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MRI and oxidative stress markers in neurological worsening of Wilson disease following penicillamine

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ABSTRACT

Background and aim: There is no report of MRI correlation with neurological worsening following chelating treatment in Wilson disease with neurological manifestation (WDN). We report radiological changes in four patients with WDN who worsen after penicillamine.

Methods: WDN was diagnosed on the basis of clinical, KF ring, serum ceruloplasmin and 24 h urinary copper. Hematological, biochemical and cranial MRI were repeated at the time of clinical deterioration following chelating treatment.

Results: Four WDN patients had neurological deterioration within 4–8 weeks of penicillamine therapy. This was associated with new lesions in white matter, thalamus, pons and mid brain and these lesions showed diffusion restriction. The neurologic deterioration was associated with increased free serum copper and malanodialdehyde and reduced glutathione. Clinical conditions stabilized after few weeks of penicillamine discontinuation.

Conclusion: Neurological worsening was associated with new lesions on MRI which revealed diffusion restriction. Increased free copper induced oxidative stress may be responsible for these changes.

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1. Introduction

Wilson disease (WD) is an autosomal recessive disease due to ATP7B mutation in the chromosome 13q14.3 and is regarded as one of the treatable hereditary metabolic disease (Bull et al., 1993; Thomas et al., 1995). Treatment in early and asymptomatic WD may be more rewarding than the WD patient with hepatic failure or severe neurological symptoms. Following chelating treatment, there is release of free copper from the liver to the circulating blood which may damage other organs. Brain is although a privileged organ to toxic and infectious injury because of its tight blood brain and blood–cerebrospinal fluid barrier, but free copper is known to penetrate the blood brain barrier resulting in brain injury (Choi and Zheng, 2009). Glutathione (GSH) is a potent water soluble antioxidant and malanodialdehyde (MDA) is an end product of lipid peroxidation and its elevated level suggests oxidative stress. Measurement of GSH and MDA levels therefore may help in assessing the free radical induced oxidative stress (Gaetke and Chow, 2003; Ozcelik and Uzun, 2009; Rossi et al., 2006; Samuele et al., 2005). Deterioration in neurological status has been reported in up to 50% of patients with WD following penicillamine and 26% following trientine treatment (Brewer et al., 1987, 2006; Kalita et al., 2014a). The clinical worsening although has been documented in earlier study but its correlation with MRI and oxidative stress markers have not been evaluated. In this communication, we report four patients with Wilson disease with neurological manifestation who had worsened following penicillamine treatment. We report their sequential MRI changes and discuss the possible mechanism in the light of serum free copper, antioxidant (GSH) and oxidative stress (MDA) markers.

2. Subjects and methods

Four patients with WD with neurological manifestation were included who deteriorated neurologically after penicillamine therapy. The diagnosis of WD was based on characteristic clinical findings, low serum ceruloplasmin (<20 mg/dl), Kayser–Fleischer ring on slit lamp examination and increased urinary excretion of copper (>40 μg/24 h) (Roberts et al., 2008). The severity of neurological manifestation was categorized into grade I to III and dystonia was assessed using Burke–Fahn–Marsden (BFM) scale (Burke et al., 1985; Grimm et al., 1991). Presence of cognitive

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impairment, various movement disorders, pyramidal and cerebellar signs was noted. Blood counts, hemoglobin, ESR, liver and kidney function tests, serum calcium, alkaline phosphatase and ultrasound abdomen were done. Cranial MRI was done using a 3 T MRI machine and T1, T2, FLAIR and DW sequences were obtained. Patients were treated with penicillamine 250 mg daily which increased every 2 weeks by 250 mg up to 1000 mg daily. Zinc carbonate (50–150 mg daily) was prescribed to all. Dystonia was treated with trihexyphenidyl, benzodiazepine, and tetrabenazine in various combinations. The patients were followed up at 1, 3 and 6 months or earlier if indicated. Their clinical, biochemical and repeat MRI findings were noted. Serum free copper and plasma GSH and MDA levels were measured at baseline, at the time of deterioration and when they stabilized (Kalita et al., 2014b). Plasma GSH was measured by spectrophotometer at 412 nm according to the method described by Tietze (1969). Plasma lipid peroxidation (LPO) was measured by assessing MDA level, according to the method described by Janero (1990). The GSH level in normal controls is 2.73 ± 0.04 mg/dl and MDA 3.03 ± 0.52 nmol/ml which were derived from 64 healthy individuals and have been reported in our earlier study (Kalita et al., 2014b).

2.1. Patient #1

A 22-years-old young male presented with declining scholastic performance for 4 years, behavioral abnormality for 10 months, and tremor and dystonia for 4 months. He was treated with antipsychotics drug due to his aggressive and violent behavior and one attempt of suicide. He did not have a history of jaundice and family history of similar disease. He had KF ring and his Mini Mental State Examination (MMSE) score was 20. He had upper limb tremor and dystonia with moderate oromandibular dystonia. Tendon reflexes were brisk. His blood counts, liver and kidney function tests, serum electrolytes, calcium and phosphorus were normal. Ultrasound abdomen revealed evidences of chronic liver disease. His serum free copper was 38 mg/dl and ceruloplasmin 15.1 mg/dl. Cranial MRI revealed frontal white matter (right -> left), bilateral medial thalami, midbrain and pontine lesions which were hyperintense on T2 and FLAIR. He was prescribed penicillamine 250 mg daily, zinc carbonate 50 mg thrice daily, trihexyphenidyl 2 mg thrice daily and clonazepam 0.5 mg twice daily. Two months later, he came with rapidly progressive visual loss, postural instability, anarthria and severe dystonia resulting in deterioration in WD severity grade from 2 to 3. His serum free copper was increased and repeat MRI revealed extensive bilateral frontal, left parieto-occipital white matter hyperintensity of T2 and FLAIR. These new lesions showed restricted diffusion on DWI and the apparent diffusion coefficient (ADC) value was high. There was no deterioration in hematological, liver and kidney function parameters. Penicillamine was stopped, at 3 months he was stabilized but was dependent for activities of daily living (ADL). At 6 months, he improved slightly and his repeat MRI revealed disappearance of thalamic, midbrain and pontine lesions. The cortico-subcortical lesions were regressed which were hyperintense on T2 and FLAIR but did not reveal diffusion restriction on DWI (Fig. 1).

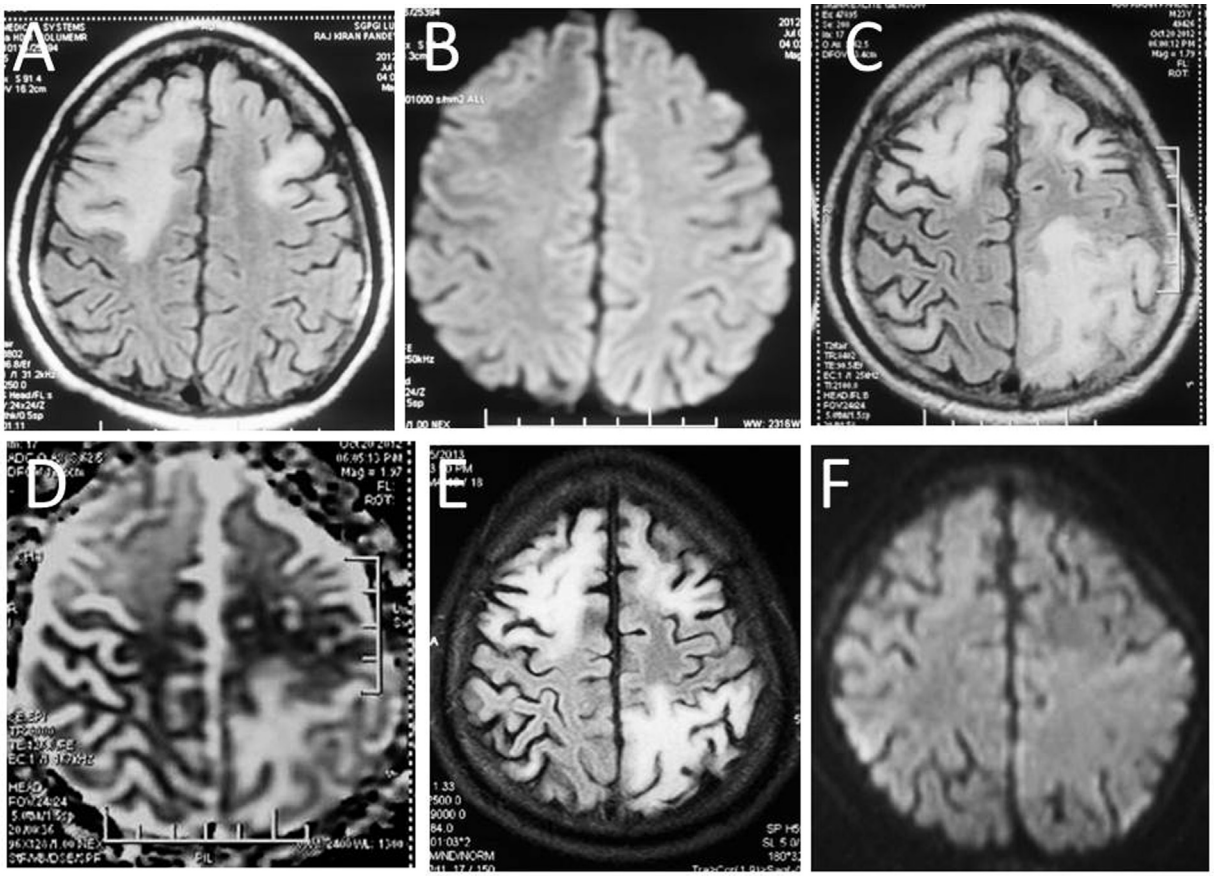

Fig. 1. MRI of patient #1. A and B are baseline MRI images showing right frontal hyper intense lesion on FLAIR but DWI did not show restriction. C and D are repeat MRI after 2 months of penicillamine when he had worsening. There are additional new lesions in left parietal region on FLAIR (C) and the left parietal lesion revealed restricted diffusion on DWI (D). E and F are MRI at 6 months and revealed mild regression of lesion on FLAIR (E) and these lesions did not reveal restriction on DWI (F).

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