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Exploring cortical atrophy and its clinical and biochemical correlates in Wilson's disease using voxel based morphometry

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ABSTRACT

Objectives: To determine cortical grey matter (GM) changes and their clinical and biochemical correlates in patients with Wilson's disease using voxel based morphometry (VBM).
Methods: Clinical and imaging data of 10 patients (all male, mean age 16.0 ± 6.3years) with Wilson's Disease were analyzed. T1W volumetric MRI data of patients without obvious cortical atrophy or signal changes on conventional MRI was compared with MRI of 11 matched control subjects using VBM analysis with Statistical Parametric Mapping 8. Results were expressed at statistical threshold of $p < 0.05$ (FWE corrected) and $p < 0.001$ (uncorrected). Multiple regression analysis was done to analyze possible relation between GM atrophy, duration of disease and biochemical abnormalities.
Results: Compared to controls, patients showed scattered areas of reduced GM volume in bilateral caudate head, medial part of right globus pallidus and body of right caudate (FWE corrected $p < 0.05$). At $p < 0.001$(uncorrected) widespread areas of cortical atrophy were also noted involving the frontal and temporal lobes, lentiform nuclei, cerebellum and thalamus. Significant positive correlation (uncorrected $p < 0.001$) were noted between (i) duration of disease and cortical GM volume of frontal, parietal and temporal lobes and cerebellum (ii) serum copper levels and GM volume of right medial frontal gyrus and paracentral lobule.
Conclusions: To the best of our knowledge, this is the first VBM study in patients with Wilson's disease. In spite of apparently normal cortex on visual inspection of MRI, decreased cortical GM volume was detected using VBM. In addition, serum copper may act as surrogate marker of cortical abnormalities in Wilson's disease.

1. Introduction

Wilson's disease is a rare autosomal disorder of copper metabolism that leads to deposition of copper resulting in neurodegeneration. Since its first description by Kinnier Wilson in 1912 [1], much has been discovered about this disease in the recent decades. It is now well established that Wilson's disease is caused by mutation of ATP 7B gene on chromosome 13 [2]. More than 400 mutations have been identified that can cause Wilson's disease [3]. These mutations impair copper transport mechanism causing an abnormal increase in the copper levels which gets deposited in different organs such as liver, brain and skeletal system. The onset of symptoms is usually in childhood or early adulthood and without adequate decoppering therapy, the disease runs an invariably fatal course due to hepatic failure.

Although not fatal, neurological Wilson's disease is a common manifestation that adds to the morbidity in these patients. Neurological manifestations of Wilson's disease are categorized into akinetic-rigid, pseudosclerotic, ataxic and dystonic types based on the predominant symptomatology [4]. Other symptoms include dysarthria, seizures, cognitive impairment and psychiatric manifestations [4]. However, in clinical practice, considerable overlaps are seen in the different neurological categories of Wilson's disease.

MRI based neuroimaging studies have reported a multitude of

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abnormalities in the brain of patients with Wilson's disease. The most commonly reported abnormality is the presence of increased signal intensity in the basal ganglia structures such as caudate, putamen and lentiform nucleus in T2 weighted images [5–8]. In addition, signal changes of substantia nigra, periaqueductal grey matter, tegmentum, thalamus and mesencephalon are also reported. Imaging features such as "face of giant panda", "face of miniature panda" and "bright claustrum" sign are described as pathognomonic signs of Wilson's disease [5–8]. Cortical changes are also reported in few studies but are not well described [5–8].

Visual interpretation of MRI is often subjective and challenging especially while studying neurodegenerative brain changes. This is particularly true in case of cortical atrophy which is often ignored unless prominent volume loss is present. Imaging techniques are now available that can objectively measure these atrophic changes and also allow comparison among different groups. Voxel based morphometry (VBM) is such a technique that measures and compares voxel wise distribution of grey matter (GM) in the brain. It involves normalization of the high resolution images into the same stereotactic space followed by segmentation and smoothing of segments followed by voxel-wise comparison of atrophic changes [9].

This study attempted to identify atrophic changes of the GM, its distribution and their clinical and biochemical determinants in patients with Wilson's disease with apparently normal cortex on conventional MRI. Information on these may have therapeutic and prognostic implications.

2. Methods

2.1. Subjects

This was a retrospective review of the clinical details and MRI of patients with Wilson's disease undergoing treatment in the Neurology department of the National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, India. Patients were evaluated by experienced neurologists and diagnosis of Wilson's disease was made based on clinical symptoms, presence of KF ring, neuroimaging finding and abnormal copper studies.

2.2. Clinical assessment

Using a predesigned proforma, detailed history and clinical examination findings were recorded. The duration of disease was considered as the number of years from the onset of first neurological symptom upto MRI acquisition. Serum copper and ceruloplasmin level of each patient was measured using standard techniques.

2.3. MRI data acquisition

Diagnostic MRI scans that were done for the patients while under clinical evaluation were used for this study. All MRI scans were done in 3-T Philips Achieva MRI scanner with 32-channel SENSE head coil. After the initial localization sequences, high-resolution three dimensional T1-weighted, anatomical MR images were obtained with 1-mm slice thickness and no inter-slice gap (TR = 8.1 msec; TE = 3.7 msec; matrix = 256 × 256; flip angle 8°; sense factor = 3.5). The MRI images were retrieved from the archive and were screened for gross cortical structural abnormalities and cortical atrophy by an experienced neuroradiologist (JS). Among the 12 patients whose MRI was analyzed, two patients were excluded from the study as they had cortical signal changes. All MR images were compared with the archived data of 11 age and gender matched healthy subjects.

2.4. MRI post-processing

MRI data analysis was performed in Statistical Parametric Mapping 8 (SPM8) (Wellcome Department of Cognitive Neurology, http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) using MATLAB R2013a. VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm/).

The raw T1-weighted anatomical data in the DICOM format were imported to SPM8 and saved as SPM compatible NIFTI format. The data of all subjects was then manually re-oriented to their respective AC-PC plane beforeVBM8 toolbox batch processing. The procedure consists of pre-processing, smoothing and statistical analysis steps. Pre-processing involves spatially normalizing the reoriented T1-weighted anatomical images from all the subjects in both the groups into the same stereotactic space. The normalised images were then segmented into GM, WM, cerebrospinal fluid (CSF) and non-CSF components. The segmented images were then spatially normalized to Montreal Neurological Institute (MNI) space and were modulated. Smoothing was applied on modulated images using an 8 mm full-width half-maximum (FWHM) gaussian kernel for subsequent statistical analysis. General linear model (GLM) was then applied on the smoothed GM images. A two-sample *t*-test was performed using age and total intracranial volume (ICV) as covariates to investigate differences between the two groups. Multiple regression analysis was performed in the patient group to correlate GM volume with age, duration of disease, serum copper and ceruloplasmin levels.

Anatomical localization of the brain areas of altered GM densities was performed using the Talairach client (www.talairach.org) after converting MNI coordinates into Talairach coordinates using Ginger ALE (http://www.brainmap.org/ale/).

3. Results

3.1. Demography

This study included ten patients of Wilson's disease (all men) with mean age of 16.0 ± 6.3 years and 11 healthy age and gender matched controls with mean age of 15.8 ± 6.0 years. There was no significant difference in the age of patients and controls.

The mean age of onset of symptoms in patients with Wilson's disease was 12.9 ± 6.9 years and mean duration was 1.4 ± 1.1 years. Among the 10 patients, 6 subjects were born out of consanguineous parentage. A positive family history of Wilson's disease was present in 6 patients. Four patients were already on de-coppering therapy at their first visit to NIMHANS and 6 patients were drug naïve. The demographic details of patients and controls are given in Table 1.

3.2. Clinical symptoms and signs

The most common clinical feature in patients with Wilson's disease was dysarthria (90%). Other common clinical features were dystonia (80%), cognitive changes (70%), parkinsonism (70%), pyramidal signs (70%), tremors (50%), behavioural disturbances (50%), gait disturbances (50%), osseo-muscular deformities (50%) and drooling of saliva (40%). Symptoms such as dysphagia (30%), chorea (30%) and seizures (20%) were present only in few patients (Table 1).

Conventional MRI in patients revealed signal changes in the putamen (70%), caudate (60%), thalamus (30%), midbrain (30%), internal capsule (20%), pons (10%) and cerebellum (10%) in FLAIR images. The control subjects were all normal and did not reveal any signal changes in the MRI.