



## Case Report

# Stroke Episode in a Young Patient with Wilson's Disease

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## Abstract

Wilson's disease is an autosomal recessive genetic disease with a copper metabolism disorder leading to hepatic, kidney, hematologic and neurologic symptoms. Stroke episodes in this pathology have not been described in the literature.

We report a 13-year-old girl with Wilson's disease discovered on neurological presentation, quickly treated with trihexyphenidyl and trientine. She was heterozygous in the *ATP7B* gene with two pathogenic variants (c.2128 G>A and c.3188C>T). Three months later, an acute neurological episode with a left capsulolenticular ischemic stroke episode occurred. Brain magnetic resonance imaging revealed a new fluid-attenuated inversion recovery hypersignal in the left internal capsule and striatum. Her neurological deficit regressed completely at six months.

Few studies have reported Wilson's disease patients with stroke-like episodes. No usual cause was found during neurologic explorations. Heart tests and coagulation were normal. Trientine and trihexyphenidyl are not known to generate stroke episodes. We here describe one of the first cases of stroke in Wilson's disease.

**Keywords:** Wilson's disease; Stroke; Childhood; *ATP7B*

## Introduction

Wilson's disease is an autosomal recessive disease of copper metabolism (*ATP7B* gene coding for ATPase copper transporting beta) characterized by toxic accumulation of copper primarily in liver and brain. *ATP7B* is localized on 13q14.3 and encodes a transmembrane protein in hepatocytes. Neurologic disorders include movement disorders (tremor, chorea, dystonia, Parkinsonism), ataxia, dysarthria, cognitive impairment, seizures, and psychiatric symptoms [1]. Presentation with acute neurologic symptoms like dysarthria may suggest a stroke-like episode and a mitochondriopathy such as mitochondrial encephalomyopathy

with lactic acidosis and stroke-like episodes (MELAS). However, few studies have reported true stroke episodes [2-6]. We report an early and atypical case of Wilson's disease with a stroke episode.

## Case presentation

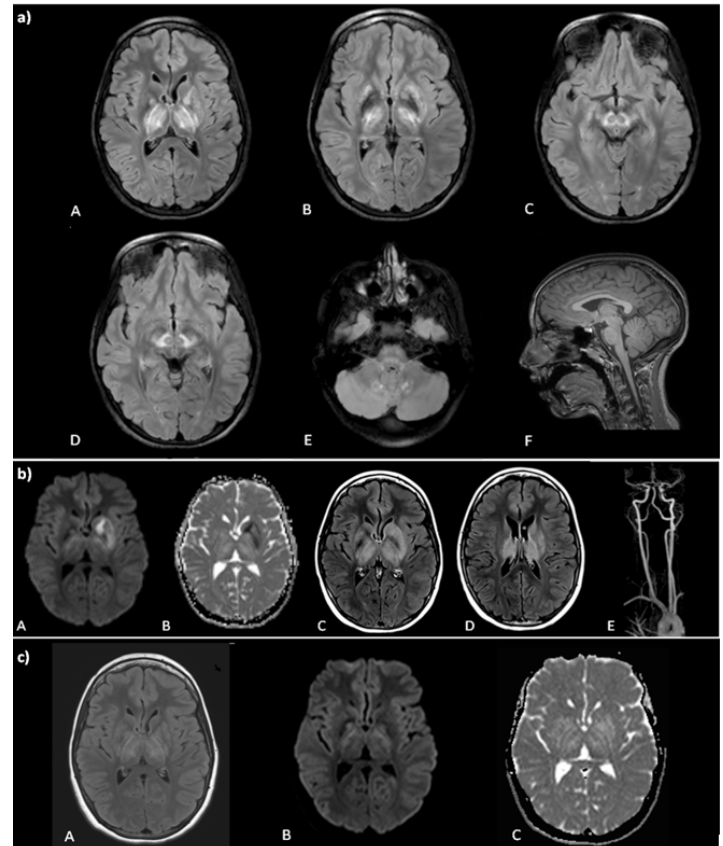
The patient was a 13-year-old girl without family, medical or surgical history. Antenatal and neonatal history was uneventful. She showed written language delay (dyslexia and slowness) from age 6 years onward and behavioral disorders (aggressiveness and emotional disorder) from 10 years. Motor development was normal. At 12 years old and 10 months, her behavior gradually deteriorated and two months later, a subacute neurological episode occurred with aphasia, ataxia, anorexia, asthenia, choreoathetosis,

swallowing disorder, walking disorder and drowsiness, appearing in a week. Clinical examination revealed extrapyramidal syndrome of the upper limbs, cerebellar syndrome, ideomotor slowdown, and nerve IX palsy, without pyramidal syndrome or motor deficit. Ophthalmologic examination revealed a Kayser-Fleischer ring in both eyes. Brain magnetic resonance imaging (MRI) using the fluid-attenuated inversion recovery (FLAIR) sequence showed bilateral hyperintensity in the basal ganglia (globus pallidus and putamen), thalamus, mesencephalon, cerebellar peduncles and dentate nucleus (Figure 1A). Skin telangiectasia was observed but no hepatomegaly, splenomegaly or icterus. Abdominal ultrasound showed liver brightness with diffuse pseudonodular heterogeneity and irregular outlines, leading to the diagnosis of cirrhosis. Blood and urinary chemistry did not show renal tubulopathy signs. 24h urinary copper was 244  $\mu\text{g}$ , plasma ceruloplasmin was 0.11 g/l and exchangeable copper was 1.87  $\mu\text{mol/l}$  (relative exchangeable copper: 21.3%). Liver function tests were normal without liver failure. Total bilirubinemia was 24.6  $\mu\text{mol/l}$ , conjugate was 7.3  $\mu\text{mol/l}$ , and the platelet count 138,000/ml without hemolytic anemia. Upper gastrointestinal endoscopy showed portal hypertensive gastritis grade 1 with no varices. The patient was treated by trihexyphenidyl hydrochloride (HCI) at 4mg/day (0.1 mg/kg/day), and trientine started at 75 mg/day with a progressive increase planned. Her motor function improved with walking recovery, but asthenia, dyspraxia, slowness and choreoathetosis persisted. Two missense pathogenic variants were detected in the *ATP7B* gene (NM\_000053.4): c.2128 G>A p.(Gly710Ser) in exon 8 and c.3188C>T p.(Ala1063Val) in exon 14, confirming the diagnosis of Wilson's disease.

Three months later, when she woke up, she discovered right facial and right upper limb paralysis. At this time, treatment was trihexyphenidyl HCI 4 mg/day and trientine 225 mg/day. The day before, plasma exchangeable copper was 2.68  $\mu\text{mol/l}$  (relative exchangeable copper 41.8%). Brain MRI revealed a new FLAIR hypersignal with diffusion restriction in the left internal capsule and left putamen (Figure 1b), indicating an acute left capsulolenticular ischemic stroke episode. The FLAIR hypersignal without diffusion restriction appeared in the left caudate nucleus. Acetylsalicylic acid 75 mg/day was administered 1 hour after the onset of stroke symptoms. At 2 hours, her National Institute of Health Stroke Score (NIHSS) was 2 and recovery was complete the following day.

Six months later, the control brain MRI showed a stable FLAIR hypersignal without diffusion restriction in the left striatum and internal capsule and a slight dilation of the left frontal ventricular horn, consistent with a sequelae of ischemic stroke. Neck and intracranial arteries had no abnormalities (Figure 1c). Cardiologic tests with Holter electrocardiogram (ECG) and echocardiography were normal. At the last examination, six months after the stroke episode, she had no neurologic deficit or asthenia,

but coordination difficulties such as disarticulated running and choreic movements of the upper right limb persisted before being treated effectively with trihexyphenidyl HCI 7.5 mg/day. Other medications were trientine 450 mg/day and acetylsalicylic acid 75 mg/day (Figure 1c).



**Figure 1:** Brain MRI of the patient at Wilson's disease diagnosis (1a), during an episode of acute neurological deficit (1b) and six months after this episode (1c); ADC: apparent diffusion coefficient; FLAIR: fluid-attenuated inversion recovery; (a) Axial T2 FLAIR A and B show bilateral hyper intensity in basal ganglia (globus pallidus and putamen) and thalamus. Axial T2 FLAIR C and D show bilateral hyperintensity in the mesencephalon. Axial T2 FLAIR E shows bilateral hyperintensity in dentate nuclei. Sagittal T1 F is normal; (b) Brain MRI revealed new FLAIR hyper signal with diffusion restriction of the left internal capsule and left putamen (axial diffusion B1000: A, axial ADC: B, axial T2 FLAIR: C and D). Hypersignal FLAIR without diffusion restriction appeared in the left caudate nuclei. Neck and intracranial arteries had no abnormality (Angio-MRI E); (c) Six months after stroke, the control brain MRI showed no diffusion restriction in the left striatum and internal capsule and a slight dilation of the left frontal ventricular horn (axial T2 FLAIR: A, axial diffusion B1000: B, axial ADC: C).

## Discussion

Wilson's disease is a rare pathology in childhood. The neurologic presentation has been well described and includes a combination of Parkinsonism, other movement disorders, dementia, ataxia, cognitive impairment, dysarthria and/or hepatic encephalopathy. The occurrence of a stroke episode is much rarer.

Five reports have described stroke or stroke-like episodes in patients with Wilson's disease. In 2016, Qi-jie Zhang et al [4] described a 17-year-old girl with progressive dysarthria and left hemiparesis over 3 months. MRI showed brain cerebral atrophy and abnormal signals in the brain stem and basal ganglia. Two pathogenic variants were detected in the *ATP7B* gene (NM\_000053.3) by Sanger sequencing: c.2828G>A p.(Gly943Asp) and c.3884C>T p.(Ala1295Val). In 2018, Pan et al [6] described a 14-year-old boy with acute neurologic events at awakening, including a high degree of difficulty in moving his legs, more severe speech problems, and limb tremor. MRI showed FLAIR hyperintensity in the right frontal lobe and the bilateral lenticular nucleus and thalamus, as well as hypointensity in the T1-weighted image in the corresponding area. Mutations in the *ATP7B* gene (NM\_000053.4) were c.525dupA p.(Val176fs) and c.3244-2A>G. For these two patients, a clinical stroke-like episode was mentioned and led to an incorrect diagnosis of MELAS until the results of brain MRI. In 2017, Javid et al [3] reported a 7-year-old boy, a priority patient on the liver transplant list, who experienced a sudden onset of decerebrate posturing and died. Cerebral computed tomography (CT) concluded that it was an acute frontal lobe venous infarct with midline shift. In 2004, Pendlebury et al [5] presented a 17-year-old boy with a stroke-like episode on awakening. Neurologic symptoms included slurred speech, difficulty swallowing solids, walking difficulties and intermittent involuntary movement of his thumbs across his palms. T2-weighted brain MRI showed hyperintensity in the midbrain, caudate nucleus, and putamen and hypointensity in the pallidum with a T1-weighted image. The patient was homozygous for mutation in *ATP7B* (NM\_000053.4): c.2297C>G p.(Thr766Arg). Last, three patients were described by Smita et al [2] in 2014. One was a 42-year-old man and the other two were 45-year-old men, all presenting acute dysarthria or dysarthria/ataxia, possibly at awakening, with normal brain CT. Brain MRIs of these patients showed symmetric T1 hyperintense lesions in the globus pallidus and/or substantia nigra with normal T2 image for patient 1 and without restriction in diffusion-weighted images for patient 2. T2 and diffusion MRI sequences are not available for others patients.

Regarding the etiological origins of ischemic stroke, Wilson's disease generates cardiac abnormalities (such as left and bi-ventricular hypertrophy, repolarization abnormalities, extrasystoles, atrial abnormalities, conduction disturbances), but the repeated heart tests were normal in our patient [7,8]. In 2017, Kouvelas et al [9] demonstrated early neurovascular involvement

despite the very young age of these patients and the concomitant copper-chelating therapy. Indeed, orthostatic hypertension, present in 73% of patients with Wilson's disease, could lead to stroke [9,10]. One might question whether stroke should be considered a treatment-emergent adverse event. According to expert opinion from the French national pharmacovigilance center (phase IV), trihexyphenidyl and trientine do not cause stroke episodes. However, plasma exchangeable copper and relative exchangeable copper had almost doubled in our patient between disease diagnosis and the day before the stroke. According to some studies [11], the risk of stroke could be related to plasma copper levels. Copper is essential for respiratory chain function, but copper overload can generate mitochondrial impairment [12] with MELAS phenotypes or stroke episodes [13]. Pathogenic variant c.2128G>A and c.3188C>T are not associated with ischemic episode in literature. We found no evidence of mitochondrial dysfunction, arterial disease, focal segmental arteritis, heart disease, rythmopathy, genotype or iatrogenic disease.

In conclusion, we here described one of the first case of stroke in Wilson's disease in a young patient with c.2128G>A p.(Gly710Ser) and c.3188C>T p.(Ala1063Val) pathogenic variants in the *ATP7B* gene. It is difficult to conclude on the pathophysiological mechanisms of this stroke, notably mitochondrial or iatrogenic. In patients with Wilson's disease, an acute neurological episode should suggest a stroke and adapt care accordingly.

### Conflict of interest

The authors declare that there is no conflict of interest.

### Ethics statement

Informed consent was obtained from the patient and her parents for being included in the study.

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### References

1. Mulligan C, Bronstein JM (2020) Wilson Disease: An Overview and Approach to Management. *Neurol Clin* 38: 417-432.
2. Smita B, Gafoor VA, Saifudheen K, Jose J (2014) Acute stroke-like presentation of acquired hepatocerebral degeneration. *Ann Indian Acad Neurol* 17: 204-206.
3. Javid K, Cg S, Khan J, Ts RK, Reddy R (2018) Stroke in a young patient with Wilson's disease: the spectre of 're balanced hemostasis. *J Clin Exp Hepatol* 8: S52-S53.
4. Zhang QJ, Xu LQ, Wang C, Hu W, Wang N, et al. (2016) Four-year follow-up of a Wilson disease pedigree complicated with epilepsy and hypopituitarism. Case report with a literature review. *Medicine (Baltimore)* 95: e5331.

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5. Pendlebury ST, Rothwell PM, Dalton A, Burton EA (2004) Strokeliike presentation of Wilson disease with homozygosity for a novel T766R mutation. *Neurology* 63:1982-1983.
6. Pan L, Ding D, Leng H, Deng X, Xu Y (2018) Recurrent stroke-like episodes of Wilson disease with a novel Val176fs mutation. *Neurol Sci* 39: 973-974.
7. Karhan AN, Aykan HH, Gümüş E, Dönmez Y, Alehan D, et al. (2019) Assessment of cardiac function and electrocardiographic findings in patients with Wilson's disease. *Cardiol Young* 29: 1183-1188.
8. Kuan P (1987) Cardiac Wilson's Disease. *Chest* 91: 579-583.
9. Kouvelas G, Bassareo PP, Pisano V, Demelia L, Nurchi AM, et al. (2017) Premature vascular deterioration in young patients affected by Wilson's disease: a pilot study. *J Pediatr Neonatal Individ Med*. 6: e060201.
10. Fessel J, Robertson D (2006) Orthostatic hypertension: when pressor reflexes overcompensate. *Nat Clin Pract Nephro* 12: 424-431.
11. Hu L, Bi C, Lin T, Liu L, Song Y, et al. (2021) Association between plasma copper levels and first stroke: a community-based nested case-control study. *Nutr Neurosci*. 25: 1524-1533.
12. Zischka H, Einer C (2018) Mitochondrial copper homeostasis and its derailment in Wilson disease. *Int J Biochem Cell Biol* 102: 71-75.
13. Liu F, Lu J, Manaenko A, Tang J, Hu Q (2018) Mitochondria in Ischemic Stroke: New Insight and Implications. *Aging Dis* 9: 924-937.