CASE REPORT

Dopamine Transporter Binding in Wilson's Disease

Chin-Chang Huang, Nai-Shin Chu, Tzu-Chen Yen, Yau-Yau Wai, Chin-Song Lu

ABSTRACT: ***Introduction:*** In Wilson's disease (WD), brain magnetic resonance images (MRI) show increased signal intensity in T2 weighted images in the lenticular nuclei, thalamus and brainstem, including the substantia nigra. A poor therapeutic response to levodopa in WD suggests the mechanism of a postsynaptic abnormality. However positron emission tomography studies show an involvement of the nigrostriatal presynaptic dopaminergic pathway. ***Case report:*** We report the clinical manifestations in a case of WD with akinetic-rigid syndrome and initial hesitation. The brain MRI showed an increased signal intensity lesion in the substantia nigra region, in addition to basal ganglion and thalamic lesions. However, dopamine transporter (DAT) imaging with ^{99m}Tc-TRODAT-1 revealed a nonsignificantly increased DAT uptake, suggesting a normal presynaptic nigrostriatal dopaminergic terminal. ***Conclusion:*** We suggest that significant heterogeneity can be found in WD patients and a normal presynaptic dopaminergic pathway may occur in some patients, even those with typical akinetic-rigid syndrome and evidence of substantia nigra involvement in the brain on MRI.

RÉSUMÉ: Liaison au transporteur de la dopamine dans la maladie de Wilson. ***Introduction***: Dans la maladie de Wilson (MW), l'imagerie par résonance magnétique (IRM) du cerveau montre une augmentation de l'intensité du signal sur les images pondérées en T2 dans les noyaux lenticulaires, le thalamus et le tronc cérébral incluant la substance noire. Une réponse thérapeutique médiocre à la lévodopa dans la MW suggère que le mécanisme est une anomalie postsynaptique. Cependant la tomographie par émission de positons montre une implication de la voie dopaminergique présynaptique nigrostriée. ***Observation***: Nous rapportons les manifestations cliniques observées chez un cas de MW présentant un syndrome akinéto-rigide et un retard à initier le mouvement. L'IRM du cerveau a montré une augmentation de l'intensité du signal dans la région de la substance noire ainsi que des lésions du noyau lenticulaire, du noyau caudé, de l'avant-mur, du noyau amygdalien et du thalamus. Cependant, l'imagerie du transporteur de la dopamine par le 99mTc-TRODAT-1 a montré une captation DAT augmentée de façon non significative suggérant que la terminaison dopaminergique nigrostriée présynaptique est normale. ***Conclusion***: Nous suggérons qu'il existe une hétérogénéité significative chez les patients atteints de la MW et que la voie dopaminergique présynaptique peut être normale chez certains de ces patients, même en présence d'un syndrome akinéto-rigide typique et de l'observation d'une lésion de la substance noire à l'IRM.

Can. J. Neurol. Sci. 2003; 30: 163-167

Wilson's disease (WD), hepatolenticular degeneration, is an autosomal recessive disorder characterized by a decreased serum concentration of ceruloplasmin and excessive deposition of copper in the brain, liver and other organs.[1] The most common neurological manifestations include motor dysfunctions such as akinetic-rigid syndrome, dystonia and ataxia with tremor.[2,3] Pathologically, the severely affected lesions are the basal ganglia involving the putamen, caudate, and globus pallidus.[4] Brain computed tomography (CT) reveals low density lesions, sometimes with cystic degeneration in the basal ganglia, particularly the globus pallidus and putamen, in addition to cortical atrophy and ventricular dilatation.[5] Brain magnetic resonance images (MRI) also show increased signal intensities in T2 weighted (T2W) images of the lenticular nuclei, thalamus, and brainstem, including the tegmentum of the pons and midbrain, and even the substantia nigra.[6-8] A poor therapeutic response to levodopa in WD suggests the mechanism of a postsynaptic abnormality.[9] However positron emission tomography (PET) studies have shown an involvement of the nigrostriatal presynaptic dopaminergic pathway.[10]

Both single-photon emission computed tomography (SPECT) with ^{123}I-iodobenzamide (^{123}I-IBZM) and PET images with [^{18}F]-methylspiperone have revealed a reduction of postsynaptic

From the Departments of Neurology (C-CH, N-SC, C-SL), Nuclear Medicine (T-CY) and Neuroradiology (Y-YW), Chang Gung Memorial Hospital and University, Taipei, Taiwan.

Received July 16, 2002. Accepted in final form November 18, 2002.

Reprint requests to: Chin-Chang Huang, Department of Neurology, Chang Gung Memorial Hospital and University, 199 Tung Hwa North Road, Taipei, Taiwan

striatal D_2 receptors reflecting striatal neuronal damage in WD.[11-13] The dopamine transporter (DAT) is a protein located in dopaminergic nerve terminals. Both (1r)-2β-carbomethoxy-3β-(4-iodophenyl)tropane(β-CIT) and TRODAT-1 are cocaine analogues that can easily bind to the DAT site on the presynaptic dopamine neuron terminal membrane.[14,15] Recently, DAT images with [^{123}I]-β-CIT have revealed a severe or differential loss of the DAT in the striatum in WD patients, suggesting significant damage in the presynaptic nigrostriatal dopaminergic nerve terminal.[14,16] However in another study, ^{123}I-IBZM was dramatically reduced, while [^{123}I]-β-CIT uptake was only slightly reduced, suggesting a postsynaptic lesion.[17] Therefore, whether the presynaptic, postsynaptic, or both nigrostriatal pathways are involved has remained unclear. Recently we encountered a patient with WD who had an akinetic-rigid syndrome feature with initial hesitation and an involvement of the substantia nigra region on the brain MRI. The results of the ^{99m}Tc-TRODAT-1 study are reported and possible mechanisms are discussed.

Case report

The patient, a 22-year-old woman, was referred to our hospital because of a gait disturbance with small steps, which began in October 1998, especially during initial walking. She was healthy until one year before this admission, when she developed a right hand tremor and gait disturbance. About six months later she had difficulty writing, followed a few months later by a swallowing disturbance and slurred speech. Neurological examination revealed bradykinesia, mild masked face, micrographia, dysphagia, and dysarthria. In addition, postural and action tremors were found. Her gait disturbance was more prominent in initial walking, which made her unable to start walking for several seconds. Dystonia was also found in the left foot with an extended toe. Tendon reflexes were normal and plantar responses were flexor. There was no sensory impairment, pyramidal signs, or cranial nerve palsy. Kayser-Fleischer rings were noted over the cornea of both eyes.

Laboratory studies showed normal complete blood counts, renal function, and lipid tests.Normal liver function was noted with albumin: 50 g/L (ref. 35-52 g/L), AST: 32.0 μ/L, total bilirubin: 13.7 μmol/L (ref.: 3.4-22.3 μmol/L) and α-fetoprotein 7 μg/L (ref.: < 20 μg/L). The prothrombin time was 13.7 seconds (control: 11.9 seconds) and activated partial thrombin time was 40.3 seconds (control: 32.0 seconds). Serum ceruloplasmin was undetectable (< 0.4 μmol/L, normal controls: 1.0-4.1 μmol/L), the serum copper level was 5.0 μmol/L (normal controls: 10.9-21.8 μmol/L) and the 24-hour urinary copper excretion was 194.7 μmol/day (normal controls: < 6.3 μmol/day). Abdominal echogram revealed a slightly enlarged liver with a coarse and deranged parenchyma, undulated liver surface, and splenomegaly indicating liver cirrhosis. A diagnosis of WD was made although neither a liver biopsy nor a genetic test was done. Brainstem auditory evoked potentials revealed a delayed latency of peak wave V and increased interpeak latencies of III-V and I-V on both sides. Pattern reversal visual evoked potentials showed prolonged peak latencies of P100 in both eyes. The data indicated bilateral impairments of visual conduction pathways. Somatosensory evoked potentials also disclosed bilateral prolongation of central conduction times of N13-N20 by median nerve stimulation, and N22-P40 by tibial nerve stimulation. In a motor evoked potential study, central conduction times were normal bilaterally. The patient was treated with D-penicillamine (300 mg), and zinc gluconate (78 mg 4 times daily). In addition, levodopa / benserazide (300/75 mg to 450 / 112.5 mg daily in divided doses) was given. However, the parkinsonian features had not improved significantly after levodopa treatment.

Brain magnetic resonance images (MRI)

Magnetic resonance images showed typical basal ganglia and thalamic lesions. In addition, the brain MRI also revealed a small brainstem with decreased signal intensity lesions in the substantia nigra on T1 weighted images (T1W). On T2W images and proton weighted images the substantia nigra lesions were hyperintense (Figure 1). Hyperintense lesions were also noted in the pretectal region of the pons. Figure 2 shows the increased signal intensity in the substantia nigra region in a magnified view of T2W as compared with those in a normal control and in a patient with Parkinson's disease (PD).

Material and methods

^{99m}Tc-TRODAT-1 Brain SPECT

The ^{99m}Tc-TRODAT-1 Brain SPECT was performed as previously described,[15, 18-20] and was prepared from a research kit from the Institute of Nuclear Energy Research. The intravenous injection dose was 925 MBq (25 mCi). Imaging was performed 4 h later. Single-photon emission computed tomography images were obtained using a MULTISPECT 3γ camera (Siemens Medical Systems, Inc., Hoffman Estates, IL) with a fanbeam collimator, 128 projections over 360°, 60s per stop, and a 128 x 128 matrix. Individual images were reconstructed with back-projection using a Butterworth filter, with a cutoff of 0.3/cm and an order of 10. The data were corrected for the effects of photon attenuation using Chang's first-order method, with the attenuation ellipses defined on the summed images of the entire data set and applied, without modification, to all the images individually. The summed image was reoriented to give transverse slices parallel to the orbitomeatal line, and then the same transformation parameters were applied to every other image in turn. Pixel size was 2.9 x 2.9 mm, and slice thickness was 2.9 mm.

The analysis of the nigrostriatal dopaminergic pathway with Tc-TRODAT-1 binding, and the ratio of specific to nonspecific binding was calculated by summing two transverse slices representing the most intense nigrostriatal DAT binding. Data analyses were performed by three investigators, blindly. A standard region-of-interest template using a stereotatic shape obtained from a MRI atlas, and including regions of the putamen, caudate, and occipital cortex, and additional regions of interest for the entire striatum, were placed bilaterally on the acquired images. Estimates of specific striatal binding were made by subtracting occipital counts from nigrostriatal counts. The ratio of specific to nonspecific striatal ^{99m}Tc-TRODAT-1 binding was then calculated by dividing the specific nigrostriatal uptake by occipital bindings.

All data were analyzed using the computer software package JMP 3.0 (SAS Institute Inc., Cary, NC) on a Macintosh personal computer (Apple Computer, Cupertino, CA). Statistical analysis was performed using the analysis of variance.

Results

The striatal specific-to-nonspecific binding ratios calculated from the ^{99m}Tc-TRODAT-1 Brain SPECT was 2.34 on the right and 2.33 on the left side, respectively (Figure 3). In comparison

https://doi.org/10.1017/S0317167100053464 Published online by Cambridge University Press

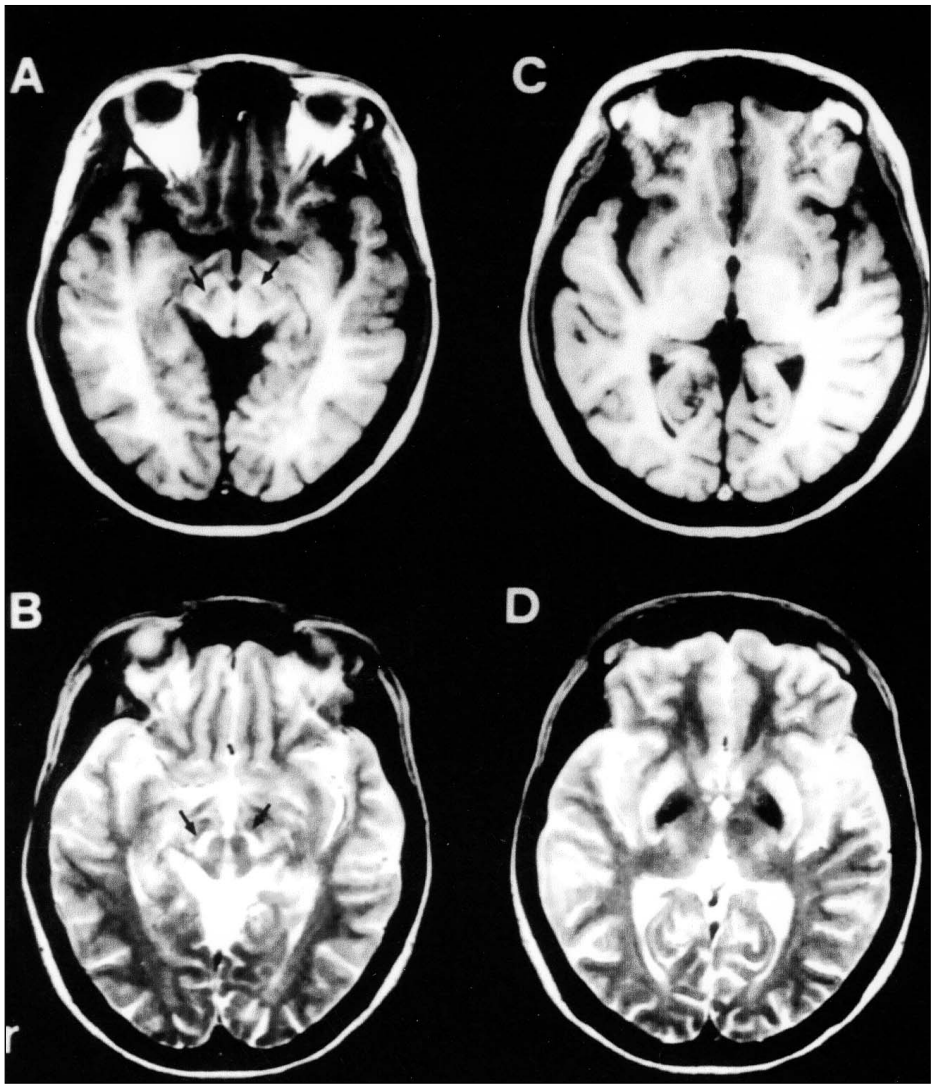

Figure 1: *Brain magnetic resonance images (MRI) revealed decreased signal intensity lesions at the midbrain, particularly the substantia nigra (arrows) on T1W (A). On T2W, the substantia nigra lesions showed hyperintensity (arrows) (B). Brain MRI also showed low signal intensities on T1W in the putamen of the basal ganglion (C). On T2W, the basal ganglia revealed hyperintensities in the putamen and hypointensities in the globus pallidus (D).*

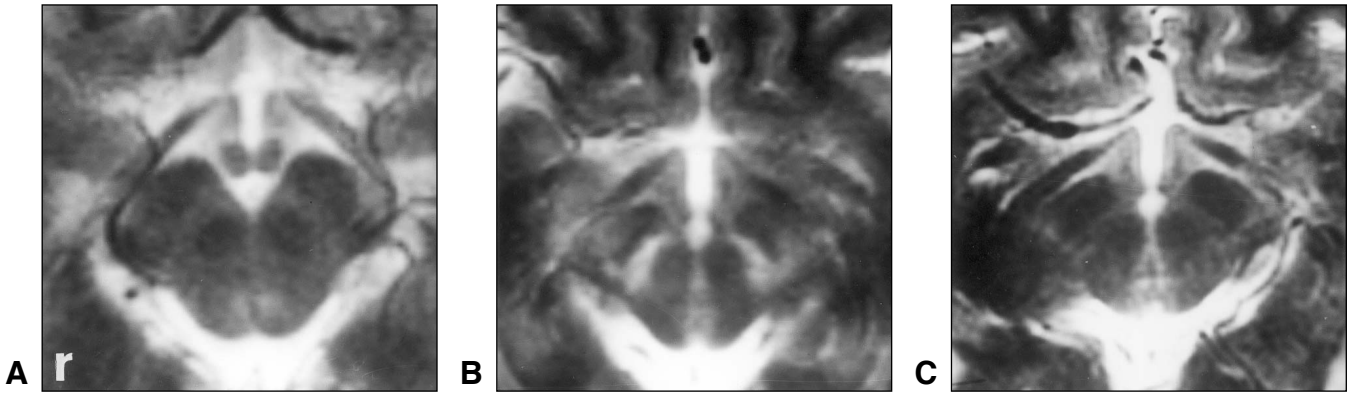

Figure 2: *A magnified brain MRI on T2W shows an increased signal intensity, particularly in the substantia nigra, in the patient with WD (B), as compared with those of a normal control (A) and a PD patient (C).*

https://doi.org/10.1017/S0317167100053464 Published online by Cambridge University Press

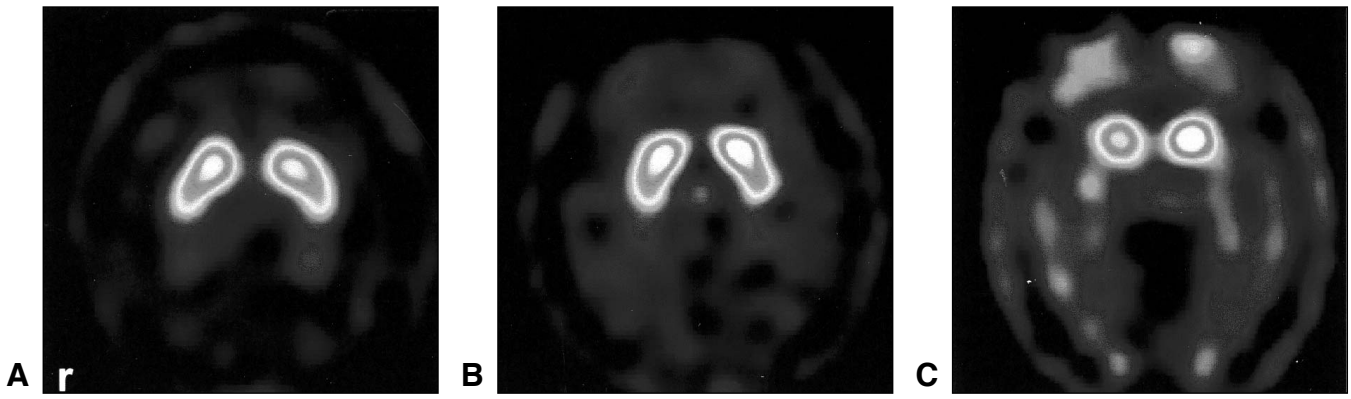

Figure 3: *Demonstration of ^{99m}Tc-TRODAT-1 uptake in an age-matched normal control (A), WD patient (B) and PD patient (C). Normal uptake of ^{99m}Tc-TRODAT-1 in the putamen and caudate nucleus was noted in the normal control and WD patient (A and B). In PD patient, there was an asymmetrically decreased ^{99m}Tc-TRODAT-1 uptake, predominantly in the putamen (C).*

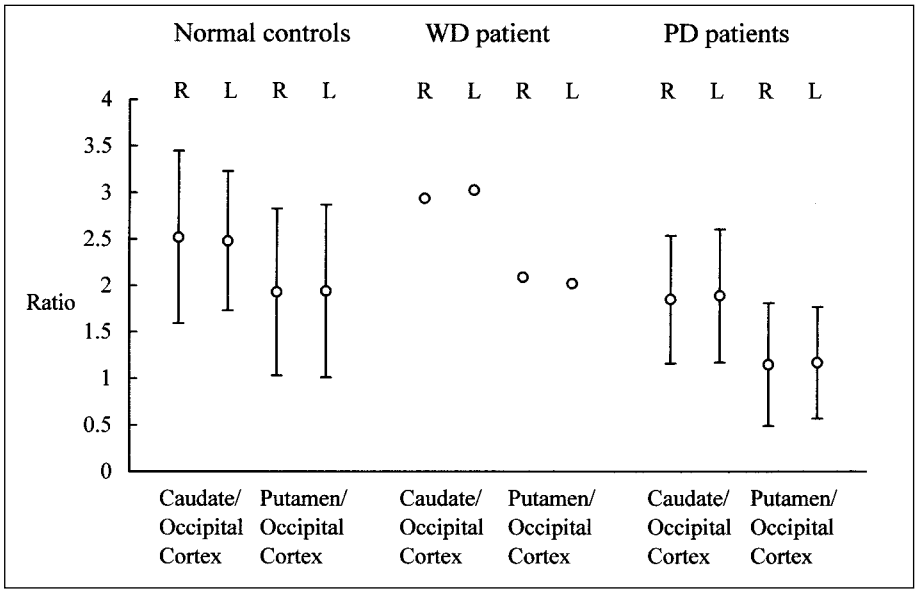

Figure 4: *Ratio of ^{99m}Tc-TRODAT-1 brain SPECT in the caudate and putamen to that of the occipital cortex in 16 normal controls, WD patient and 10 patients with PD. The error bars indicate confidence interval with 3 standard deviations. The data indicate a nonsignificantly increased uptake of ^{99m}Tc-TRODAT-1 in the WD patient as compared with the normal controls and a significantly higher uptake of DAT as compared with the PD patients.*

with 16 age-matched normals (age range: 20 to 40 yrs) and 10 PD patients (age range: 35 to 45 yrs), the data indicate a non-significant trend towards increased DAT binding (right: 2.15 ± 0.35, left: 2.14 ± 0.32) in the corpus striatum for the normals. However, the data also show a higher DAT binding in the corpus striatum than those in PD (right: 1.38 ± 0.18, left: 1.41 ± 0.20). Figure 4 shows the results of the ^{99m}Tc-TRODAT-1 brain SPECT in the caudate and putamen in the WD patient, 16 normals and 10 PD patients.

Discussion

The present study reports a WD patient with akinetic-rigid syndrome whose MRI findings showed an involvement of the substantia nigra with high signal intensities in T2W images, in addition to basal ganglion and thalamic lesions. However, a measurement with ^{99m}Tc-TRODAT-1 showed a normal DAT binding as compared with those of the normal controls. The data indicate normal dopaminergic nerve terminals despite involvement of the substantia nigra region on MRI.

Lesions of the basal ganglion have been considered to be commonly affected in WD.[4] Akinetic-rigid syndrome and dystonia have been the common manifestations.[2,3,21] In addition, postsynaptic damage in the striatum has been shown in pathological studies, neuroimages and D2 receptor images.[4,5-8,11-13] Poor therapeutic response to L-dopa also suggests a postsynaptic mechanism. However, the brain MRI revealed structural lesions in the midbrain, including the nigral region.[8] In some [^{18}F]-6-fluorodopa PET studies, the fluorodopa uptake was decreased in

https://doi.org/10.1017/S0317167100053464 Published online by Cambridge University Press

WD patients with neurological symptoms.[10] Similarly, striatal binding of [^{11}C]-(+)-nomifensine was reduced in neurological WD patients.[22] In addition, some reports showed that L-dopa might improve the neurological symptoms in WD patients.[23,24] These data suggest that presynaptic dopaminergic damage may also play an important role in WD patients.

The DAT may directly reflect the normal function of nigrostriatal dopaminergic terminals.[14,15] In our study, the patient had an involvement in the substantia nigra region on the MRI. However, the DAT with the ^{99m}Tc-TRODAT-1 study showed a normal result. Our findings were very similar to those of the study by Bettin et al,[17] who reported a dramatic reduction of the basal ganglia/medial frontal cortex ratio for ^{123}I-IBZM and only a slight reduction in the [^{123}I]-β-CIT study. These data suggested a prominent postsynaptic D2 receptor lesion rather than a presynaptic dopaminergic terminal lesion. In contrast, in the study by Jeon et al,[14] a severe loss of DAT in the striatum indicated significant damage in the presynaptic membrane. Surprisingly, the loss of DAT is very severe, similar to that of the control patients with PD. Most of them also showed some lesions in the substantia nigra but the important MRI were not shown. The discrepancy between our case and Jeon's patients may be due to the differences in severity of the clinical manifestations. In addition, our WD patient was also different from patients with dopa responsive dystonia. In dopa responsive dystonia patients, DAT studies are also normal but their responses to dopamine treatment have been excellent.[25]

In our patient, despite typical akinetic-rigid syndrome features and lesions in bilateral substantia nigra on the MRI scan, the DAT results were still within normal limits. An alternative explanation may be put forward. The MRI lesions may represent damage to the nondopaminergic neurons or glial cells, or a demyelinating process.[8,26] We conclude that there is significant heterogeneity in terms of the pathological substrate for parkinsonian symptoms in WD. In some patients, this may be related to a presynaptic abnormality, whereas in other patients the symptoms are presumably related to a postsynaptic abnormality. A further large series study is warranted to elucidate the problem.

Acknowledgement

The study was supported by a grant from the National Science Council (NSC 90-2314-b-182A-063). The development of the TRODAT-1 kit at INER was supported by a grant from the Ministry of Economic Affairs, ROC (EC-2A-17-0304). The authors are grateful to Ms. Y-C Hsieh for typing the manuscript.

References

1. Walshe JM. Wilson's disease In: Vinken PJ, Bruyn GW, Klawans HL,(Eds.). Handbook of Clinical Neurology. Vol 49. Extrapyramidal Disorders. Amsterdam: North-Holland. 1986:223-238.
2. Scheinberg IH, Sternlieb I. Wilson's disease. Philadelphia: WB Saunders. 1984: 25-31 and 64-69.
3. Marsden CD. Wilson's disease. Q J Med 1987;248:959-966.
4. Duchen LW, Jacobs J. Nutritional deficiences and metabolic disorders. In: Adams JH, Duchen LW (Eds.). Greenfield's Neuropathology. 5th ed. London: Edward Arnold;1992:838-841.
5. Williams JB, Walshe JM. Wilson's disease: an analysis of the cranial computerized tomographic appearances found in 60 patients and the changes in response to treatment with chelating agents. Brain 1981;104:735-752.
6. Roh JK, Lee TG, Wie BA, et al. Initial and follow up brain MRI findings and correlation with the clinical course in Wilson's disease. Neurology 1994;44:1064-1068.
7. Aisen A, Martel W, Gabrielsen T, et al. Wilson's disease of the brain: MR imaging. Radiology 1985;157:137-141.
8. Huang CC, Chu NS. Acute dystonia with thalamic and brainstem lesions after initial penicillamine treatment in Wilson's disease. Eur Neurol 1998;39:32-37.
9. Morgan JP, Preziosi TJ, Bianchine JR. Ineffectiveness of L-DOPA as a supplement to penicillamine in a case of Wilson's disease. Lancet 1970;ii:659.
10. Snow BJ, Bhatt M, Martin WRW, Li D, Calne DB. The nigrostriatal dopaminergic pathway in Wilson's disease studied with positron emission tomography. J Neurol Neurosurg Psychiatry 1991;54:12-17.
11. Oertel WH, Tatsch K, Schwavz J, et al. Decrease of D2 receptors indicated by ^{123}I-Iodobenzamide single-photon emission computed tomography relates to neurological deficit in treated Wilson's disease. Ann Neurol 1992;32:743-748.
12. Schlaug G, Hefter H, Nebeling B, et al. Dopamine D2 receptor binding and cerebral glucose metabolism recover after D-penicillamine therapy in Wilson's disease. J Neurol 1994;241:577-584.
13. Oder W, Brucke T, Kollegger H, et al. Dopamine D2 receptor binding is reduced in Wilson's disease: correlation of neurological deficits with striatal ^{123}I-iodobenzamide binding. J Neural Trans 1996;103:1093-1103.
14. Jeon B, Kim JM, Jeong JM, et al. Dopamine transporter imaging with [^{123}I]-β-CIT demonstrates presynaptic nigrostriatal dopaminergic damage in Wilson's disease. J Neurol Neurosurg Psychiatry 1998;65:60-64.
15. Kung HF, Kim HJ, Kung MP, et al. Imaging of dopamine transporters in humans with technetium-^{99m} TRODAT-1. Eur J Nucl Med 1996;23:1527-1530.
16. Barthel H, Sorger D, Kuhn HJ, et al. Differential alteration of the nigrostriatal dopaminergic system in Wilson's disease investigated with [^{123}I]-ß-CIT and high-resolution SPECT. Eur J Nucl Med 2001;28:1656-1663.
17. Bettin S, Kampfer I, Seese A, et al. Striatal uptake of I-123-β-CIT and I-123-IBZM in patients with extrapyramidal symptoms. Nuklearmedizin 1997;36:167-172.
18. Mozley PD, Schneider JS, Acton PD, et al. Binding of [^{99m}Tc]-TRODAT-1 to dopamine transporters in patients with Parkinson's disease and in healthy volunteers. J Nucl Med 2000;41:584-589.
19. Tzen KY, Lu CS, Yen TC, Wey SP, Ting G. Differential diagnosis of Parkinson's disease and vascular parkinsonism by [^{99m}Tc]-TRODAT-1. J Nucl Med 2001;42:408-413.
20. Yen TC, Lu CS, Tzen KY, et al. Decreased dopamine transporter binding in Machado-Joseph disease. J Nucl Med 2000;41:994-998.
21. Huang CC, Chu NS. Wilson's disease: clinical analysis of 71 cases and comparison with previous Chinese series. J Formosan Med Assoc 1992;91:502-507.
22. Westermark K, Tedroff J, Thuomas KA, et al. Neurological Wilson's disease studied with magnetic resonance imaging and with positron emission tomography using dopaminergic markers. Mov Disord 1995;10:596-603.
23. Barbeau A, Friesen H. Treatment of Wilson's disease with L-DOPA after failure with penicillamine. Lancet 1970;I:1180-1181.
24. Berio A. Favorable results from the association of L-DOPA, amantadine and penicillamine in a child with Wilson's disease. IRCS J Med Sci 1974;2:1326.
25. Huang CC, Yen TC, Weng YH, Lu CS. Normal dopamine transporter binding in dopa responsive dystonia. J Neurol 2002;249:1016-1020.
26. Huang CC, Chu NS. Psychosis and epileptic seizures in Wilson's disease with predominantly white matter lesions in the frontal lobe. Parkinson Relat Disord 1995; 1:53-58.