Can talamus diffusions on magnetic resonance imaging predict the differential diagnosis of multiple sclerosis from ischemic cerebral small vessel disease when the white matter is involved?

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Aims and objectives

Multiple sclerosis (MS) plaques and ischemic gliotic foci of cerebral small vessel disease (CSVD) located in the cerebral white matter may cause similar appearance on MRI, and clinical, laboratory and conventional MRI findings are sometimes insufficient to differentiate these two pathological entities.

Small penetrating artery infarctions account for approximately 20-25% of all ischemic strokes [1]. Fibrohyalinosis affecting the small penetrating arteries cause ischemic lesions in the deep gray matter together with the ischemic gliotic foci in the white matter, since penetrating arteries are located in the cerebral white matter and deep gray matter. On the other hand, MS is primarily due to the deterioration of myelin sheath and oligodendrocytes. However, the pathologic events causing degeneration of axons may affect the small arteries and may lead to infarction in advanced stages of the disease. Periventricular and pericallosal white matter and corpus callosum are most commonly involved in MS. But in recent years, with new methods of MRI, it was understood that the pathological process is not limited to the areas identified by conventional MRI sequences, but more widespread [2, 3]. From this perspective, deep gray matter areas may be expected to be affected in MS. However, this influence is likely to be significantly lower than in case of CSVD, since CSVD is a primary vascular disease unlike MS in which vascular structures are secondarily involved.

The aim of this study was to identify the microstructural changes in normal-appearing thalami on conventional MRI using DWI, and to determine the difference between MS and CSVD quantitatively with the apparent diffusion coefficient (ADC) values. According to our hypothesis the ADC values of thalamus might be different from each other since the degree of arterial involvement in these two pathologies are different. We expected to obtain data to distinguish these two pathologies even though the white matter lesions appear the same.
Methods and materials

This prospective case-control study was approved by the Ethics Committee of Cumhuriyet University School of Medicine (No: 2007-4/8. Decided May 1, 2007).

50 patients with CSVD and 35 patients with MS who underwent MRI in our radiology department between May 2007 and April 2013 were included in our study. Since there is significant difference between CSVD and MS patients in terms of age and gender, two different control groups which are statistically comparable with patient groups were conducted. The control groups constituted of 50 patients for CSVD group, and 35 patients for MS group who were sent to our department for different reasons and had normal findings on conventional MRI.

Revised McDonald criteria were used for the diagnosis of MS. 31 (89%) of MS patients were previously diagnosed and were undergone MRI before at least once. 4 (11%) patients were admitted with the suspicion of MS and diagnosed as MS with clinical, laboratory and imaging findings. MS patients were included in the study regardless of the clinical subtypes and stages of the disease. Patients who did not have the definite diagnosis of MS throughout the course of the study were excluded.

Since standard diagnostic criteria do not exist for CSVD, the patients were selected among those who had multiple hyperintense foci in the cerebral white matter on conventional T2-weighted and FLAIR MR images. The presence of some risk factors such as hypertension, diabetes mellitus, dyslipidemia, history of smoking was searched in the selection of patients, and among these patients whose clinical, laboratory and imaging findings could not rule out such pathologies as thromboembolic disease, vasculitis, infection, demyelinating disease, trauma and intracranial space-occupying lesions were excluded from the study.

14 male and 21 female subjects whose ages ranged between 21 and 53 composed the control group of MS patients. On the other hand, the control group of CSVD patients consisted of 26 male and 24 female individuals whose ages ranged from 29 to 76. There were no history of any cardiac, metabolic or hematologic disorder in the control groups. Patients and controls were informed about the study. No special preparation before the examination was done.

Image Acquisition

MR imaging was done with a 1.5 tesla MR unit using standard head coils. The conventional MRI protocol included axial, coronal and sagittal T1-weighted SE (TR: 550ms; TE: 15ms; FA: 70/180; NEX: 1.2; FOV: 180 x 220 mm; matrix: 160 x 256; slice thickness: 5mm; interslice gap: 1 mm); axial and sagittal T2-weighted fast SE (TR: 5000, TE: 94; FA: 90/180; NEX: 2; FOV: 180 x 220 mm; matrix: 224 x 320; slice thickness:
Diffusion-weighted images were acquired using EP imaging sequences (TR: 5000 ms; TE: 130 ms; FA: 90/180; NEX: 1; FOV: 270 x 320 mm; matrix: 128 x 128; slice thickness: 5 mm; interslice gap: 2 mm; b value: 0 and 1000 s/mm$^2$). Diffusion gradients were applied in three orthogonal planes in order to measure diffusion in three planes (x, y and z) (Fig 1. a-d).

Postprocessing and Image Analysis

Thalamus is selected for the measurement of ADC values of deep gray matter containing penetrating arteries, since the area of thalamus is larger than basal ganglia and measurement without contamination is more easily provided. Besides, Virchow-Robin spaces which may change ADC numbers are common in basal ganglia. The presence of these spaces is rare in thalamus. Thus, thalamus is considered to be the most suitable site to measure ADCs.

DW images are transferred to a separate workstation after the observation of absence of any signal change in conventional MR images of the thalami of both patient and control groups. Direction-independent isotropic diffusion images are obtained by postprocessing of diffusion images acquired from x, y and z axes (Fig 1. e). ADC maps were constructed via substraction of SE EP b=0 images from these isotropic images (Fig 1. f).

The regions of interest (ROIs), the areas from where the ADC values quantitatively measured on ADC maps, were selected from the central portions of thalami far away enough from the ventricles medially and internal capsules laterally to avoid contamination of these tissues. Standard oval ROIs, compatible with the anatomic shape of thalamus, with an area of 0.5 cm$^2$ which were oriented parallel to the long axis of thalamus were used (Fig 1. f). ADC values of right and left thalami were calculated by the MR device automatically for each case. The difference between thalamic diffusions of patient and control groups was determined.

Statistical Analysis

The data obtained were analysed using SPSS software. The difference between the ages, ADC values of right and left thalami and mean ADC values of patient and control groups was analysed with the t-test for the significance of the difference of the means. The chi-square test was used for the comparison of the gender of patient and control groups. p values less than 0.05 were considered to be statistically significant.
Fig. 1: Acquisition of axial DW images and ADC maps. a. T2-weighted axial EP SE image without application of diffusion gradient. b-d. Images obtained in three orthogonal planes with the application of diffusion gradients in x (b), y (c) and z (d) axes. e. Direction-independent isotropic image formed using DW images obtained from three directions. f. ADC map and standard ROIs placed on thalami for quantitative measurement of ADC values.

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Results

52 % (n:26) of patients with CSVD were women, 48% (n:24) were men, and their mean age was 58.7 ± 12.6 (29-80). 48% (n:24) of patients in the control group of CSVD were women, and 52% (n:26) were men with a mean age of 58.1 ± 11.7 (29-80). The difference between the patient and control groups in terms of age (p=0.842) and gender (p=0.806) was not statistically significant.

On the other hand, 71% (n:25), of patients with MS were women and 29% (n:10) were men, with a mean age of 36.1 ± 8.5 (21-52). 21(60%) women and 14 (40%) men with a mean age of 35.5 ± 8.3 (21-53) consisted the control group of MS. No statistically significant difference was found between these two groups in terms of age(p=0.755) and gender (p=0.450).

On the basis of ADC values, there was no statistically significant difference between right and left thalami in patient and control groups (p>0.05) (Table).

Table: Mean ADC numbers in patients with CSVD; MS and controls

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Mean ADC-R</th>
<th>Mean ADC-L</th>
<th>Mean ADC-M</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSVD</td>
<td>50</td>
<td>0.98 ± 0.17 X 10^{-3}</td>
<td>0.99 ± 0.16 X 10^{-3}</td>
<td>0.99 ± 0.16 X 10^{-3}</td>
</tr>
<tr>
<td>CSVD control</td>
<td>50</td>
<td>0.78 ± 0.07 X 10^{-3}</td>
<td>0.78 ± 0.08 X 10^{-3}</td>
<td>0.78 ± 0.06 X 10^{-3}</td>
</tr>
<tr>
<td>p</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>MS</td>
<td>35</td>
<td>0.79 ± 0.09 X 10^{-3}</td>
<td>0.77 ± 0.08 X 10^{-3}</td>
<td>0.78 ± 0.08 X 10^{-3}</td>
</tr>
<tr>
<td>MS control</td>
<td>35</td>
<td>0.77 ± 0.09 X 10^{-3}</td>
<td>0.74 ± 0.08 X 10^{-3}</td>
<td>0.75 ± 0.08 X 10^{-3}</td>
</tr>
<tr>
<td>p</td>
<td>p=0.317</td>
<td>p=0.108</td>
<td>p=0.160</td>
<td></td>
</tr>
</tbody>
</table>

CSVD: Cerebral small vessel disease, MS: multiple sclerosis , ADC-R: apparent diffusion coefficient of the right thalamus , ADC-L: apparent diffusion coefficient of the left thalamus , ADC-M: mean apparent diffusion coefficient.
All patients with CSVD and MS involved in the study showed multiple T2-hyperintense lesions in bilateral cerebral deep white matter, which is more prominent in the periventricular regions. (Figures 1 and 2).

There was statistically significant difference in mean thalamic ADC values ($\text{ADC}_{\text{mean}}$) between CSVD patients and their controls ($p<0.001$). On the other hand, there was no statistically significant difference between patients with MS and their controls in terms of mean thalamic ADC values ($\text{ADC}_{\text{mean}}$) ($p=0.160$).
Fig. 2: MR images of a patient with CSVD obtained from the level of lateral ventricles. T2-weighted (a) and FLAIR (b) images reveal multiple hyperintense foci in periventricular and deep white matter. Thalami appear normal on T2-weighted (c) and FLAIR (d) images, as well as on ADC map.

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Fig. 3: MR images of a patient with MS. T2-weighted (a) and FLAIR (b) images demonstrate multiple periventricular and deep white matter hyperintensities. Thalami show normal signal on T2-weighted (c) and FLAIR (d) images and on ADC map (e).

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Conclusion

CSVD, MS, widened Virchow-Robin areas, migraine, infarction, vasculitides, hypoxic-ischemic changes, hemorrhagic foci, inflammatory disorders, central pontine and extrapontine myelinolysis, metastases, changes secondary to radiotherapy and chemotherapy, neurometabolic diseases, degenerative diseases of the central nervous system, eclampsia and many other pathologies may manifest as T2-hyperintense lesions in the brain. Dilated Virchow-Robin spaces, CSVD and MS are the most common causes of these lesions. While some of these T2-hyperintense foci are the cause of the clinical signs and symptoms, others are incidentally found and may lead to challenges in diagnosis. CSVD and MS are the most common pathologies that require differential diagnosis showing T2-hyperintensities. Although clinical and laboratory findings provide important data in differential diagnosis, they may not always be sufficient in equivocal cases.

Age is an important parameter clinically, but it may be misleading. Although MS is primarily a disease of young adults, it may affect all age groups from infancy to eighth decade [4]. On the other hand, CSVD is more frequently seen in advanced age, but 3-17% of patients are young, therefore, occurrence of lesions of these two pathologies in the same age group is not rare [5]. Diffusion studies showed increased diffusion in T2-hyperintense areas in CSVD and MS [6-8], which is also nonspecific.

In last decades, normal-appearing white matter is being investigated. Brown et al. [9] examined white matter which showed normal intensity on conventional MRI in CSVD patients histologically in their autopsy series, and they found decreased vascularity. Similar studies were done with DWI in MS, and obtained ADC values showed increased diffusion which supported demyelination in normal-appearing white matter [3].

Oliveira-Filho et al. [5] found penetrating artery infarctions in normal-appearing thalami and basal ganglia of patients with CSVD using DWI. They reported that these lesions which are missed with T2-weighted and FLAIR images were either acute or too small to be seen. We found increased diffusion in thalami in CSVD, which is in concordance with the findings of Oliveira-Filho et al. [5], and which shows that there are in fact some microstructural changes in normal-appearing thalami on conventional MRI. This is probably due to tissue damage resulting from penetrating artery involvement, gliosis and increased extracellular fluid motion as a result. In contrast to our study, Chun et al. [10] found normal thalamic diffusion in 9 individuals who had less than five small focal ischemic white matter lesions in their study to evaluate age-related diffusion changes in 38 subjects. However, healthy subjects and patients were both included in their study, and the number of patients and lesions were too limited to exemplify CSVD with white matter T2-hyperintensities.

Mean ADC values that we obtained from MS patients and matched controls were within normal limits similar to Helenius et al.’s [8] results in normal subjects in different age
groups. We can interpret this result as; normal-appearing thalamus is not affected from demyelination to a degree to change ADC values, or no small vessel involvement is present in MS, or if present, it is not to a degree to affect ADC numbers. Some reports, such as Griffin et al.'s [11] and Ciccarelli et al.'s [12], support our findings, whereas some others such as a diffusion tensor imaging study by Tovar-Moll et al., revealed thalamic involvement, which may be attributable to the lesion load or subtype of MS patients as well as the higher resolution of high-field MR scanner [13-15].

This study revealed diffusion differences in normal-appearing thalami between CSVD and MS with similar T2-hyperintense lesions on conventional MRI. DWI may contribute to radiologic differentiation of equivocal cases. However, there are some limitations of our study: Patients were included in our study irrespective of the subtype of MS, and the phase of the disease which might affect the results was also ignored. Further investigations with increased specificity and reproducibility are needed.
References


