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Does brain degeneration in Wilson disease involve not only copper but also iron accumulation?

Czy neurodegeneracja w chorobie Wilsona jest związana tylko z akumulacją miedzi czy także żelaza?

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Abstract

Background and purpose: Wilson disease (WD) is an autosomal recessive inherited disorder of hepatic copper metabolism. Clinical manifestations of WD include neurologic, hepatic and psychiatric symptoms. Most WD patients with the neuropsychiatric form, and some with the hepatic and presymptomatic forms have both hypointense and hyperintense lesions in basal ganglia on T2-weighted magnetic resonance imaging (MRI), which can be iron and copper accumulation. It has been established that T2* and susceptibility-weighted imaging (SWI) are highly sensitive in demonstrating brain iron accumulation, showing decreased signal intensity. Hypointense globus pallidus (GP) signal has been described on T2-, T2*-weighted images and on SWI as typical MRI lesion for patients with neurodegeneration with brain iron accumulation (NBIA). We investigated whether WD patients have MRI changes suggesting iron accumulation using T2*-weighted and VEN_BOLD SWI imaging protocols.

Material and methods: Standard MRI with additional sequences (T2*-weighted and VEN_BOLD SWI) was performed in consecutively admitted, clinically stable, and treated patients.

Results: Twenty-eight patients entered the study. Hypointensity in the GP was observed on T2*-weighted images in 10 pa-

Streszczenie

Wstęp i cel pracy: Choroba Wilsona jest genetycznie uwarunkowanym, dziedziczonym autosomalnie recesywnie schorzeniem powodującym upośledzenie metabolizmu miedzi. Wyróżnia się następujące postacie kliniczne: neurologiczną, psychiatryczną i wątrobową. U większości pacjentów z postacią neurologiczną choroby Wilsona, a także u części osób z postacią wątrobową i bezobjawową stwierdza się hipointensywne i hiperintensywne zmiany w jądrach podkorowych w obrazach T2-zależnych rezonansu magnetycznego (RM) mózgu, które mogą świadczyć o gromadzeniu zarówno miedzi, jak i żelaza. Wiadomo także, że badanie RM w sekwencjach T2*-zależnej i VEN_BOLD SWI (*susceptibility-weighted imaging*) pozwala z dużą czułością wykrywać gromadzenie żelaza w tkance. Hipointensywny sygnał gałki bladej w RM mózgu w obrazach T2*-zależnych i w sekwencji VEN_BOLD SWI jest typowy dla neurodegeneracji z gromadzeniem żelaza (*neurodegeneration with brain iron accumulation* – NBIA). Celem niniejszej pracy było stwierdzenie, czy pacjenci z chorobą Wilsona mają zmiany w RM mózgu w sekwencjach T2*-zależnych i VEN_BOLD SWI sugerujące gromadzenie żelaza.

Materiał i metody: Badanie RM, standardowe oraz w sekwencjach T2*-zależnych i VEN_BOLD SWI, zostało wykonane u wszystkich kolejnych pacjentów przyjętych do II Klini-

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tients. Using the VEN_BOLD SWI technique, we found hypointense signal in GP in 20 patients.
Conclusions: MRI data suggest not only copper but also iron accumulation in GP in WD patients.

Key words: Wilson disease, magnetic resonance imaging, copper, iron.

ki Neurologii w okresie obserwacji. Wszyscy pacjenci byli w stabilnym stanie i leczono ich z powodu choroby Wilsona.
Wyniki: Do badania włączono 28 pacjentów. Hipointensywne zmiany w gałce bladej w obrazach T2*-zależnych stwierdzono u 10 z nich. W sekwencji VEN_BOLD SWI zmiany hipointensywne zaobserwowano u 20 osób.
Wnioski: Wyniki wskazują na gromadzenie nie tylko miedzi, lecz także żelaza w gałce bladej u pacjentów z chorobą Wilsona.

Słowa kluczowe: choroba Wilsona, rezonans magnetyczny, miedź, żelazo.

Introduction

Wilson disease (WD) is an autosomal recessive inherited disorder of hepatic copper metabolism that is caused by malfunction of a putative copper-transporting P-type APTase (ATP7B). The cellular damage associated with this disorder is thought to be due to copper deposition in affected tissues, principally the liver and brain [1]. Clinical manifestations of WD include neurologic, hepatic and psychiatric symptoms.

Abnormal findings in magnetic resonance imaging (MRI) – including brain atrophy; hyperintense lesions on T2-weighted images in putamen, pons, midbrain, and thalamus; and hypointense signals of basal ganglia on T2-weighted images – are observed in most WD patients with the neuropsychiatric form, and in some patients with the hepatic and presymptomatic forms [2-7]. Simultaneous involvement of basal ganglia, thalamus and brainstem seem to be pathognomonic for WD [8]. Of those abnormalities, the hyperintense T2 lesions are believed to be gliosis or edema, whereas the hypointense T2 lesions likely indicate ion accumulation [9]. MRI T1-hyperintensity in the pallidum is also observed in WD patients, probably due to manganese accumulation in cases of liver failure [10].

Brain ion accumulation has recently become a topic of great interest. The role of brain iron deposition in normal aging and neurodegeneration has been recognized. Iron deposition has been demonstrated within the substantia nigra in Parkinson disease, and in structures affected by β-amyloid plaques in Alzheimer disease [11]. Iron is thought to play a role in the pathogenesis of common neurodegenerative diseases, probably via increased oxidative stress [12,13].

Since ions are paramagnetic, MRI techniques such as T2*-weighted imaging and BOLD imaging seem to be very sensitive tools for detecting *in vivo* ion accumulation. It has been established that T2*-weighted images are highly sensitive to brain iron accumulation [11], which causes decreased signal intensity. T2* imaging could also be highly sensitive to copper depositions [7]. Currently available MRI blood oxygenation level-dependent (BOLD) techniques, like susceptibility-weighted imaging (SWI; VEN_BOLD SWI), are useful for vessel imaging, but seem to be more sensitive for detecting ion deposits (especially iron) than conventional MRI [14,15].

Hypointense signals of basal ganglia, primarily hypointense globus pallidus, have been described on T2-weighted images from WD patients similarly to the typical MRI changes of neurodegeneration with brain iron accumulation (NBIA) [11]. Therefore, in this study we aimed to observe the presence of MR changes typical of NBIA in WD patients, using the standard T1- and T2-weighted imaging and T2*- and BOLD-weighted imaging protocols.

Material and methods

Patients

All WD patients admitted to our department between March and August 2011 were subjected to MR examination with an established protocol. This study was approved by the Ethical Committee of the Institute of Psychiatry and Neurology and written consent was obtained from all subjects.

Wilson disease diagnosis was based on typical neurological and/or hepatic symptoms, biochemical markers (decreased ceruloplasmin level, raised 24-hour urinary copper concentration, and decreased plasma copper concentration), and genetic examination, as described previously [16]. A predominant symptom scoring system was used to classify symptomatic patients, as described previously [17]. As the number of patients in the study was small, we did not compare different clinical groups (hepa-

tic vs. neurologic) as well as disease duration and kind of treatment (zinc sulfate vs. penicillamine). All patients were on therapy and were clinically stable for at least 6 months prior to the start of the study.

Imaging study

All images were acquired on a 1.5 T MRI unit (Philips). T1-weighted (TR = 596 ms, TE = 15 ms) and T2-weighted (TR = 6783 ms, TE = 140 ms) images were taken in axial planes with 5-mm slice thickness. Gradient echo T2*-weighted images were obtained as a single-echo sequence (TR = 693 ms, TE = 23 ms; flip angle = 20°). The VEN_BOLD SWI (TR = = 34 ms, TE = 49 ms) were performed for all patients. Lenticular nucleus (putamen and globus pallidus) was assessed. Other structures (putamen, pons, thalamus, cerebellum, substantia nigra [SN], red nucleus [RN], caudate and cortex) were also assessed, but this data is not presented in this paper. The MRI were analyzed by the neurologist blinded to the clinical examination.

Results

Twenty-eight patients (11 males) entered the study. The mean age was 32 years (standard deviation [SD], 10). All subjects underwent the full MRI protocol. Mean time from onset of symptoms to MRI study was 9.32 years (SD, 7.28). Clinical presentation and MR changes are shown in Table 1.

No MRI abnormalities on T1- and T2-weighted images were observed in 13 patients. One patient suffering from previously described liver failure exhibited hyperintense changes in globus pallidus on T1-weighted images. On T2-weighted images, 11 patients had only hyperintense changes in putamen, 9 had hypointense changes in globus pallidus and 6 patients had both hyperintense changes in putamen and hypointense changes in globus pallidus. T2*-weighted images showed hypointensity in the globus pallidus in 10 patients. Using the VEN_BOLD SWI technique, we found hypointense signals in globus pallidus in 20 patients (Fig. 1).

Discussion

The presence of basal ganglia iron deposition in neurodegenerative diseases has been established; globus pallidus MR hypointensity on T2- and T2*-weighted sequences is a typical abnormality for all NBIA [11]. Our study showed globus pallidus hypointensity on T2*-weighted images in 10 patients and in VEN_BOLD SWI in 20 patients. The exact nature of these observed hypointense lesions is still unclear. Since copper is paramagnetic, it is possible that copper shortens the T2 relaxation time and causes decrease of signal intensity [7], but some authors believe that copper typically results in increased T2 signal abnormalities [10]. Symmetric hypointense lesions in basal ganglia have been described despite long-term copper chelating therapy [7,15], while high signal changes in T2-weighted images usually improve or totally disappear under sufficient medical treatment [7,18,19]. While the contribution of copper to hypointense effects on T2*-weighted and BOLD images has not yet been determined, the utility of these sequences in demonstrating iron deposition has been described [11,14]. Copper-iron interactions in WD patients are logical, as ceruloplasmin is the major ferroxidase and is essential for iron metabolism, and aceruloplasminemia is related to a heavy iron load [20]. Liver biopsy has detected both iron and copper deposition in WD patients [20]. Our results suggest that VEN_BOLD SWI imaging is more sensitive than T2-weighted sequences for detecting globus pallidus intensity changes in WD. The only published data about

Table 1. Clinical presentation and magnetic resonance imaging (MRI) abnormalities in 28 examined patients

	Clinical presentation		
	Neurological *n* = 9	Hepatic *n* = 13	Presymptomatic *n* = 6
No MRI changes	2	8	3
Lenticular nucleus hyperintensity in T2-weighted image	7	3	1
Lenticular nucleus hypointensity in T2-weighted image	6	0	3
Lenticular nucleus hypointensity in T2*-weighted image	7	0	3
Lenticular nucleus hypointensity in VEN_BOLD sequence	9	6	5

VEN_BOLD – blood oxygenation level dependent imaging venography

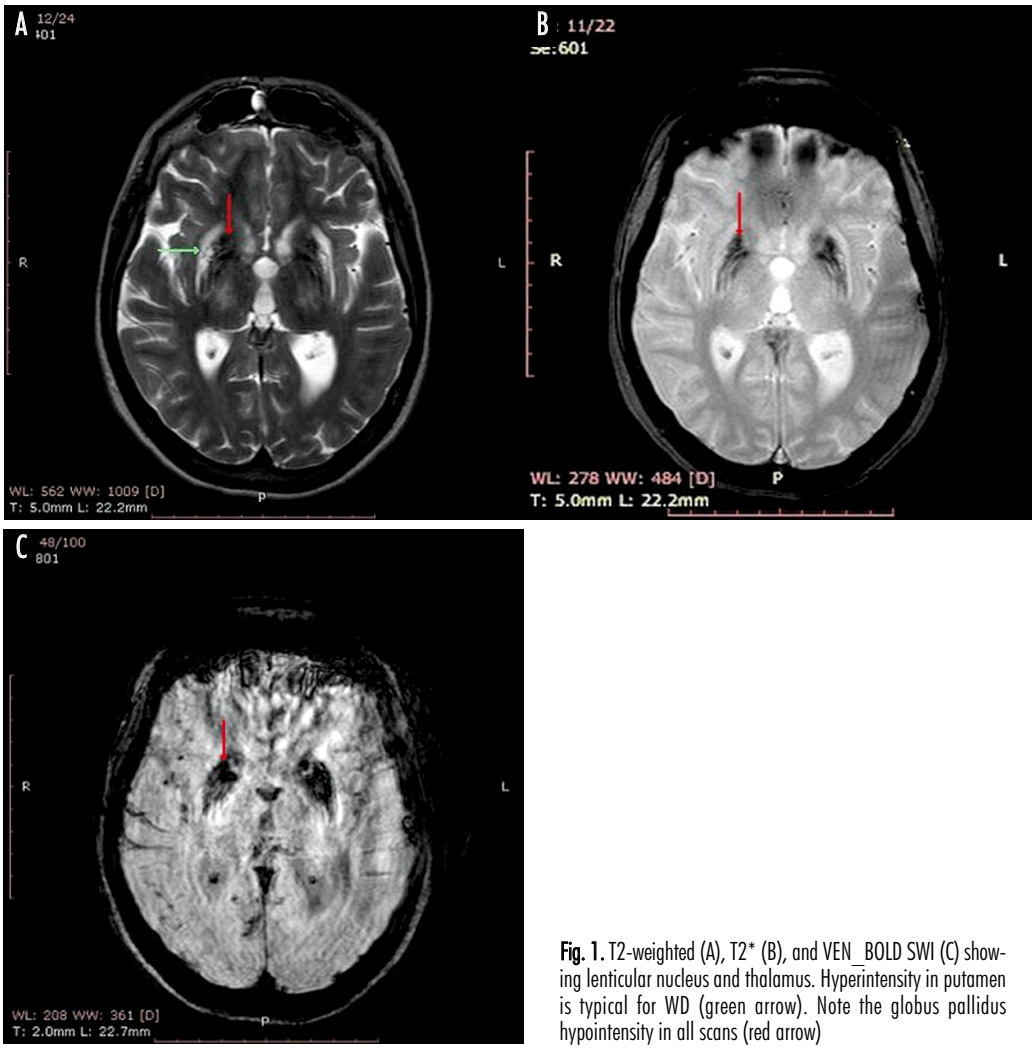

Fig. 1. T2-weighted (A), T2* (B), and VEN_BOLD SWI (C) showing lenticular nucleus and thalamus. Hyperintensity in putamen is typical for WD (green arrow). Note the globus pallidus hypointensity in all scans (red arrow)

SWI in WD patients is a case study in which paramagnetic signals on SWI remained unchanged despite therapy during a six-month follow-up [15].

Our study has number of limitations, including the small number of patients in each clinical group and that MR imaging was performed at different time points for each patient. Additionally, all patients were treated with one of two different protocols, which might influence our results; long-term penicillamine treatment compared to zinc sulfate seems to be responsible for more severe hepatic iron accumulation [21].

Conclusions

We find interesting the idea that WD seems to involve accumulation of not only copper but also iron. This hypothesis is supported by the presence of hypointense lesions on T2*-weighted images and SWI sequences that are sensitive for iron depositions in patients under de-coppering therapy. Further studies, including larger groups of patients, and post-mortem studies are necessary.

Disclosure

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Authors report no conflict of interest.

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