Clinical manifestations and imaging features of white matter demyelination in older patients

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Abstract

Objective: To investigate the clinical manifestations and imaging features of older patients with white matter demyelination diagnosed by magnetic resonance imaging (MRI).

Methods: Ninety-six patients with leukoaraiosis diagnosed by MRI were divided by their clinical diagnoses into a demyelinating group (40 cases) and a non-demyelinating group (56 cases). The imaging and clinical features of the patients in the two groups were analyzed.

Results: Compared with the non-demyelinating group, there were significantly more women in the demyelinating group than men. There was no significant difference in age between the two groups. Of the 37 cases who had an imaging report of “white matter demyelination and multiple sclerosis,” 36 cases had a clinical diagnosis in accordance with white matter demyelination (97.3%). Of the 59 cases who had an imaging report of “white matter demyelination”, only four cases had a clinical diagnosis in accordance with demyelination (6.8%).

Conclusion: In older patients with headaches, vertigo, other head symptoms, and unilateral numbness as the chief complaints, a clinical diagnosis of demyelinating disease is very unlikely when the imaging report states white matter demyelination only.

Keywords
Magnetic resonance imaging, demyelinating degeneration of white matter, headache, dizziness, paroxysmal numbness and weakness of unilateral limb, imaging report, clinical diagnosis

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Introduction

Among older patients who complain of head and limb discomfort in the neurology outpatient department, many are worried about the occurrence of organic brain
diseases, such as stroke or brain tumors. In magnetic resonance imaging (MRI) examinations, many patients have dotlike or patchy equal T1 or long T1 signals, high T2 signals, and high fluid-attenuated inversion recovery (FLAIR) signals, with the imaging reports stating “white matter demyelination.” Because of a general misunderstanding of the concept of demyelination, some patients associate their symptoms with the imaging results. In some cases, this causes patients to experience psychological reactions, such as tension, anxiety, and fear, which can affect their daily work and life.

The purpose of this study was to retrospectively analyze the clinical manifestations and imaging features of older patients who were diagnosed with white matter demyelination by MRI, to provide a basis for clinicians to make diagnoses based on patients’ clinical manifestations and examination results. In this way, we hope to avoid and relieve unnecessary psychological burdens on these patients.

**Materials and methods**

**Subjects**

Patients with brain MRI reports diagnosing “mild white matter demyelination,” “white matter demyelination,” or “white matter demyelination and multiple sclerosis (MS),” together with the re-examination of the MR images in the outpatient department of our hospital from January 2014 to July 2018, were included in the study. These patients were divided according to their clinical diagnosis into a demyelinating group and a non-demyelinating group. The 2017 McDonald criteria for the diagnosis of MS were used to diagnose MS and clinical isolated syndrome (CIS). To diagnose neuromyelitis optica spectrum disorders (NMOSD), the 2015 international consensus diagnostic criteria for neuromyelitis disorders were used. The present study was approved by the ethics committee of our institute (project no. IRB00006761-m2019097) and informed consent was signed by all patients.

**Inclusion and exclusion criteria**

Inclusion criteria: (1) patients with white matter demyelination diagnosed by brain MRI; (2) patients ≥60 years old; and (3) patients with signed informed consent. Exclusion criteria: (1) patients with severe infections; (2) patients with severe cardiac, hepatic, and/or renal dysfunction; (3) patients with late-stage malignant tumors; (4) patients without thorough brain MRI results; and (5) patients with incomplete case data.

**Brain MRI analysis**

With an observation of high FLAIR signals, the periventricular white matter and deep white matter were graded using the Fazekas scale. The two scores were then added together. Scores of 1 to 2 were regarded as mild, while scores of 3 to 4 were regarded as moderate. In the periventricular region, 0 means no lesion, 1 refers to cap-like or pencil-like lamellar lesions, 2 refers to a lesion presenting as a smooth halo, and 3 refers to irregular white matter hyperintensities extending to the deep white matter. In the deep white matter, 0 means no lesion, 1 refers to a dotlike lesion, 2 refers to a lesion starting to fuse, and 3 refers to a lesion with a large area of fusion.

A 3.0 T MR unit was used for imaging. All patients underwent cranial MRI at the time of admission, which included T1-weighted imaging, T2-weighted imaging, FLAIR, and diffusion-weighted imaging (DWI). In addition, some patients underwent susceptibility-weighted imaging (SWI; no abnormalities in SWI were observed). The first imaging report was
used to analyze all patients, and mainly targeted the T1, T2, and FLAIR descriptions.

**Statistical analysis**

The measurement data are expressed as means ± standard deviations, while count data are presented as percentages. The *W* test was used for normality tests, the *F* test was employed for analyzing the homogeneity of variance, and the *T* test was used for comparisons between two groups. Nonparametric testing was used to compare the mean values of samples that did not obey a normal distribution, or that obeyed a normal distribution but had different variances. The chi-squared test was used for count data. *P* < 0.05 was considered statistically significant.

**Results**

**General data**

As shown in Table 1, 96 patients who had brain MRI reports stating “mild white matter demyelination,” “white matter demyelination,” and “white matter demyelination and MS” together with the re-examination of the images were included in this study. The ages of the patients ranged from 60 to 74 years old. Patients were divided into a demyelinating group and a non-demyelinating group according to their clinical diagnoses. There were 40 patients in the demyelinating group (12 men and 28 women), with a mean age of 64.5 ± 3.3 years. There were 56 patients in the non-demyelinating group (30 men and 26 women), with a mean age of 65.5 ± 4.2 years. There were significantly

| Index                              | Demyelinating group | Non-demyelinating group | *P*  |
|------------------------------------|---------------------|--------------------------|------|
| *n*                                | 40                  | 56                       |      |
| Sex (male/female)                  | 12/28               | 30/26                    | 0.036|
| Age (years)                        | 64.5 ± 3.3          | 65.5 ± 4.2               | 0.212|
| Multiple sclerosis                 | 35                  |                          |      |
| Neuromyelitis optic spectrum disease| 3                   |                          |      |
| Clinical isolation syndrome        | 2                   |                          |      |
| Transient ischemic attack          | 19                  |                          |      |
| Anxiety/depressive state           | 13                  |                          |      |
| Benign paroxysmal positional vertigo| 4                   |                          |      |
| Sudden deafness                    | 4                   |                          |      |
| Fatigue-induced symptoms           | 4                   |                          |      |
| Parkinson’s disease                | 3                   |                          |      |
| Neurological tinnitus              | 3                   |                          |      |
| Ménière’s disease                  | 2                   |                          |      |
| Essential tremor                   | 2                   |                          |      |
| Facial paralysis                   | 1                   |                          |      |
| Cough syncope                      | 1                   |                          |      |
| Fazekas score = 1                  | 7                   | 7                        |      |
| Fazekas score = 2                  | 28                  | 48                       |      |
| Fazekas score = 3                  | 5                   | 1                        |      |
| Clinical recurrence or new symptoms| 1                   | 0                        |      |
| Dynamic changes in magnetic resonance | 11                  | 3                        |      |
more women in the demyelinating group than in the non-demyelinating group ($\chi^2 = 4.410, P = 0.036$). There was no significant difference in age between the two groups ($t = 1.256$).

**Clinical manifestations**

The most common clinical manifestations of patients in the demyelinating group were limb weakness, abnormal sensation, anesthesia, and decreased vision (Table 2). Patients in the demyelinating group also reported sphincter dysfunction, ataxia, dizziness, diplopia, nausea, dysarthria, vertigo, and vomiting. The most common clinical manifestations in the non-demyelinating group were vertigo, headaches, dizziness, and nausea (Table 2). Patients in this group also complained of vomiting, paroxysmal unilateral limb weakness, decreased hearing, tinnitus, tremors, paroxysmal unilateral limb numbness, weakness, slow actions, paroxysmal speech impairment, paroxysmal loss of consciousness, paroxysmal unilateral amaurosis, and peripheral facial paralysis. The first symptoms noted by each patient in the two groups are given in Table 3.

**Case histories**

In the demyelinating group, nine cases had been previously diagnosed with hyperlipidemia, three cases with hypertension, two with diabetes mellitus, one with renal

| Table 2. Clinical symptoms. |
|-----------------------------|
|                            |
| Demyelinating disease group | Non-demyelinating disease group |
| Weakness of the limbs       | 40                           | 0       |
| Paresthesia                 | 40                           | 0       |
| Anesthesia                  | 40                           | 0       |
| Vision loss                 | 37                           | 0       |
| Sphincter dysfunction       | 11                           | 0       |
| Ataxia                      | 4                            | 0       |
| Double vision               | 2                            | 0       |
| Dysarthria                  | 1                            | 0       |
| Vertigo                     | 1                            | 18      |
| Headache                    | 0                            | 16      |
| Dizziness                   | 4                            | 15      |
| Nausea                      | 2                            | 13      |
| Vomiting                    | 1                            | 8       |
| Paroxysmal limb weakness    | 0                            | 7       |
| Hearing loss                | 0                            | 6       |
| Tinnitus                    | 0                            | 4       |
| Tremor                      | 0                            | 4       |
| Weak paroxysmal limb numbness | 0                        | 3       |
| Slow movement               | 0                            | 3       |
| Paroxysmal speech adverse   | 0                            | 1       |
| Episodic loss of consciousness | 0                        | 1       |
| Paroxysmal monocular blackness | 0                        | 1       |
| Peripheral facial paralysis | 0                            | 1       |
| Imaging report of demyelination + multiple sclerosis | 36 | 1 |
| Imaging report of demyelination | 4 | 55 |
tubular acidosis, and 37 with one to eight episodes of neurological deficits from 2 to 39 years. In the non-demyelinating group, 16 cases had previously been diagnosed with hyperlipidemia, 11 with hypertension, eight with diabetes mellitus, and six with hyperhomocysteinemia. Four cases were smokers and one case had a history of carbon monoxide poisoning without sequelae. There was no history of alcoholism, brain injuries, stroke, or central nervous system infections in any of the patients.

**Auxiliary examinations**

In the demyelinating group, 40 cases had demyelinating lesions of the spinal cord by spinal MRI, three cases were positive for the aquaporin 4 (AQP4) antibody (37 cases were negative), and one case was positive for anti-SSA and anti-SSB antibodies (39 cases had no abnormalities in rheumatic immune blood tests). In the non-demyelinating group, 56 cases had carotid artery ultrasounds and brain magnetic resonance angiography (MRA) examinations. Seven cases had decreased high-frequency hearing in audiometry, and four cases were positive for benign paroxysmal positional vertigo. The Hamilton Anxiety Scale was performed in 13 cases.

**Brain MRI changes**

Figure 1 and Figure 2 show representative MRI scans from two patients. In the demyelinating group, four cases had subcortical round lesions, 36 cases had oval and patchy white matter lesions in the deep part of the brain lobes and the semioval center (lesions with fusions in five cases), 35 cases had lesions around or perpendicular to the lateral ventricle (at least five lesions), seven cases had patchy lesions in the brainstem, and one case had a patchy lesion in the cerebellum. Three cases had four to six dotlike lesions in the frontal, parietal, and temporal lobes; one case had three dotlike lesions in

| Initial symptoms | Demyelinating disease group | Non-demyelinating disease group |
|------------------|-----------------------------|---------------------------------|
| Numbness in one leg | 19                          | 0                               |
| Weakness of one leg | 9                           | 0                               |
| One measure of vision loss | 7                        | 0                               |
| Numbness of lower limbs | 4                        | 0                               |
| Weakness of lower limbs | 1                        | 0                               |
| Vertigo          | 0                           | 18                              |
| Headache         | 0                           | 10                              |
| Paroxysmal side limb weakness | 0                      | 7                               |
| Hearing loss     | 0                           | 4                               |
| Episodic limb numbness and weakness | 0              | 3                               |
| Tremor           | 0                           | 3                               |
| Tinnitus         | 0                           | 3                               |
| Slow             | 0                           | 2                               |
| Dizziness        | 0                           | 2                               |
| Paroxysmal speech is not good | 0                 | 1                               |
| Episodic loss of consciousness | 0              | 1                               |
| Paroxysmal monocular blackness | 0            | 1                               |
| Peripheral facial paralysis | 0                | 1                               |
| Total            | 40                          | 56                              |
the frontal lobe; and 33 cases had thin-layer lesions in the margin of the frontal and/or occipital angle. In the non-demyelinating group, five cases had three to six dotlike lesions in the frontal, parietal, temporal, and occipital lobes, and two cases had dotlike patchy lesions in the frontal and occipital lobes (four and seven lesions, respectively). Lesions in the frontal, parietal, temporal, and occipital lobes were found in six, four, four, and three cases, respectively, with Fazekas scores of 1. Thirty-eight cases had thin-layer lesions of the frontal and/or occipital angle, with dotlike lesions (three to nine lesions) of the frontal, parietal, temporal, and occipital lobes. Ten cases had thin-layer lesions of the frontal and occipital angle margins, with dotlike patchy lesions (five to nine lesions) of the frontal, parietal, temporal, and occipital lobes. Lesions in the frontal, parietal, temporal, and occipital lobes were found in 49, 34, 31, and 24 cases, respectively, with Fazekas scores of 2 and patchy lesion diameters of <0.9 cm. One case had thin-layer lesions of the frontal and occipital angle, with multiple dotlike patchy lesions and fusion in the center of the frontal, parietal, temporal, and occipital lobes, and the semioval center (Fazekas scores of 3). There was no significant difference in the incidence of thin-layer lesions in the frontal and/or occipital angle between the two groups ($\chi^2 = 0.468$). In addition, the DWI signals of all patients in the non-demyelinating group were normal, whereas two patients in the demyelinating group had high DWI signal.

In the non-demyelinating group, one case had a brain MRI similar to that of MS but was clinically diagnosed with an anxiety/depression status. The diagnosis of MS had been excluded through this patient’s clinical manifestations and dynamic re-examinations. The patient had no history of hypertension, diabetes mellitus, alcoholism, or smoking, but they did have a history of carbon monoxide poisoning. No abnormalities were found in the carotid ultrasound or brain MRA. There

Figure 1. Magnetic resonance images from a female patient, 63 years old, with a clinical diagnosis of sudden deafness and an imaging report of “white matter demyelination degeneration.” a: T2-weighted long-point signal in the parietal frontal lobe. b: Fluid-attenuated inversion recovery (FLAIR) parietal dotlike hypersignal. c: T1-weighted thin-layer long T1 signal at the edge of the dual frontal angle. d: T2-weighted phase-two frontal edge thin-layer long T2 signal. e: FLAIR phase hyperintensity signal on both frontal edges.
were no complaints of recognition dysfunction, with a normal score (28 score) in the Montreal Cognitive Assessment.

**MRI follow-ups**

In the demyelinating group, one case relapsed after 8 months, and the new and original lesions were partially reduced on brain MRI. In three cases without clinical relapse, new lesions in the semioval center were found on brain MRI after re-examination 1 year later, and the original focus was partially reduced. In another seven cases without clinical relapse, no new lesions were found in brain MRI at the 1-year re-examination, and the original lesions were partially reduced. In the remaining 29 cases without clinical relapse, no changes were found in brain MRI at the 1-year re-examination. A thin-layer lesion of the frontal angle margin was found in two cases. In one case without new-onset symptoms, a focus of lacunar infarction of the basal ganglia was found on brain MRI at the 1-year re-examination, with normal SWI phase.

**Clinical diagnoses**

In the demyelinating group, 35 cases were diagnosed with MS, with imaging reports of “white matter demyelination degeneration, multiple sclerosis.” Two cases each were diagnosed with NMOSD and CIS, with imaging reports of “mild white matter demyelination.” One case was diagnosed with optic neuromyelitis pedigreedisease, with an imaging report of “white matter demyelination and MS.” In the non-demyelinating group, the most common diagnosis was of transient ischemic attack. Patients in this group were also diagnosed with benign paroxysmal positional vertigo, sudden deafness, Parkinson’s disease, neurological tinnitus, Ménière’s disease, benign tremors, cough syncope, facial paralysis, anxiety/depression, and fatigue (Table 1). Furthermore, 56 patients had imaging reports stating “mild white
matter demyelination” or “white matter demyelination,” and one case had an imaging report of “white matter demyelination and MS.” In the 37 cases with imaging reports stating “white matter demyelination and MS,” 36 had a clinical diagnosis in accordance with white matter demyelination (97.3%), and in the 59 cases with imaging reports stating “mild white matter demyelination” or “white matter demyelination,” only four cases had a clinical diagnosis in accordance with demyelination (6.8%; \( \chi^2 = 76.656; P < 0.001 \)).

**Discussion**

Demyelinating diseases in neurology mainly include MS, NMOSD, acute disseminated encephalomyelitis, CIS, and other immune-mediated inflammatory demyelinating diseases. These diseases have mainly young and middle-aged onsets. The diagnosis of demyelinating diseases is based on clinical manifestations and a comprehensive range of auxiliary examinations, and is not merely based on the MRI diagnosis.\(^5\) Cerebral small vessel disease\(^6\) can also cause serious demyelination, a decline in cognitive function, and gait disorder, and with an increase in age, cerebral arteriosclerosis causes chronic ischemia. Some demyelination in MRI is a common physiological change that is observed in older individuals, and has no clinical significance. Ischemia, hypoxia, and poisoning, among other causes, can all lead to demyelination. For example, in the present study, one non-demyelinating case with a brain MRI similar to that of MS was clinically diagnosed with anxiety/depression status, and had a history of carbon monoxide poisoning. No new lesions were found by image re-examination in this patient, suggesting that the imaging changes might be related to poisoning.

The clinical manifestations of demyelinating diseases are complex and changeable in nature, with multiple lesions. Atypical cases or patients in the early phases of these diseases can be easily misdiagnosed.\(^7\) Chronic ischemia from arteriosclerosis can cause demyelination in older individuals, especially in patients with stroke risk factors. Mild white matter changes may not cause cognitive impairment.\(^8\) Clinically, for older patients in whom autoimmune demyelinating disease is excluded, it is important to focus on the risk factors for stroke as well as on the prevention and treatment of cerebrovascular diseases.\(^9\) In the present study, 10 patients with Fazekas scores of 2 had patchy lesions and normal scores in the Montreal Cognitive Assessment, but none of these patients had diagnoses in accordance with cerebrovascular disease.\(^10\)

There were some limitations in the current study. First, this was a retrospective study, rather than a randomized controlled trial, so there is a certain risk of bias. Second, this study was a single-center clinical study, with a small number of samples. Future studies should increase the sample size in a multi-center clinical study. Finally, the correlations between white matter demyelination on MRI images and patients’ clinical manifestations need further study.

In conclusion, a diagnosis of demyelinating disease requires a combination of clinical manifestations and auxiliary examinations. There are many reasons for demyelination in brain MRI scans. In older patients suffering from headaches, vertigo, other head symptoms, and unilateral numbness as the chief complaints, a clinical diagnosis of demyelinating disease is very unlikely when the imaging report simply states white matter demyelination.

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Declaration of conflicting interest

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