Wilson’s Disease: Clinical, Brain MRI and Tc-99m HMPAO SPECT Correlation

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ABSTRACT

Background: Brain damage secondary to Wilson’s disease leads to several psychiatric and neurological manifestations. However, little research has been published about the role of anatomo-functional diagnostic modalities in the evaluation of the disease course. Objective: To evaluate and compare the role of brain MRI and Tc-99m HMPAO SPECT in assessing brain involvement in Wilson’s disease and correlating these findings with the clinical presentations. Methods: Eighteen patients with established Wilson’s disease were included. The clinical picture was of neurologic type (nWD) in 11 patients (61.1%), and of the hepatic type (hWD) in 7 patients (38.9%). All patients were subjected to clinical assessment, cognitive assessment, ophthalmic slit lamp examination, biochemical tests including urinary copper and serum ceruloplasmin levels, abdominal ultrasound, liver biopsy (only in 5 patients), MRI of the brain and Tc-99m HMPAO brain SPECT. Results: Brain MRI was abnormal in 11/18 patients (sensitivity 61.1%). It was abnormal in 9/11 nWD patients (sensitivity 81.8%) and 2/7 of hWD patients (sensitivity 28.6%). Brain Tc-99m HMPAO SPECT was abnormal in 15 out of 18 patients (sensitivity 83.3%). The scan was abnormal in 10/11 patients with nWD (sensitivity 90.9%) and in 5/7 of patients with hWD (sensitivity 71.4%). There was a good correlation between the clinical presentation of the disease and radiological and SPECT findings. Conclusion: In Wilson’s disease brain SPECT has a higher sensitivity than brain MRI in detecting brain damage. There was also a good clinic-anatomical correlation but it was still not clear yet in explaining some clinical aspects in some cases. (Egypt J Neurol Psychiat Neurosurg. 2010; 47(1): 29-35)

Key Words: Wilson’s disease, Brain MRI, Brain SPECT

INTRODUCTION

Wilson’s disease is an autosomal recessive genetic disorder characterized by excessive copper accumulation in the liver, brain, cornea and kidneys. Excess copper attacks the brain results in psychiatric and neurological symptoms. Neurological manifestations include resting and intention tremors, spasticity, rigidity and chorea. Dystonic signs include slowness of speech, unsteady gait, dystonic facies and posturing. Psychiatric disturbances are present in the majority of patients with symptomatic disease, and include several forms of psychoses and neuroses. No matter how the disease begins, it is always fatal if not diagnosed or treated.

Besides biochemical changes in Wilson’s disease better assessment can be obtained with other imaging diagnostic modalities such as magnetic resonance imaging (MRI) and single photon emission tomography (SPECT). Brain MRI shows symmetrical lesions in the putamen, caudate, pons, globus pallidus, thalamus, mesencephalon and cerebellum.

Asymmetrical white matter involvement is also present.

In Wilson’s disease SPECT using dopamine D2 ligands such as I-123 iodo benzamide (IBZM) has shown reduction in the striatal binding. Tc-99m HMPAO is trapped by cerebral grey matter and the basal ganglia on its first pass through the brain. Patients with Wilson’s disease had varying degrees of basal ganglia underperfusion as demonstrated by Tc-99m HMPAO SPECT scan. Recently, in Wilson’s disease, a disturbed glucose metabolism determined by F-18 Fluodoreoxyglucose positron emission tomography in the striatal and cerebellar areas has been also reported and this correlated with the severity of the extrapyramidal motor symptoms.

The aim of this study is to detect and compare the sensitivity of brain MRI and Tc-99m HMPAO SPECT of the brain in the evaluation of patients with Wilson’s disease and correlating these findings with the clinical presentation of the disease.

PATIENTS AND METHODS

This study included 18 Egyptian patients with established Wilson’s disease, 10 males (55.6%) and 8 females (44.4%). The age of the patients ranged from 21 to 53 years (mean age 30±9.4 years). All patients...
were hospitalized and studied at the Neurology and Tropical Medicine Departments at Kasr El-Aini hospital. The diagnosis of Wilson’s disease was based on the physical examination, urinary copper levels (>100 mcg/24h), with or without serum ceruloplasmin levels (<20 mg/dl), hepatic copper concentration (>250 mcg/g dry tissue) only in 5 cases and the presence of Kayser-Fleischer corneal ring.

Family history was positive for Wilson’s disease in 10 patients (55.6%). Eleven patients (61.1%) had neurologic involvement (nWD), and 7 patients (38.9%) presented with hepatic manifestations (hWD). The mean duration of the clinical manifestations at the time of the study was 3.5±2.7 years. Twelve patients (66.7%) were under D-penicillamine treatment on average at a dose of 1.5 gm/day for 1-8 years (mean 4.2±2.9 years). The remaining 6 patients had not started specific treatment yet.

Patients included in the current study were subjected to:

- Careful history taking including family history.
- Full general and neurological assessment.
- Cognitive functions assessment: Mini-Mental State Examination scale (M.M.S.E)\(^{12}\) and Trial Making Test\(^{13}\).
- Ophthalmic slit lamp examination to detect Kayser-Fleischer corneal ring.
- Laboratory investigations including CBC, urea, creatinine, liver function tests, in addition to biochemical tests for diagnosis of Wilson’s disease including 24 h urinary copper and serum ceruloplasmine.
- Abdominal ultrasound.
- Liver biopsy (only in 5 patients).
- MRI of the brain was performed with T\(_1\), T\(_2\) and proton density weighted sequences. Contrast media of Gadolinium at a dose of 2 ml/kg were administered to all patients. MRI images were evaluated by specialized radiologist with respect to the presence of brain atrophy and focal signal changes in the cerebellum, pons, midbrain, putamen, globus pallidus, caudate nucleus and thalamus. Areas of involvement in the cortex and subcortical white matter were also noted.
- Tc-99m HMPAO brain SPECT was performed 30-60 minutes following intravenous injection of 740 MBq (20 mCi) of Tc-99m HMPAO. Images were acquired on dual head gamma camera (ADAC vertex version); data were collected on 64x64 matrix through 360 degree rotation, 6 angle interval for 40 seconds per arc interval. Images were filtered using Butterworth filter. The images were reoriented in the transaxial, coronal and sagittal planes. Images were assessed visually as well as semiquantitatively.

Normal findings of Tc-99m HMPAO brain images consisted of homogenous uptake in the cerebral cortex, basal ganglia and cerebellum without visible asymmetry. Semiquantitative analysis of each cerebral lobe, basal ganglia and cerebellum was performed by drawing 6 regions of interest (ROIs) including frontal, parietal, temporal, occipital lobes, basal ganglia and cerebellum on each hemisphere.

Statistical Methods:
Data were entered onto SPSS version 11 for analysis. Simple frequencies were used for data checking, descriptive statistics (arithmetic mean and standard deviation) were used for summary of quantitative data while percentage were used for qualitative data.

RESULTS

I. Clinical results:

The presenting clinical manifestations of the 18 patients diagnosed as having established Wilson’s disease were illustrated in table (1). Hepatic manifestations in the form of jaundice and vomiting were recorded in all patients with hWD (7/7), while observed only in 2/11 patients (18.2%) of those with nWD, tremors in 10/11 patients (90.9%), Dysarthria or scanning speech in 7/11 patients (63.6%), gait impairment (unsteady gait) in 6/11 patients (54.5%), dystonia in 4/11 patients (36.4%), drooling in 4/11 patients (36.4%), seizures and chorea, each in only 1/11 patient (9.1%), finally behavioral and/or cognitive changes were observed in 7/11 patients (63.6%). None of the hWD patients showed any neurologic abnormalities.

II. Radiological finding:

Brain MRI studies showed abnormal findings in 9/11 patients with neurological manifestations (81.8%). Abnormalities in different combinations were found in the putamen, caudate, pons, globus pallidus, dentate nucleus, substantia nigra, claustrum region, thalamus, mesencephalon, internal capsule, supra and subtentorial white matter, medial and lateral lemniscus and corpus callosum. The lesions appeared hypointense in T\(_1\) weighted images and hyperintense in T\(_2\) weighted images. However, MRI image couldn’t detect any focal brain lesions in patients with hWD. Four out of eighteen patients (22.2%) had diffuse brain atrophy, 2 of them had nWD (2/11; 18.2%) and the other 2 had hWD (2/7; 28.6%). The sensitivity of MRI brain in nWD was 81.8% (9/11 patients) and the sensitivity in all patients with WD was 61.1% (11/18).
Brain Tc-99m HMPAO SPECT was abnormal in 15 out of 18 patients (83.3%). The abnormalities were detected in 10/11 patients with nWD (90.9%) and 5/7 patients with hWD (71.4%). The abnormal scans showed diffuse or focal hypoperfusion in the affected brain tissue. Basal ganglia was the most common areas of hypoperfusion it was involved in 10 patients; (66.7%), Temporal hypoperfusion was found in 6 patients; (40%), and parietal hypoperfusion was found in 5 patients; (33.3%). Cerebellum was involved in 4 patients; (26.7%). Frontal and occipital lobes were the least brain lobes involved 2 patients; (13.3%) and one patient; (6.7%) respectively. One patient had cerebral atrophy in MRI, didn’t show any abnormalities in SPECT. However, 5 patients with abnormal brain SPECT showed normal MRI. The detailed areas of lesion abnormalities in both brain MRI and SPECT were reported in Table (2) and Figures (1 and 2).

Table 1. Clinical manifestations at the time of presentation in 18 patients with Wilson’s disease.

<table>
<thead>
<tr>
<th>Clinical manifestation</th>
<th>hWD (7 patients)</th>
<th>nWD (11 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaundice &amp; vomiting</td>
<td>7 (100%)</td>
<td>2 (18.2%)</td>
</tr>
<tr>
<td>Tremors</td>
<td>--</td>
<td>10 (90.9%)</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>--</td>
<td>7 (63.6%)</td>
</tr>
<tr>
<td>Unsteady gait</td>
<td>--</td>
<td>6 (54.5%)</td>
</tr>
<tr>
<td>Dystonia</td>
<td>--</td>
<td>4 (36.4%)</td>
</tr>
<tr>
<td>Drooling</td>
<td>--</td>
<td>4 (36.4%)</td>
</tr>
<tr>
<td>Seizures</td>
<td>--</td>
<td>1 (9.1%)</td>
</tr>
<tr>
<td>Chorea</td>
<td>--</td>
<td>1 (9.1%)</td>
</tr>
<tr>
<td>Behavioral/cognitive changes</td>
<td>--</td>
<td>7 (63.6%)</td>
</tr>
</tbody>
</table>

WD = Wilson’s disease, hWD = Wilson’s disease with hepatic involvement, nWD = Wilson’s disease with neurologic involvement.

Table 2. Findings of brain MRI and brain Tc-99m HMPAO SPECT.

<table>
<thead>
<tr>
<th>No.</th>
<th>Brain MRI</th>
<th>Brain Tc-99m HMPAO SPECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bilateral lesions at dentate nucleus, substantia nigra, corpus callosum and Lt claustrum</td>
<td>Marked hypoperfusion of Lt T/P Cx</td>
</tr>
<tr>
<td>2</td>
<td>Cerebral atrophy</td>
<td>Diffuse hypoperfusion of cerebellum</td>
</tr>
<tr>
<td>3</td>
<td>Lesions at Lt lenticular, Lt thalamic nuclei, substantia nigra, and subcortical atrophy</td>
<td>Diffuse hypoperfusion of Lt BG</td>
</tr>
<tr>
<td>4</td>
<td>Lesions at bilat thalamic nuclei, putamen more on right, substantia nigra, and supra &amp; infratentorial white matter</td>
<td>Moderate hypoperfusion of Rt BG &amp; Lt F/P Cx</td>
</tr>
<tr>
<td>5</td>
<td>Symmetrical lenticular lesions</td>
<td>Marked hypoperfusion of Rt BG &amp; Lt T/P Cx</td>
</tr>
<tr>
<td>6</td>
<td>Cerebral atrophy</td>
<td>Moderate hypoperfusion of Lt BG &amp; Lt cerebellum</td>
</tr>
<tr>
<td>7</td>
<td>Negative</td>
<td>Marked hypoperfusion of Rt T Cx</td>
</tr>
<tr>
<td>8</td>
<td>Lesions at Lt lenticular, Lt thalamic nuclei, substantia nigra, and subcortical atrophy</td>
<td>Moderate hypoperfusion of Lt BG &amp; Lt cerebellum</td>
</tr>
<tr>
<td>9</td>
<td>Lesions at Lt globus pallidus</td>
<td>Moderate hypoperfusion of Rt BG &amp; Lt T/P Cx</td>
</tr>
<tr>
<td>10</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>11</td>
<td>Lesions at Lt globus pallidus</td>
<td>Diffuse hypoperfusion of cerebellum</td>
</tr>
<tr>
<td>12</td>
<td>Negative</td>
<td>Diffuse hypoperfusion of Rt BG &amp; Lt T Cx</td>
</tr>
<tr>
<td>13</td>
<td>Negative</td>
<td>Moderate hypoperfusion of Lt F/T Cx</td>
</tr>
<tr>
<td>14</td>
<td>Cerebral atrophy</td>
<td>Negative</td>
</tr>
<tr>
<td>15</td>
<td>Negative</td>
<td>Diffuse hypoperfusion of Lt BG</td>
</tr>
<tr>
<td>16</td>
<td>Cerebral atrophy</td>
<td>Moderate hypoperfusion of Rt BG &amp; Lt O/P Cx</td>
</tr>
<tr>
<td>17</td>
<td>Negative</td>
<td>Moderate hypoperfusion of Lt BG</td>
</tr>
<tr>
<td>18</td>
<td>Negative</td>
<td>Negative</td>
</tr>
</tbody>
</table>

No. = patient’s number, BG = Basal ganglia; T= Temporal; P = Parietal; F = Frontal; O = Occipital; Rt = Right side and Lt = Left side, CX = Cortex; Bilat= bilateral
Wilson’s disease involves primarily the corpus striatum but also the thalami, brain stem nuclei, cerebral cortex, cerebral and cerebellar white matter and dentate nucleus are frequently involved. Neurological abnormalities results directly from deposition of copper in these areas. The lesions detected by brain MRI in our patients were found in 9 out of 11 patients presented with neurological symptoms, and in only 2 out of 7 patients suffered from hepatic symptoms. These MRI findings were consistent with the previously reported results of other authors regarding its diagnostic value, lesion localization as well as being mostly limited to the group of patients presented with neurological manifestations. Similar results were also reported by Hermann et al., Kozic et al. and Saatci et al., where authors reported MRI hypodense abnormalities in all patients in the basal ganglia regularly combined with atrophy of the cerebral and cerebellar cortices. In contrast, Giagheddu et al.
reported no MRI abnormalities have been observed in patients with hepatic manifestations.  

Tc-99m HMPAO SPECT of the brain in the current study showed hypoperfused lesions in 15 out of 18 patients included in the study (83.3%). Comparable results have been previously reported by Watanabe et al. However, Giagheddu et al. reported a little higher detection rate than our results (86%). The high incidence of basal ganglia involvement is a typical presentation to the classical lesional model of the disease.

The advantage of Tc-99m HMPAO is that it can detect dysfunctional lesions through addressing the regional cerebral blood flow abnormalities accurately. The areas of brain hypoperfusion detected with Tc-99m HMPAO SPECT depend on the vascular changes, which are caused by pathological deposition of copper that characterizes this disease. In fact, in Wilson’s disease, the vascular changes in the brain such as swelling, thickening, proliferation, fibrosis and neoformation of capillaries and arterioles with vascular congestion, hypertrophy of the cells of the endothelium and the adventitia as well as calcification of the artery wall has often been suggested to be the cause of functional changes detected by Tc-99m HMPAO. However, excess copper deposition in the brain tissue and its effect on the stability of the lipophilic form of the Tc-99m HMPAO and glutation interaction have been alternatively proposed.

The best sensitivity for detection of the brain abnormalities in patients with neurological as well as hepatic involvement has been addressed in the current study to brain Tc-99m HMPAO SPECT in comparison to brain MRI. This was also reported by Giagheddu et al. and Piga et al. The authors suggested that this method should be routinely used in monitoring patients with Wilson’s disease.

Clinically all our patients had extrapyramidal symptoms and signs secondary to basal ganglia involvement. Seven out of eleven patients had also behavioral and/or cognitive impairment; none of them had clinically overt hepatic encephalopathy, so the abnormalities detected could be interpreted as a result of cognitive impairment secondary to brain changes. Similar finding was reported by Page et al.

Correlation between neurological symptoms and signs and MRI, and SPECT findings varied greatly and in concordance with these reports, 9/11 and 10/11 of nWD included in our study had abnormal MRI and SPECT scanning respectively. There was a fairly good correlation between clinical presentation and MRI findings as the basal ganglia were the most frequently affected in MRI. However, these MRI findings failed to explain some clinical manifestations especially the behavioral and cognitive ones.

Being more sensitive than MRI in detecting brain lesions in Wilson’s disease, SPECT findings correlated at a higher level than that with MRI with the clinical symptoms and signs of the disease especially the behavioral and cognitive signs reported in our cases. This was attributed not only to the high sensitivity of SPECT in demonstrating areas of brain involvement other than basal ganglia (cerebral and cerebellar cortices) but also to its ability to detect small sized lesions. Similar findings were also observed by Page et al.

Although, there was a good correlation between the anatomical involvement in MRI and functional abnormalities in SPECT examination. Moreover, many clinical symptoms and signs observed in clinical evaluation and cognitive assessment could be explained by the MRI and/or SPECT abnormalities. However, in some cases correlation between some clinical manifestations and the findings of these radiological tools did not reach the same level indicating a non obvious pathology responsible for the occurrence of these clinical manifestations. Similar findings were observed by Page et al., Akil and Brewer and Seniow et al.

On the other hand, a percentage of patients with hWD, who had no evidence of clinical neurological manifestations showed MRI changes (2/7 brain atrophy) and SPECT changes (5/7 areas of hypoperfusion). A finding which suggested the subclinical brain pathology even in neurologically free WD patients.

**Conclusion**

In conclusion, brain MRI and Tc-99m HMPAO brain SPECT are useful tools for evaluating Wilson’s disease with higher sensitivity for brain SPECT over brain MRI in detecting brain abnormalities. Also, anatomo-functional studies have a significant role in detecting brain abnormalities not appreciated clinically in patients with hepatic type of Wilson’s disease. There was a good clinico-anatomical correlation but it was still not established yet in some clinical aspects of the disease in some cases.

**REFERENCES**


الملخص العربي

مرض ولسون: العلاقة بين الحالة الإكلينيكية والأشعة的日نغ المغناطيسية على المخ والأشعة المقطعية على المخ باستخدام التطور المشعة أحادية الفوتون.

تهدف هذه الدراسة لتقييم وتقييم تأثير الفوتون على المخ، وعلاقة هذه المظاهر بالحالة الإكلينيكية للمريض.

تمت هذه الدراسة على 18 مريض مصاب بمرض ولسون، وتم ترقب أعمارهم بين 21 و53 سنة. وكانت الحالة الإكلينيكية هي من النوع العصبي في 11 مريض (61.1%) والنوع الكبدي في 7 مريض (38.9%). تم عمل التحليل للمرضى: كشف تقنيًا، قياسات التوافق النتائج الصعوبة على العينين، اختبارات عملية، ونتائج المحاكاة في أوقات مختلفة، ونسبة سير ونظام الحمض النووي، و结果显示 أن الفوتونات أحادية الفوتون على المخ وآخذة بالكمبووتر على المخ. 

وباستخدام التطور المشعة أحادية الفوتون.

وقد أوضح النتائج أن هناك تغييرات غير طبيعية في أشعة الرينغ المغناطيسية على المخ في 18/11 مريض ولسون (61.1%) وف. 9/11 من مرضى ولسون من النوع العصبي وفي 7/2 من مرضى ولسون من النوع الكبدي. وتعتبر المشعة أحادية الفوتون في 15 من 18 مريض ولسون من النوع العصبي و7/5 من مرضى ولسون من النوع الكبدي. كما أوضحت الدراسة أن العلاقة بين الحالة الإكلينيكية والتفكير في أشعة الرينغ المغناطيسية على المخ وآخذة الفوتونات أحادية الفوتون في كل حالة.

وبهذا نستنتج أن الأشعة المقطعية على المخ باستخدام التطور المشعة أحادية الفوتون أكثر حساسية من أشعة الرينغ المغناطيسية على المخ في توضيح تغييرات المخ المصاحبة لمرض ولسون، هناك علاقة جيدة بين الحالة الإكلينيكية والتشخيصية وأن كانت ليست واضحة بعد في تفسير بعض الجوانب الإكلينيكية للمريض في بعض الحالات.