM_H were detected along with medullary arteries/veins and thrombi often cause high-intensity signals on T1W1. In addition, SCME indicated microvascular inflammation because SCME reflected the increase of permeability of blood-brain barrier. The present study suggests that SCM_H and SCME at 7 Tesla MRI might be

early lesions that are not detected by conventional MRI and serve as useful indices to diagnose NPSLE with 7 Tesla MRI.

The pathogenesis of NPSLE has been thought to involve the impairment of microcirculation in the brain. Pathologically, the hyalinization of vessels, proliferation of endothelial cells, and gliosis in perivascular area have been detected in autopsies (15, 16). Sibbitt WL Jr., et al reported that microscopic pathological findings in the patients with fatal NPSLE were diverse in the post mortem analysis (17). Their findings included global ischemic changes, parenchymal edema, microhemorrhages, glial hyperplasia, diffuse neuronal/axonal loss, resolved cerebral infarction, microthromboemboli, blood vessel remodeling, acute cerebral infarction, and acute macrohemorrhages. These histopathological findings were thought to contain both acute and chronic changes. Consistent with these findings, some cases were thought to have relapsed NPSLE symptoms. In addition, myocardial infarction and infection were included in the causes of death in some cases. In this regard, determining which lesion was

responsible for the cause of death in the NPSLE patient seemed difficult. However, thromboembolism and hypercoagulability were suggested to be dominant mechanisms for fatal NPSLE based upon the histological findings of the frequent presence of arterial macro- and microthrombi, focal lesions of infarct and vascular remodeling, edema, hemorrhages, and glial hyperplasia.

Because the major pathogenesis of NPSLE has been thought to be vasculopathy or vasculitis, MRI is currently the most suitable modality to detect CNS lesions in NPSLE patients (7, 8, 18, 19). MRI is exceptionally sensitive for cerebral infarcts, CNS hemorrhage, and transverse myelitis in NPSLE. In fact, Sibbitt WL Jr, et al investigated the *pre mortem* cases of 14 patients with fatal NPSLE and reported the MRI findings in all cases (17). Their findings included small focal white matter lesions, cortical atrophy, ventricular dilation, cerebral edema, diffuse white matter abnormalities, focal atrophy, cerebral infarction, acute leukoencephalopathy, and intracranial hemorrhages. Those findings were drastic, widespread and very

prominent in the CNS. In comparison with those findings, the findings obtained with 7 Tesla MRI in our study were very minute. We think this difference between the study of Sibbitt WL Jr., et al (17) and ours could be attributed to the severity and history of the patients with NPSLE. All cases studied by Sibbitt WL Jr., et al were fatal and had severe SLE with a history of relapses. In contrast, the 5 cases of NPSLE in our study were new cases experiencing their first episodes of NPSLE and all cases improved. In this regard, we think that the findings obtained with 7 Tesla MRI in our study might indicate early microvascular events in NPSLE.

Luyendijk J., et al. reported that although MRI detected focal hyperintensities in the white matter in 49% of patients, MRI abnormalities were absent in 42% of the patients, despite signs and symptoms of NPSLE (12). It is possible that these authors could not detect small microvascular lesions by conventional MRI (0.5T, 1.5T, and 3T). **It is important to compare the CNS findings of the NPSLE patients at 7 Tesla MRI with those at 3 Tesla MRI. However, we did not perform this comparison in our**

study. It needs to be done in next step. We performed conventional MRI examination by 1.5 Tesla MRI on the same patients with NPSLE and could not detect the CNS findings obtained by 7 Tesla MRI. However, we cannot exclude the possibility that 3 Tesla MRI might detect the SCMH and SCME obtained by 7 Tesla MRI with the same methods of the present study. However, we assume that only 7 Tesla MRI can detect the SCMH and SCME shown in our study because both spatial resolution and signal-to-noise ratio are remarkably increased at 7 Tesla MRI and the prolongation of T1 relaxation at 7 Tesla MRI can augment the hyperintensity and contrast enhancement on T1W1 when compared with 3 Tesla MRI. In the present study, we detected small microvascular lesions by 7 Tesla MRI, which have never been detected by conventional MRI. Despite the small number of NPSLE cases, 7 Tesla MRI findings, such as SCMH on T1WIs were detected in 4 of 5 NPSLE patients (80%), which was significantly more frequent compared with the SLE patients without NPSLE. This result suggests that 7 Tesla MRI might be a useful tool to

distinguish the patients with NPSLE from the SLE patients without NPSLE.

To date, markers in serum or CSF to indicate NPSLE have been studied. The immune complexes induced by auto-antibodies are assumed to be the causes of the vasculopathy resulting in NPSLE (20). Among the auto-antibodies, anti-phospholipid antibodies were reported to be associated with cerebrovascular stroke in SLE patients (21, 22). Cytokines enhanced immunoreactions are also assumed to induce vasculitis in CNS. The IL-6 concentration in CSF has been reported to be a useful marker to evaluate NPSLE (23). In our study, the anti-cardiolipin antibody, anti-double-stranded DNA antibody, and lupus anticoagulant were not different between the SLE patients with NPSLE and those without NPSLE. The measurement of IL-6 in the CSF was incomplete in our study (data not shown). The SLEDAI, a disease activity index of SLE, was significantly associated with NPSLE in our study. However, SLEDAI included 8 of 24

scoring items related to NPSLE and vasculitis. Consequently, the SLEDAI score was expected to be associated with NPSLE (24).

The early recognition and evaluation of NPSLE is critically important as NPSLE represents 7–13 % of deaths from SLE (6). Conventional MRI is valuable in detecting CNS lesion in acute focal NPSLE manifestations.

However, detecting the lesions responsible for NPSLE in all cases is difficult. To date, there have been reports that various nonspecific findings were found in the NPSLE patients, however, no CNS findings by conventional MRI were detected in the NPSLE patients. Nomura et al. reported that 38 of 100 SLE patients without neurological deficits showed an abnormality in the CNS detected by 1.0 Tesla MRI (25). These findings were thought to include subclinical lesions of NPSLE and nonspecific lesions unrelated to the pathogenesis of SLE. In this regard, to prevent deaths from NPSLE, we need to detect the early lesions responsible for NPSLE by distinguishing them from nonspecific findings. The present study demonstrated that SCMH and SCME on T1WIs at 7 Tesla were

significantly frequent in the patients with NPSLE compared with the SLE patients without NPSLE.

In conclusion, high-resolution T1WIs at 7 Tesla **detects** minute findings indicating intracerebral microvascular lesions in patients with NPSLE.

Seven Tesla MRI might therefore be a useful tool to diagnose NPSLE in the early stages.

Acknowledgements

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Table 1.

Clinical characteristics and imaging findings in NPSLE and non-NPSLE patients

		NPSLE (n = 5)	Non-NPSLE (n = 15)	<i>p</i> -value*
Demographics				
Women	(%)	4 (80)	13 (87)	0.718
Age	(median)	15–39 (29)	16–54 (35.5)	0.114
SLEDAI	(median)	8–26 (18)	0–24 (10)	0.023
Serum				
dsDNA-Ab	(median)	3.5–400 (36.5)	6.4–394.2 (54.9)	0.860
Sm-Ab	(median)	2.6–113.3 (17.4)	0.6–153.3 (8.5)	0.662
CL-Ab	(median)	2.1–26.3 (24.3)	1.2–50.8 (17.3)	0.667
LA	(median)	0.96–1.19 (0.98)	0.88–2.15 (1.03)	0.526
7 Tesla MRI				
SCMH	(%)	4 (80)	1 (7)	0.001
SCME	(%)	3 (60)	0 (0)	0.001
Infarct	(%)	1 (20)	3 (20)	1.000
DWMH	(%)	1 (20)	4 (27)	0.766

anti-cardiolipin antibody; L-Ab, anti-double-stranded DNA antibody; dsDNA-Ab, deep white matter hyperintensity; DWMH, interleukin-6; IL6, lupus anticoagulant; LA, neuropsychiatric SLE; NP-SLE, subcortical/cortical micro-enhancement; SCME, subcortical/cortical micro-hyperintensity; SCMH, systemic lupus erythematosus; SLE, SLE disease activity index; SLEDAI, anti-Smith antibody; Sm-Ab, *Fisher's exact test or Mann-Whitney's test

Figure legends

Figure 1: Subcortical/cortical micro-hyperintensity (SCMH) in 7 Tesla MRI Images.

On high-resolution T1WIs at 7 Tesla, minute punctate/linear hyper-intense lesions were found in subcortical areas in the NPSLE patient (39 year-old woman)(yellow arrows). Panel a and b, T1WIs; panel c and d, CE-T1WIs; panel e and f, T2WIs.

Figure 2: Subcortical/cortical micro-enhancement (SCME) in 7 Tesla MRI Images.

On high-resolution contrast-enhanced T1WIs, minute punctate enhanced lesions were found in cortical and subcortical areas of the NPSLE patients (orange arrows). Panel a and b, T1WIs; panel c and d, CE-T1WIs; panel e and f, T2WIs; panel a, c, e, 34 year-old woman; panel b, d, f, 15 year-old woman.