Magnetic Resonance Imaging Findings in the Brains of Patients with CADASIL.

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Abstract

Cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an inherited microangiopathy caused by mutations in the Notch3 gene. Typical findings from magnetic resonance imaging (MRI) include multiple subcortical lacunes, extensive white matter change and multiple cerebral microbleeds (CMBs). Whereas MRI findings are well described in Caucasian patients with CADASIL. There is a paucity of data on Asian patients. We aim to characterized imaging findings in Asian patients with CADASIL. The study population comprised 73 patients who underwent brain MRI between March 2012 and May 2013. T1-weighted image, susceptibility weighted image (SWI), and fluid attenuated inversion recovery (FLAIR) images were analyzed by visual inspection. Clinical information at time of imaging was available for all patients. The mean age of patients (44 men, 29 women) was 63.2±11.8 (SD). In patients with CADASIL, lacunes (76.7%, 56 of 73), CMBs (74%, 54 of 73), and area of white mater hyperintensities (98.6%, 72 of 73) were observed. Lacunes, CMBs, and WMHs were located predominantly in the cortical-subcortical lesion (57.5%, 54.8%, and 98.6%, respectively). These findings suggest that cortical-subcortical area is the most frequently injured area of brain in CADASIL. Further studies are needed to validate our findings. **(J Med Life Sci 2014;11(1):82-86)**

Key Words : Cerebral Autosomal-dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL), Lacunes, Cerebral Microbleeds (CMBs), White Matter Change, Cortical-subcortical Area.

Introduction

Cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an inherited microangiopathy caused by mutations in the Notch3 gene[1]. The main clinical manifestations are recurrent stroke, cognitive decline, chronic headache, mood disturbances, and seizure[2,3]. Magnetic resonance imaging (MRI) is crucial in the diagnosis of CADASIL. Typical MRI findings include multiple subcortical lacunes, extensive white matter change, and multiple cerebral microbleeds (CMBs)[4,5].

There seems to be some difference between Caucasian patients with CADASIL and East Asian patients concerning clinical phenotypes and neuroimaging features. East Asian patients have higher rates of intracranial hemorrhage (ICH) than Caucasian patients[6-8]. Also, hyperintensities of the anterior temporal pole, considered a characteristic magnetic resonance imaging (MRI) feature in CADASIL, are found less often in East Asian patients[6-8]. Although the profile of MRI findings in CADASIL has been described previously for Caucasians, those of Asian patients has not been thoroughly evaluated. We performed a detailed analysis of the frequency and distribution pattern of lacunes, CMBs, and WMHs to characterize brain MRI findings in East Asian patients with CADASIL.

Methods

Between April 2012and December 2013, 73consecutive patients with genetically confirmed CADASIL were enrolled. The vascular risk factors were recorded, including hypertension, diabetes mellitus, and hypercholesterolemia. Hypertension was defined as blood pressure > 140/90 mmHg on different occasions or use of an antihypertensive agent. Diabetes mellitus was defined as fasting glucose level ≥ 126 mg/dl or PP2 test level ≥ 200 mg/dl or use of antidiabetes medication. Hypercholesterolemia was defined as total serum cholesterol level > 240mg/dl. This study was approved by the institutional review board and informed

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consent was obtained from patients.

All scan were acquired on a 3T MRI scanner (Achieva, Philips Healthcare, Best, the Netherlands) by using an 32-channerl array head coil. A volume isotrophic TSE (turbo spin echo) acquisition (VISTA) technique was used for 3D FLAIR imaging. The paremeters for 3D FLAIR imaging were the following: TR/TE, 4800/320 ms; TI, 1650 ms, turbo factor, 240; spatial resolution, 1x1x1mm; reconstructed resolution, 1x1x0.5mm; and SENSE factor;5. The acquisition time for 3D FLAIR was about 6minutes 48 seconds. A 3D T1-weighted turbo field echo (TFE) acquisition technique was used for 3D T1-weighted imaging. The parameters for 3D T1 TFE were the following; TR/TE, 8/4 ms; flip angle, 15°, spatial resolution, 1x1x1mm; reconstructed resolution, 1x1x0.5mm; and SENSE factor;2. The acquisition time for 3D TFE was 5 minutes. Susceptibility weighted imaging (SWI) was performed for evaluation of microbleeds. The detailed image parameters for SWI were as follows: flow-compensated three-dimensional gradient-echo sequence; TR/TE, 15/21 ms; flip angle, 15°; FOV, 210 × 210 mm; matrix, 280 × 280; section thickness, 2 mm; slab thickness, 150 mm; SENSE factor;2, and total acquisition time, 2 min 51 s. Axial TSE T2-weighted imaging was acquired (TR/TE. 3200/80 ms).

Lacunes were defined as parenchymal defect not extending to the cortical gray matter with a signal intensity of CSF in all sequences and more than 2 mm in diameter The lesions located in the lower third of the corpus striatum of the basal ganglia were excluded[16]. Cerebral microbleeds (CMB) were defined as focal areas of round signal loss on T2*-weighted gradient echo planar images with a diameter of less than 10 mm[17]. The total number of CMBs was manually countered by two observers (J.S.L., C.K.). Areas of symmetric hypointensity in the basal ganglia were excluded. WMHs were scored by two raters (J.S.L., C.K.), using the semiquantitative rating scale devised and validated by Scheltens et al[9]. For each region, a score of 0 to 6 is assigned according to the following scale: 0 = absent; 1 = up to five lesions of 〈3 mm diameter; 2 = six or more lesions of 〈3 mm; 3 = up to five lesions of 4 to 10 mm in diameter; 4 = six or more lesions of 4 to 10 mm; 5 = one or more lesions 〉10 mm in size; and 6 = confluent hyperintensity. In addition, frontal and occipital periventricular "caps" and periventricular "bands" are scored: 0 5 absent; 1 = 0 to 5 mm; 2 = 〉5 mm. The Scheltens' scale was modified for this study by the addition of three further anatomic regions for assessment: the corpus callosum, the external capsule－internal capsule region, and the anterior-posterior temporal lobe. The posterior margin of the amygdala was taken as the boundary between anterior and posterior temporal lobe[10, 11].

Results

Details of demographics of the patients with CADASIL are presented in Table 1. Of the 73 patients, 44 were men (60.3%). The mean age of the patients was 63.2±11.8 years. Among the 66 patients who were diagnosed genetically, 62 patients (85.0%) had a R544C mutation, followed by R578C in 2 patients (2.7%) and R75P in 2 patients (2.7%). Sixty two subjects were symptomatic and eleven were asymptomatic (15.1%).

Table 1. Patient demographics

variable	n=73
Male	44(60.3%)
Age (years±SD)	63.2±11.8
Hypertension	45 (61.6%)
Diabetes Mellitus	10 (13.7%)
Hypercholesterolemia	20(27.4%)
Current or previous smoking	28 (38.4%)
Atrial fibrillation	3(4.1%)

Data are mean±SD or n(%) values.

Lacunes were present in 56 (76.7%) of the patients (Table 2). Lacunes were observed in cortical-subcortical regions in 42 patients (57.5%), in the basal ganglia in 31 patients (42.5%), in the thalamus in 17 patients (23.3%), in the brainstem in 18 patients (24.7%), and in the cerebellum in 5 patients (6.3%).

Table 2. Frequencies of CMBs, lacunes, and WMHs (n=73)

locations	CMBs	Lacunes	WMHs
Any location	54 (74.0)	56 (76.7)	72 (98.6)
Subcortical-cortical	40 (54.8)	42 (57.5)	72 (98.6)
Thalamus	38 (52.1)	17 (23.3)	46 (63.0)
Basal ganglia	27 (37.0)	31 (42.5)	51 (69.9)
Cerebellum	16 (21.9)	5 (6.3)	20 (27.4)
Brainstem	20 (27.4)	18 (24.7)	37 (50.7)

values are n(%). CMBs cerebral microbleeds; WMHs white matter hyperintensities.

WMHs were present in 72 (98.6%) of the patients (Figure. A-C). WMHs were observed in cortical-subcortical regions in 72 patients (98.6%), in the basal ganglia in 51 patients (69.9%), in the thalamus in 46 patients (63.0%), in the brainstem in 37 patients (50.7%), and in the cerebellum in 20 patients (27.4%).

CMBs were present in 54 (74.0%) of the patients (Figure. D-F). CMBs were observed in cortical-subcortical regions in 40 patients (54.8%), in the basal ganglia in 27 patients (37.0%), in the thalamus in 38 patients (52.1%), in the brainstem in 20 patients (27.4%), and in the cerebellum in 16 patients (21.9%).

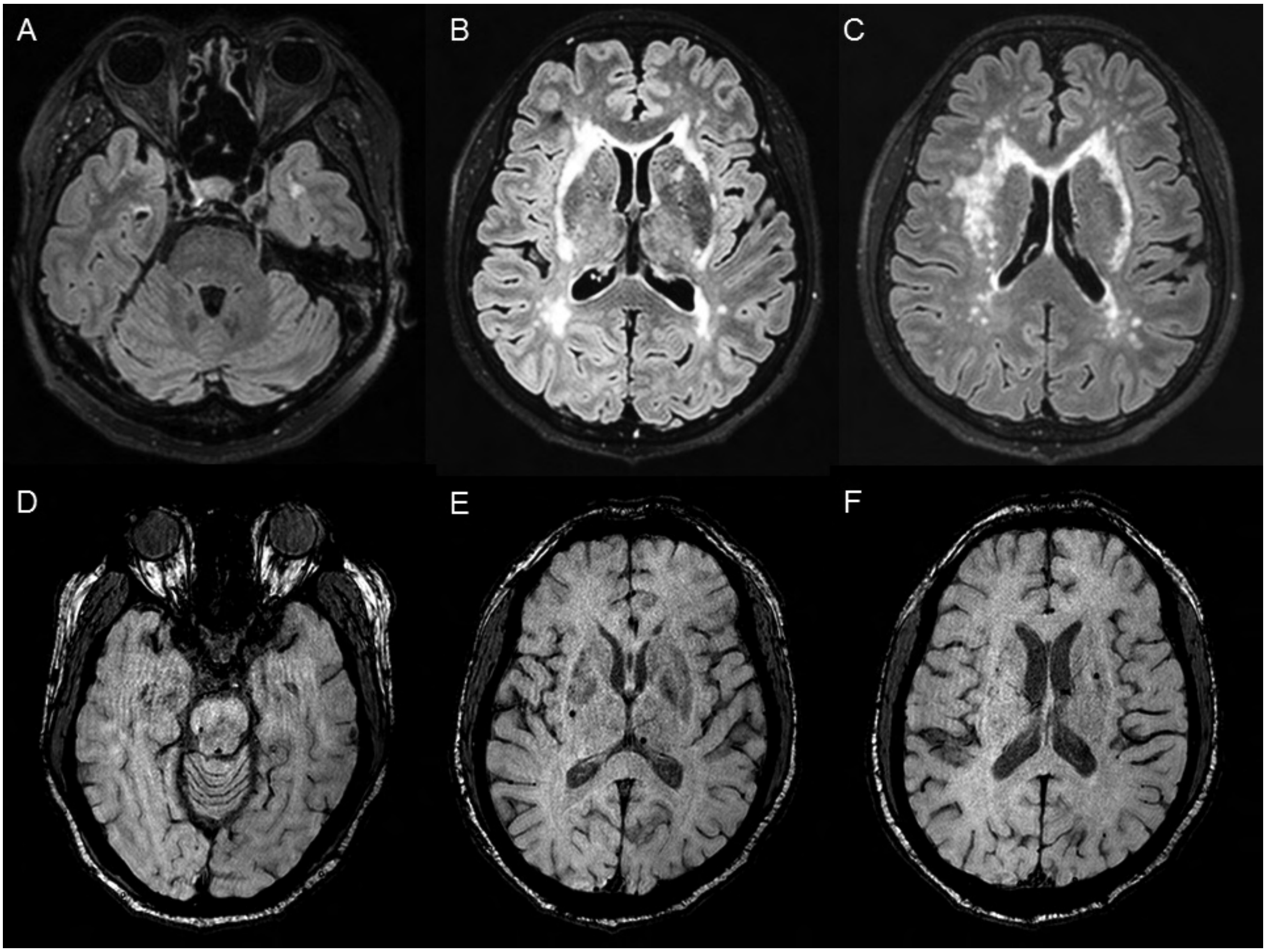

Figure 1. Figure. Fluid-attenuated inversion recovery (FLAIR) image and Susceptibility weighted imaging (SWI) in the patients with CADASIL showing periventricular and deep white matter hyperintensities (A-C) and cerebral microbleeds (D-E).

Discussion

We found that lacunes, CMBs, and WMHs were most common in the cortico-subcortical region in CADASIL. CMBs had similar occurrence indices in the cortico-subcortical region (54.8%) and the thalamus (52.1%). Basal ganglia were the second most common location for lacunes (42.5%). The lowest occurrence index of lacunes was observed in the cerebellum. This findings has never been elucidate in non-Caucasian patients with CADASIL, though it has been previously reported[4].

Lacunes were presently observed in 76.7% of patients on T1-weighted MRI. The frequency of lacunes ranges from 72.5% to 95.9% in Caucasian CADSIL cohort, as reported previously[12,13]. The prevalence of hypertension in our study was relatively high (61.6%) compared with the previous studies (7.5%–27%)[14-16]. The most frequent locations of lacunes were the cortico-subcortical lesion (57.5%) and basal ganglia (42.5%), similar to previous descriptions[12-16]. CMBs were found in 74.0% of patients on SWI. A prior study reported CMBs in 11 (69%) of 16 patients with CADASIL[17]. Except for this study, the reported frequency of CMBs in patients with CADASIL on T2*-weighted gradient echo sequences ranged from 25% to 35%[14,15]. The most frequent locations of CMBs were the cortico-subcortical lesion (54.8%) and thalamus (52.1%), similar to previous descriptions[14,15,17]. With respect to the WMHs, the cortico-subcortical lesion (98.6%), basal ganglia (69.9%) and thalamus (63.0%) had higher indices than the brain stem (50.7%) and cerebellum (27.4%).

In our study, the occurrence index of the CMBs was found to be highest in the cortico-subcortical region. This is important, because CMBs is known to have different etiologies depending on the basis of their location in the brain. Hypertensive arteriopathy is associated with CMBs in basal ganglia, thalamus, and brainstem[18]. However, isolated lobar CMBs were more closely linked to Apo E genotyping[19]. Therefore, CADASIL is characterized by CMBs in cortico-subcortical distribution. However, the mean patient age in our study was 63.2 years, making a significant admixture of Cerebral Amyloid Angiopathy (CAA). It is known to show a lobar distribution of CMBs[18].

Our study was subject to several limitations. First, this study was cross-sectional. Second, R544C in exon 11 accounted for 85.0% of the mutations. Thus, our findings may not be fully representative of the wider CADASIL population.

In conclusion, our results suggest that cortical-subcortical area is the most frequently injured area of brain in CADASIL. Further studies are needed to elucidate specific MRI pattern in patients with CADASIL.

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Disclosure of conflict of interest

The authors declare no financial or other conflict of interest.

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