

# Status epilepticus in Wilson's disease

Elia M. Pestana Knight<sup>1</sup>, Sid Gilman<sup>2</sup>, Linda Selwa<sup>2</sup>

<sup>1</sup> Division of Pediatric Neurology, Department of Pediatrics

<sup>2</sup> Department of Neurology, University of Michigan, Ann Arbor, USA

Received January 16, 2009; Accepted April 23, 2009

**ABSTRACT** – *Rationale.* Seizures occur in Wilson's disease (WD), with prevalence figures as high as 4-6% in specialized academic centers, but status epilepticus is rare. We report a patient with WD who developed non-convulsive status epilepticus (SE) during therapy with Tetrathiomolybdate (TTM) and review the last 20 years of the relevant literature. *Case report.* A 55 year-old right handed man with WD who had parkinsonian features and hepatic cirrhosis was admitted for seizures. Seizures began on week 4 of treatment with TTM (Phase III Study of Tetrathiomolybdate Dose Regimen in Neurological Wilson's Disease). Seizures were characterized by forced clonic eye, head deviation to the right and right arm posturing followed by unresponsiveness, bilateral eye blinking and right hand automatisms. EEG confirmed frequent left frontal seizures. He developed non-convulsive status epilepticus (NCSE) with electrographic seizures every 5-10 minutes, lasting for 1-2 minutes each. Seizures were controlled within 24 hours with fosphenytoin, midazolam and levetiracetam. Brain MRI showed diffuse atrophy, mineralization of the basal ganglia, and patchy FLAIR increase signal in the left frontal lobe. *Literature review.* We found reports of 6 WD patients with SE, two upon presentation of the disease and before copper removing treatment, and four after months to years of treatment with D-penicillamine. *Conclusion.* SE occurs rarely in WD, and our case is the only one reported to develop SE during treatment with TTM. As the literature documented two patients with WD who developed SE prior to copper deposit treatment, our hypothesis is that seizures in WD can be the result of the progression of the disease or a combination of factors but not necessarily due to its treatment alone.

**Key words:** Wilson's disease, seizures, status epilepticus, Tetrathiomolybdate, EEG, MRI

Seizures occur in Wilson's disease (WD), but are unusual. Denning *et al.* (1988) described epilepsy in 15 of 200 patients with WD, a prevalence of 6.2%. The annual incidence rate was 4.3/1 000 per year (Denning *et al.* 1988). Another study reported a prevalence of seizures in 4.2% of 119 patients with WD with neurological manifestations (Machado *et al.* 2006). One of these patients had status epilepticus (SE) (Machado *et al.* 2006). SE appears to be very rare in WD, as only few cases have been reported. We describe a patient with WD and neurological symptoms who developed non-

convulsive SE during therapy with Tetrathiomolybdate (TTM) and review the last 20 years of literature.

## Case report

A 55 year old right handed man with the recent diagnosis of WD (low serum ceruloplasmin 0.11 g/L; high 24 hour urine copper excretion 1.33 micromol/dL; bilateral Kayser-Fleischer (K-F) rings, parkinsonian features, hypokinetic speech and frequent freezing with walking and speaking) presented to the

### Correspondence:

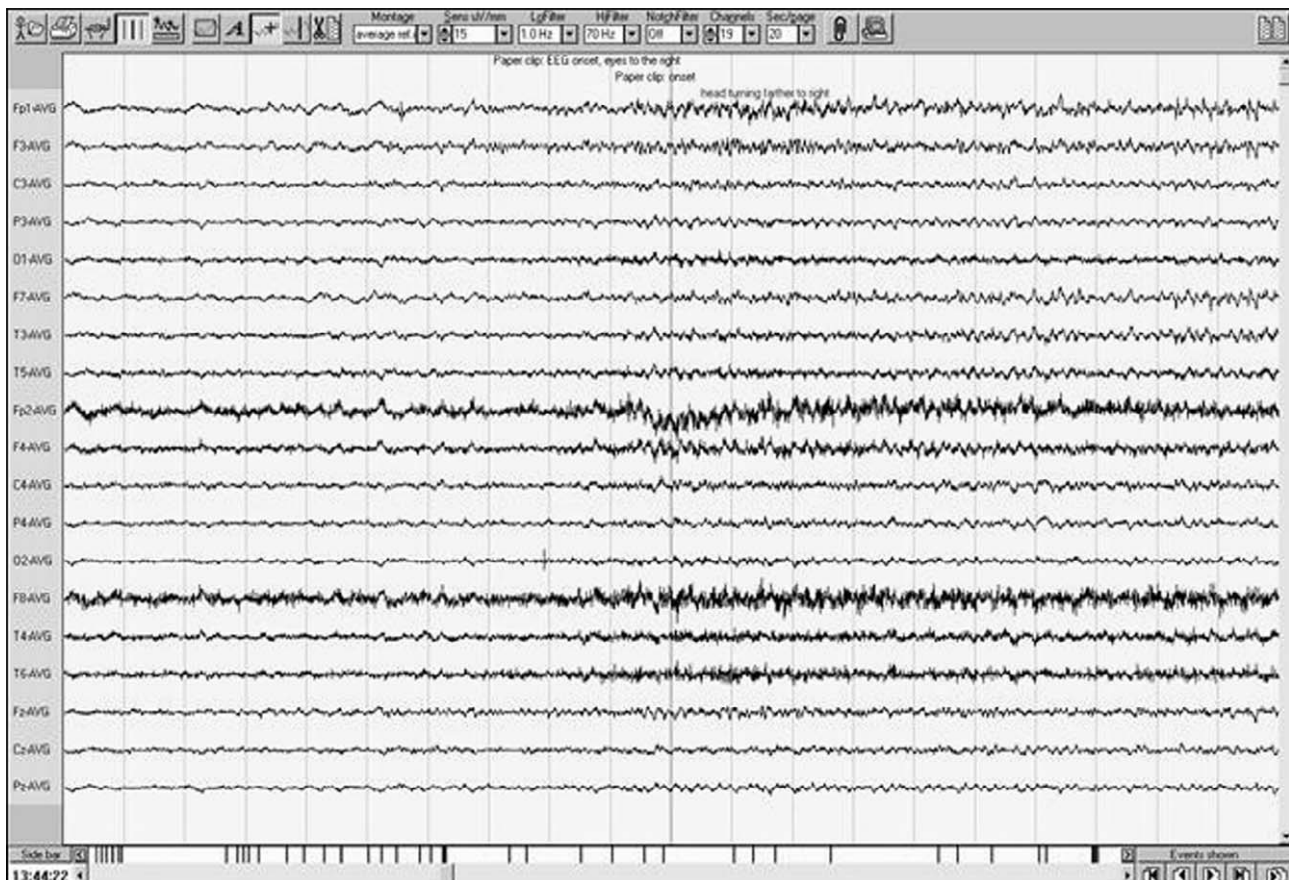
L. Selwa, MD  
Associate Chair for Clinical Activities,  
Director, Clinical Neurophysiology Program,  
Co-Director, EEG/Epilepsy Program,  
Alfred Taubman Health Care Center,  
1500 East Medical Center Drive, Room 1324,  
Ann Arbor, MI 48109-5322, USA  
<lmselwa@med.umich.edu>

Emergency Department after developing recurrent episodes of forced eye deviation to the right, head turning to the right and elevation of the right arm. TTM was his first medical treatment for WD and his seizures began after week 4 of treatment (phase III study of Tetrathiomolybdate dose regimen in neurological Wilson's disease).

On presentation the frequency of the seizures was 4-5 per day and the duration was less than half a minute. In the next 4 days the episodes became more frequent, one every 15-20 minutes. Initially during the seizures, he had saccadic movements of the eyes to the right followed by head deviation to the right. His right arm extended and elevated in a posturing position. During this period he was able to follow commands. Afterwards, his eyes returned to midline position, he stared ahead and became unresponsive. He had rhythmic blinking of the eyes and right hand picking automatisms. His resting tremor completely disappeared during the seizures. The episode ended after 30 seconds with a sigh, and he immediately regained consciousness until the next episode 15-20 minutes later. Between the seizures, he was able to talk and walk.

On physical examination (before and after the SE), he had hypophonic, bradykinetic and spastic speech. When the

seizures were frequent, he was disoriented to place and time. He had K-F rings covering the inferior and superior border of the limbus of the corneas bilaterally. Extra-ocular movements revealed small square-wave jerks, and saccadic interruptions of pursuit movements. Up-gaze and down-gaze were limited to 20 degrees from the horizontal meridian. His blink-rate was reduced, and he had a masked face. He had cogwheel rigidity in all extremities, and rapid alternating movements were slow bilaterally. He had bilateral resting tremor in both arms and both hands, and the left leg. He had bilateral upper extremity postural and kinetic tremor. The tremor had low amplitude and high frequency distally and larger amplitude with slower frequency proximally mainly at the shoulders. Finger-nose-finger testing showed an intention tremor. He has dystonia with hyperextension and rotation of the fingers in both hands. He had difficulty walking, with extremely short steps and shuffling of the feet that worsened when he was going under a door or near obstacles such as chairs. He took more than 15 short steps to turn around with an en bloc turn and he required help. He had decreased arm swing bilaterally in the upper extremities.



**Figure 1.** EEG shows a seizure arising from the left frontal region.

Video-EEG confirmed frequent clinical seizures that were arising from the left frontal region (*figure 1*). He received treatment with diazepam 5 mg IV and levetiracetam 1 000 mg IV BID but a few hours later became unresponsive and developed non-convulsive status epilepticus with electrographic seizures lasting 1-2 minutes and occurring about every 5-10 minutes. He was loaded with fosphenytoin 1 900 mg IV (20 mg/kg/dose). He also received midazolam in continuous IV infusion at the rate of 11 mg/hr. After the fosphenytoin load, Serum total Dilantin level was 22.9 and free Dilantin 2.1. Despite the presence of hepatic cirrhosis, he tolerated treatment with fosphenytoin. Seizures were controlled within the following 24 hours. Treatment was continued with phenytoin at the dose of 300 mg PO at bedtime and levetiracetam at 1 500 mg PO BID. Treatment with phenytoin was discontinued due to the cirrhosis and transient mild elevation of liver enzymes [AST 32 IU/L (8-30) and ALT 43 IU/L (7-35)]. He remained seizure free and was discharged home on monotherapy with levetiracetam, TTM and zinc.

During treatment with TTM, serum ceruloplasmin was 18.8 (reference 16-36 mg/dL) and 24 hours urine copper was 333 (reference < 55 UG/TV) (please note that discrepancy in the measurement of the ceruloplasmine and urine copper are due to differences in the reporting systems of the two laboratories where the tests were done). During this hospitalization, CBCD, electrolytes and renal function tests were normal. Direct bilirubin 0.7 mg/dL (> 0.3), total bilirubin 1.9 mg/dL (0.2-1.2) and PT 12 seconds (9.5-11.7) were slightly elevated. He had *Citrobacter* urinary tract infection that was treated successfully. Cerebrospinal fluid (CSF) study was normal.

MRI of the brain showed generalized brain volume loss with prominence of the cortical sulci and mild generalized atrophy of the brainstem and caudate heads. There was mineralization of the basal ganglia, substantia nigra, red nuclei and periaqueductal gray matter (*figure 2A*). There was prominent FLAIR and T2 increase signal noted throughout the white matter, mainly in the left frontal lobe (*figure 2B*) but also the splenium of the corpus callosum (*figure 2C*).

After he was discharged home, the patient remained seizure free for almost two months and then developed seizure breakthrough in the course of another urinary tract infection. His gait and cognition has continued to deteriorate.

## Literature review

We reviewed the medical literature relevant to WD with particular interest in cases that developed SE. To review the literature related to WD and seizures before 1988, we refer the readers to the excellent paper by Denning *et al.* (1988).

We used MEDLINE as the main search engine. We looked for the combination of terms "status epilepticus and Wilson disease". In addition, a second search was done using the terms "seizures and Wilson disease". All these papers were reviewed in detail looking for additional reports of patients with WD and SE.

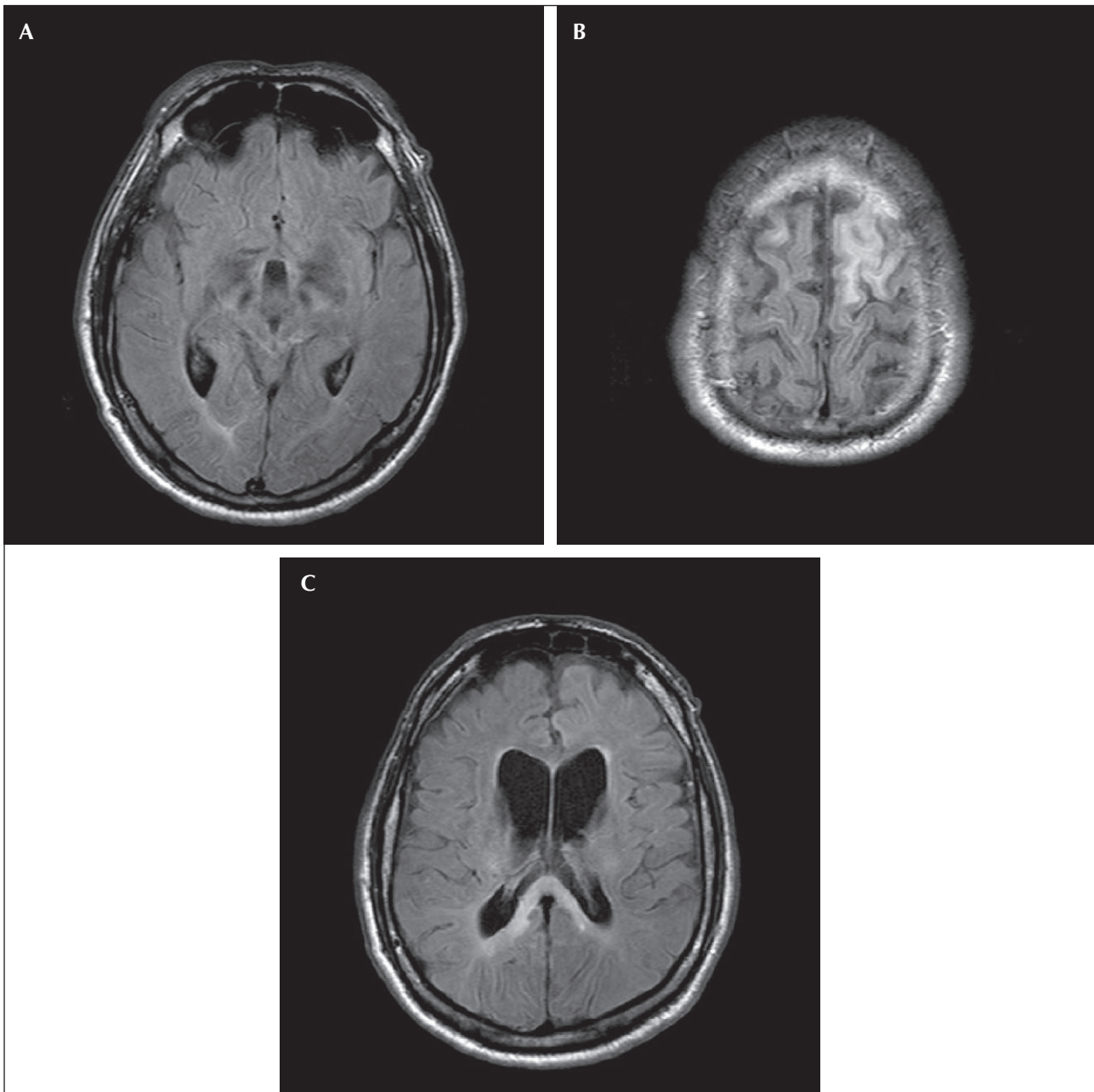
We found six patients with WD who developed SE, 3 females and 3 males (*table 1*). Four out of the six patients developed SE in the second decade of life (Kumar 2005, Shukla *et al.* 2006, Türk-Borü *et al.* 2003, Yoshida *et al.* 1989). Seizures were generalized tonic clonic in two patients (Kumar 2005, Shukla *et al.* 2006), partial with secondary generalization in two (Machado *et al.* 2006, Türk-Borü *et al.* 2003), a combination of generalized and partial seizures in one patient (Denning *et al.* 1988), and partial followed by loss of consciousness (most likely non-convulsive) in another (Yoshida *et al.* 1989). EEG foci were localized to the left fronto-central region in two (Shukla *et al.* 2006, Yoshida *et al.* 1989), left posterior in one (Denning *et al.* 1988), bifrontal in one (Türk-Borü *et al.* 2003) and diffuse slow in one (Kumar 2005).

Brain MRI findings were described in 4 patients. Three had white matter lesions in the both frontal lobes (Kumar 2005, Shukla *et al.* 2006, Türk-Borü *et al.* 2003) and one in the left hemisphere (Yoshida *et al.* 1989). In addition, the four patients had findings related to mineralization of the basal ganglia. Cerebrospinal fluid was studied in 2/6 patients only and it was normal (Shukla *et al.* 2006, Türk-Borü *et al.* 2003).

Two of the patients developed SE at disease presentation of the WD and before chelating treatment (Kumar 2005, Shukla *et al.* 2006). Four patients developed seizures after 5 months to 3 years of D-penicillamine (Denning *et al.* 1988, Machado *et al.* 2006, Türk-Borü *et al.* 2003, Yoshida *et al.* 1989). Information about the treatment of SE was available in three patients (Kumar 2005, Shukla *et al.* 2006, Türk-Borü *et al.* 2003). SE was treated with a combination of phenytoin and benzodiazepines. Two patients were seizure free at the time of the report (Shukla *et al.* 2006, Türk-Borü *et al.* 2003), and one had slight improvement in seizure control (Denning *et al.* 1988).

## Discussion

SE is, by far, less frequently found when treating patients with WD. We consider it clinically important to point out this rare effect of WD, as late recognition of seizures can delay treatment leading to prolonged SE. Dystonias can be present in up to 69% of patients with WD (Machado *et al.* 2006). In our patient and others in the literature, seizures presented with focal posturing of the arms that could resemble dystonias. Consequently, seizures in WD could be mistaken for abnormal movement disorders. The



**Figure 2.** FLAIR images. **A)** Shows mineralization of the basal ganglia, substantia nigra, and periaqueductal gray matter (“face of the giant panda” sign). There is also increase signal in the white matter of the right occipital lobe. **B)** and **C)** show increase signal noted in the left frontal lobe and the splenium of the corpus callosum respectively. Brain MRI was done after the resolution of the SE.

association of sudden saccadic eye deviation to the right and head deviation to the right with posturing of the right arm and the fact that the episodes were stereotypical gave the initial clinical clues that these episodes represented seizures and not dystonia. The initial features of the seizures in our patient with eye first and then head version to the right, suggested that the seizure onset was in the left frontal lobe. Video-EEG was key on confirming the pres-

ence of recurrent left frontal seizures. Considering that patients with WD have a higher prevalence and incidence of seizures than in the general population (Denning *et al.* 1988), poor awareness and poor recognition of the presence of seizures among physicians, put patients with WD at a higher risk of developing SE.

SE in WD can occur either at the time of presentation of the WD or during treatment of copper deposits. Seizures

**Table 1.** Status epilepticus in Wilson's disease.

Author/Year/Country	Gender/Age (years)	SE type/ Duration	EEG/MRI/CSF	Treatments A) Before SE B) SE C) Post SE	Seizures Follow-up
Dening TR/1988/UK	Female/29 <sup>#</sup>	Right focal, Generalized/ unknown	EEG: left posterior focus	A) Penicillamine $\leq$ (3 years) pyridoxine C) Carbamazepine, clonazepam	Slight improvement at 3 yrs
Yoshida K/1989/Japan	Female/13	Right focal clonic $\rightarrow$ LOC/ unknown	EEG: spikes left centro-parietal and SWC left frontal, generalized slow MRI: left frontal, parietal and occipital	A) Penicillamine: $\leq$ (5 months) B) Antiepileptic drugs (not described which ones)	Not reported
Türk-Borü U/2003/Turkey	Male/19	Right clonic $\rightarrow$ automatism $\rightarrow$ GTCS/2 days	EEG: BG slow, Bifrontal spikes MRI: WML bifrontal CSF normal	A) D) penicillamine $\leq$ (3 years) B) IV Diazepam and Phenytoin C) Carbamazepine 1 400 mg/day	Seizure free at 2 years
Kumar S/2005/India	Female/16 <sup>*</sup>	GTCS/1 day	EEG: diffuse slow MRI: WML bifrontal left > right	A) None B) IV Phenytoin load and midazolam C) Phenytoin 200 mg/day, D-penicillamine, Pyridoxine	Not reported
Shukla R/2006/India	Male/17 <sup>*</sup>	GTCS/2-3 days	EEG: left frontal focus MRI WML bifrontal Contrast Head CT: bifrontal WM hypodensities CSF: normal	A) None B) IV phenytoin and lorazepam C) D-penicillamine 500 mg/day $\leq$ (0); Zinc sulphate 150 mg/day and Phenytoin 300 mg/day	Seizure free at 3 months
Machado A/2006/Brazil	-	Focal $\rightarrow$ Gen	-	A) Penicillamine $\leq$ (1.5 years) B) Antiepileptic drugs (not described which ones)	Not reported
Our case/2008/USA	Male/55	Non-convulsive SE/24 hours	EEG: left fronto-temporal (see EEG picture) MRI: WML multifocal (see MRI picture) CSF: normal	A) TTM $\leq$ (4 weeks) and Zinc B) IV Levetiracetam 1 000 mg BID, Fosphenytoin 20 mg/kg and Midazolam 11 mg/hr C) TTM, Zinc, Levetiracetam 1 500 mg BID	Recurrent seizures with UTI @ 2-3 months, gait and cognition deteriorating

$\rightarrow$  indicates the evolution of the seizures ; GTCS: generalized tonic-clonic seizure;  $\leq$  (time of treatment with D-penicillamine before SE onset); SE: status epilepticus.

<sup>#</sup> Original paper mentioned 2 patient with SE but described only one.

<sup>\*</sup> SE before treatment for WD.

during WD can have been attributed to: (a) toxic effect related to the chelating agent, (b) liver toxicity, or (c) progression of the disease itself. SE at the presentation of WD challenges the hypothesis that seizures in WD are related to pyridoxine deficiency or treatment with D-penicillamine. The literature review does not support the possibility that the seizures are related to liver toxicity since liver enzymes were reported elevated in only one case (Kumar

2005). Brain autopsy of two patients with WD who also had seizures (Meenakshi-Sundaram *et al.* 2008, Barbosa *et al.* 2007) documented neuronal loss, gliosis and astrogliosis. These findings are similar to the findings in other causes of seizures such as mesial temporal sclerosis, suggesting at least a common end point in the pathology of both diseases. It is unclear to us if the development of seizures in our patient was due to treatment with TTM,

the neurotoxicity related to the cooper deposit or a combination of both. Our patient is the only one reported in the literature who had developed seizures and SE during treatment with TTM.

In summary, we presented a patient with late onset WD who developed seizures and SE in the course of treatment with TTM. In our patients, seizures could have been aggravated by a late recognition combined with infectious disease. New onset of stereotyped movements in patients with WD should raise the suspicion of seizures and expedited treatment could avoid the development of SE. □

#### Acknowledgments.

We thank Dr Masaki Iwasaki for his translation from Japanese and Dr Jayanti Mani for providing articles that were published in the Indian medical literature.

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