Review Article

Magnetic resonance imaging findings in diagnosis and prognosis of Wilson disease

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Wilson disease (WD) is a rare autosomal recessive disorder characterized by excessive copper deposition in the body, principally in the liver and the brain. There is a wide spectrum of clinical presentations, but the most significant and basic symptoms of the disease can be divided into hepatic, neurologic, and psychiatric manifestations. Magnetic resonance imaging (MRI) provides more detailed anatomical information than computed tomography of the brain, especially of the structure of the basal ganglia and brain stem. In this review, we want to evaluate the correlation between MRI findings and clinical features of WD.

Key words: Hepatocerebral degeneration, magnetic resonance imaging, Wilson disease

How to cite this article: Salari M, Fayyazi E, Mirmosayyeb O. Magnetic resonance imaging findings in diagnosis and prognosis of Wilson disease. J Res Med Sci 2018;23:23.

INTRODUCTION

Wilson disease (WD) is a rare autosomal recessive disorder characterized by excessive copper deposition in the body, principally in the liver and the brain. The involved gene ATP7B encodes a copper-transporting P-type ATPase. More than 500 ATP7B mutations have recently been identified. Less common genetic pathways, including complete exon deletions, promoter region mutations, simultaneous presence of three pathogenic variations, and monogenic disomy have also been detected but are relatively rare. Loss of ATP7B function results in reduced hepatic biliary copper excretion reduced assimilation of copper into ceruloplasmin and the accumulation of copper in many tissues.[1]

There is a wide spectrum of clinical presentations, but the most significant and basic symptoms of the disease can be divided into hepatic, neurologic, and psychiatric manifestations. The neurologic presentation develops in almost 40%–50% of patients and typically begins in the second or third decade. Tremor is the most common neurologic symptom occurred in about 80% patients with the neurologic manifestation. The diagnosis of WD is based on the detection of Kayser–Fleischer rings, low ceruloplasmin, raised urine and hepatic copper level, signs of liver and/or neurologic deficit, and related histologic alterations in the liver.[2]

Magnetic resonance imaging (MRI) is the most important neuroradiological instrument for the monitoring of both diagnosis and treatment in WD. The typical MRI finding is designated as symmetric hyperintensity or mixed intensity in T2-weighted (T2W) images in the pons, midbrain, and basal ganglion. The cerebellum, corticospinal tracts, cortex, and subcortical area are also affected. Theoretically, pathognomonic MRI findings include "the faces of the giant and miniature panda" and the "trident" signs was also reported in other neurodegenerative disorders.[3]

In this review, we want to evaluate the correlation between MRI findings and clinical features of WD.

Access this article online

Quick Response Code:

Website: www.jmsjournal.net

DOI: 10.4103/jrms.JRMS_362_16

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Received: 29-04-2016; **Revised:** 03-01-2017; **Accepted:** 18-03-2017

METHODS

Two of authors (OM and EF) independently searched the Medline, Central Register of Controlled Trials, and clinicaltrials.gov databases (published between January 01, 2000, and July 31, 2016) using the terms WD, MRI, and hepatolenticular degeneration. A comprehensive literature search was performed by an author with expertise in neurology and systematic review methodology. Review articles and references of all papers were assessed for potentially related studies.

Inclusion criteria

The following criteria were used to include studies:

1. WD was defined according to accepted international diagnostic criteria
2. MRI findings in WD were calculated
3. Papers were published in English.

After removing duplicate data, abstracts, and in some cases, full text of paper, were screened by two reviewers independently to assess the eligibility of the study to be included in our study. All potentially eligible studies were reviewed independently by the two trained reviewers (OM and EF). Any discrepancies following full article review were solved by a third reviewer (MS).

MAGNETIC RESONANCE IMAGING FINDINGS OF WILSON DISEASE

WD is an inherited autosomal recessive disease of copper metabolism resulting in copper toxicity. This was first described in 1912 by Kinnier Wilson as "progressive lenticular degeneration."[4] Inborn defect in copper metabolism characterized by abnormal accumulation of copper in several tissues, particularly in the liver and the brain. MRI findings were used in the clinical treatment of patients with WD.[5] Brain MRI in WD patients takes a main place for the diagnosis of these neurological forms. Structural brain MRI demonstrates extensive atrophy, and hypersignals in fluid-attenuated inversion recovery (FLAIR) and diffusion sequences in basal ganglia, cerebellar peduncles, and midbrain.[6] Hyposignals in FLAIR sequences can be seen at a later stage of the disease after several years of treatment. In hepatic forms with portacaval shunt, nonspecific bilateral striatal hypersignals are observed on T1 sequences.[7] Abnormalities of corticosubcortical white matter, compared with the deep nuclear structures, have received less consideration in WD. White-matter changes are observed in about 25%–40% of patients, often asymmetrical with frontal preference.[8] MRI revealed abnormalities in the basal ganglia, cerebral white matter, midbrain, pons, and cerebellum. The paramagnetic effects of copper were found only in untreated patients. Patients with a longer duration of WD had less severe changes in signal intensity. The most commonly affected site seen on MRI was the putamen, with a distinctive lateral rim of high-signal intensity on the T2W images. Abnormalities in the remainder of the basal ganglia, namely, the ventral nuclear mass of the thalami, caudate, and globus pallidus, were found only in the presence of an abnormal putamen. The second most commonly affected site was the pons, followed by the midbrain, cortical white matter, and cerebellum. Abnormalities in signal intensity were most commonly seen on the T2W images.[6] MRI provides more detailed anatomical information than CT of the brain, especially of the structure of the basal ganglia and brain stem. It also provides biochemical information on the distribution of heavy metal in the brain substance; MRI is clearly a useful method for assessing heavy metal storage disease.[9] Hence, there are known signs of WD on MRI. On T2W images, the signal intensities of the basal ganglia may change. An increased signal is considered as a correlate of toxic damage and can be partly reversible.[10] In the study of Alanen *et al*., MRI of the patients showed high-signal intensity areas in posterior thalamus, general atrophy, and pontine myelinolysis were present in the patients with clinical manifestations. The T2 measurement of these areas confirmed the result of image analysis. Apart from general atrophy, the changes in the patients with clinical disease were largely reversible.[11] Published MRI studies of WD have shown a number of abnormalities, including focal atrophy, high-intensity lesions, as well as hypodense areas on T2W imaging. Attempts have formerly been made to correlate these MRI changes with clinical progression or diagnosis, with varying degrees of success. Other imaging modalities have also been used in conjunction with MRI, including positron emission tomography and single-photon emission computed tomography.[12] Further, abnormalities may occur in the brainstem (e.g., the face of the giant panda's sign).[13] The T2W horizontal section of the midbrain in these patients showed the "face of giant panda" appearance, which we describe for the first time and is specific for WD. Hyperintensity in the T2W image was also observed in the pontine tegmentum, medulla oblongata, and the cerebellar white matter around the dentate nucleus; the latter structures were thought to be normal. The superior colliculus, which in normal controls show the same signal intensity as cerebral white matter, showed a remarkable decrease in signal intensity in the patients with WD.[9] In some WD patients treated with D-penicillamine with reduced dietary copper, T2W MRI showed high-intense integrities symmetrically in the bilateral lenticular nuclei and thalami in the right frontal subcortical white matter. In one study found that the basal ganglia was the most frequently affected site and always involved the putamen, with abnormality in the globus

pallidus, caudate, and thalami occurring in about half of the WD patients.[6] Hence, the MRI findings in WD patients represent the neuropathologic spectrum of spongy to cystic degeneration of gray matter nuclei; central pontine myelinolysis; and softening, gliosis, and demyelination of nerve fibers [Table 1].

CORRELATION OF MAGNETIC RESONANCE IMAGING FINDINGS WITH CLINICAL CHARACTERISTICS OF WILSON DISEASE

There are the ranges of abnormalities seen on cranial MRI of patients with WD, and they correlate the findings with clinical severity, duration of disease, and duration of neurologic signs and symptoms before treatment.[6]

Regarding to dysarthria, most consistent pathological feature was globus pallidus and then thalamus, also about tremor. Chorea mostly accompanying with caudate lesions, nystagmus with lentiform lesions and thalamus, rigidity with lentiform, white matter and thalamus lesions, and dystonia with globos pallidus and putamen. In one study about a few patients with WD, T2W MRI of the midbrain in all three revealed the characteristic "face of the giant panda" sign, consisting of high signal intensity in the tegmentum except for red nucleus, preservation of signal intensity of the lateral portion of the pars reticulata of the substantia nigra, and hypointensity of the superior colliculus. There clinical manifestations in these patients with these MRI pattern were rigidity, dysarthria, and also showed tremor and dystonia.[9] In another study brain, MRI revealed symmetrical hyperintensities on T2/T2 fluid attenuation inversion recovery images in the putamen, thalami, midbrain, pons, and subcortical white matter of both frontal lobes in one patient with decreased sleep, irrelevant speech, aggressive, and bizarre behavior.[14]

Table 1: Clinical studies on the correlation of magnetic resonance imaging findings in Wilson disease

Author	Year	Clinical features	MRI findings (site of the lesion)	Mean age/ age (year)	Sample size (patients/controls)	Study design
Lawler	1983	Dysarthria, tremor, spasticity, weakness, ataxia, chorea, nystagmus, rigidity	Thalamus, lentiform nucleus, caudate	24.5	13 patients 12 controls	Case-control
De Haan	1987	Dysarthria, horizontal diplopia, and blurred vision, chorea, tremor	Thalamus, lentiform nucleus	18	1 patient	Case report
Starosta-Rubinstein, *et al.*	1987	Dysarthria (97%), dystonia (65%), dysdiadochokinesia (58%), rigidity (52%), gait and postural abnormalities (42%), and tremor (32%). Chorea and dementia were rare	Caudate, putamen, subcortical white matter, midbrain, and pons. Generalized brain atrophy common. Lesions were less common thalamus, cerebellar vermis, midbrain tegmentum, globus pallidus, red nucleus, and dentate nucleus	28	31 patients	Case series
Prayer *et al.*	1989	Dysarthria, tremor, ataxia, rigidity, bradykinesia, chorea, dystonia	Lenticular, thalamic, caudate, brain stem, white matter	-	38 patients	Case series
Linne	1990	Dysarthria, chorea, tremor	Lentiform nucleus	13	1 patients	Case report
Hitoshi	1991	Sialorrhea, dysarthria, tremor, rigidity, dystonia	Putamen, globus pallidus, superior colliculus, substantia nigra, white matter, thalamus, midbrain, pons, medulla	29.75	4 patients	Case series
Nazer	1992	Slow mentation, dysarthria, rigidity, bradykinesia, choreoathetosis, tremors, diplopia, ataxia, weakness, behavior disturbance, dystonia	Around aqueduct, putamen, lentiform, striatum, thalamus, internal and external capsule, brainstem	17.5	8 patients	Case series
Brugieres	1992	Manic depression, tremor, slow mentation	Putamen, caudate	53	1 patients	Case report
Thumas	1993	Dysarthria, dystonia, tremor, ataxia	Thalamus, caudate, lentiform	19-60	15 patients	Case series
Sener	1993	Tremor, dystonia, bradykinesia, dysarthria	External capsule/ claustrum, putamen, globus pallidus, caudate, thalamus	13	1 patients	Case report

Contd...

Table 1: Contd...

Author	Year	Clinical features	MRI findings (site of the lesion)	Mean age/ age (year)	Sample size (patients/controls)	Study design
Sener	1993	Dysarthria, dystonia, tremor, ataxia	Calaustrum, lentiform, thalamus	13.3	100 patients 100 controls	Case-control
Magalhaes *et al*.	1994	Dystonia, bradykinesia, postural abnormality, gait disturbance, dementia, rigidity, hyperreflexia, cerebellar tremor, dysarthria, dysdiadochokinesia	Putamen, caudate, red nucleus, thalamus, superior cerebellar peduncle, globus pallidus, substantia nigra	19.5	10 patients	Case series
Schlaug	1996	Dysarthria, tremor, rigidity, dystonia	Striatum, cerebellum, thalamus, cortex, white matter, midbrain	31.3±8.8	18 patients	Case series
van Wassenaer-van Hall	1996	Parkinsonism, dystonia, cerebellar tremor	Globus pallidus, putamen, caudate, thalamus, claustrum, subthalamic, white matter	30.0	50 patients	cross-sectional
Yoshii	1996	Personality change, tremor, dysarthria, dysphasia, incoordination, ataxia	Lenticular nucleus, thalamus, frontal-subcortical	22	1 patients	Case report
King	1996	Parkinsonism, dystonia, cerebellar tremor	Putamen, globus pallidus, thalamus, subthalamic nucleus, midbrain, pons, cerebellum, claustrum, white matter	31	25 patients	Case series
Mochizuki	1997	Tremor	Globus pallidus	18.6	3 patients	Case series
Sener	1997	Dystonia, dysarthria, seizure, mental function change	Globus pallidus, putamen, claustrum, caudate, thalamus, cortical, subcortical, mesencephalon, pons	12	1 patient	Case report
Alanen	1999	Dysarthria, tremor	Putamen, white matter, thalamus, globus pallidus	38.25	4 patients 4 controls	Case-control
Kuruvilla	2000	Tremor, dysarthria	Midbrain, superior colliculus, substantia nigra	24	1 patients	Case report
Jayasundar	2002	Impaired mental functions, dystonia, dysarthria, bilateral horizontal nystagmus, ataxia, tremor, drooling, rigidity	Basal ganglia, parietal white matter, putamen	12	3 patients	Case series
Sener	2003	Dystonia	Putamen, caudate, parenchyma	11	6 patients	Case series
Kozic	2003	No neurologic sign	Putamen, globus pallidus, caudate nucleus, thalamus, claustrum, mesencephalon, pons	26	16 patients	Case series
Kawamura	2004	Chorea	Striatum, thalamus, midbrain	15	1 patients	Case report
Page	2004	Dysarthria, drooling, gait impairment, dystonia, behavioral and cognitive change	Basal ganglia, white matter, midbrain, pons, cerebellum	44.0	17 patients 17 controls	Case-control
Juan	2005	Clumsiness, hemichorea, dystonia, rigidity	Putamen, globus pallidus, occipital periventricular and subcortical, corona radiata	12	1 patients	Case report
Semnic	2005	Parkinsonian, dystonic, cerebellar feature, dysarthria, dysphagia	Midbrain atrophy	32.2±8.3	47 patients 51 controls	Case-control
Sinha	2006	Dysarthria, drooling, gait abnormality, dystonia, bradykinesia and rigidity, tremor, ataxia and chorea	Caudate, putamen, globus pallidus, internal capsule, thalamus, midbrain, pons, medulla, cerebellum, cerebellar white matter, cortical lesion	13.5±7.3	100 patients	Case series

Contd...

Table 1: Contd...

Author	Year	Clinical features	MRI findings (site of the lesion)	Mean age/ age (year)	Sample size (patients/controls)	Study design
Strecker	2006	Dystonia, dysarthria, emotional lability, tremor	Midbrain	38	41 patients 23 controls	Case-control
Favrole	2006	Dysarthria, tremor, rigidity, parkinsonism, chorea, dystonia	Putamen, pallidum, internal capsule, corpus callosum, mesencephalon, pons, dentate nucleus, white matter	25.7±9.0	13 patients 10 controls	Case-control
Taly	2007	Parkinsonism, dystonia, ataxia, pyramidal signs, athetosis, chorea	Caudate, globus pallidus, midbrain, cerebellar, pons, medulla, white matter, thalamic	15.93±8.10	182 patients	Cohort
Thapa	2008	Dystonia, dysarthria, emotional lability, tremor	Midbrain, superior colliculus, substantia nigra	16	1 patient	Case report
Piga	2008	Dysarthria, dystonia, nystagmus, tremor	Putamen, midbrain, pons, globus pallidus, frontal lobe, cerebellum, parietal lobe	30.6±9.4	25 patients	Case series
Sankhyan	2008	Dysarthria, rigidity, dystonia, drooling	Corpus striatum, external capsules, thalamus, and posterior deep and subcortical white matter	12	1 patient	Case report
Sinha	2010	Dysarthria and drooling, gait abnormality, dystonia, bradykinesia and rigidity, tremor, ataxia, and chorea	Putamen, thalami, caudate, midbrain, cerebral white matter, pons, cortex, and medulla	20.6±8.1	40 patients 40 controls	Case-control
George	2010	Decreased sleep, irrelevant speech, bizarre behavior	Putamen, thalamus, midbrain, pons, subcortical white matter, field of floral, internal medullary lamina	32	1 patients	Case report
Trocello	2011	Parkinsonism, dystonia, ataxia, pyramidal signs, athetosis, chorea	Basal ganglia, cerebellum, midbrain, white matter, corpus callosum	34.8	81 patients 10 controls	Case-control
Fritzsch	2014	Dysarthria, dystonia, nystagmus, tremor	Putamen, red nucleus, globus pallidus, substantia nigra	44	11 patients 10 controls	Case-control
Seungyoo Kim	2014	Head and hand tremors, dystonic component	Periaqueductal region, dorsal midbrain, dorsal upper pons	34	1 female	Case report
Litwin	2014	Dysarthria, oromandibular dystonia, gait disturbances, positional hand tremor	Globus pallidus, putamen	41	1 male	Case report
Yu Liu	2015	Dysarthria, dystonia, nystagmus, tremor	Putamen, globus pallidus, caudate, thalamus	24	42 males, 32 females	Cohort
A. Ranjan	2015	Focal with secondary generalized seizure, generalized tonic-clonic seizure patients, drooling, dementia, dystonia, tremor, choreoathetosis, myoclonus	Putamen, caudate, brainstem, globus pallidus, thalamus, cerebral cortex, subcortical white matter, cerebellum	14	34 patients	Case series
Jinjing Yang	2015	Dysarthria, dystonia, nystagmus, tremor	Caudate nuclei, globus pallidus, putamen, thalamus, substantia nigra, red nucleus	21.18±7.35	33 patients 18 control	Case-control
Shivraj Goyal	2015	Exaggerated deep tendon reflexes, positive bilateral Babinski's sign, difficulty in walking and sitting, difficulty in speaking, tremors, dysphasia, dysarthria, ataxia	Bilateral thalami, basal ganglia, claustrum, red nucleus, bilateral frontal white matter	26	1 patient	Case-report

MRI=Magnetic resonance imaging

The severity of changes in signal intensity on MRI was inversely related to the duration of untreated disease and similarly related to the overall duration of disease. In contrast, no significant relationship was found between the extent of disease seen on MRI and the total duration of disease or its untreated duration. Neurologic severity was unrelated to the duration of untreated disease or to total duration of disease.[6]

CONCLUSION

MRI is the most important neuroradiological instrument for the monitoring of both diagnosis and treatment in WD. MRI studies of WD have demonstrated a number of abnormalities, including focal atrophy and high-intensity lesions, as well as hypodense areas on T2W imaging. Attempts have formerly been made to correlate these MRI changes with clinical progression or diagnosis, with varying degrees of success. More clinical studies should be done to clarify the role of MRI findings in the diagnosis and prognosis of WD.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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