MRI OF THE BRAIN IN WILSON'S DISEASE PRESENTING WITH NEUROPSYCHIATRIC MANIFESTATION

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ABSTRACT

A 32- year old female patient is described presenting with neuropsychiatric manifestation of wilson's disease which was initally diagnosed on the basis of MR findings. MRI findings are reviewed.

CASE REPORT

A 32 year old woman who emigrated from Bosnia in 1994, first came to medical attention via an antenatal clinic in 1995 where she was noted to have mild thrombocytopenia [107 x10 / L]. This combined with her past obstetric history of three first trimester miscarriages raised the possibility of anti-phospholipid syndrome. On haematology review, an illness said to be haemolytic anemia in Bosnia in1989 was revealed.The illness spontaneously resolved in 2 weeks with no treatment. Further haemotology investigation showed a mild leucopenia [3.9X10 /L] as well as thrombocytopenia. ANA was 1:40. Anticardiolipin antibodies and lupus anticoagulant were negative. In early 1996 she had noted tremulousness, unsteadiness and poor concentration. The only abnormality on examination was a fine action tremor. She was refered to a psychiatrist for depression and was commenced on an selective serotonin reuptake inhibitor. This led to improvement in mood but after being on the drug for a month she developed generalised dystonia and rigidity. This persisted despite cessation of the drug.She had her first MRI which was reported as cerebral atrophy. She subsequently underwent electro-convulsive therapy with marked improvement in her mental state and in the dystonia and rigidity. She remained well for about 6 months but then developed progerssively worsening abnormal movements over the next 3 months. Her mobility was declining to the stage of requiring 2 people to assist her. She was admitted to the neurology unit for investigation.On examination she had fine action tremor of both hands, choreo-athetosis of all limb, and dystonic posturing of the limbs and trunk. There were no Kayser-Fleisher ring on opthalmoscopy. Her general examination finding was normal except for splenomegaly. Laboratory investigations showed persisting mild thrombocytopenia and leucopenia, a mild rise in liver transminase [ALT 36u/L] and ANA 1:160]. An MRI was performed on 1.5 T superconducting system [Siemens : with a 256 x 256 matrix.] Sagital T1 repitition time/ echo time/excitation 462/12/2, axial proton density, 4000/22/2, and axial T2 4000/90/2 and axial T2-weighted inversion recovery 7000/119/1, and inversion time of 2200msec. T2 weighted images showed increased

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signal intensities in the caudate nucleus, putamen particularly the lateral border, globus pallidus, the thalamus, the tegmentum, red nucleus and periaqueductal region of the midbrain and ventral pons, the claustrum, the superior and middle cerebeller peduncle and adjacent white matter and asymetric focal increase signal intensities in centrum semiovale (Fig 1-5) Areas of low signal intensity were peresent within the hyperintense basal ganglia. Inversion recovery sequences showed increased signal intensity in the dentate nucleus, superior cerebeller peduncle and sub-cortical white matter. (Fig 5B)

Serum cerruloplasmin was 77 [range 280-573 mg/L], 24 hour urinary copper was 11.3 [normal less than 1.6 micromol]. Slit- lamp examination did reveal the presence of Kaiser-Fleisher rings. The diagnosis of Wilson's disease was confirmed and penicillamine and zinc were commenced.

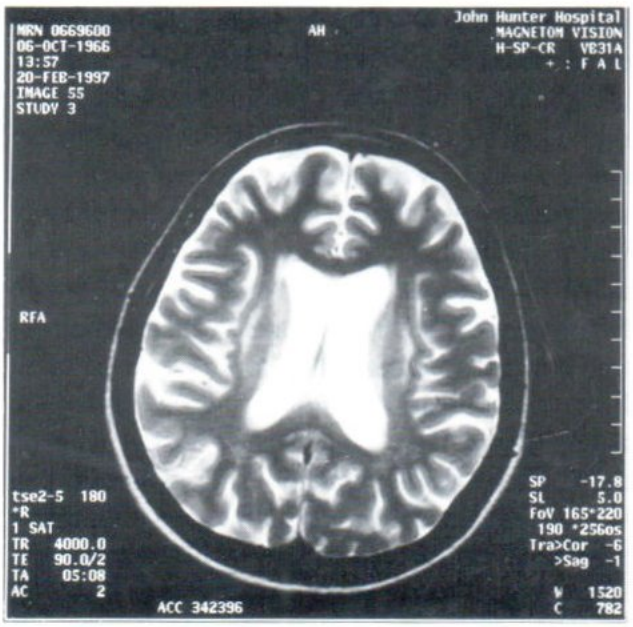

Fig.1 T2 -weighted MR image shows a thick hyperintense claustrum. Both caudate nuclei are hyperintense..

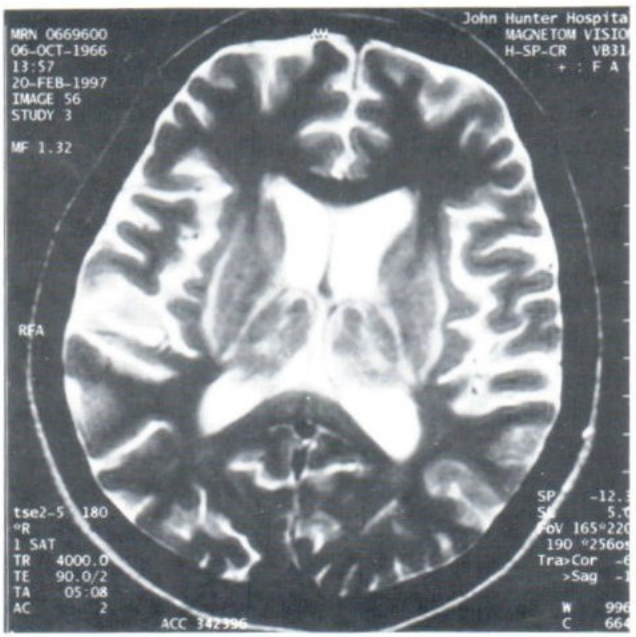

Fig.2 Axial T2-weighted image. High signal intensity in putamen particularly involving the outer rim, caudate nuclei and thalami. Low signal intensity areas are present within the hyperintense basal ganglia.

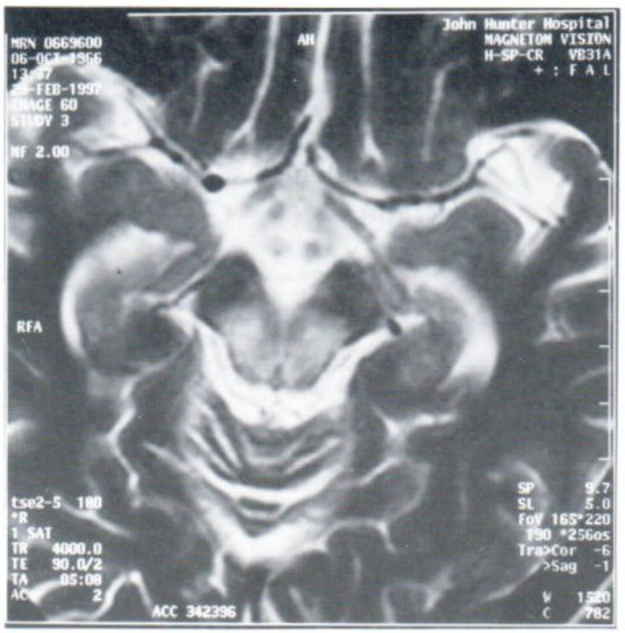

Fig.3 T2-weighted axial MR image through mid-brain shows diffuse increase signal intensity in tegmentum .

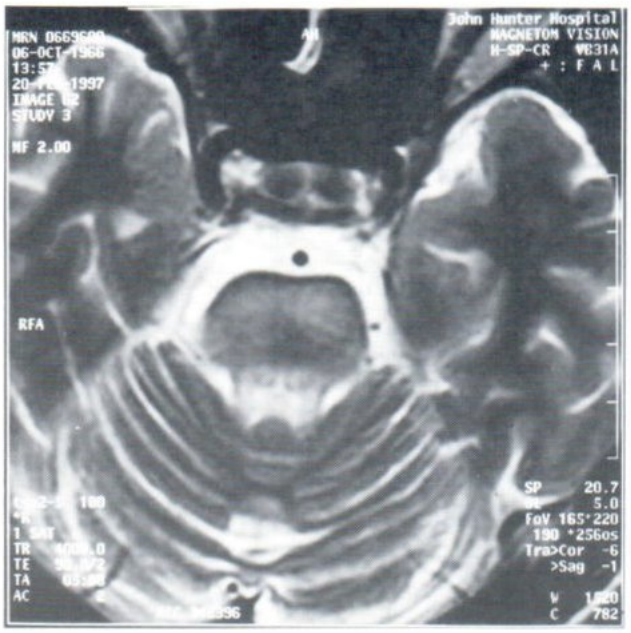

Fig.4 T2-weighted axial MR image through pons reveal increase signal intensity in central pons and superior cerebeller peduncle

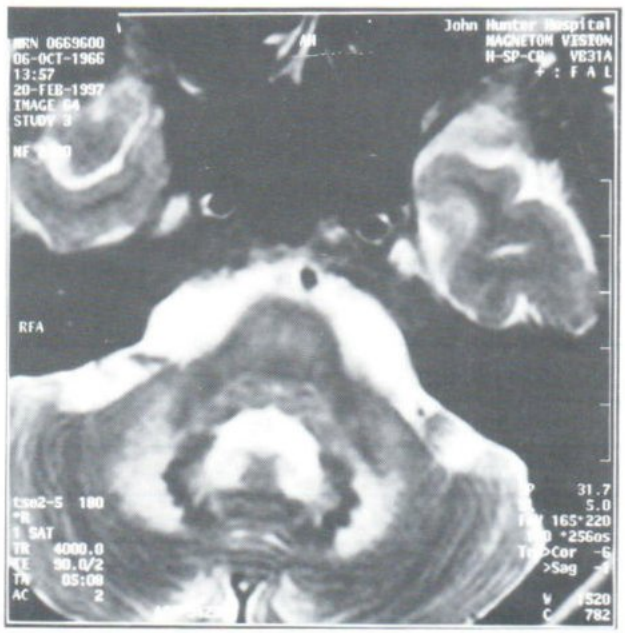

Fig.5 T2-weighted axial MR through cerebellum shows increased signal intensity in middle cerebeller peduncle

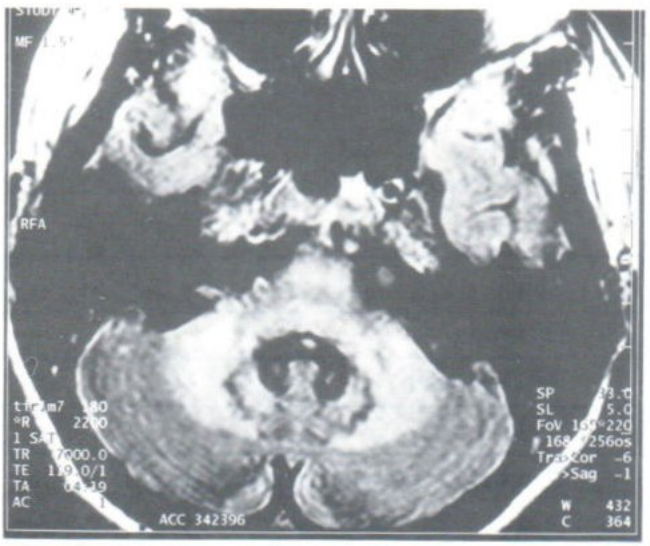

Fig.5 B Inversion recovery sequence demon strate increased signal intensity in cerebellar peduncle and adjacent white matter and dentate nuclei.

SUMMARY OF MRI FINDINGS

Basal ganglia	
Caudate nuclei	Diffuse
Putamen	Diffuse with high signal intensity outer rim
Glubus pallidus	
Thalami	Diffuse
Midbrain	
Tegmentum	
Periaqueductal gray matter	
Red nuclei	
Pon	Ventral
Cerebellum	
Superior peduncle	
Middle peduncle	
Dentate nuclei	
Sub-cortical white matter	Asymmetric
Centum semiovale	Asymmetric

Table 1 Correlation between Neurological signs and brain MRI lesion (REF 6)

Sign	MRI lesion
Dystonia	Putamen
Bradykinesia	Putamen
Dysarthria	Putamen and Caudate
Cerebeller sign and Postural tremor	Dentate nucleus, superior cerebeller peduncle red nucleus
Distractibility of gaze fixation	Frontal lobe

Table 2 Location of MR Abnormalities in Wilsons' Disease (REF 4)

Basal ganglia	Most frequently affected
Putamen	High SI outer rim on T2-W
Globius pallidus	Frequent
Caudate Nucleus	Frequent
Thalamus	Frequent: ventro-lateral aspect
Sub-thalamic region	Rare
Mid brain	Frequent
Tegmentum	
Substantia niagra	
Periaqueductal grey matter	
Red nuclei	
Tectum	
Crura	Rare
Pons	Second most commonly involved
Tegmentum	Frequent
Cerebellum	
Superior cerebeller peduncle	Frequent
Middle cerebeller peduncle	Frequent
Dentate Nucleus	
Vermis	
Medulla	Rare
Subcortical white matter	Asymmetric
	Parietal/Frontal
Claustrum	Frequent
Atrophy	Common
Cerebral	Vary mild to severe
Cerebellum	Mild

DISCUSSION

Wilson's disease is an uncommon autosomally recessive inherited disorder of copper metabolism caused by a deficiency of ceruloplasmin, the serum transport protein for copper. There is excessive deposition of copper in various tissues, especially the liver and brain.

Although it is a rare disease early diagnosis is particularly important as prompt therapy can prevent the irrevisible damage to vital organs such as the liver and the brain and may be reversible if therapy is commenced early. Because it has a variety of clinical manifestation, early diagnosis may be difficult and the first clue to the diagnosis may be made by a radiologist based on MRI findings as was in our patient. Neuropsychiatric manifestation are frequently the first symptoms. Psychiatric symptoms are common and the patient suffers depression, and emotional instability. Neurological symptoms include tremors, dystonia, rigidity, dysarthria, incordination and gait difficulty. There is correlation of dystonia and bradykinesia with lesion of putamen, dysarthria with lesion in putamen and caudate nucleus, cerebeller sign and

postural tremor with dentate nucleus, superior cerebeller peduncle and or red nucleus, distractibility of gaze fixation with frontal lobe involvement.[1,2,3] (Table 1)Patient usually have Kayser-Fleischer ring in the eyes due to deposition of copper in Descement membrane. Biochemical studies will confirm the diagnosis of Wilson's disease.

MR imaging is a sensitive modality for defining the normal anatomy and pathological changes of brain parenchyma and correlates better with clinical symptoms than CT does.

Wilson's disease may have a wide spectrum of abnormality on neuroimaging involving both gray matter and white matter with a predilection for the extrapyramidal system. Lesions have been reported in basal ganglia, thalami, subcortical white matter, mesencephalon, pons, dentate nucleus, vermis and claustrum.

Some of the neuroimaging findings may be related to neurological sign or to the presence of portosystemic shunt. The basal ganglia are the most frequently affected site with the putamen, globus pallidus, caudate nuclei and thalami being involved in up to 50 % of patients.[4] There is bilateral, symmetric involvement in gray matter in contrast to asymmetric white matter disease. The pons is the second most commonly affected structure, with the the pontine tegmentum being the prefered site. Midbrain is frequently abnormal [3,5,6,7] with the tegmentum being the most commonly affected site in the midbrain. Abnormality is present in the substantia nigra, red nucleus, inferior tectum and crura.[4] Thalami are symetrically affected. Maximal involvement is confined to the ventro-lateral nuclei. Minimal abnormal signal intensity was demonstrated in one patient in the subthalamic region.[4] Medulla was rarely involved[8] Half the number of patient had superior cerebeller peduncle and middle cerebeller peduncle involvement. There was symmetric involvement of middle cerebeller peduncle extending into adjacent white matter.[4] There were mild sub-cortical white matter involvement with asymmetrical focal changes or more symmetric diffuse changes in the parietal and frontal lobes.[4] There is relatively high incidence of claustral involvement with thickened and bright signal intensity.[9] Cerebral atrophy was common (Table2)

Histopathological changes in cerebral lesion of Wilson's disease include odema, gliosis, demyelination, neuronal loss and spongiform degeneration and cavitation especially in the putamen. These has been attributed to excessive copper deposition or ischemia or both.

Findings on CT are low density lesion in basal ganglia and widespread brain atrophy. On MRI, the most frequent findings is an increase signal intensity on T2- weighted images and decrease signal intensity on T1-weighted images which reflect underlying odema, gliosis and cavitation. Subtraction techniques enable cavitation to be distinguished from gliosis. The cavities in subtraction images appears as areas of very low signal intensity.[10] High signal intensity of white matter on T2 could be explained by demyelination, spongiformation or cavitation. Hypointensity on T2-weighted images has been reported and has been attributed to the paramagnetic effect of copper deposition.[7,11,12] Another possible cause of decrease T2 signal is iron deposition from previous haemorrhage which may occur in association with basal ganglionic destruction.[7,10,13] Low signal intensity in gray matter nuclei is diffcult to differentiate normal from abnormal low signal intensity as there is a wide variation in signal intensity in normal aging population. There is a physiological and age dependent accumulation of iron in basal ganglia and brain stem nuclei. Occasionally basal ganglia may be normal in signal intensity due to the potential balance effect of gliosis, odema and paramagnetic effect.[14]

Copper deposition in untreated patients had shorten T1 relaxation time that produced diffusely increase signal intensity on T1 weighted images.[4] Hyperintensity on T1 weighted images have been described in globus pallidus in patient with chronic

liver disease [non-Wilson] and has been attributed to accumulation of manganese.[15] High signal intensity on globus pallidus on T1 or high signal intensity in claustrum and frontal white matter on T2 has been associated with severe liver disease in Wilson's.[16] Contrast enhacement of brain lesion on MR images has been reported[17] and has been attributed to hypersensitivty to penicillamine therapy.

There has been conflicting reports ,some authors find good MRI correllation with neurologic examination[10] and other reports found no correlation between MR abnormality and severity of neurological impairment.[4,5,18] King et al[4] noted patient with longer duration of untreated disease had significantly less severe changes in signal intensity on MR images. Clinical response begin three to six months after initiation of therapy and even in the presence of severe neurologic disease a complete recovery may occur.[4,5,10] There were improvement of MR findings on follow up study under therapy.[4,5,10]

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