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Corpus callosum abnormalities in Wilson's disease

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ABSTRACT

Introduction Wilson's disease (WD) with neurological presentation is associated with brain lesions classically localised in globus pallidus, putamen, thalamus, mesencephalon, pons and dentate nucleus. Lesions of corpus callosum (CC) have not been studied in a broad population of patients with WD.

Objective Evaluation of the frequency of CC lesions in patients with neurological symptoms related to WD.

Method The authors included all patients with neurological expression of WD, followed in the French national centre for WD who had a brain MRI between March 2006 and December 2008. The localisation of brain lesions was analysed and the frequency of lesions in CC evaluated. All patients were assessed using the Unified Wilson's Disease Rating Scale. For patients with abnormalities located in CC, a clinical dysconnexion syndrome was investigated.

Results Among 81 patients (45 men, mean age: 34.8 years, from 12 to 74 years) with neurological expression, 42% had white-matter lesions on fluid-attenuated inversion recovery MRI. 23.4% of patients presented CC lesions, limited to the posterior part (splenium). The severity of disability estimated by Unified Wilson's Disease Rating Scale was correlated with the presence of CC lesions on MRI.

Conclusion Abnormalities in CC are not unusual (23.4%). Together with lesions of basal ganglia, CC signal changes should suggest the diagnosis of WD.

INTRODUCTION

Wilson's disease (WD) is an autosomal recessive disorder caused by a mutation of the *ATP7B* gene mapped to chromosome 13. The ATP7B protein plays an essential role in copper homeostasis.[1 2] Diagnosis of WD with neurological expression can be made at various stages in the illness with a mean delay of 25 months after first symptoms.[3] Brain MR imaging takes a main place for the diagnosis of these neurological forms. Structural brain MRI reveals widespread atrophy and hypersignals in fluid-attenuated inversion recovery (FLAIR) and diffusion sequences in basal ganglia, cerebellar peduncles and midbrain.[4] Hyposignals in FLAIR sequences can be seen at a later stage of the illness after several years of treatment. In hepatic forms with portacaval shunt, non-specific bilateral striatal hypersignals are observed on T1 sequences.[5]

Abnormalities of corticosubcortical white matter, compared with the deep nuclear structures, have received less attention in WD. White-matter changes are observed in about 25–40% of patients, often asymmetrical with frontal predilection.[5] Abnormalities in the corpus callosum (CC) have rarely been addressed in previous studies.[5 6] The aim of this study is to evaluate the frequency of CC lesions in patients with neurological symptoms related to WD.

METHODS

Patients

We conducted this current study in the French National Wilson's disease Centre (CNR Wilson). The diagnosis of WD was based on clinical symptoms, Kayser Fleischer rings on slit-lamp examination, low serum copper and ceruloplasmin, increased 24 h urinary excretion of copper and molecular genetic studies. Data on patients with neurological symptoms who underwent brain MRI between March 2006 and December 2008 were reviewed retrospectively to analyse the localisation of lesions.

The Unified Wilson Disease Rating Scale (UWDRS) was used to evaluate the handicap due to neurological symptoms and realised at the same time of brain imaging.[7] UWDRS is a component of the EuroWilson patient registry (http://www.eurowilson.com/) which combines items from the Unified Parkinson's disease rating scale (UPDRS part III), the Barthel index, the Burke Fahn Marsden scale (BFM scale), the Clinical Rating Scale for Tremor and the Unified Huntington's Disease Rating Scale (UHDRS). For Wilson patients with abnormalities in the CC (WCC+ group), a clinical dysconnexion syndrome was investigated: left tactile anomia, left agraphia, left apraxia and pseudolateral homonymous hemianopsia.

MR imaging

All images were acquired on a 1.5 T MR unit (GE Medical System, Milwaukee, Wisconsin, USA) parallel to the CA-CP used as the reference plane using at least the following sequences: (1) T2-FLAIR: imaging time, 4.16 min; axial interleaved sections, 5 mm with 1.5 mm gap; matrix, 256×192; field of view, 24×24 cm; repetition time (TR)/effective echo time (TEeff)/inversion time (TI)/excitations, 8002/155/2000/2 and bandwidth, 31.2 kHz; (2) diffusion-weighted imaging: imaging time, 30 s; multisection single shot spin-echo diffusion echo planar with a pair of diffusion gradient centred around the 180° pulse; axial section thickness, 5 mm with 1.5 mm gap; matrix, 128×128; field of view, 24×24 cm; TR/TEeff, 7.500/99, and 20 sections acquired with echoplanarT2 imaging acquisition (b=0 s/mm^2) and b=1000 s/mm^2 (diffusion gradient G×22 mT/m, duration×32 ms, separation time=39 ms). Dedicated software was used to generate quantitative apparent diffusion coefficient (ADC) maps (FuncTool V.2.2.49, GE Medical System).

The ADC was measured in hyperintense areas on FLAIR images of Wilson patients. The region of interest was positioned in the CC.

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Table 1 Description of the group of patients with corpus callosum lesions (WCC+) and group of patients without corpus callosum lesions (WCC−): numbers of patients with fluid-attenuated inversion recovery MRI abnormalities

	No of patients	Male/ female ratio	Age (years)	Age at diagnosis (years)	Delay between MRI and diagnosis	Wilson Disease Rating Scale score	White matter	Basal ganglia	Cerebellum	Midbrain
WCC+	19	2.2	34	22.7	10.11	23.7	5	19	11	17
WCC−	62	1.1	35	21.1	12.98	12.27	10	52	22	37
p Value			0.77	0.4	0.19	0.03*	0.38	0.001*	0.1	0.003*

*Significant results ($p<0.05$).

MR analysis

The MRI data were reviewed by a board-certified neuroradiologist blinded to the subject's clinical condition. The presence of lesions on MRI in the following structures was collected: basal ganglia, cerebellum, midbrain, CC and other localisations in white matter.

Statistical analysis

ADC values in Wilson patients with CC lesions were compared with a control group composed of 10 patients referred to our institution for a diagnosis of atypical headaches (eight women and two men; mean age: 29.3 years (range 19–42 years)) with normal MRI results (on T1, T2, FLAIR and diffusion-weighted images).

UWDRS scores in the two groups of patients (with or without CC lesions) were compared. We used non-parametric tests (Wilcoxon/Kruskal–Wallis tests). p Values <0.05 were considered significant.

RESULTS

The mean age of these 81 patients (45 males, 36 females) was 34.8 years (12 to 74 years). The mean age at diagnosis was 21.5 (5 to 51 years). The mean delay between cerebral MRI and diagnosis was 12 years (0 to 34 years). All patients were treated by copper-chelating agents or zinc. White-matter lesions on FLAIR MRI were present in 42%. CC lesions were detected in 23.4% (13 males; six females) with a mean age of 34 years (from 20 to 57 years). The lesions were limited to the posterior part (splenium) of CC. In the group of patients with CC lesions, brain MRI abnormalities were more diffuse, reaching basal ganglia in 100% of cases and midbrain in 89.5% (table 1). No signal abnormalities were observed in CC on T1 (figure 1). No difference was found between the two groups of patients (with or without CC lesions) with the age, age of onset of the disease and treatment duration. The UWDRS value (mean±SEM) in the WCC+ group (23.7±5.9) was significantly higher than in the WCC− group (12.3±2.07) ($p=0.02$). No callosum dysconnexion syndrome was found on clinical examination in patients with CC lesions. The apparent diffusion coefficient value ($\times 10^{-6}$ s/mm^2; mean±SD) was 791±9 in CC lesions, without any significant difference from the control group (830±73).

DISCUSSION

Brain lesions observed in WD are usually bilateral and symmetrical. The structures mostly involved are the globus pallidus, putamen, thalamus, mesencephalon, pons and dentate nucleus.[5] The bilateral and symmetrical aspect of basal ganglia lesions could be a pitfall for the radiologist. We demonstrated

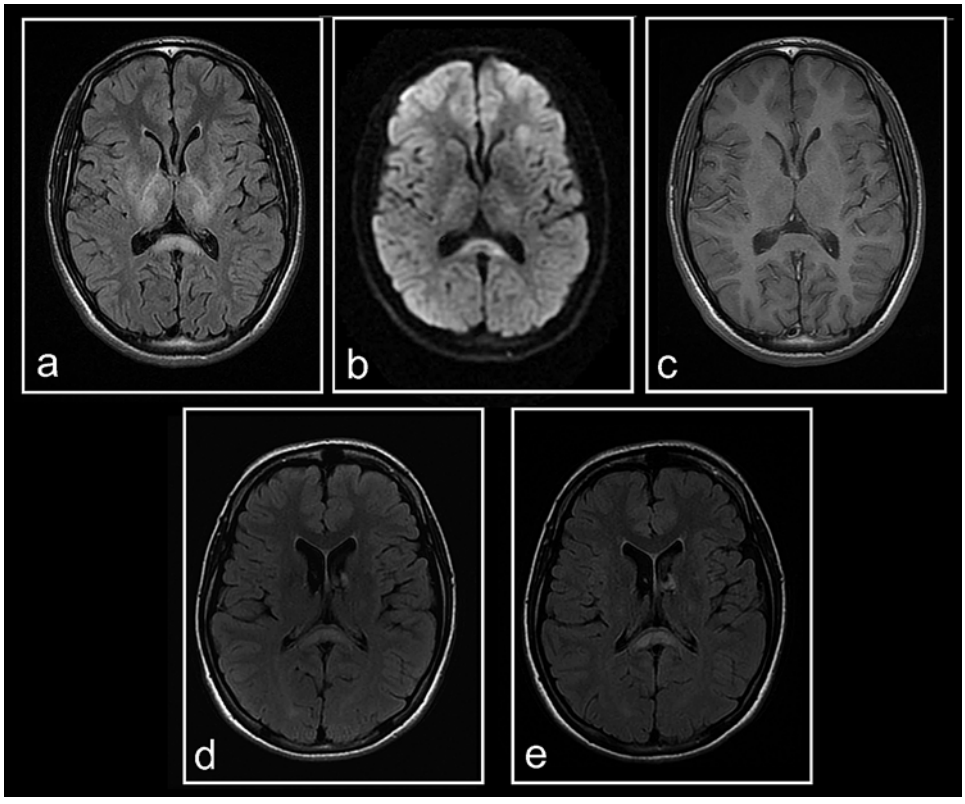

Figure 1 Brain MRI of patients with Wilson's disease. Patient 1: (A) fluid-attenuated inversion recovery (FLAIR); (B) diffusion; (C) T1-weighted. Patient 2: (D) FLAIR in 2005; (E) FLAIR 3 years later.

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that abnormalities in CC are not unusual (23%), limited to its posterior part (splenium). Together with lesions of the basal ganglia, CC signal changes should suggest WD diagnosis.

White-matter abnormalities were detected in 42% of patients in our series. They are reported in the literature in 25–40% on brain MRI of WD patients.[5] Autopsy studies have confirmed the implication of white matter in WD.[8] To our knowledge, no previous study has specifically analysed the frequency of CC lesions in WD, which were included in white-matter abnormalities.

Abnormalities of CC have already been reported in other diseases such as epilepsy or hypoglycaemia.[9] In those situations, abnormalities of CC are often limited to the splenium. The special vulnerability of this part of the CC is still unclear. Different hypotheses are discussed: direct consequence of seizure, antiepileptic treatment or vascular domage.[10] In our patients, no one presented with a seizure. There was no recent deterioration or biological abnormalities to the time of imaging. The follow-up of CC lesions of few patients shows no modifications (figure 1). The stability of CC abnormalities is therefore an argument against a transient change.

No clinical signs of dysconnexion were observed probably due to the slowly progressive pathway (copper toxicity) of brain lesions. Pathological changes in WD are associated with increased copper concentrations in the brain. Abnormalities include atrophy, spongy softening, cavitations, neuron loss and the presence of Opalski cells, probably resulting from an increase in extracellular copper, which causes oxidative stress.[11 12] High diffusion coefficient values correspond to increased mobility of water molecules and indicate the presence of a vasogenic oedema-like pattern.[12] Increased ADC values have already been reported in structures such as the putamen, correlated with the severity of the disease.[6] No significant difference was observed between ADC values in the CC of our patients and controls. The compact nature of white-matter tracts in CC constitutes a relative barrier to the flow of interstitial oedema and could explain the lack of ADC abnormalities observed in this study. It can however be due to the limited number of patients included in this study. Indeed, we have noticed a wide interindividual variability in ADC values in the CC area, suggesting different histopathological states corresponding to different stages of the disease as has already been observed in other structures.[12]

The severity of disability, estimated by UWDRS values, is correlated with the presence of CC lesions on MRI. We have however observed more extended lesions on MRI in the group with CC lesions. This localisation apparently adds no supplementary symptoms. Further studies should evaluate the prognostic value of CC injuries in WD.

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

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