

Extensive Gray & White Matter Abnormalities In Wilson's Disease: A Case Report

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INTRODUCTION

Wilson's Disease is a recessively inherited disorder of copper metabolism in individuals, traced to the ATP-7B gene locus on long arm of Chromosome 13 which codes for the synthesis of ceruloplasmin, a copper protein transporter [1]. Normally, copper loss occurs through bile and into faeces. In Wilson's disease biliary excretion of copper is impaired and body copper progressively increases, especially in the liver, brain, kidneys and cornea. The serum Ceruloplasmin is low and excessive copper exists in the plasma and urine [1, 2]. The excess copper leads to tissue injury and if not effectively treated, may lead to death [1, 2].

Clinical presentation of Wilson's Disease is between 5 to 50 years [2]. However, early childhood Wilson's disease usually presents with chronic liver disease or hemolytic anemia and neurological manifestations are rare before the age of ten years [1]. Most radiologists are well aware of the frequently described basal ganglia and brainstem abnormalities as well as cerebral atrophy in Wilson's Disease. However, besides the better known basal ganglia lesions, extensive gray matter and even white matter lesions may occur, though much less frequently [3,4]. We report a child of Wilson's Disease with extensive gray and white matter abnormalities and briefly discuss the relevant literature.

CASE REPORT

A 14 year old boy presented with increasing difficulty in walking, speech articulation, swallowing and resting tremors of 3 years duration. These complaints were observed by relatives to be accompanied by vacant staring, masklike facies, mild behavioral and mental abnormalities. There was no history of similar complaints or other major illness in the patient's family. On

examination there was bradykinesia, and slow response to commands, drooling of saliva and gaze fixation distractibility. Motor examination revealed abnormal rigidity and posturing with exaggerated deep tendon reflexes. Sensory and systemic examination were normal except for mild hepatomegaly. Ophthalmological study showed bilateral Kayser Fleischer rings. A provisional clinical diagnosis of Wilson's Disease was considered.

Laboratory investigations revealed Serum Ceruloplasmin = 4mg/dl (N = 18-35mg/dl); Serum Copper = 57.9 µg/dl (N=70-140 µg/dl) 24 hours Urine Copper = 766 µg (N = 20-35 µg).

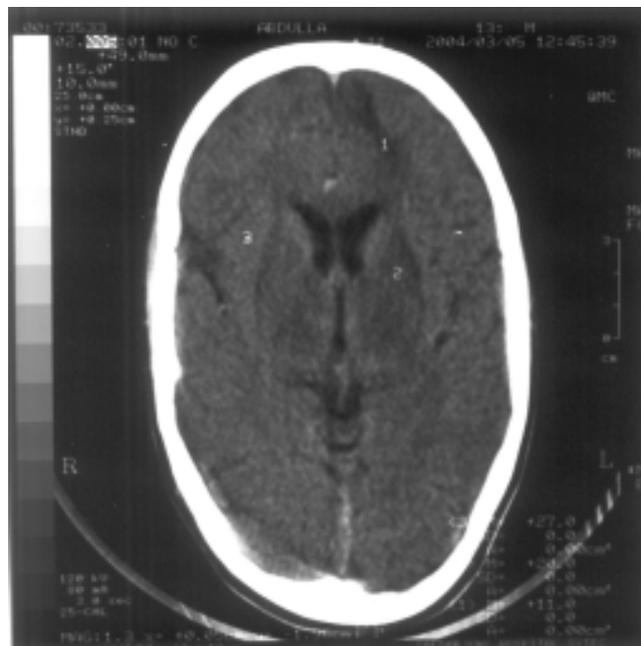


Fig 1. NCCT Scan shows hypodensity in left frontal lobe and bilateral basal ganglia.

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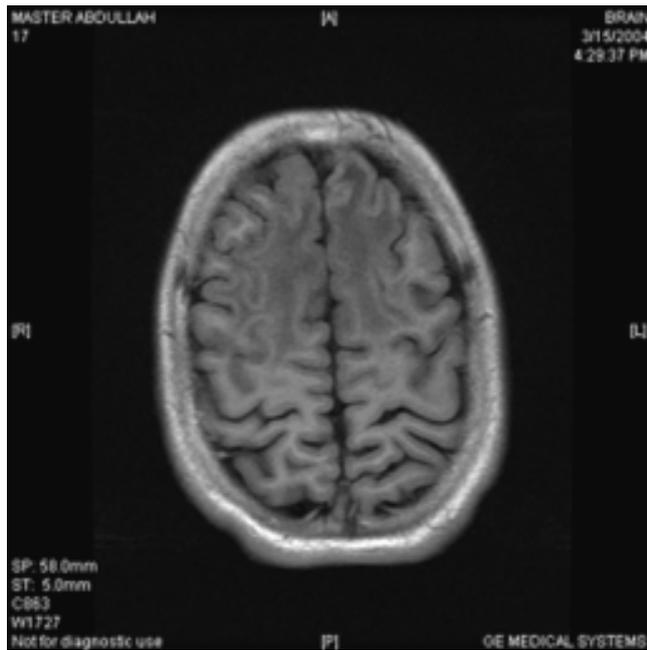


Fig 2a. T1-weighted image shows confluent hypointensities in the cortical gray matter and subcortical white matter of frontoparietal lobes.

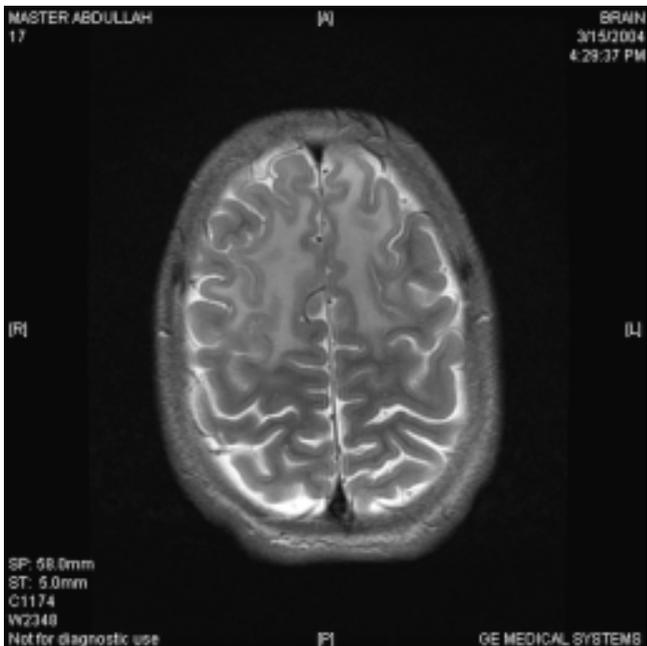


Fig 2b. T2- weighted axial image reveals altered signal intensity in bilateral fronto-parietal lobes.

Gray scale sonography revealed coarse echotexture of the liver with hepatomegaly. CT Scan brain revealed hypodensity in left frontal lobe and hypodensities in bilateral basal ganglia and thalami (Fig.1). On MRI, the T1 & T2weighted images revealed altered signal intensity in the cortical gray matter and subcortical white matter of frontoparietal lobes (Fig.2a,2b). T2-weighted images in axial, coronal and sagittal planes revealed confluent hyperintensities in the cortical gray matter and subcortical

white matter of frontal, parietal and temporal lobes with partial effacement of adjacent sulci. Bilateral basal ganglia, thalami, mid brain and pons showed symmetrical hyperintensity (Figs 3,4&5). Skeletal survey revealed mild osteopenia with periarticular osteoporosis. Hence a final diagnosis of Wilson's Disease was made and treatment with penicillamine 750mg/day along with anticonvulsant and other supportive measures was initiated.

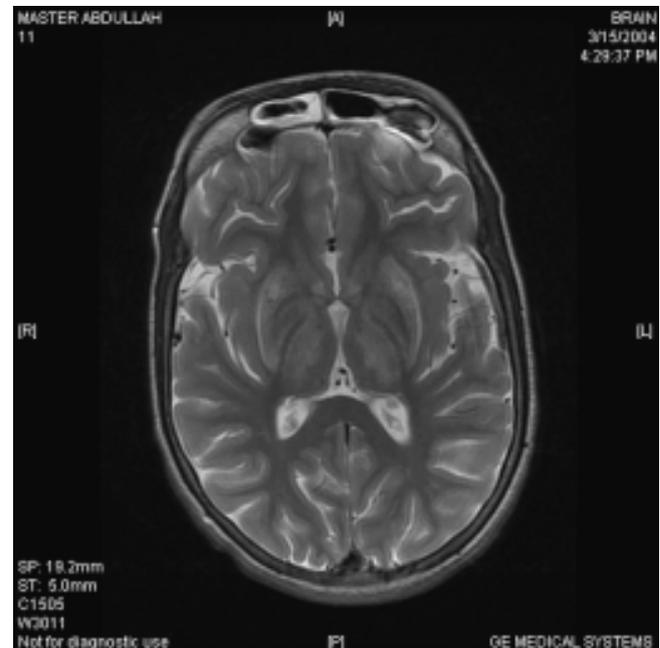


Fig 3. Axial T2- weighted image reveals hyperintensity in bilateral basal ganglia and thalami.



Fig 4. Sagittal T2- weighted image reveals increased signal intensity in frontoparietotemporal subcortical white matter with partially effaced gyri and sulci.

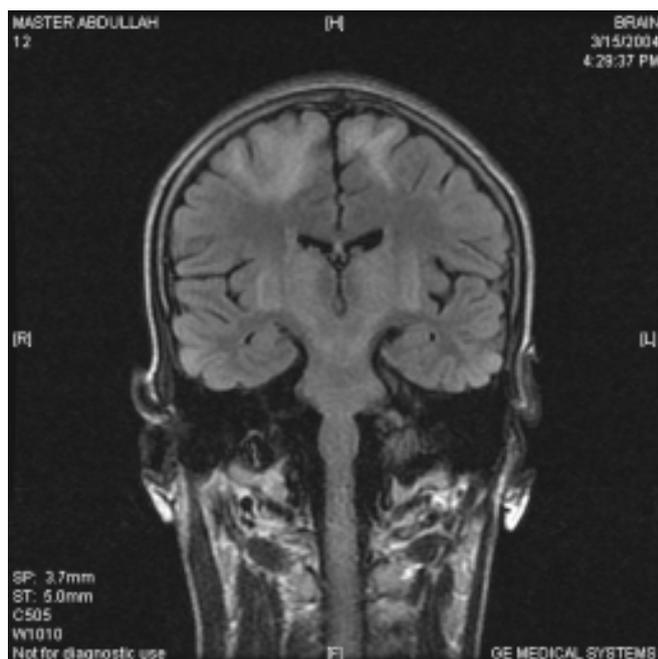


Fig 5. T2-weighted FLAIR coronal image shows increased signal intensity in the cortical gray matter and subcortical white matter of both frontal lobes and centrum semiovale along with increased signal intensities in the cortical gray matter of both temporal lobes, both basal ganglia, thalami, midbrain and pons.

DISCUSSION

Clinical presentation of Wilson's Disease is mostly hepato - neuro-ocular, ranging from the asymptomatic to a fulminant variety with hepatitis, portal hypertension, protean neurological and psychiatric symptoms. Diagnosis is based on clinical evaluation along with biochemical and neuroimaging confirmation. Biochemical studies reveal a low serum ceruloplasmin level (<20 mg/dl) and increased urinary copper excretion (more than >100 µg copper per 24 hours). Hepatic copper estimation, of more than 250 µg/g of dry tissue (Normal 15-55 µg/g) is the most definitive method of diagnosis[2].

In patients with Wilson's Disease, neuroimaging abnormalities occur in gray matter of lentiform, caudate and thalamic nuclei [3,4]. Our patient also had gray matter abnormalities in the thalami, temporal lobes, midbrain and pons. Cerebral atrophy with ventricular dilatation especially of the frontal horns and cerebellar atrophy are also frequently observed in Wilson's Disease [4]. Our patient did not have significant ventricular dilatation or cerebellar atrophy.

On CT, gray matter abnormalities manifest as hypodensities. On MRI, they are hypointense on T1-weighted images and hyperintense on T2-weighted sequences. The high signal intensity on T2 weighted images is believed to be due to edema, gliosis, necrosis and cystic degeneration[4,5]. Hypointensities on long TR

sequences have also been observed and are postulated to occur due to the paramagnetic effect of copper deposition [5].

White matter abnormalities were seen in our patient in the subcortical regions of frontal, parietal and temporal lobes manifesting as high signal intensity on T2W images. The striking white matter abnormalities as observed in our patient are unusual and have been infrequently reported. In Nazer et al's series of 6 patients, none had white matter lesions [6]. In one Indian report by Jha et al, a frequency of 10% incidence of white matter lesions was reported [7].

However, van Wassenauer-van Hall et al in 1995 had reported an incidence of 41% which was unusually high [3]. These investigators reported that white matter changes can occur in pyramidal and extra pyramidal system and primarily involve 3 tracts:- dentatorubrothalamic, pontocerebellar and corticospinal in a patchy or a continuous manner [3]. In contrast to gray matter lesions, which are mostly symmetrical, those in the white matter are usually asymmetrical as was seen in our patient [5]. On CT these appear as hypodense areas and MR imaging reveals decreased signal intensity on T1-weighted images and high signal intensity on T2-weighted images. This MR appearance is explained by investigators as occurring due to demyelination, softening, spongy degeneration and cavitation [3,4].

van Wassenauer-van Hall attempted to correlate the neuroimaging observations with clinical symptomatology. They observed that bradykinesia, rigidity and cognitive impairment correlated with 3rd ventricular dilatation; ataxia and tremors with thalamic abnormalities, dyskinesia and dysarthria corresponded to lentiform nuclear pathology [4].

However, whether extent of neuroimaging findings correlate with clinical prognosis and post therapeutic response, remains an ongoing debate in the literature. Nazer et al also observed that CT & MRI changes may lack correlation with neurological status and even worsen despite clinical improvement which occurs following therapy [6]. Prayer et al had reported that there is no correlation between morphological and functional alterations of the brain, and proposed that this was because impairment of cell metabolism precedes changes which are morphologically demonstrable [8].

Through our report we highlight that besides the basal ganglia and brainstem lesions in Wilson's Disease, gray matter lesions may be more extensive and furthermore that white matter abnormalities may also exist. Hence neuro-physicians, surgeons and radiologists should not only evaluate suspected patients of Wilson's Disease for

basal ganglial abnormalities but for more extensive gray matter pathology and also for white matter defects.

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