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Letter to the Editor

Detection of dentate nuclei abnormality in a patient with dentatorubral-pallidoluysian atrophy using the quantitative susceptibility mapping

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Dear Editor,

Dentatorubral-pallidoluysian atrophy (DRPLA) is a polyglutamine disease caused by a cytosine-adenine-guanine (CAG) repeat expansion in the DRPLA gene, resulting in a protein with a long polyglutamine tract that has a toxic effect on neuronal populations [1]. Huntington's disease (HD) is another polyglutamine disease caused by a CAG repeat expansion in the Huntingtin gene [2]. These two entities share overlapping clinical features, so making a diagnosis purely on clinical grounds may be challenging. Although no definitive treatment has yet been developed for either, it is clinically important to differentiate DRLPA from HD because the symptomatic treatment is different; tetrabenazine is used for HD, while taltirelin hydrate and protirelin tartrate hydrate are used for DRPLA.

Useful neuroimaging findings have been established for the diagnosis of HD, with brain atrophy mainly in the striatum and globus pallidus (GP) common magnetic resonance imaging (MRI) features. In contrast, the MRI findings of DRPLA seem slightly non-specific, including atrophy in the cerebellum and brain stem (particularly the pontine tegmentum) and diffuse T2-weighted high-signal-intensity lesions in the cerebral white matter [1].

Recent developments in quantitative susceptibility mapping (QSM) techniques have made it possible to directly map brain tissue magnetic susceptibility. QSM is believed to give a more accurate and more specific measure of the tissue magnetic susceptibility than previous techniques, characteristics that have been shown to correlate well with the tissue iron concentration in most gray matter regions [3]. Previous QSM studies of HD have shown that the susceptibility values of the basal ganglia (caudate nuclei [CN], GP, and putamen) are higher in HD patients than in healthy controls, due to the iron deposition with degeneration and/or neuronal loss [4]. To our knowledge, however, there are no reports evaluating DRPLA using QSM.

To clarify the utility of QSM for diagnosing DRPLA, we herein report a case of DRPLA comparing 3 female HD patients (genetically confirmed) (age [average ± standard deviation], 50.3 ± 10.1 years; age range, 41–62 years) and 10 female normal controls (NCs) (age [average ± standard deviation], 46.4 ± 6.9 years; age range, 38–57 years).

1. Case report

A 44-year-old woman was referred to our hospital. A clinical examination showed marked choreoathetosis, dysarthria, and dementia. The patient had a disease duration of three years. A genetic analysis revealed an abnormal CAG trinucleotide in the ATN1 gene, which suggested a diagnosis of DRPLA. She was therefore diagnosed with early adult-type DRPLA.

A 3.0-T MR system (Signa EXCITE; GE Healthcare, Milwaukee, WI, USA) with an 8-channel head coil was used for conventional MRI and QSM. QSM was performed with a three-dimensional multi-echo spoiled gradient echo sequence and reconstructed using the complex data obtained during the sequence using morphology-enabled dipole inversion sequencing [5].

For the quantitative assessment, we averaged the susceptibility values of both sides for subcortical regions of interest (dentate nuclei [DN], red nuclei [RN], GP, subthalamic nuclei [STN], Putamen, CN, and substantia nigra). For HD patients (n = 3) and NCs (n = 10), we then averaged the values of each subject, and the obtained values were used in the comparison. QSM images showed higher susceptibility values for the DN and RN in DRPLA than in HD patients and NCs (Fig. 1A, B, C, and Table 1). However, conventional T2*WI showed non-specific mild hypointensity for the DN (Fig. 1D). The GP showed higher susceptibility values in DRPLA and HD patients than in NCs. However, for the STN, the susceptibility values were nearly equal among the three groups (Table 1). Conventional MRI showed mild atrophic changes in the cerebellum and mild T2-weighted high-signal-intensity lesions in the cerebral white matter (not shown).

2. Discussion

A previous pathological study of DRPLA revealed neuronal loss in the DN, STN, and external segment of the GP [6]. Degeneration of the dentatorubral systems is one of the major pathological features of DRPLA but not of HD [7,8]. This evidence supports our findings; the magnetic susceptibility values in the DN and RN were higher in the patients with DRPLA than in the patients with HD and NCs. Moreover, the patient had no factors increasing susceptibility values at DN and RN such as a history of use of gadolinium-based contrast agents. The conventional MRI findings of DRPLA are somewhat non-specific and show no abnormality in the DN, suggesting the usefulness of QSM for diagnosing DRPLA.

The increased susceptibility values may be attributed predominantly to

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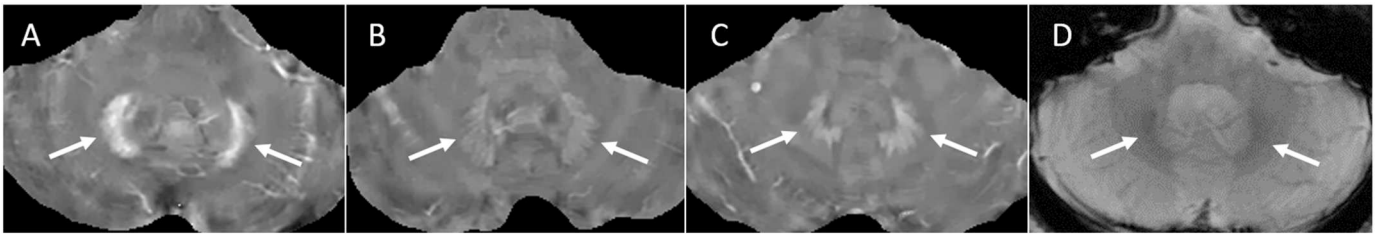

Fig. 1. The comparison of the QSM images at the level of the DN between DRPLA patients (A), HD patients (B), and NCs (C). T2*WI are also shown at the same level for DRPLA (D). For the DN (arrows), QSM showed a higher signal intensity in DRPLA patient than in HD patients or NCs, while T2*WI of DRPLA patient revealed non-specific slightly low signal intensity. DRPLA indicates dentatorubral-pallidoluysian atrophy; HD, Huntington's disease; NCs, normal controls; DN, dentate nuclei.

Table 1
Mean susceptibility values in subcortical regions of interest.

	DRPLA	HD	NCs
DN	193.2	54 (28.2)	76.1 (12.9)
RN	174.9	110 (8.1)	111.5 (32.1)
GP	179.5	193.8 (17.9)	86.4 (15.2)
STN	57.6	79.1 (20.4)	61 (20.9)
Pu	31.9	167.7 (7.2)	52.4 (22.2)
CN	52.4	139.9 (4.9)	48.6 (16.7)
SN	85.2	78.5 (10.6)	107.1 (35.7)

Mean susceptibility value (standard deviation) ($\times 10^{-3}$ ppm)

DRPLA indicates dentatorubral-pallidoluysian atrophy; HD, Huntington's disease; NCs, normal controls; DN, dentate nuclei; RN, red nuclei; GP, globus pallidus; STN, subthalamic nuclei; Pu, putamen; CN, caudate nuclei; SN, substantia nigra; ppm, parts per million.

the increase in the tissue iron content in these regions associated with DRPLA and HD [9]. Microglia, the brain-resident immune cells, are emerging as a central player in regulating key pathways in CNS inflammation. Recent insights into neuroinflammation indicate that microglia modulate the transport and metabolism of the essential metal iron in response to pro-inflammatory environmental cues [10]. Activated microglia lead to an influx of intercellular iron through an iron transporter, which further leads to increased oxidative damage in cases of HD [10]. Similar to HD, the microglia-induced increased uptake of iron into the cells might damage the neurons, inducing inflammation and neuronal loss leading to the degradation of the dentatorubral and pallidoluysian systems in DRPLA.

The quantitative assessment showed that the difference in the susceptibility values between DRPLA and HD was greater in the DN than in RN. Although the DN is consistently involved in DRPLA, showing loss of neurons and astrocytosis, the RN shows only astrocytosis with no loss of neurons, which may support our results [8]. We therefore suggest that assessing the DN using QSM is useful for diagnosing DRPLA. It has been shown the clinical subtypes of DRPLA such as early adult-type and late adult-type may provide pathological differences of the brain. Therefore, it may be an important topic to assess the susceptibility values of the brain regions regarding the clinical subtypes of DRPLA.

In conclusion, QSM showed increased magnetic susceptibility values, particularly in the DN, of DRPLA patient compared to HD patients and NCs, reflecting iron deposition that was not obvious on conventional MRI.

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