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LETTER TO THE EDITOR

Six-year clinical and MRI quantitative susceptibility mapping (QSM) follow-up in neurological Wilson's disease under zinc therapy: a case report

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To the Editor,

Wilson's disease (WD) is an inherited disorder of copper metabolism, resulting in pathological accumulation of copper, principally in the liver, brain and cornea. The causative gene is ATP7B (13q14.3) that encodes a copper-transporting P-type ATPase. Liver or neuropsychiatric involvement is a hallmark of the disease [1]. Copper chelators or zinc salts are commonly given as therapy, although there is no international consensus on first-line therapy. Improvement in T2-signal alterations in follow-up brain MRI have been documented in WD patients undergoing zinc treatment (zinc sulfate) [2]. Recent studies have shown that copper deposit may result in a measurable difference in quantitative susceptibility mapping (QSM) at brain MRI of neurological and non-neurological WD patients compared to healthy controls at field strength of 7T [3], as well as in young patients with neurological WD even before T1 or T2 brain signal alteration at 1.5T [4]. Herein, we report a significant improvement in clinical and neuroradiologic findings, including QSM at 1.5 T, after a switch from D-penicillamine (DPA) to zinc acetate therapy in an adult patient with neurological WD.

A 39-year-old male carrying a homozygous mutation c.3207C>A in exon 14 of the ATP7B gene was diagnosed with WD. His medical history included mild mental retardation. Progressive phobic and obsessive disorder was reported in the previous 18 months leading up to diagnosis. On admission to our department, neurological examination showed a severe akinetic-rigid syndrome, generalized dystonia, abnormal posture of the trunk, torticollis and spastic flexion of hands and feet, with secondary skeletal changes and inability to move. Severe bulbar dystonia was associated with facial grimacing, anarthria and dysphagia. Sphincter incontinence was also present. Ophthalmological examination by slit lamp excluded the Kaiser-Flesher ring. Normal liver function was demonstrated, although ultrasonography revealed unspecific chronic damage. Before referral to our department, the patient had been treated with DPA (600 mg/die) and a restricted-copper diet for 7 months. On presentation, laboratory tests showed serum ceruloplasmin 12 mg/dl (n.v. 20–60 mg/dl), serum "free" copper 391.43 μg/L (n.v. 600–1660 μg/L) and 24-h urinary copper excretion 1014.98 μg/day (n.v. 4–15 μg/day). Poor clinical response prompted us to switch therapy to zinc acetate (150 mg/day). Rapid reduction in hypertonia and dystonia allowed the patient to recover sitting position and begin physical therapy. Six years later, the patient is interacting with his environment, dystonic flexion of the limbs is reduced, and voluntary movement of the upper limbs enables him to read the paper and feed himself. Deglutition has improved, allowing a semisolid diet per os. Severe speech disorder persists, although the patient is now able to say a few words. Laboratory examination showed 24-h urinary copper excretion constantly below 75 μg/day. Brain MRI (Fig. 1a–c) performed on admission to our department showed typical findings, including a "giant panda face" pattern in the midbrain and a "miniature panda face" in the pons. MRI findings with quantitative susceptibility mapping revealed a diffuse increase in susceptibility changes in the basal ganglia and brainstem in susceptibility-weighted (SWI) magnitude- and phase-weighted images on a 1.5T MR scanner (Fig. 1c) [4]. At 6-year follow-up brain MRI showed reduction in abnormal findings in T2- and T1-weighted images (Fig. 1d–f). To measure differences in susceptibility changes during follow-up, QSM was evaluated with "MEDI_toolbox"

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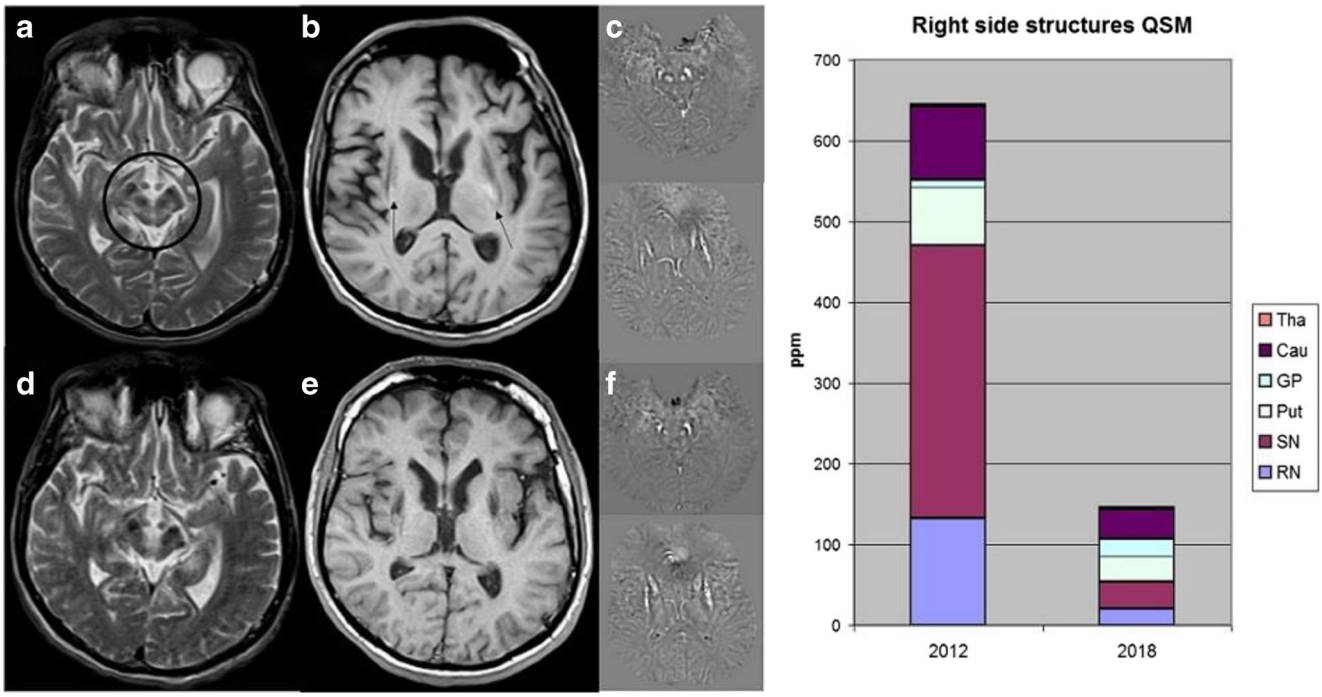

Fig. 1 Brain MRI and quantitative susceptibility map (QSM) follow-up from 2012 to 2018. Left: in March 2012, T2-weighted axial images (**a**) of the midbrain showed the "panda sign" (*black circle*), resulting from preservation of normal signal intensity in the red nuclei and lateral portion of the pars reticulata of the substantia nigra, high signal in the tegmentum, and hypointensity of the superior colliculus; T1-weighted axial images (**b**) showed diffuse bilateral signal intensity in the putamina and external capsules, including areas of subtle high signal intensity (*arrows*) in the posterior putamen, more pronounced on the left side. Non-consecutive axial QSM (**c**) showed an increase in susceptibility in red nuclei, substantia nigra, caudate nuclei, and lenticular nuclei. Note also diffuse cerebral atrophy. Despite different inclination planes and patient's motion artifacts, T2-weighted axial image obtained in March 2013 (**d**) and T1-weighted axial image obtained in December 2015 (**e**) showed clearcut improvement in signal alterations, without increase of cerebral atrophy. QSM obtained in December 2015 (**f**) showed a reduction in susceptibility, more evident in red nuclei, substantia nigra, and caudate nuclei. Right: findings from QSM in right-side structures evaluated from March 2012 to March 2018. Cau caudate nucleus, GP globus pallidus, Put putamen, SN substantia nigra, Tha thalamus, RN red nucleus

software. Region of interest (ROI) analysis was performed bilaterally in the substantia nigra, red nucleus, caudate nucleus and lenticular nucleus and thalamus. ROIs were drawn manually on a single slice where they were best visible by two neuroradiologists (I.C., A.C.) in double blind and consensus using freely available software. Cerebrospinal fluid (CSF) measurements were obtained using a circular ROI in one lateral ventricle; for each QSM study, CSF values were used as zero references, subtracting them from the other measured values. Comparison of QSM measurements from different examinations was performed using paired sample Wilcoxon signed-rank tests. A p value <0.05 was considered significant. In 2012, there were no significant differences between right- and left-side structures. Between 2012 and 2018, QSM showed a decrease in susceptibility changes (mean value in 2012: 91.96 ppm vs 22.81 ppm in 2018), with borderline significance (p=0.062). Results were significant in right side structures (mean values in 2012: 123.33 vs 20.81 ppm in 2018, p=0.02).

The wide age of onset and clinical heterogeneity of WD may delay diagnosis and therapy, influencing prognosis. The aim of therapy is to restore a negative copper balance. Copper chelators (DPA, trientine, tetrathiomolybdate) bind copper and promote its urinary excretion; zinc salts (zinc sulfate or zinc acetate) induce metallothionein formation, reducing intestinal copper absorption [1]. Liver transplant is a life-saving treatment for patients unresponsive to medical therapy. Newer therapies are available, such as cell-based and gene therapies. As in other rare neurological diseases, knowledge of different therapies arises from clinical experience and no prospective studies comparing alternative therapies have been conducted. According to literature [5], copper chelators are the first-line therapy in symptomatic patients. DPA may have severe side effects, causing drop out in up to 30% of cases. Side effects include neuropsychiatric worsening, probably due to a rapid mobilization of toxic copper and its transient increase in blood and CSF. Zinc salt therapy is used for pre-symptomatic patients and pregnant women and as maintenance therapy after chelators. Because of its delayed-action, it is not proposed as a first-line choice in symptomatic patients. To our knowledge, only one study compares neurological outcomes in WD patients, with similar baseline liver function, treated with DPA vs zinc salts. It showed more invalidating impairment of daily

living activities in patients on DPA therapy [5]. Herein, we describe an important response to zinc therapy in a case of neurological WD, in absence of clinical response to chelator. Although neurological signs such as dysphagia and dysarthria changed slightly, dystonic postures and bradykinesia improved dramatically. The effectiveness of the therapeutic switch was supported not only by clinical improvement but also by a remarkable reduction of lesions at follow-up brain MRI. Improvement was noted not only in T2-signal alterations [2] but also at QSM. The asymmetric response at QSM has no certain explanation. Distribution patterns of susceptibility changes consistent with copper deposit have been reported as different among healthy controls and WD patients with or without neurological involvement. At 7T brain MRI, in a series of neurological or hepatic WD patients in decoppering therapy, the differences between the susceptibility values in substantia nigra, red nucleus, globus pallidus and putamen resulted asymmetric, with variable significance levels [3]. At 1.5-T brain MRI, in a series of pediatric neurological WD patients treated with DPA and zinc, susceptibility changes of the entire right globus pallidus and the left anterior part, the entire right putamen and the left posterior part and the right thalamus showed significant differences, explained by artefactual images on QSM maps [4].

QSM is a post-processing technique which allows differentiation between paramagnetic and diamagnetic influences on SWI signal. Only paramagnetic minerals alter the phase of local MRI signal resulting in susceptibility differences at SWI and QSM. Increased susceptibility value generally indicates paramagnetic minerals such as iron and copper stored in the nervous tissue. A possible explanation of the asymmetry of QSM findings might rely in the highly complex physiopathology of such processes.

To the best of our knowledge, this is the first report which demonstrates the effectiveness of zinc salt therapy in WD through a quantifiable parameter, such as QSM. Although further evaluations are needed, we confirm the potential of QSM also for longitudinal follow-up of treatment effectiveness in patients with WD.

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Compliance with ethical standards

Patient consent was obtained. Details have been removed from this case report to ensure anonymity.

Conflict of interest The authors declare that they have no conflicts of interest.

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