中文題目：以神經學合併精神學症狀表現的威爾森氏症-病例報告

英文題目：Neurological symptomes combined with psychiatric symptoms presenting as Wilson disease: A case report

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Introduction: Wilson disease is a genetic disorder of copper metabolism with an autosomal recessive pattern of inheritance due to mutations that lead to impaired function of the intracellular copper transporter *ATP7B.* In Europe, the disease is most frequently diagnosed in Austria (3.0 per 100,000 inhabitants) and Germany (2.5 per 100,000 inhabitants)[2,3]. The prevalence is higher in China (58.7 per 1,000,000) and Asian countries than in western countries[4]. It can appear at any age, although it is most prevalent in patients before the age of 40. Most cases are diagnosed between 5 and 35 years of age[5]. Impaired biliary copper excretion leads to accumulation of copper in several organs,including liver, brain, and cornea. Predominant patterns of presentation include hepatic, neurologic, and psychiatric disorders.

Case presentation: A 22-year-old woman without systemic diseases presented with progressive dysarthria and difficulty swallowing, ataxia and dystonia which lead to inability of ambulation for two weeks. Initially, she presented with impairment of memory, comprehension and declining of study performance in college since one year ago. She soon visited a psychiatric clinic for help and was told to have depression due to depressed mood, insomnia, and poor study performance. However, her symptoms showed no improvement under antidepressant used for several months. Finally, she quit school. Multiple neurological symptoms including limbs resting tremor, gait ataxia, parkinsonism, dysarthria, dysphagia, and drooling appeared in recent one month. She was brought to the neurologist for her continuous worsening of neurological symptoms and personality change one month ago(Ex: imitation of her mother's movement, childish behavior). Under the impression of movement disorder, she received a brain MRI which revealed symmetric high intensity signals over bilateral putamen, bilateral caudate nucleus, thalamus, midbrain and tegmentum which is referred to a "double panda sign". So Wilson disease was highly suspected. (Figure 1). Abdominal ultrasound revealed liver cirrhosis with splenomegaly. Laboratory examination found low levels of serum ceruloplasmin(2.6 mg/dL), low blood Cu (385 PPB), and high 24 hours urinary copper excretion(174.7 mcg/day),

which supported the diagnosis of Wilson disease. She was then transferred and admitted to our hospital for further evaluation and management. Kayser-Fleischer rings(Figure 3) were noted by the ophthalmologist. Genetic testing revealed two heterozygous mutations of *ATP7B* and liver biopsy showed focally strong positive Copper stain which both proved the diagnosis of Wilson disease. The Leipzig scoring system for Wilson disease was more than 4, thus diagnosis was established[6]. Penicillamine was administered, but adverse effects including fever, elevated liver enzyme and multiple erythematous maculopapular rash(Figure 2.) were developed. D-penicillamine related early drug eruption was impressed by dermatologists. The dose of D-penicillamine was tapered and Zinc acetate was added as combined therapy. Skin eruptions persisted after tapering D-penicillamine during the period of follow-up, so D-penicillamine was shifted to Trientine hydrochloride. Her 24 hours urinary copper excretion gradually decreased and her neuropsychiatric symptoms improved under trientine hydrochloride and Zinc acetate combined therapy for three months. Currently, she is on soft diet and rarely chokes while drinking. She is able to use chopsticks and walk without assistance.

Discussion: There is wide variability in the reported rates of the manifestations seen in Wilson disease including 18~73% of neurologic and 10~100% of psychiatric symptoms. While children are more likely to present with hepatic manifestations and rarely with neurologic symptoms, adolescents and adult patients present more neurologically. The mean age of onset with neurologic symptoms ranges between 15 and 21 years. The clinical categories encompass the neurologic Wilson disease are, dysarthric, dystonic, tremor, pseudosclerotic or parkinsonian[7]. In studies that categorize initial manifestations, dysarthria is the most common (57.6%), followed by dystonia (42.4%), abnormal gait (37.8%), tremor (36.2%), parkinsonism (17.3%), chorea or athetosis (15.3%), and seizures (4.7%)[8]. Among the types of dystonia, focal dystonia of the vocal cords, muscle of articulation, and swallowing frequently results in dysphonia, dysarthria, and dysphagia. As the disease progresses focal dystonia can progress to segmental, multifocal, hemidystonia, and generalized dystonia. Bradykinesia, imbalance, and cogwheel rigidity are the more common parkinsonian features. Chorea is more common in young onset disease. In patients with neurologic disorders, the symptoms disappear more slowly and remission may require up to 3 years[9]. One of the largest series of Wilson disease patients (n = 327)

from Euro Wilson consortium, showed hepatic forms had 91% response compared to only 68% in neurological forms after a median follow up duration of 13.3 years[10]. The frequency of neurologic symptoms deterioration after starting chelation therapy occurs between less than 10% and 50% of patients[11]. The neurologic status of patients may worsen after initiation of treatment with D-penicillamine and trientine which appears less commonly with D-penicillamine. It has been suggested that chelating therapy increases free copper, which creates free radicals and contributes to further neurological damage. Therefore, chelating therapy should be started at low dose. In addition, behavioral and psychiatric symptoms are more common in patients with neurologic involvement than in patients with hepatic involvement. The most common behavioral and psychiatric symptoms include depression , personality change, incongruous behavior, and irritability[12]. However, behavioral and psychiatric symptoms are often overlooked misdiagnosed (eg, they may be attributed to puberty). Fortunately, our patient had neurological symptoms soon after behavioral and psychiatric symptoms that raised our awareness of this disease. We suspected her depressive mood was induced not merely by external influences but also definite brain injury by copper. It is uncommon for patients to be diagnosed of Wilson disease only with behavioral or psychiatric symptoms, and diagnosis may be delayed significantly in these individuals.

Conclusion: Wilson disease is a diagnosis of consideration in young age patients presenting with depression and movement disorder, especially in those with typical neurological, behavioral symptoms, typical images and laboratory findings. We can use the Leipzig scoring system to assist in diagnosis. Symptomatic patients should be treated initially with a chelating agent. Maintenance therapy can be achieved with zinc or with a lower doses of a chelating agent Patients should be monitored at least twice annually with serum copper, ceruloplasmin, liver biochemistries, international normalized ratio, complete blood count, urinalysis, and a thorough physical examination.

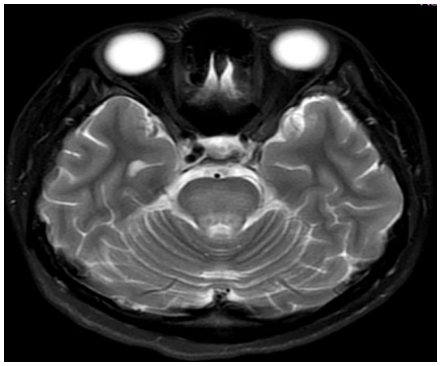

Figure 1 The face of miniature panda within the pontine tegmentum in T2-weighted image

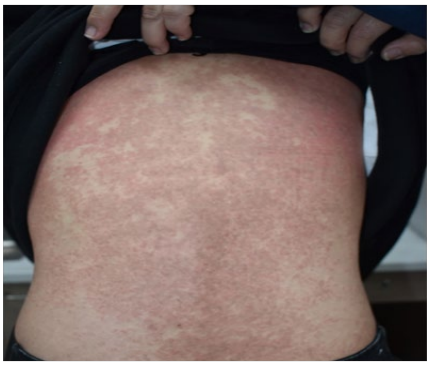

Figure 2 Multiple erythematous maculopapular rash(D-penicillamine related eruption) over the back, limbs and trunk

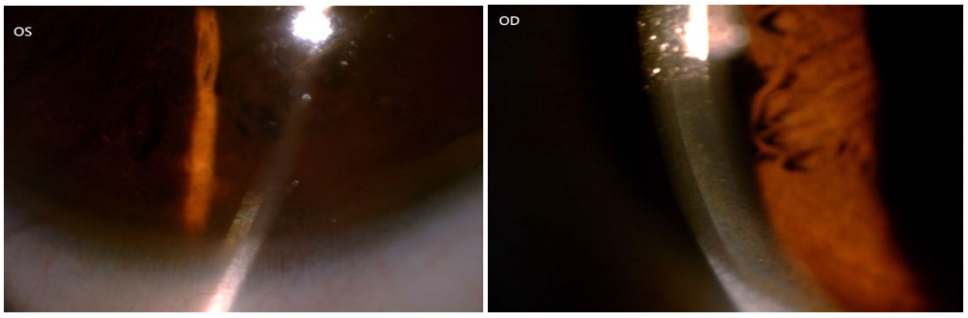

Figure 3 Kayser Fleischer ring, OU, under slit lamp view

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