Clinical Neurology and Neurosurgery 138 (2015) 31–36

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

A study of MRI changes in Wilson disease and its correlation with clinical features and outcome

A. Ranjan[a], J. Kalita[a,*], S. Kumar[b], S.K. Bhoi[a], U.K. Misra[a]

[a] Department of Neurology, Sanjay Gandhi Post Graduate medical Sciences, Lucknow, India
[b] Department of Radiology, Sanjay Gandhi Post Graduate medical Sciences, Lucknow, India

ARTICLE INFO

Article history:
Received 9 June 2014
Received in revised form 12 January 2015
Accepted 5 July 2015
Available online 21 July 2015

Keywords:
Wilson disease
MRI
DRI
ADC
FLAIR
Movement disorder
Cognitive impairment
Chorea
Athetosis
Worsening

ABSTRACT

Objective: To evaluate the sensitivity of different MRI sequences in Wilson disease (WD) with neurological manifestations and its correlation with clinical features and outcome.
Methods: 34 WD patients with neurological manifestation with a median age of 14 years were included. Their Mini Mental State Examination (MMSE) score, movement disorders and laboratory findings were noted. Cranial MRI in T1, T2, FLAIR and DW sequences were done. Outcome at 6 months was categorized into improved (>1 grade improvement), static or worsening.
Results: MRI was abnormal in all and revealed involvement of putamen in 29 (85.3%), caudate in 23 (67.6%), brainstem and globus pallidus in 21 (61.8%) each, thalamus in 20 (58.8%), cerebral cortex in 9 (26.5%), subcortical white matter in 8 (23.5%), and cerebellum in 2 (5.9%) patients. The overall sensitivity of T2 and FLAIR was 97.1% each, DWI 38.2% and T1 31.4%. None had contrast enhancement and 4 had reduced ADC value. Choreoathetosis correlated with thalamic, pallidal and putaminal lesions; MMSE with subcortical white mater. MRI load correlated with age, tremor, psychiatric disorder, choreoathetosis, and severity of WD. At 6 months 9 (26.5%) patients improved, 18 (52.9%) remained static and 6 (17.6%) deteriorated.
Conclusion: In neurologic WD, putaminal involvement is the commonest; T2 and FLAIR sequences have similar sensitivity and number of MRI lesions correlated with disease severity but not with outcome.

1. Introduction

Wilson disease (WD) is an autosomal recessive disease due to mutation of ATP7B gene in chromosome 13q 14.3. This genetic defect results in impaired excretion of copper into the bile resulting in accumulation of copper in liver, kidney, cornea, brain and other body organs. Neurological manifestation in WD occurs in the second decade and manifests with cognitive decline, drooling, extrapyramidal and pyramidal features. Cranial MRI reveals characteristic signal changes which are reported to correlate with neurological symptoms and severity of illness [1]. In a large study on cranial MRI, putaminal involvement was the commonest (72%) followed by cerebral atrophy (70%), brainstem (66%), caudate (61%) and thalamic (58%) involvement. Cerebellum was least affected in this study. MRI changes correlated with disease severity but not with duration of illness [2]. The sensitivity of different MRI sequence may vary in revealing the pathological changes. MRI changes may also suggest the disease severity and predict the outcome. There is paucity of studies evaluating the sensitivity of various MRI sequences in WD. In a study, FLAIR sequence revealed abnormality in all symptomatic WD but DW1 was abnormal in 84.6% patients [3]. Abnormality in DW1 correlated with clinical disability [3]. The diagnostic and prognostic role of different MRI sequences therefore may be different. There is no study evaluating the role of MRI sequence in the prognosis of WD. In this study, we therefore evaluate the sensitivity of different MRI sequences in revealing abnormality in WD patients with neurological manifestations and their correlation with disease severity and outcome.

2. Subjects and methods

2.1. Inclusion

Consecutive patients with WD having neurological manifestations who attended to the neurology service of Sanjay Gandhi Post Graduate Institute of Medical Sciences during last 6 years were included. The patients enrolled during 2009–2013 were

* Corresponding author at: Department of Neurology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Raebareily Road, Lucknow-226014, India. Tel.: +91 522 2494177; fax: +91 522 2668811.
E-mail addresses: jayanteek@yahoo.com, jkalita@sgpgi.ac.in (J. Kalita).

http://dx.doi.org/10.1016/j.clineuro.2015.07.013
0303-8467/

prospectively evaluated. Those patients who were enrolled prior to 2009 were retrospectively analyzed from a prospectively maintained WD registry. Their data were retrieved from the computerized hospital information service and their MRI scans were reanalyzed by a neuroradiologist (S.K.). The diagnosis of WD was based on characteristic clinical findings, presence of KF ring on slit lamp examination, low serum ceruloplasmin level (<20 mg/dl) and 24 h urinary excretion of copper >40 μg/day [4].

2.2. Exclusion

WD patient with incomplete clinical data or not having cranial MRI scans for reevaluation were excluded. The patients with only hepatic manifestations were also excluded.

2.3. Evaluation

A detailed clinical history and examination were carried out. The age at onset of neurological symptoms, duration of illness and prior history of hepatic dysfunction were noted. Pedigree chart was drawn and presence of anemia, jaundice, edema, ascites, and hepatosplenomegaly were noted. Cognitive examination was evaluated by Mini Mental State Examination (MMSE) scale. The severity of dystonia was measured by Burke-Fahn-Mardsen (BFM) score [5]. Presence of chorea, athetosis, dystonia, rigidity, tremor and myoclonus were noted and their severity on a 0–4 scale was assessed. The neurological severity of WD was assessed on a I–IV grade based on various movement disorders and activity of daily living [ADL] [6,7]. Muscle power, tone, tendon reflexes and cerebellar signs were noted. Sensations of touch, pinprick, joint position and vibration were noted.

2.4. Investigation

Blood count, hemoglobin, ESR, fasting blood sugar, serum creatinine, bilirubin, transaminases, lactate dehydrogenase, albumin, calcium, alkaline phosphatase, potassium and sodium were measured. Ultrasound abdomen was done. Activated partial thromboplastin and prothrombin time, slit lamp examination for KF ring and ocular examination were done for sunflower cataract. Cranial MRI was done using 3T scanner (Signa, GE medical system, Wisconsin, USA) in the patients who were enrolled after 2008 and those enrolled earlier using 1.5T scanner (Echospeed Plus, Signa, Milwaukee, WI). The 3T MRI parameters for various sequences were as follows: T1 [repetition time ((TR) 1254, echo time (TE) 11.6, matrix 512 × 256, NEX 1], T2 (TR 5600, TE 95.5, matrix 320 × 320, NEX 1) and fluid attenuated inversion recovery [FLAIR; TI 2250, TR 8802, TE 86.1, matrix 256 × 160, NEX 1), diffusion weighted imaging [DWI; TR 5600, TE 73.3, matrix 128 × 160, NEX 1] with two *b* values (0 and 1000 s/mm^2) taken in three orthogonal directions. The specifications of 1.5T scanner were as follows: T1 (TR 440, TE 9), T2 (TR 4300, TE 81), FLAIR (T1 2200, TR 9002, TE 133), DWI (TR 10,000, TE 101) and *b* value was set at 1000 s/mm^2. Field of view of 24 × 24 was applied to all sequences and matrix size was 256 × 256. All images in all sequences were 5 mm thick and inter-slice gap was 0.5 mm. Acquisition was done after one excitation.

Gadolinium enhanced T1 contrast was done in some patients. The presence of abnormal signal changes in different MR sequences and its location were noted. For assessing MRI lesion load, the total number of MRI lesions on T2/FLAIR in both supra and infra tentorial location was calculated in individual patient.

2.5. Treatment and fellow up

The patients were treated with zinc (50 mg daily) with or without penicillamine. Penicillamine was started in a dose of 250 mg daily and increased very slowly (at 4–5 weeks interval) depending on the tolerability and response. The patients were followed up at 3 and 6 months or earlier if needed. The severity of WD and BFM score were recorded at 3 and 6 months follow up. Blood count and liver function tests were also carried out at follow up.

2.6. Statistical analysis

The sensitivity of MRI abnormality on T1, T2, FLAIR and DWI was calculated. The severity of WD, BFM score were correlated with location and total number of lesions. The correlation of various movement disorders were also correlated with location of MRI lesion such as thalamic, caudate, corpus striatum, globus pallidus and brainstem. The outcome of the patients at 6 months (improved, static or worsened) was correlated with location and total number of MRI lesions. The categorical data were compared using Fisher Exact test and continuous variable using independent t or Mann–Whitney *U* test. The predictors of outcome were evaluated using binary logistic regression analysis including the variables having a *P* value of <0.1 on univariate analysis. The variable having a 2 tailed *P* value <0.05 was considered significant. The statistical analysis was done using SPSS 16 version software.

3. Results

There were 34 patients with neurologic WD in whom all the four sequences of MRI were available for review. Their age ranged between 9 and 41 (median 14) years and 6 were females. Family history of WD was present in 12 patients. The median duration of neurological symptoms was 18 (range 2–156) months and median age of onset of neurological symptoms was 11 (range7–39) years. Fifteen patients had jaundice in the past. Five patients had seizure; focal with secondary generalized in 1 and generalized tonic clonic in 3 patients. Twenty-five patients had drooling and MMSE was abnormal in 13 patients but none had severe dementia (MMSE score < 11).

Movement disorder was present in all the patients; dystonia in 32, tremor in 18, choreoathetosis in 13 and myoclonus in 5. The BFM score ranged between 0 and 90 (median 49). Majority of the patients had moderate to severe WD; the severity of WD was grade III in 16, grade II in 16 and grade I in 2 patients.

3.1. Investigations

Sixteen patients were anemic (<12 gm/dl), 6 had leukopenia (<4000/mm^3) and 25 had thrombocytopenia (<1 lac/mm^3). SGPT was although raised (>40 IU/L) in 22 patients but bilirubin was high (>1.3 mg/dl) in 1 patient only. Seven patients had hypoalbuminemia (<3.5 gm/dl) and 16 had features of chronic liver disease on ultrasound abdomen.

3.2. Cranial MRI

Cranial MRI was abnormal in all the patients. The commonest site of involvement was putamen in 29 (85.3%) followed by caudate in 23 (67.6%), brain stem in 21 (61.8%; mid brain in 11, mid brain and pons in 10), globus pallidus in 21 (61.8%), thalamus in 20 (58.8%), and cerebral cortex in 10 (29.5%; frontal 6, frontoparietal 2, occipital 2), subcortical white matter in 8 (23.5%) and cerebellum in 2 (5.9%) patients (Fig. 1). Cortical atrophy was present in 7 (20.5%) patients. In 14 patients, there was abnormality in DWI but only 4 patients showed diffusion restriction with mean ADC value of 6.4×10^{-3} mm^2/s. The MRI lesions were hypointense in T1 and hyperintense in T2 and FLAIR sequence. Details of basal ganglia lesion with various movement disorders are summarized in Table 1. Thalamic, basal ganglia and brainstem lesions were bilateral in all