Journal of Clinical Neuroscience xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Case Report

Delayed appearance of wing-beating tremor after liver transplantation in a patient with Wilson disease

Joong-Seok Kim [a,*], Su-Young Kim [b], Jong-Young Choi [c], Hee-Tae Kim [d], Yoon-Sang Oh [a]

[a] Department of Neurology, College of Medicine, The Catholic University of Korea, Seoul St. Mary's Hospital, 505, Banpo-dong, Seocho-gu, Seoul 137-701, Republic of Korea
[b] Department of Pathology, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea
[c] Division of Hepatology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea
[d] Department of Neurology, Hanyang University School of Medicine, Seoul, Republic of Korea

ARTICLE INFO

Article history:
Available online xxxx

Keywords:
Delayed
Orthotopic liver transplantation
Tremor
Wilson disease

ABSTRACT

Orthotopic liver transplantation (OLT) is the sole etiological treatment for Wilson disease (WD), but several neurological complications after OLT have been reported. We report a WD patient who developed a unilateral wing-beating tremor 6 years after OLT. New neurological symptoms develop immediately after OLT in most cases. In our patient, the onset of extrapyramidal symptoms was at a prolonged interval after OLT. To our knowledge this is the first patient with delayed extrapyramidal symptoms after OLT in WD where the pathophysiology of these late extrapyramidal symptoms is still unknown.

1. Introduction

Orthotopic liver transplantation (OLT) is the sole etiological treatment for Wilson disease (WD), but the efficacy of transplantation in improving the neurologic symptoms of WD is still debated [1]. Several neurological symptoms after OLT have been reported; most are related to immunosuppressive therapy and the remainder are acute neurological symptoms such as dystonia subsequent to surgery [2,3]. Only a few patients have been reported with new extrapyramidal symptoms [3]. We present a 45-year-old WD patient who developed a wing-beating tremor 6 years after OLT.

2. Case report

A 45-year-old woman was referred to our Movement Disorders Clinic for evaluation of a 3 month history of left arm tremor when holding a cup. She was diagnosed with a hepatic form of WD 8 years previously (genetically confirmed recently by ATP7B gene mutations in c.[2200G>T]+[3443T>C] (p.[V734F]+[I1148T]), and she had undergone OLT 6 years prior to this presentation. Her diagnosis at that time was made on the basis of biopsy-proven cirrhosis, low ceruloplasmin level, increased urinary copper excretion and presence of corneal Kayser-Fleischer ring. Prior medical records before OLT revealed no tremor, bradykinesia, dysarthria, or gait disturbance. The patient also underwent removal of a left parotid cancer 5 years ago and, thereafter, a left facial palsy and left hemifacial spasm developed and remained. The patient was on immunosuppressive therapy with cyclosporine; however, the plasma level was undetectable because of her compliance. Her younger brother had died 10 years previously due to acute hepatic failure from WD and her elder sister (patient's donor) had been treated for 2 years for major depression without a confirmed diagnosis for WD.

On examination, the patient had a coarse wing-beating tremor of the left arm with a frequency of 3–4 Hz measured clinically. Mild hemifacial spasms of the left face were noted. No resting tremor, bradykinesia, dystonia, or gait disturbance was observed (Supp. Video 1).

Biochemical examination of copper metabolism parameters were performed, showing a low serum ceruloplasmin of 14 mg/dl (laboratory norm, 16–60 mg/dl), normal serum copper of 84.14 μg/dl (laboratory norm, 64.0–134.0 μg/dl), and a mild increase in copper excretion in urine of 76.82 μg/day (laboratory norm, 0–50 μg/day). An ophthalmologic examination revealed persistent Kayser-Fleischer rings bilaterally. A penicillamine (PCN) challenge test was performed after loading with 1500 mg PCN which showed a borderline increase in copper excretion in urine of 414.09 μg/day.

MRI of the brain, including diffusion-weighted images, did not show any definite abnormalities. Additionally, positron emission tomography using ^{18}F-N-(3-fluoropropyl)-2beta-carbon ethoxy-3beta-(4-iodophenyl) nortropane also showed no abnormalities.

A liver biopsy was performed to confirm disease status and was compared with pre-OLT specimens and the donor using

* Corresponding author. Tel.: +82 2 2258 6078; fax: +82 2 599 9686.
E-mail address: neuronet@catholic.ac.kr (J.-S. Kim).

http://dx.doi.org/10.1016/j.jocn.2013.10.036
0967-5868/

hematoxylin and eosin (H&E) and rhodianine staining. The pre-OLT specimen showed cirrhotic changes on H&E staining (Fig. 1A) and a marked positive reaction to copper in the rhodianine-stained specimen (Fig. 1B). In contrast, that of the donor showed mild leukocyte infiltration, which was probably due to surgical stress (Fig. 1C) and a very mild degree of copper reactivity (Fig. 1D). The specimen obtained after the new neurological symptoms appeared showed a very mild cirrhotic change (Fig. 1E) and mild to moderate copper positivity (Fig. 1F).

3. Discussion

This patient's history was very intriguing. The patient's donor was her elder sister. Because of the donor's unconfirmed WD diagnosis and as the patient suffered from a newly developed tremor, we firstly inferred that her symptoms were caused by a recurrence of WD, although the transplanted liver was free of genetic defects responsible for WD [4]. The patient did exhibit persistent Kayser-Fleischer rings, and liver biopsy performed after the patient presented with neurological symptoms showed mild to moderate copper positivity, suggestive of copper accumulation. However, 24 hour urinary copper excretion and PCN challenge test results did not support WD recurrence [5]. Another possibility is that the development of neurological symptoms in our patient represents a delayed manifestation, resulting from the initial hepatic disease.

Nearly 100% of patients with neurologic WD are reported to have Kayser-Fleischer rings [6]. The patient's relative late age of onset of symptoms (diagnosed at age 37) may explain why tremor onset was also so delayed.

Tremor in one or both hands is one of the most common initial symptoms of WD. One of the characteristic components is proximal tremor activity with a wing-beating quality [4].

However, several reports have indicated that this type of tremor is associated with other structural and metabolic lesions [7,8]. Furthermore, the development of mild cirrhotic changes and mild copper accumulation in the liver can influence these neurological symptoms. Finally, we should consider other naturally occurring diseases such as an essential tremor or drug-induced tremors, including that induced by cyclosporine.

In summary, we report, to our knowledge, the first patient with delayed appearance of extrapyramidal symptoms after OLT in WD for which the pathophysiology is still unknown.

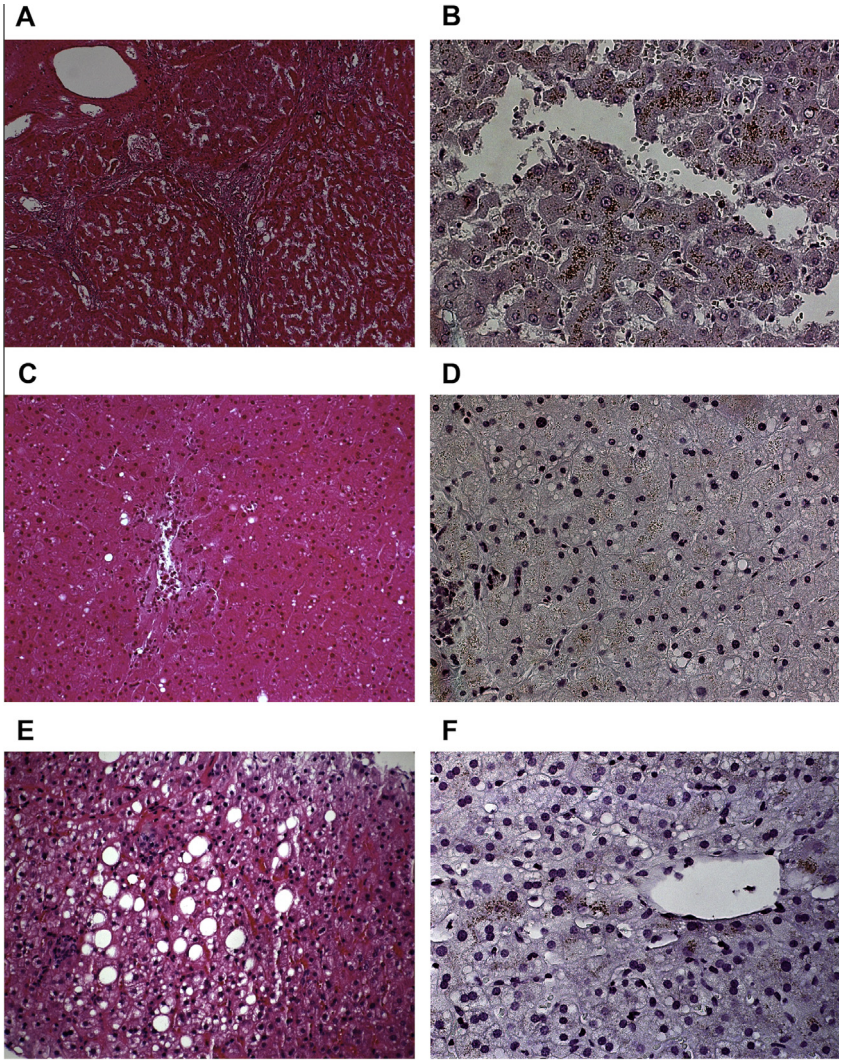

Fig. 1. The patient's pre-orthotopic liver transplantation liver specimen showed marked cirrhotic changes on hematoxylin and eosin staining (A; original magnification × 100) and marked reactivity to copper on rhodianine staining (B; original magnification × 400). That of the donor showed mild leukocyte infiltrations, which were probably due to surgical stress (C; original magnification × 100) and a very mild degree of copper reactivity (D; original magnification × 400). Finally, a specimen obtained from the patient's donor liver after the new neurological symptoms appeared showed a mild cirrhotic change (E; original magnification × 100) and mild to moderate copper positivity (F; original magnification × 400).

Conflicts of Interest/Disclosures

The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jocn.2013.10.036.

References

[1] Guarino M, Stracciari A, D'Alessandro R, et al. No neurological improvement after liver transplantation for Wilson's disease. Acta Neurol Scand 1995;92:405–8.

[2] Litwin T, Gromadzka G, Członkowska A. Neurological presentation of Wilson's disease in a patient after liver transplantation. Mov Disord 2008;23:743–6.

[3] Erol I, Alehan F, Ozcay F, et al. Neurologic complications of liver transplantation in pediatric patients with the hepatic form of Wilson's disease. J Child Neurol 2008;23:293–300.

[4] Pfeiffer R. Wilson's disease. In: Watts RL, Koller WC, editors. Movement disorders: neurologic principles and practice. New York: McGraw-Hill Medical Publishers; 2004. p. 779–97.

[5] Martins da Costa C, Baldwin D, Portmann B, et al. Value of urinary copper excretion after penicillamine challenge in the diagnosis of Wilson's disease. Hepatology 1992;15:609–15.

[6] Lorincz MT. Neurologic Wilson's disease. Ann N Y Acad Sci 2010;1184:173–87.

[7] Manji H, Sweeney B, Connolly S, et al. Movement disorders in AIDS: infective, neoplastic and iatrogenic causes. Parkinsonism Relat Disord 1995;1:13–9.

[8] Ghika J, Bogousslavsky J, Henderson J, et al. The "jerky dystonic unsteady hand": a delayed motor syndrome in posterior thalamic infarctions. J Neurol 1994;241:537–42.