Peer reviewed article

# Status epilepticus in a case of Wilson's disease during D-pencillamine treatment

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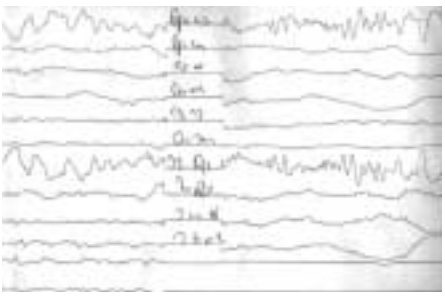
We report on a case of Wilson's disease in a young male presenting with status epilepticus during D-pencillamine treatment. The patient was admitted to our neurogical clinic for status epilepticus and was successfully treated with antiepileptic drugs. He had been on regular D-pencillamine treatment for three years. Magnetic resonance imaging showed lesions bilaterally in subcortical areas of frontal lobes, putamen, thalamus, globus pallidum and caudate nuclei. Wilson's disease had been diagnosed. Few patients with Wilson's disease presenting with epilepsy and status epilepticus have been reported. Although the patient had received D-pencillamine treatment, the diagnosis of Wilson's disease should be considered in patients who present with status epilepticus.

## Introduction

Wilson's disease (WD), or hepatolenticular degeneration, is a neurodegenerative disease of copper metabolism. WD is a treatable autosomal recessive disease localised to chromosome 13, leading to an excessive accumulation of copper in the liver, cornea, kidneys and the basal ganglia of the brain [1]. Other brain structures, such as the thalamus, the cerebellum and the cerebral white matter, may also be affected. Dysarthria, dystonia, cerebellar signs, rigidity, gait and postural abnormalities, tremor, chorea, and dementia are neurological findings seen in WD [2]. Seizures are a relatively rare feature of WD [3–5].

**Figure 1**

EEG recording.



## Case report

A 19-year-old male was admitted to our neurological outpatient clinic for status epilepticus with right-sided focal onset. The focal motor onset – right-sided and firstly clonic in nature, then becoming generalised tonic-clonic seizures – continued for two days. Each seizure complex with frontal automatisms continued for 10–15 minutes and was repeated sixteen times over two days; status epilepticus was diagnosed. The patient was unconscious due to generalised convulsive status epilepticus of the intermittent type and was treated with intravenous diazepam and phenytoin. From the third day the patient's level of consciousness improved and he responded to verbal stimulation. He also exhibited explosive dysarthric speech, rigidity, dystonia and bilateral pyramidal signs. Tandem walking was ataxic. Cognitive examination showed emotional lability and a mini-mental examination score of 18/30. Slit-lamp examination disclosed Kayser-Fleischer rings. He had been diagnosed with WD five years previously and had received 400 mg/day D-pencillamine regularly for 3 years. Routine biochemical tests, including liver function tests, were normal. He had low plasma copper (24 mg/ml [100 mg/ml]) and caeruloplasmin (10 mg/100 ml [N: >20 mg]) concentrations. The 24-hour excreted copper concentration was very high (256 mg/dl [40–80 mg/dl]). Cerebrospinal fluid findings were normal. No provocation factor was involved. The patient was followed in intensive care and due to a technical problem with the EEG equipment an EEG was taken 2 days after the status epilepticus had ended and showed slow background activity, bifrontal slow theta waves and spikes (fig. 1). Ultrasound of the liver was normal. Cranial MRI showed that bilateral subcortical area of frontal lobe, putamen, thalamus, globus pallidus, and caudate nucleus involved lesions that were hypointense on T1 weighted and hyperintense on T2 images. Additionally lesions on pons, mesenzefalon, and periaquaductal gray matter, which were hypointense on T1 weighted images and hyperintense on T2 weighted images, were seen (fig. 2a, b). Following acute hospitalisation he received 1400 mg/day carbamazepine and 400 mg/day D-pencillamine, and has remained seizure-free for two years.

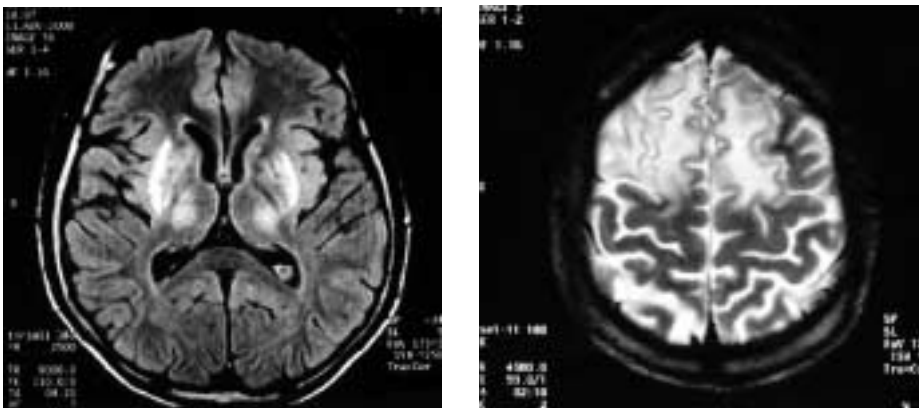
## Discussion

The symptoms of WD may be variable, with neurological and psychiatric findings associated with liver disease predominating. Epileptic seizures are rarely seen in WD. Epileptic seizures in various forms, e.g. generalised tonic-clonic, absence, focal motor and psychomotor, occur as an early or late manifestation of WD [5, 6]. Several mechanisms have been suggested for increased seizure activity. As shown in animal studies, copper deposition in the brain may cause ictus by inhibition of membrane ATPase [7], and thus focal and generalised seizures may be related to copper deposition in the brain. Copper deposition occurs in the lentiform nuclei, thalamus, brainstem nuclei, cerebral cortex, and cerebral and cerebellar white matter. Neuronal loss, gliosis, laminar necrosis, spongy degeneration and cavitation may also be responsible for focal seizure activity [8]. D-penicillamine induces pyridoxine deficiency, which may be a predisposing factor for seizures [6, 9]. Patients with neurological symptoms and signs of Wilson's disease, and even presymptomatic patients, may experience worsening of their condition after starting therapy with D-penicillamine [10]. Dystonia and bradykinesia correlated with the striatum and especially putamen lesions, and dysarthria correlated with both putamen and caudate lesions. Penicillamine treatment in Wilson's disease may cause dystonia with thalamic and brainstem lesions [10, 11]. We conjectured that in the present case the severe seizure problem, and especially dystonia, could be related to D-penicillamine therapy.

Our patient had status epilepticus with

**Figure 2**

Cranial MRI showed hyperintense $T_2$-weighted images in putamen, thalamus, globus pallidus, and caudate nucleus (a) and bilateral subcortical area of frontal lobe and periaquaductal gray matter (b).



a b

focal and secondary generalised tonic-clonic seizures for 48 hours. The EEG recording taken after two days indicated focal epileptiform activity in the frontal regions. In the English-language literature we were unable to find any report of status epilepticus in WD under D-pencillamine treatment. A case report in Japanese was found via MEDLINE [12]. Cerebral MR findings correlate well with neurological findings in WD. The majority of patients without neurological symptoms have normal MR scans, while those with neurological symptoms have abnormal scans [13, 14]. The MRI study in our case showed bilateral subcortical white matter lesions of the frontal lobe, and other classic lesions in which copper may be deposited. We postulate that the frontal lesions may have an aetiological relationship with the seizures in our patient. Because of the existence of frontal automatism and the EEG focus on the frontal regions, the patient's seizures were thought to originate from the frontal lobe. As far as we know this is the second reported case of WD associated with status epilepticus under D-penicillamine treatment. The diagnosis of Wilson's disease should be considered in patients presenting with seizures and status epilepticus.

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## References

1 Finelli PF. Kayser-Fleischer ring: Hepatolenticular degeneration (Wilson's disease). Neurology 1995;45:1261–2.
2 Oder W, Prayer L, Grimm G et al. Wilson's disease: Evidence of subgroups derived from clinical findings and brain lesions. Neurology 1993; 43:120–4.
3 Iwasaki Y, Sone, Kato T, Yoshida E. A young adult female case of Wilson's disease presenting with mental disorder and frontal lobe signs. Rinsho Shinkeigaku 2000;40:576–81.
4 Saka ET, Elibol B, Saygi S. Circling seizures in a case with Wilson's disease. Clinical electroencephalography. 1999;30:1–4.
5 Smith CK, Mattson RH. Seizures in Wilson's disease. Neurology 1967;17:1121–3.
6 Denning TR, Berrios GE, Walshe JM. Wilson's disease and epilepsy. Brain 1988;111:1139–55.
7 Peters RA, Shorthouse M, Walshe JM. The effect of $Cu^{+2}$ on the membrane ATPase and its relation to initiation of convulsions. J Physiol 1965;181: 27–8.
8 Duchen LW, Jacobs JM. Nutritional deficiencies and metabolic disorders. In: Adams JH, Duchen LW (eds.). Greenfield's neuropathology. 5th ed. London: Edward Arnold; 1992. p. 838.
9 Gibbs K, Walshe JM. Penicillamine and pyridoxine requirements in man. Lancet 1966/I:175–9.
10 Glass JD, Reich SG, DeLong MR. Wilson's disease. Development of neurological disease after beginning penicillamine therapy. Arch Neurol 1990;47:595–6.
11 Huang CC, Chu NS. Acute dystonia with thalamic and brainstem lesions after initial penicillamine treatment in Wilson's disease. Eur Neurol 1998;39:32–7.
12 Yoshida K, Maruyama K, Hasimato T, Shindo M, Shoji S, Yangasawa N. A patient with Wilson's disease who developed status epilepticus during D-pencillamine therapy. Nippon Naika Gakkai Zasshi 1989;78:70–4.
13 Aisen AM, Martel W, Gabrielsen TO, et al. Wilson's disease of the brain: MR imaging. Radiology 1985;157:137–41.
14 Prayer L, Wimberger D, Kramer J, et al. Cranial MRI in Wilson's disease. Neuroradiology 1990; 32:211–4.

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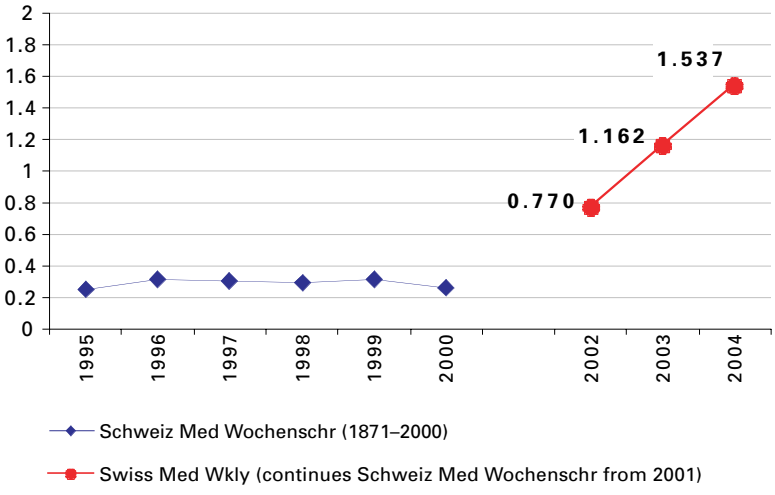


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