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A STUDY ON MAGNETIC RESONANCE IMAGING CHANGES OF BRAIN IN WILSON'S DISEASE AND ITS CORRELATION WITH CLINICAL FEATURES

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ABSTRACT

Introduction: Wilson's disease is inherited in autosomal recessive pattern and can manifest in the form of hepatic, neurological or psychiatric symptoms. The neurological manifestations are still a clinical enigma and are being studied continuously for a better understanding.

Aims: To describe the range of abnormalities in brain magnetic resonance imaging (MRI) of patients with Wilson's disease having neurological manifestations and their correlation with clinical findings and to evaluate the sensitivity of different MRI brain sequences in identifying the lesions in these patients

Materials and Methods: A descriptive cross-sectional study was conducted in the department of radiology, Nil Ratan Sircar Medical College and Hospital for a duration of one year from August 2021 to July 2022. A total of 23 patients of Wilson's disease having neurological manifestations who attended the medicine or neuro-medicine outpatient department of Nil Ratan Sircar Medical College and Hospital, Kolkata were included in the study.

Result: The present study revealed abnormalities in the brain MRI of all the patients of Wilson's disease with neurological manifestations. The sequences having highest sensitivity for the lesions were T2-weighted (96.4%) and T2-weighted FLAIR (96.4%) (Fluid-attenuated inversion recovery). Putamen (86.9%) was the most common site of involvement. Lesions in the region of thalamus, globus pallidus and putamen correlated with choreoathetosis. Number of MRI lesions correlated with age at presentation (p-value = 0.032).

Conclusion: Neurological symptoms are a common form of Wilson's disease manifestation. Patients with neurological manifestations have characteristic signal intensity alterations on MRI study of brain especially in basal ganglia region. These signal alterations can be best picked up by T2-weighted and T2-weighted FLAIR sequences. MRI lesions show association with clinical features like tremors and choreoathetosis, and age at presentation.

Keywords: wilson's disease, brain MRI, movement disorders and Neurological symptoms.

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INTRODUCTION

Wilson's disease is an inherited condition caused by a mutation in the ATP7B gene on chromosome 13q 14.3. This genetic defect results in impaired copper excretion into the bile, which in turn causes copper buildup in the liver, kidney, cornea, brain, and other body organs.

The chromosome 13q 14.3 encodes for a copper-transporting ATPase that facilitates the combination of copper and alpha-2 globulin into ceruloplasmin in liver.

Prevalence of Wilson's disease in Asian countries is estimated to be around 33 to 68 per 100,000 of the population [1].

Wilson's disease is usually diagnosed via its multiple manifestations involving multiple organs and systems which include neurological and hepatic manifestations along with biochemical tests for copper and presence of Kayser-Fleischer rings in the cornea. Neurological manifestations include both extrapyramidal and pyramidal systems of the brain as well as cognitive and psychiatric symptoms [2].

Neurological manifestations usually occur in 40-50% of the affected individuals and are usually seen in the second or third decade. Most common manifestation seen is movement disorders which includes dystonia, tremors, ataxia and quite often are also associated with dysarthria and drooling. Of these, tremors are the most characteristic manifestation [3].

The presence of classical "wing beating tremor" or "flapping tremor" in combination with dysarthria strongly suggests the diagnosis of Wilson's disease. Pyramidal features seen typically are brisk deep tendon reflexes. Dysarthria can also be seen along with slow tongue movements. Slowness of movement, shuffling gait, impaired finger movements and hypomimia are further typical features. Seizures can sometimes be the presenting feature of Wilson's disease which can be seen at any stage of the illness.

Psychiatric features commonly seen include abnormal behavior (irritability and disinhibition), personality changes, anxiety and depression. Psychosis is a less common feature in Wilson's disease.

Diagnosis of Wilson's disease can be made through assessment of serum ceruloplasmin. A serum ceruloplasmin level of <10mg/dl is diagnostic. Urinary excretion of copper > 100 microgram per 24 hours in absence of cholestatic liver disease is also diagnostic.

Magnetic resonance imaging (MRI) is the most important neuroradiological instrument for both diagnosis and follow up of treatment of Wilson's disease. Wilson's disease commonly affects the putamen but can also involve the cerebellum, cortex, subcortical area, pons and midbrain. Typical manifestation as seen on MRI T2-weighted images appears as symmetric hyperintensities on the affected part of the brain [4].

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MATERIALS AND METHODS

A descriptive cross-sectional study was conducted in the department of radiology, Nil Ratan Sircar Medical College and Hospital for a duration of one year from August 2021 to July 2022. A total of 23 patients of Wilson's disease having neurological manifestations who attended the medicine or neuro-medicine outpatient department of Nil Ratan Sircar Medical College and Hospital, Kolkata were included in the study.

Inclusion Criteria-

Patients of Wilson's disease having neurological manifestations attending the medicine or neuro medicine outpatient department and referred to the department of radiology for brain MRI were primary candidates of the study. The diagnosis of Wilson's disease was made based on-characteristic clinical findings, presence of Kayser-Fleischer (KF) ring on slit lamp examination, low serum ceruloplasmin level (<10mg/dl) and 24 hours urinary excretion of copper >100 μg/day.

Exclusion Criteria-

Patients of Wilson's disease with incomplete clinical data or not having cranial MRI scans and patients having only hepatic manifestations were excluded from the study.

After screening the patients according to inclusion and exclusion criteria, a detailed clinical history and family history was taken. Thorough neurological examination was done. Presence of dystonia, chorea, rigidity, tremor and myoclonus was noted and graded on a scale of 0-4. Necessary clinical investigations like serum ceruloplasmin, urinary copper excretion, slit lamp examination for KF ring and routine blood count were done. All the patients were screened for contraindications to MRI scan before the procedure. Following that the patients underwent MRI study of brain on GE Signa HDe 1.5T MRI scanner. The pulse sequences used in the examination were T1-weighted sequence, T2-weighted sequence, T2-weighted FLAIR sequence and Diffusion Weighted Imaging (DWI). Abnormal signal intensities and their location in different MRI sequences were noted. For estimation of total number of lesions in a patient on MRI, supratentorial as well as infratentorial lesions on T2-weighted and T2-weighted FLAIR sequences were calculated.

Statistical Analysis

The data collected from the participants was recorded in a patient data collection form and then was transferred to a Microsoft Excel spreadsheet. The analysis was done using SPSS (version 26.0; SPSS Inc., Chicago, IL, USA). For categorical data, description was given using frequencies and percentages. Chi-square test or Fisher exact test were used for comparison of categorical data. For continuous variables, mean and standard deviation was used. The comparison of continuous data was done using independent t-test. A p-value of < 0.05 was considered significant. For p-value > 0.05 the null hypothesis was rejected.

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RESULT AND DISCUSSION

This study focuses on MRI changes of brain in patients of Wilson's disease with neurological symptoms in a tertiary care hospital in eastern India. The neurological symptoms in Wilson's disease occur either as a direct result of copper accumulation in the brain or indirectly due to dysfunctioning of the liver. A combination of the two exists in quite a few cases. There is a predilection for accumulation of copper in the extrapyramidal tracts resulting in disorders of movement [5]. Despite the extensive involvement of brain, it has been noted that treatment with copper chelating agents leads to reversal of symptoms and significant improvement of patients, thus making early diagnosis and treatment initiation crucial for them.

In this study, patients diagnosed with Wilson's disease based on the diagnostic criteria and having neurological manifestations attending the medicine or neuro medicine outpatient department and referred to the department of radiology for brain MRI were included as per the inclusion and exclusion criteria.

Detailed clinical and family history was taken and a thorough neurological examination was done. Brain MRI study was performed for all the patients and the site, number and intensity of signal change in the lesions were noted and later correlated with the clinical findings.

A total of 23 patients were included in the study of which 15 were male and eight were female. The range for age of onset of illness in the study was from nine years to 48 years. Członkowska A, Rodo M, and Gromadzka G in their study on Wilson's disease also stated that the disease is more common in men than women and the clinical symptoms develop between the age of three years to 40 years [6]. The age range in our study is slightly higher than theirs.

The duration of illness was found to be varying between two months to 145 months, with a mean duration of 19.2 months. The age of onset of neurological symptoms ranged from eight years to 35 years with the median age being 12 years. The findings are similar to the findings of the study by Taly et al on 282 patients of Wilson's disease who were evaluated over three decades[7].

All the patients included in the study had some form of neurological symptoms with the most common being oromandibular dystonia and myoclonus being the least common. Walshe JM and Yealland M in their study on Wilson's disease also found dystonia and movement disorders to be the most common neurological manifestation[5].

Brain MRI showed abnormal signal intensities in all the patients. The lesions were hyperintense on T2-weighted and T2 FLAIR sequences and hypointense on T1-weighted sequence. The commonest site of involvement noted on MRI study of brain was putamen, seen in 20 patients which accounts for 86.9%. Caudate nucleus was involved in 17 patients and brainstem and globus pallidus lesions were noted in 14 patients. Thalamic lesions were noted in 13 patients. Cerebellar involvement was noted only in one patient. Cerebral cortex involvement was most common in frontal region. Putamen has been found to be the most commonly involved site in various previous studies such as those by Kim et al. [8] and Aisen AM et al [9].

In the present study, choreoathetosis as a clinical symptom correlated with lesions in thalamus, putamen and globus pallidus. Putaminal lesions also correlated with dystonia. Myoclonus was mostly seen in patients having involvement of cerebral cortex and subcortical white matter. The

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number of lesions on MRI correlated with age at presentation and the severity of changes in signal intensity on MRI study correlated with overall duration of illness. These findings of our study were comparable to those by M. Südmeyer et al. and Ranjan A et al [10, 11]. The results for association of MRI brain findings with clinical symptoms in Wilson's disease have been variable. In study by Ranjan A et al. it was established that the MRI findings associated strongly with disease severity but not with disease duration whereas in another study by S Sinha, AB Taly, LK Prashanth et al. the location of lesion had no correlation with number of lesion or disease prognosis. Pulai et al in their study also found a positive correlation between severity of clinical symptoms and the anatomical extent of MRI signal abnormalities [12, 13]. In the present study we could establish that the duration of disease affected the severity of brain changes, and the number of lesions were affected mainly by age of disease onset and duration of untreated disease.

On comparing the sensitivity of various sequences of MRI for assessment of lesions in different regions of brain it was noted that T2-weighted FLAIR and T2-weighted images have the highest sensitivity and T1-weighted images have the least sensitivity. Despite having the same sensitivity lesions are more prominent on T2-weighted FLAIR than on T2-weighted sequence. DWI restriction with low ADC values was noted only in two patients. Favrole. P et al in their study also found T2-weighted FLAIR to be more sensitive in detecting lesions of Wilson's disease as compared to other sequences [14].

CONCLUSION

From the present study we can conclude that neurological symptoms are a common form of Wilson's disease manifestation. Patients with neurological manifestations of Wilson's disease have characteristic symmetrical signal intensity alterations on MRI study of brain especially in the basal ganglia region. These signal alterations can be best picked up by T2-weighted and T2-weighted FLAIR sequences. MRI lesions correlate with age at presentation and clinical features like tremors and choreoathetosis. Therefore, magnetic resonance imaging study of brain can be an important tool in studying the neurological involvement in patients of Wilson's disease.

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Table 1: Movement disorders and site of MRI lesions in patients of Wilson's disease with neurological manifestations

	Dystonia (n=23)	Choreoathetosis (n=13)	Tremors (n=15)	Myoclonus (n=3)
Putamen	19 (82.6%)	13 (100%)	11 (73.3%)	02 (66.6%)
Caudate	17 (73.9%)	10 (76.9%)	10 (66.7%)	01 (33.3%)
Globus Pallidus	13 (56.5%)	12 (92.3%)	07 (46.6%)	02 (66.6%)
Thalamus	16 (69.5%)	12 (92.3%)	09 (60.0%)	02 (66.6%)
Brainstem	12 (52.2%)	09 (69.2%)	07 (46.6%)	02 (66.6%)
Cerebral Cortex	05 (21.7%)	03 (23.0%)	04 (26.7%)	03 (100%)
Subcortical White Matter	05 (21.7%)	03 (23.0%)	05 (33.3%)	03 (100%)

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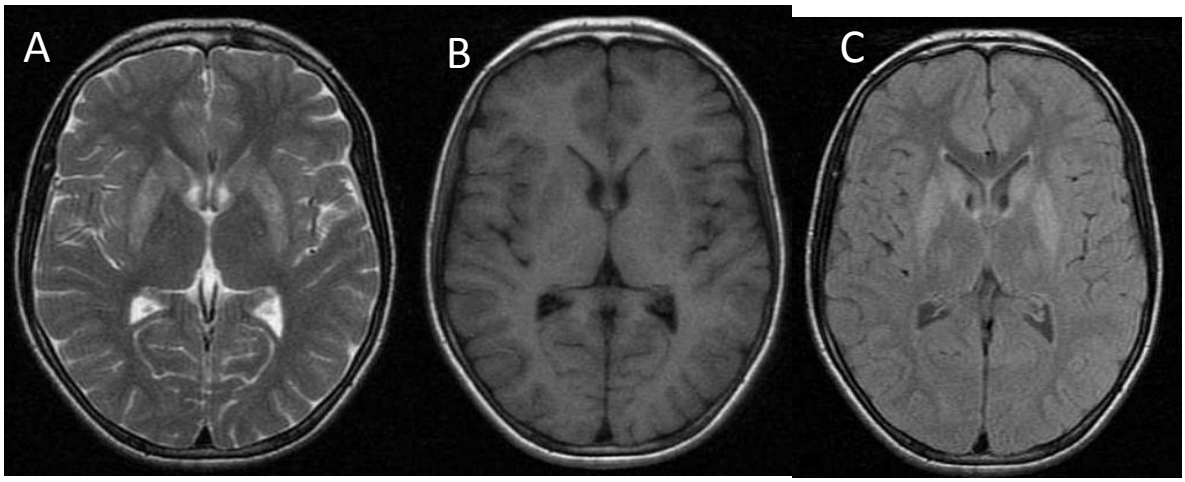
Table 2: Sensitivity of MRI sequences for detection of lesions	
Sequence	Sensitivity
T2-weighted	96.4%
FLAIR (T2-weighted)	96.4%
DWI	35.9%
T1-weighted	32.1%

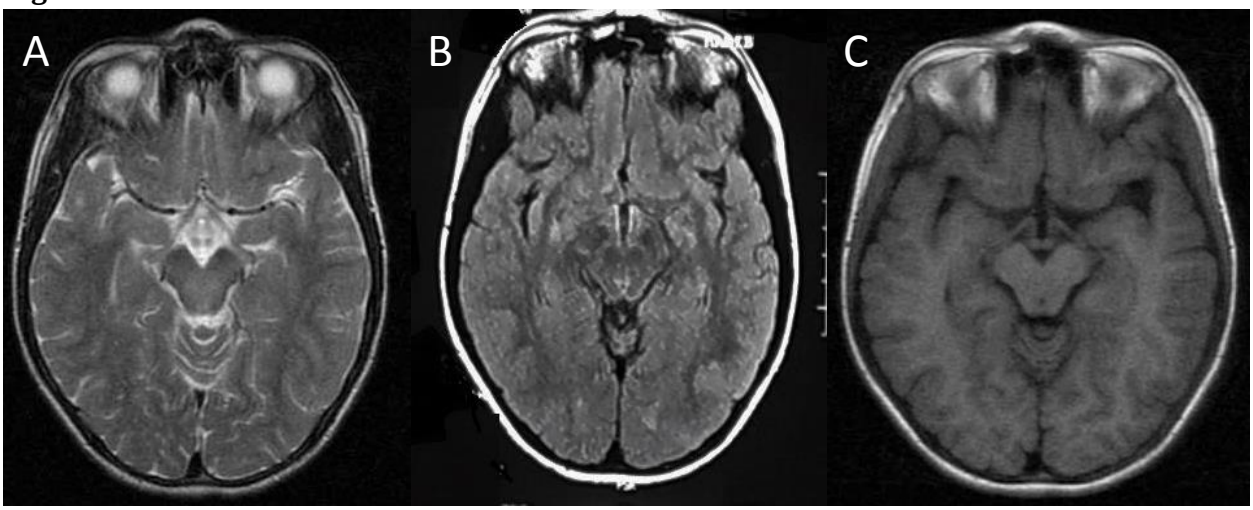
Representative Cases:

Figure 1:



Axial T2-weighted(A) and T2-FLAIR(B) image showing hyperintensity in bilateral putaminal and caudate region. Similar level T1-weighted image(C) with ill-defined hypointensities.

Figure 2:



Axial T2-weighted(A) and T2-FLAIR(B) images showing hyperintensity in midbrain, with giant panda sign. T1-weighted image however doesn't show prominent hyointensity.