An unusual and devastating presentation of neurologic Wilson's disease with extensive brain MRI lesions

Une présentation neurologique inhabituelle et gravissime d'une maladie de Wilson avec lésions extensives à l'IRM encéphalique

Wilson's disease (WD) is a rare autosomal recessive disorder involving copper transport leading to its deposition in various tissues, chiefly the liver, brain and cornea. WD is caused by a mutation in the ATP7B gene located on chromosome 13, which encodes the copper-transporting transmembrane protein ATPase7B that is mostly expressed in the liver. In WD, brain copper accumulation predominantly occurs, but not exclusively, in the basal ganglia and brainstem [1,2]. We report here an atypical and fatal case of WD, presenting subacutely with unusual and severe neurological manifestations, in association with extensive cortical and frontal white matter lesions.

A 22-year-old man, born from a consanguineous marriage, came to our hospital because of recurrent, generalized motor seizures that were experienced for 1 month. He also developed, since 1 year, psychiatric symptoms such as delusion of grandiosity, delusion of reference, auditory hallucinations, inappropriate affect and abstract thinking, excessive irritability, insomnia and disinhibited behaviors. At this time, a diagnosis of schizophrenia was made for him after visiting a psychiatrist. Therefore, he has started to take olanzapine 10 mg/day, but without resulting in any significant changes in his symptoms. After admission to our hospital, a physical examination revealed an apyretic, alert and awake patient with normal respiratory and cardiovascular examinations. A neurological examination was also normal. His CT scan of brain and cerebrospinal fluid (CSF) study revealed no abnormalities. The intercritical electroencephalogram (EEG) showed generalized discharges of spikes. In order to control generalized seizures, we added valproate 1500 mg/day. However; three days after hospitalization; somnolence, pyrexia (temperature 39.5 °C), diaphoresis, tremor, rigidity, tachycardia and oscillation of blood pressure were observed. Laboratory investigations revealed leukocytosis: 15×10^9/L (N: 4.00–11.0 $\times 10^9$/L) with a neutrophil count of 13×10^9/L (N: 2.5–7.5 $\times 10^9$/L). Creatine kinase (CK) level was markedly elevated: 5753U/L (N: 52–336 U/L), also urea: 2.4 g/L (N: 0.10–0.55 g/L), creatinine: 78.4 mg/L (N: 9–14 mg/L) and serum sodium: 158 mmol/L (N: 135–145 mmol/L). Glycemia and other electrolyte levels were normal.

A diagnosis of neuroleptic malignant syndrome (NMS) was made. Therefore, olanzapine was stopped and the patient was transferred to the medical intensive care unit for management. Within 2 weeks, the patient's NMS symptoms were improved and his CK level and other hematological and biochemical parameters returned to normal. However, a severe akinetic mutism (AM) with generalized tremor was occurred.

Upon examination, the patient was noted to be unresponsive to visual, auditory, and verbal commands but noted to be alert. Although he was not responding by emotional or motor movements, ocular movements and the ability to follow visual stimuli were intact.

Thus, magnetic resonance imaging (MRI) of brain was performed (3 days after CT scan of brain) (*figure 1* a–d) and it showed many abnormalities on T2-weighted, fluid-attenuated inversion recovery (FLAIR) and diffusion weighted imaging (DWI) which revealed diffuse hyperintensities in pons with central pontine myelinolysis (CPM)- like changes; symmetrical hyperintensities in both halves of midbrain and periaqueductal gray matter with hypointense red nuclei and subtantia nigra forming 'face of giant panda' sign; hyperintensities in bilateral thalami; hypointensities in bilateral globus pallidus, hyperintensities in bilateral putamen and increased signal intensity in the left caudate nuclei and claustrum (Bright claustrum sign).

Bilateral and diffuse hyperintensities were observed in the frontal and temporal cortex. We also noted extensive hyperintensities in the subcortical white matter in frontal lobe. These cortical and white matter lesions were seen mainly in the left hemisphere.

Slit-lamp examination revealed Kayser-Fleischer (KF) rings in both eyes. Serum ceruloplasmin level was low: 0.04 g/L (N: 0.15–0.30 g/L); 24 hours urinary copper excretion was high:194 µg/24 h (N: less than or equal to 60 µg/24 hrs) with decreased serum copper level: 0.10 mg/L (N: 0.70–1.27 mg/L). CT of abdomen and liver function tests were all normal. Genetic testing was not done.

Using the scoring system for WD diagnosis developed at the international WD meeting in Leipzig, Germany, in 2001 [3], our patient achieved a score of 8 (severe neurological symptoms with typical abnormalities on brain MRI: 2, K-F rings present: 2, serum ceruloplasmin < 0.10 g/L: 2, urinary copper > 2x upper limit of normal: 2) and thus, a diagnosis of WD was established.

Treatment was started with a copper-chelating agent, D-penicillamine at a lower initial dose of 125 mg/day with upward titration by 250 mg at 3 week intervals to a goal of 1500 mg/day. Symptomatic therapy included levodopa (1000 mg/day), bromocriptine (30 mg/day), physiotherapy and orthophonic support. However, 3 months after the occurrence of the NMS, our patient succumbed to sepsis related to long-term decubitus. At the time of his death, he was at 900 mg/day of D-penicillamine without significant improvement of AM symptoms.

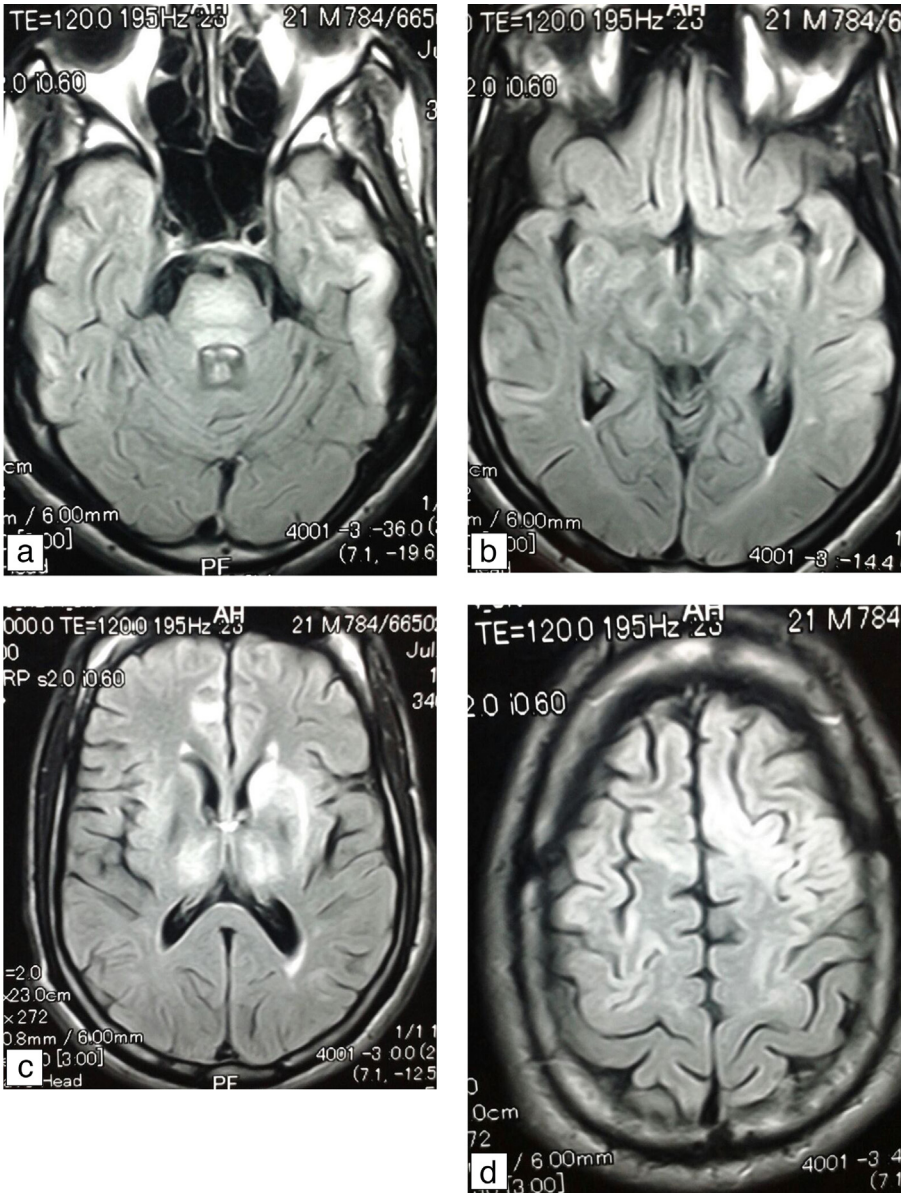

FIGURE 1

a: axial FLAIR - diffuse hyperintensities in pons with central pontine myelinolysis (CPM) - like changes with the characteristic hypointense horizontal line "bisected pattern". Bilateral and asymmetric hyperintensities in the cortex of the temporal lobe, predominantly in the left hemisphere, are also seen; b: axial FLAIR - "the face of a giant panda" sign :, increased signal intensity in the midbrain tegmentum with normally hypointense red nucleus (eyes), preservation of signal intensity of the pars reticulate of substantia nigra (ears) and low signal intensity of superior colliculous (chin); c: axial FLAIR - hyperintensities in bilateral thalami; hypointensities in bilateral globus pallidus, hyperintensities in bilateral putamen and increased signal intensity in the left caudate nuclei and claustrum "Bright claustrum sign". Hyperintensities in the cortex of the frontal lobe (particularly the right anterior cingulate cortex) are also observed; d: axial FLAIR - diffuse and asymmetric hyperintensities in the cortex and the white matter of the frontal lobe, predominantly in the left hemisphere