Wilson's Disease in Taiwan

Nai-Shin Chu and Chin-Chang Huang

Abstract- Wilson's disease (WD) has been studied in Taiwan since 1960s. The study can be divided into three periods: (1) The first period was 1960s, represented by the work of Dr. JB Tu who worked in the U.S. Naval Medical Research Unit No. 2 (NAMRU-2); (2) The second period was 1970s, represented by the work of Dr. ML Leu who also worked in NAMRU-2. During these two periods, d-penicillamine was introduced to Taiwan via NAMRU-2, primarily as study drug; and (3) The third period was 1980s and afterwards.

Tu and Leu reported the clinical manifestations, tissue concentrations of copper, and therapeutic effects of d-penicillamine including cupriuresis, reduction of copper content in tissues, and prognosis. Our studies after 1980s included clinical manifestations, evoked potentials to detect the extent of CNS involvement, effect of superimposed hepatitis B infection on clinical manifestations and prognosis, and WD with cerebral white matter involvement. The present review highlights above investigations.

Key Words: Wilson's disease, Hepatolenticular degeneration, Taiwan, Cerebral white matter degeneration, Evoked potentials

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INTRODUCTION

In 1912, Kinner Wilson reported in Brain his classic study entitled "Progressive lenticular degeneration: a familial nervous disease associated with cirrhosis of the liver"[1]. In this rare disease which bears his name, he established the familial nature of the disease, described the clinical characteristics of involuntary motor symptoms, and demonstrated its unusual association with cirrhosis of the liver.

Wilson considered this neurological disorder "a pure syndrome of the corpus striatum", and that "in pure cases, the affection constitutes an extrapyramidal motor disease, for the reflexes are normal from the point of view of the function of the pyramidal tracts"[1].

The discovery of Wilson's disease (WD) is one of the milestones in the history of neurology. It introduces the terms of extrapyramidal system and extrapyramidal disease, and establishes the pathogenetic concept of an inborn error of metabolism. In 1948, Cumings demon-

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strated accumulation of copper in the brain and the liver[2]. The major therapeutic advance was achieved in 1956 when Walshe introduced d-penicillamine, an oral chelating agent, to effectively treat WD[3].

Interest in WD started early in China, probably because Wilson's parents were Scottish missionaries in China and the first neurologist in China, Dr. A.H. Woods, was also a missionary physician in China. In 1904, Dr. Woods was a visiting neurologist to the Canton Christian College which later moved to a new site at Lingnan as the Christian Association of Pennsylvania University[4]. In 1919, Dr. Woods moved to Peking Union Medical College as an associate professor of neurology and psychiatry[4]. In 1925, Woods and Pendleton reported 14 cases of "an acute degenerative striatal disease" in Archieve of Neurology and Psychiatry[5]. These striatal diseases were thought to be WD. After 1930s, several reports on WD had come out from China[6-9].

STUDY OF WD IN TAIWAN

In 1959, Cheng and Lee first reported two cases of WD in Taiwan[10]. However, systematic study of this disease was not initiated until 1960s when the U.S. Navy established a Naval Medical Research Unit No. 2 (NAMRU-2) in Taipei. This research unit was situated within the building complex of the National Taiwan University Hospital (NTUH). There were research collaborations between NTUH and NAMRU-2.

The study of WD in Taiwan may be divided into three periods:

a. The first period－1960s[11-18]

b. The second period－1970s[19-25]

c. The third period－1980s and afterwards[26-48]

In 1960s, Dr. JB Tu of the department of neuropsychiatry, NTUH, collaborated with Dr. RQ Blackwell and others of NAMRU-2, looking into the clinical manifestations, genetic and metabolic analysis, and treatment with penicillamine in Chinese patients with WD[11-18]. At that time, penicillamine was very expensive and also not on market. Therefore, the clinical manifestations of those patients represented the pre-penicillamine era.

From their studies, the clinical symptoms of WD in Chinese patients were found to be similar to those of previous reports except that skeletal and joint abnormalities (66%) and epileptic seizures (33%) were more common. Penicillamine-induced cupriuresis was seen in homozygotes and heterozygotes with the former showing a distinctly higher output[17]. This penicillamine-induced cupriuresis was thought a useful adjunct to serum ceruloplasmin for diagnosis of presymptomatic WD.

They also determined tissue copper concentrations on autopsy specimens from 4 patients with WD, one asymptomatic patient, and 4 controls. Higher tissue concentrations were found in WD cases, particularly marked in the liver, brain, kidney and cornea[12]. Interestingly, copper levels of the cerebral cortex were higher than those of the basal ganglia, suggesting that the latter is more vulnerable to copper toxicity[12].

In 1970s, Dr. ML Leu of the department of medicine, NTUH, collaborated with Dr. G.T. Strickland of NAMRU-2 to investigate clinical features as well as renal functions in WD and their response to penicillamine[19-25]. They also determined tissue levels of copper, zinc, and manganese in WD by neutron activation analysis[21]. Only copper was found elevated, particularly in the brain, liver, spleen and skeletal muscle (Unfortunately renal tissue was not analyzed). Penicillamine therapy reduced tissue levels of copper, most rapidly from the kidney, more slowly from the liver, and slowest from the brain.

As the result of a collaboration between Taiwan and the United Kingdom, they published an important paper, comparing general clinical characteristic and genetic analysis of 142 cases (55 cases from Taiwan and 87 cases from UK) between Taiwan and UK[23]. Prognosis after penicillamine therapy was also investigated[23]. Although there were minor differences, clinical manifestations were in general similar. One thing stood out was the excellent response of Chinese patients to penicillamine treatment. Among 88 patients with follow-up up to 16 years, 35 of 36 patients who had not received penicillamine treatment had died; In contrast, 31 of 35 patients who had received penicillamine therapy were alive, and furthermore 18 of those alive patients were

asymptomatic.

In 1980s, study of WD in Taiwan had changed direction: mainly on clinical and electrophysiological aspects[26-48]. Although the original description of WD stressed CNS lesions in the basal ganglia, there are also lesions in claustrum, thalamus, subthalamus and red nucleus; degeneration of myelinated fiber bundles; abnormalities of blood vessels; and a variable degree of involvement of the cerebral and cerebellar cortices as well as the white matter[1]. Cumings also stated that "It is also known that the cerebral cortex and the white matter may be as severely affected as the basal ganglia."[49]. Brain MRIs show not only involvement of the putamen, globus pallidus and caudate nucleus, but also lesions of subcortical white matter[30,35,38,42,45,50-52]. These findings raise the possibility that copper cytotoxicity in the CNS affects not only gray matter, but also white matter. Therefore, evoked potentials study might show slowed conduction and/or poor response. Furthermore, clinical manifestations related to white matter involvement could also be explored.

1. Clinical studies

Although Tu and Leu had reported clinical manifestations of WD in Taiwan, their patients came from NTUH, a tertiary referral center, and might not be representative of general population. In contrast, our hospital is a general hospital with an open-door policy, allowing free access to patients.

We analyzed 71 patients with WD who were seen in our hospital from 1979 to 1990[34]. The mean age of onset was 18.1 years, with 17.0 years for males and 20.2 years for females. Hepatic WD was the most frequent mode of presentation in childhood with a mean age of 15.5 years, while neurologic WD tended to occur in adolescence with a mean age of 21.0 years. The mean ages of onset were 12.5 years for renal WD and 25.3 years for psychiatric WD. The common initial symptoms were neurologic (46.5%) and hepatic (45.1%). The neurologic symptoms at the time of diagnosis were tremor (66.2%), dysarthria (56.3%), gait disturbance (46.5%), dystonia (45.3%), masked face (40.8%), personality change (38%), rigidity (33.8%), and grimace (23.9%). Less frequent but notable neurological presentations were psychosis (11.3%), epileptic seizures (5.6%), and hypokalemic periodic paralysis (1.4%). It was also noted that epileptic seizures were often associated with cerebral white matter lesions.

When compared to previous large Chinese series[9], our study showed an earlier age of onset (18.1 years vs. 23.5 years) and higher incidences of hepatic and hematologic abnormalities, while the incidences of skeletal involvement and psychiatric symptoms were much lower. On the other hand, when compared to previous large Taiwan series[23], our study showed a male predominance (M/F ratio: 1.7 vs. 0.8), a later age of onset, particularly for the females (20.2 years vs. 11.8 years), higher incidences of hepatic, hematologic and renal abnormalities, but lower incidences of mostly skeletal involvement and psychiatric symptoms; and less prominently in rigidity and masked face. These differences seemed to reflect different clinical presentations between post- and pre-penicillamine eras.

2. Electrophysiological studies

In electrophysiological studies including motor, somatosensory, brainstem auditory, and pattern-reversal visual evoked potentials (EPs), abnormalities of those EPs were frequent in patients with neurologic symptoms, whereas those abnormalities were not observed in patients with hepatic form and in the family members[27,29-31,37]. These studies seemed to indicate that the majority of patients with neurologic symptoms had subclinical dysfunction in the cortico-spinal motor pathway as well as major sensory pathways. These data are consistent with neuropathological and neuroradiological findings of widespread degeneration of the brain, both gray and white matters, in WD[1,49].

Another study compared the brainstem auditory EP (BAEP) among different chronic hepatic diseases, including chronic hepatitis B infection, liver cirrhosis from hepatitis B, liver cirrhosis from alcoholism, and liver cirrhosis from WD[29]. BAEP was normal in patients with hepatitis B infection only, but it was progressively worse from hepatitis B cirrhosis, to alcoholic cirrhosis, and finally to Wilsonian cirrhosis. These findings sug-

gest that copper cytotoxicity has the worse effect on the brainstem function.

Finally, blink reflex was studied in WD to further investigate the degree and extent of brainstem abnormalities[37]. The data showed that R1 and R2 latencies as well as R2 duration were prolonged in the patient group, but not in the family member group. Those blink reflex abnormalities in WD differed from those in Parkinson's disease, Huntington disease and torsion dystonia by having abnormalities in both R1 and R2 components. These findings are in some aspects similar to those seen in multiple sclerosis, suggesting involvement of the white matter. Because abnormal R1 response is usually indicative of functional or structural abnormality in the pons, whereas abnormal R2 response is usually indicative of suprabulbar influences, these data seem to be again consistent with extensive conduction abnormalities in motor and sensory pathways as demonstrated in our EP studies.

3. Cerebral white matter involvement

Although WD has been thought to primarily involve gray matter with the main target on the lenticular nuclei, white matter degeneration has been reported[30,35,38,45,49-52]. From review of the literature and our studies, cerebral white degeneration is estimated to be 6-20% of patients with WD and mainly affects the frontal lobe (Fig.) [45].

Our studies have revealed certain characteristic clinical presentations[30,35,38,45]. The majority of the patients were adolescents or young adults who usually had WD for several years. The patients were often not treated, poorly treated, or induced or aggravated by penicillamine therapy. Clinical features were characterized by

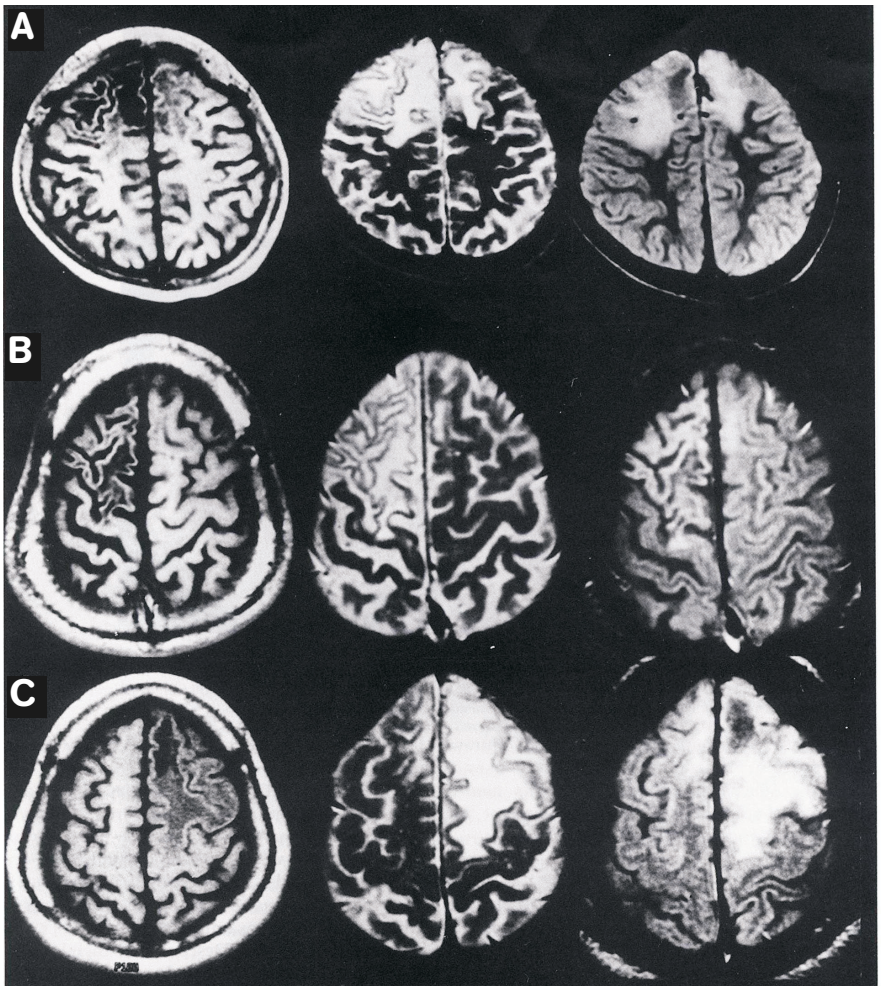

Figure. MRI scans of 3 patients (A, B, C) with cerebral white matter lesions predominantly in the frontal lobe. The first, second, and third columns are T1, T2 and proton weighted images, respectively.

contralateral weakness, tremor, and/or dystonia. Psychiatric symptoms, particularly schizophrenia-like psychosis, were common. Epileptic seizures were also common and might be the initial presentation. The seizures would respond to antiepileptic and decoppering drugs. The long-term prognosis appeared to be favorable when patients had regular and proper treatment.

4. WD with hepatitis B infection

Taiwan is an endemic area of hepatitis B with a prevalence rate of 15-20% for carriers in general population. We retrospectively investigated the occurrence of type B viral hepatitis in patients with WD and the clinical manifestations of this particular group of patients[44].

Among 61 patients who had tests for HBsAg and HBsAB, 10 patients (16%) were positive for HBsAg. Their mean age of disease onset was 15.3±9.2 years; the initial presentation was hepatic in 8 (80%); hepatic encephalopathy occurred in 8 (80%) and death from hepatic cause occurred in 5 (50%) within 2.4 ± 1.5 years after disease onset; In contrast, 51 HBsAg-negative patients had onset age of 18.5±7.1 years; initial hepatic presentation occurred in 15 (29%); hepatic encephalopathy occurred in 4 (7%); and hepatic cause of death occurred in 12 (24%) within 5.7±3.1 years.

These data indicate that the occurrence of hepatitis B infection in WD is not different from that of general population, but will aggravate the clinical manifestations and prognosis of WD. An incidental finding of the study was that none of the patients, HBsAg positive or negative, had primary hepatocellular carcinoma, despite having cirrhosis of the liver, consistent with previous observations that primary hepatic malignancy is extremely rare in WD, suggesting a protective role of copper[53,54].

CONCLUSIONS

WD has been studied in Taiwan since 1960s. Clinical manifestations were analyzed in both pre- and post-penicillamine eras. Pencillamine was demonstrated to induce cupriuresis, to lessen clinical symptoms, and to improve prognosis.

Electrophysiological studies, particularly EPs, revealed frequent conduction abnormalities in both central motor and sensory pathways, suggesting widespread white matter involvement in WD. The cerebral white matter lesions were often associated with epileptic seizures, psychosis and dystonia. Those patients were usually not treated, delayed in treatment, or induced by penicillamine therapy. Further study is needed to delineate the pathophysiology of cerebral white matter degeneration in WD.

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