

# Liver transplantation for hypoparathyroidism secondary to Wilson's disease

Zhi-Bin Zhang<sup>1</sup>, Xin Zhao<sup>1</sup>, Jun-Jie Li<sup>2</sup>, Qi Han<sup>3</sup>, Lu-Si A<sup>3</sup>, Ming-Sheng Huai<sup>1</sup>

<sup>1</sup>Department of General Surgery, Tianjin First Central Hospital, Tianjin 300192, China;

<sup>2</sup>Department of Transplantation Surgery, Tianjin First Central Hospital, Tianjin 300192, China;

<sup>3</sup>Graduate School of Tianjin Medical University, Tianjin 300070, China.

*To the Editor:* A 19-year-old man was admitted to the hospital presenting with “skin and sclera yellow staining for 18 years, accompanied by growth retardation.” The patient developed scleral yellowing at 4 months of age, at which time he was diagnosed as having Wilson's disease (WD) and received symptomatic treatment for liver protection. At 9 years of age the patient developed a pale nail bed, clubbing of the fingers and toes, and accompanying growth retardation. A spontaneous fracture of the right upper limb and left pubic bone occurred at 16 years of age. At 17 years of age the patient developed neuropsychiatric symptoms consisting of fatigue, personality changes, mental retardation, numbness, epileptic seizures, and constipation. He required daily glycerin to assist with defecation. At 5 months prior to admission, obvious sternal malformations and anterior sternal processes were present. Family history revealed that his parents were close relatives (cousin-sister relationship) and the patient's cousin died as a result of WD at age of 12 years. The patient's younger brother was 3 years old and also had a history of WD.

On admission, physical examination were: height 153 cm, weight 63.9 kg. Notable observations included abnormal development, an indifferent expression, poor nutrition, passive posture, limited movement, and an inability to stand unaided. Kayser-Fleischer (K-F) ring was positive in both eyes. The patient also displayed alopecia, a rounded face, short neck, rickets of the chest and coarse skin, particularly obvious in the hands and feet. Other examination at admission were: ultrasonography, hypoechoic nodules on the posterior pole of the right lobe of the thyroid (two nodules, parathyroid gland sources cannot be excluded); dual-phase technetium-99m-labelled methoxyisobutyl isonitrile (<sup>99m</sup>Tc-MIBI) imaging of the parathyroid gland, two low-density nodules on the posterior pole of the right lobe of the thyroid, and no abnormal

concentration of MIBI radiation [Figure 1A]; Thoracic magnetic resonance thoracic scoliosis with T7, T9, and T10–L2 vertebral wedge deformation, especially at T7 and T9 [Figure 1B]. Lumbar magnetic resonance, straightened lumbar curvature with L1–2, L4–5 vertebral wedge-shaped changes [Figure 1C]. Parathyroid hormone (PTH) <2 pg/mL, blood calcium 2.09 mmol/L, blood inorganic phosphorus 1.78 mmol/L, albumin 25.4 g/L, ceruloplasmin (CP) 17.1 mg/dL, and 25-hydroxyvitamin D 6.96 ng/mL. The patient underwent orthotopic liver transplantation due to liver failure at 7 weeks following admittance. Levels of PTH [Figure 1D], blood calcium, blood phosphorus [Figure 1E], and CP were reviewed regularly following surgery. Substantial increase in CP levels (39.1 mg/dL) was observed at 3 weeks post-surgery.

WD is a disorder of copper metabolism and deficiency of copper transporters, resulting in excessive copper deposition at abnormal sites within the body. The liver is the main organ site of involvement and symptoms are most frequently observed in the eyes and brain.<sup>[1]</sup> Rare manifestations include hypoparathyroidism.<sup>[2]</sup> This present case was diagnosed as WD, which not only affected the liver, but to a lesser extent, the parathyroid gland. Notably, in this patient typical clinical manifestations of hypoparathyroidism were observed.

There are many causes of hypoparathyroidism, of which WD represents one of the most rare. WD is an autosomal recessive hereditary disease characterized by mutations in the P-type copper transporter ATPase.<sup>[3]</sup> Such mutations lead to a decrease of CP synthesis in serum and obstruction of biliary copper excretion, which then results in copper deposition *in vivo*.<sup>[4]</sup> Although copper is an essential cofactor for enzymes, deposition of excessive amounts can be destructive.

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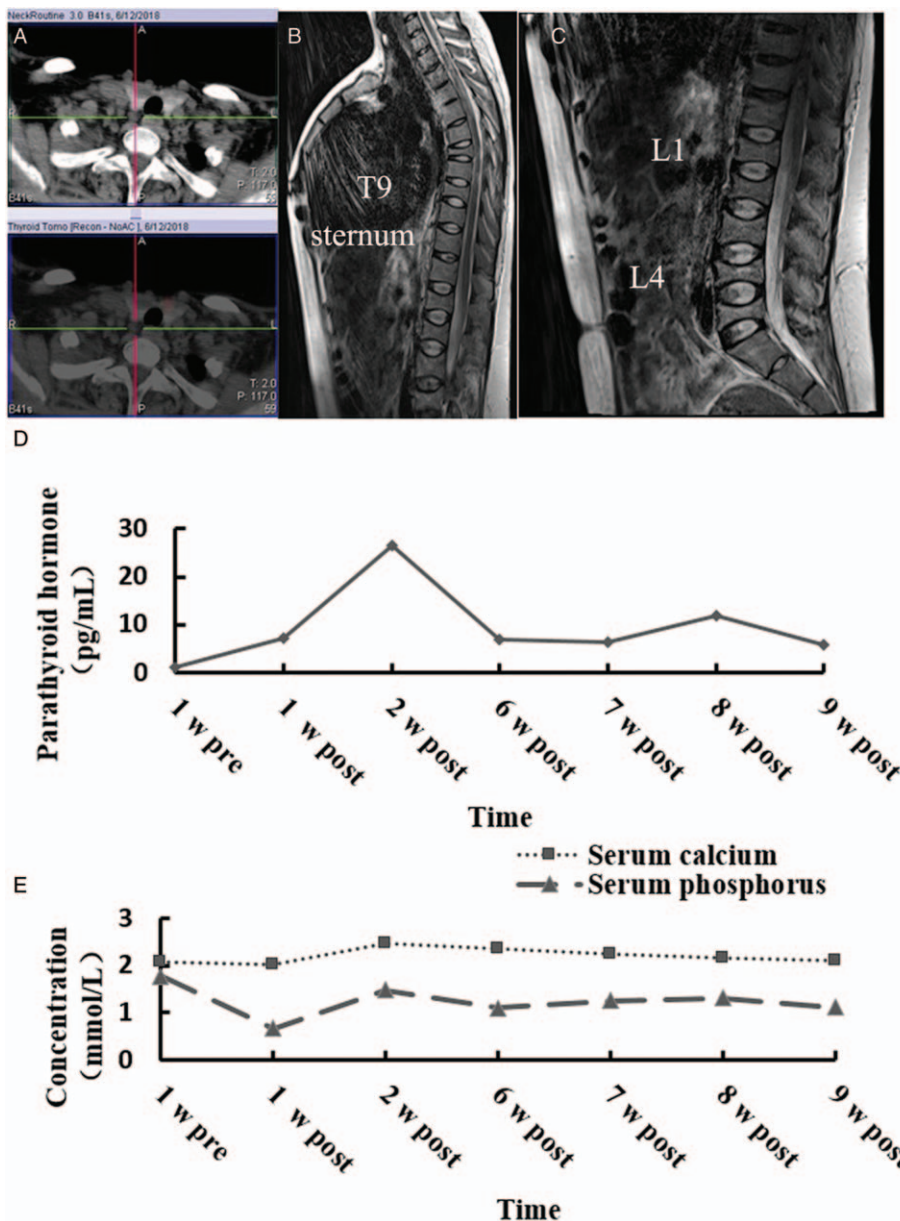
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**Correspondence to:** Prof. Ming-Sheng Huai, Department of General Surgery, Tianjin First Central Hospital, No. 24 Fukang Road, Nankai District, Tianjin 300192, China  
E-Mail: huaimingsheng\_19@163.com

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**Figure 1:** Represent images of the patient. (A) Dual-phase 99mTc-MIBI imaging of the parathyroid showing low-density nodules at the posterior pole of the right lobe of the thyroid, and no abnormal concentration of MIBI radiation (arrows). (B) Thoracic magnetic resonance showing sternal protrusion and wedge deformation of thoracic vertebrae, especially at T7 and T9 (arrows). (C) Lumbar magnetic resonance showing a straightening of lumbar curvature and L1–2, L4–5 vertebral wedge-shaped changes (arrows). (D) Changes in parathyroid hormone. (E) Serum calcium and phosphorus as determined pre- and post-operatively. 99mTc-MIBI: Technetium-99m-labelled methoxyisobutyl isonitrile.

The hypoparathyroidism secondary to WD is due to destruction of the parathyroid gland from copper deposition. Due to the decreased secretion of PTH, a hyperplasia of the parathyroid gland results, which is accompanied with a reduction in parathyroid gland function. Therefore, 99mTc-MIBI dual-phase imaging showed no abnormal concentration of MIBI radioactivity in these hyperplastic parathyroid glands.

As WD is a liver disease characterized by a metabolic copper deficiency in hepatocytes, liver transplantation represents the only possible approach to restore copper homeostasis. According to the recommendations of the European Association for the Study of Liver Diseases/American Association for the Study of Liver Diseases, liver

transplantation may be considered with liver failure or decompensated liver cirrhosis in patients with WD that fail to respond to pharmacological treatments.<sup>[2]</sup> In such patients, CP gradually returns to normal after liver transplantation. Specifically, CP levels have been reported to show a time-dependent increase after liver transplant in patients with WD.<sup>[5]</sup> In the case report, CP recovered to 39.1 mg/dL at 3 weeks post-transplant, which was remarkably increased as compared to that of the 17.1 mg/dL recorded prior to surgery.

Although dysfunction of bile duct copper excretion was restored after CP returned to normal, the issue of whether copper deposited in the parathyroid gland could be metabolized remains unclear. At present, no relevant

literature has been reported on this eventuality. Due to ethical considerations, it was not possible to perform the necessary procedures (eg, electron microscopy, immunohistochemistry) to compare pre- vs. post-surgical changes in copper ions deposited within parathyroid tissue. In the present case report, we observed changes in PTH levels as determined before and at 9 weeks after surgery. With the exception of the period at 2-week after surgery, when a substantial increase in PTH to 26.6 pg/mL was observed, PTH remained relatively stable and at low levels when sampled at 1, 6, 7, 8, and 9 weeks post-surgery with levels ranging between 5.9 and 11.8 pg/mL. In addition, beginning at 2 weeks after surgery and continuing thereafter, serum calcium increased to normal levels, being maintained between 2.11 and 2.47 mmol/L. Serum phosphorus levels dropped below the lower limit of normal during the first week after surgery (0.66 mmol/L) but increased after week two and were then maintained between 1.1 and 1.48 mmol/L. Although levels of PTH failed to return to normal after surgery, blood calcium and phosphorus values did return to normal values. Due to the short observation time after surgery, it remains unclear as to whether the liver transplantation had any effects on the hypoparathyroidism secondary to WD, therefore further follow-up observations are warranted.

Based upon this study, we propose that an immediate parathyroid transplantation may not necessarily be required in patients with hypoparathyroidism secondary to WD who require liver transplant due to liver failure resulting from WD. In such patients, the liver transplant might provide a sufficient condition for the recovery of parathyroid function.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understand that this name and initial will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

### Conflicts of interest

None.

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