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Clinical Study

Non-Wilsonian hepatolenticular degeneration: Clinical and MRI observations in four families from south India

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ABSTRACT

Non-Wilsonian hepatolenticular degeneration (NWHD) is a heterogeneous neurological disorder occurring secondary to chronic acquired liver disease. Genetically determined familial NWHD is rare, poorly understood, and often mistaken for Wilson's disease (WD). We analysed clinical and MRI profiles of NWHD patients who did not have obvious cause for acquired liver disease, such as alcohol intake or hepatitis. Six patients from four families (four males, two females, mean age: 17.0 ± standard deviation 7.9 years), presenting with chronic extrapyramidal disorder resembling WD and imaging (abdominal ultrasound/MRI) evidence of cirrhosis were studied. They lacked Kayser–Fleischer rings or biochemical and/or genetic evidence of WD. Clinical features included dystonia (n = 6), parkinsonism (n = 3), tremor (n = 1), cerebellar ataxia (n = 3), orofacial dyskinesia (n = 1), behavioural abnormalities (n = 3), and cognitive decline (n = 1). Brain MRI revealed T1-weighted hyperintensity in the pallidum (n = 6), crus cerebri (n = 4), putamen (n = 1), caudate (n = 1), thalamus (n = 1), and red nucleus (n = 1) with T2-weighted shortening in some of these regions. Additional findings included giant cisterna magna (n = 1), face of giant panda sign (n = 1) and thin corpus callosum (n = 1). Areas of "blooming" on susceptibility weighted images were noted in two patients in the caudate (n = 2) and putamen (n = 1). The finding of T1 shortening is distinct from that of WD where the majority of lesions are T1-hypointense and T2-hyperintense. Extrapallidal T1-hyperintensity is also an exceptional observation in NWHD. The MRI appearance of intense T1 shortening coupled with the lack of increased susceptibility changes suggests that the most likely mineral deposited is manganese. The association of this neurological disorder and cirrhosis of the liver in the absence of an acquired liver disease is a distinct disease entity. This syndrome may represent a disorder of manganese metabolism resulting in its toxic deposition.

1. Introduction

Non-Wilsonian hepatolenticular degeneration (NWHD) is a heterogeneous neurological disorder resulting from chronic hepatic dysfunction and is characterised by neuropsychiatric, cerebellar and extrapyramidal disorders occurring in varying combinations. This entity was first recognised nearly a century ago by van Woerkem, whose seminal work almost coincided with that of Sir S.A.K. Wilson [1]. While there has been a tremendous progress in the treatment of Wilson's disease (WD), the pathophysiological basis and specific and effective treatment for NWHD remains enigmatic and elusive. NWHD is purported to be more prevalent than WD, yet it continues to be an ill-defined and under-recognised disorder. NWHD in the absence of acquired liver disorder is a recently recognised entity [2,3]. We describe the clinical and imaging features in six patients with NWHD from four families.

2. Patients and methods

The National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, India, is a large university teaching hospital and a tertiary care referral centre for neuropsychiatric patients in south India. A specialty clinic for WD is run at NIMHANS that provides treatment to these patients free of cost, including decoppering agents, namely zinc sulphate and d-penicillamine. Between January 2001 and December 2012, six patients were

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referred to the WD clinic with a diagnosis of WD based on the presence of (i) a neurological disorder dominated by an extrapyramidal syndrome, reminiscent of WD; and (ii) a chronic liver disease in the form of symptomatic jaundice and/or radiological evidence of cirrhosis. However, these patients did not have biochemical and/or genetic evidence of WD. None of the patients had a history of alcohol abuse. Tests for other causes of liver dysfunction were undertaken based on clinical suspicion. These patients did not have episodes of encephalopathy associated with acute hepatic decompensation or hepatic myelopathy as the lone neurological manifestation.

The clinical features and brain MRI features of these patients were studied. Data regarding the demography and clinical features were collected, namely detailed history, family pedigree, sex, age at onset, duration and evolution, course, type of extrapyramidal features, clinical diagnosis, follow-up data, laboratory tests, specific tests such as slit lamp examination for Kayser–Fleischer (KF) ring, serum copper, serum ceruloplasmin, 24 hour urinary copper excretion, and abdominal ultrasound. Clinical information was extracted from the archived medical records. Ethical approval was obtained from local Institute Ethics Committee and written informed consent was obtained.

Brain MRI of these patients were retrieved from the Picture Archival and Communication System. All patients underwent cranial MRI in a 1.5 Tesla (Siemens-Magnetom; Siemens AG, Erlangen, Germany) or 3.0 Tesla (Philips-Achieva Royal; Philips Electronics, Amsterdam, The Netherlands) scanner after providing informed consent. Images were acquired using standard protocols (acquisition time 2.5 minutes, matrix 256 × 256 and 230 mm field of view), axial and sagittal spin echo T1-weighted images (repetition time [TR] = 650 ms, echo time [TE] = 14 ms), axial, sagittal and coronal T2-weighted images (TR = 12,000 ms, TE = 120 ms), axial fluid attenuation and inversion recovery sequences (TR = 9000 ms, TE = 119 ms), post-gadolinium T1-weighted sequences and susceptibility weighted images (SWI; TR = 40 ms; TE = 23 ms). The abnormal findings in T1, T2 and SWI sequences were recorded separately. MRI observations were recorded by two authors (M.N., S.S.) and in case of disagreement consensus was arrived at by discussion with the other authors. The data thus obtained was incorporated into a Microsoft Excel spreadsheet for analysis (Microsoft, Redmond, WA, USA).

3. Results

3.1. Clinical features

Six patients (four males, two females) from four families were studied. The mean age at presentation was 17.0 years (standard deviation: 7.9; median: 14 years; range: 10–30 years) and mean duration of symptoms was 40.7 months (standard deviation: 55.0; median: 21 months; range: 1–120 months). All had normal developmental milestones. All patients had extrapyramidal involvement. None had KF rings on slit lamp examination or acanthocytes in peripheral smear. The clinical course was progressive in two and fluctuating in the rest. Additional investigations in the form of muscle biopsy (n = 2) and bone marrow aspirate (n = 2) tested for mitochondrial and storage disorders drew negative results. Genetic studies for WD were done in four patients from two families, but revealed no mutations in the *ATP7B* gene. The MRI findings are summarised in Table 1.

3.2. Patient 1

Patient 1 presented with progressive difficulty in walking, frequent falls, dysphagia, dysarthria and intellectual decline since 6 years of age. He was found to have dystonia, facial hypomimia, rigidity, bradykinesia, pseudobulbar affect and ataxia on examination. There was a history of similar illness in his older brother. There was a history of jaundice but his current liver function test (LFT) was normal. The serum copper (156 mcg/dl; reference [ref]: 75–160 mcg/dl), serum ceruloplasmin (18 mg/dl; ref: 15–35 mg/dl), serum parathyroid hormone (44.1 pg/ml; ref: 10–62 pg/ml) and serum total hexosaminidase (1333 nmol/hour/ml; ref: 333–750 nmol/hour/ml) were normal. Tandem mass spectrometry screening for inborn errors of metabolism showed mild non-specific elevation of alanine (593.79 μmol/l; ref: 112–480 μmol/l). Bone marrow aspirate and biopsy of the biceps muscle did not reveal evidence of a storage disorder or mitochondrial cytopathy. Brain MRI showed T1 hyperintensity in the caudate, lentiform nuclei, red nuclei, crus cerebri and periventricular white matter. There was T1 hyperintensity running antero-posteriorly along the middle of the thalamus. SWI showed "blooming" of the caudate and putamen (Fig. 1A–D). Additional findings included a thin corpus callosum and reduced white matter volume.

3.3. Patient 2, 3, 4

The proband was Patient 2 (Table 1), a 10-year-old boy, who presented with recurrent episodes of jaundice, abdominal pain, and nausea. He had hepatosplenomegaly and dystonia of extremities. He was born to non-consanguineous parents and had a normal birth and developmental milestones. Haemogram showed bicytopenia: haemoglobin 11.1 g/dl, total count 3900/mm^3; platelet count 100,000/mm^3. LFT were abnormal, with bilirubin 2.7 mg/dl; aspartate transaminase 274 U/l and alanine transaminase 120 U/l. Serum copper (113 mcg/dl), and ceruloplasmin (28 mg/dl) were normal. Endoscopic evaluation of the upper gastrointestinal tract showed grade II oesophageal varices. At the age of 16 years, he developed transient painful swelling of his knees. He developed psychiatric manifestations at the age of 17 years in the form of

Table 1
MRI findings in seven patients with non-Wilsonian hepatolenticular degeneration

Patient	Hyperintensity on T1W	Hyperintensity on T2W/FLAIR	Hypointensity on T2W/blooming on SWI	Other
1	Caudate, putamen, globus pallidus, red nucleus, thalamus, crus cerebri	–	T2W hypointense: caudate, putamen, globus pallidus, red nucleus SWI blooming: caudate, putamen	Thin corpus callosum
2	Globus pallidus, crus cerebri	Discrete white matter changes	–	Diffuse atrophy
3	Globus pallidus, crus cerebri	–	–	–
4	Globus pallidus	–	T2W hypointense: globus pallidus	–
5	Globus pallidus, crus cerebri	–	–	–
6	Globus pallidus	Discrete white matter changes	SWI blooming: caudate	Giant cisterna magna, face of giant panda sign, mild cerebellar atrophy

FLAIR = fluid attenuated inversion recovery imaging, SWI = susceptibility weighted imaging, T1W = T1-weighted imaging, T2W = T2-weighted imaging.