Wilson’s Disease and Hyperornithinemia-hyperammonemia-homocitrullinuria Syndrome in a Child: A Case Report with Lessons Learned!

Meranthis Fernando1, Suresh Vijay2, Saikat Santra3, Mary A Preece4, Rachel Brown5, Astor Rodrigues6, Girish L Gupte7

ABSTRACT
Background: Wilson’s disease (WD) is a rare disorder of copper toxicosis. Hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome is even rarer. The coexistence of these two disorders and their clinical implications are not yet reported. We report on a child who succumbed to death due to liver disease caused by both disorders, documenting their disease-causing mutations and highlighting the lessons learnt out of this case.

Case description: A child who was diagnosed to have WD soon after birth due to known parental heterozygosity was later found to have developmental delay, seizures, and hyperammonemia. Subsequent evaluation confirmed hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome as a comorbidity. Though this child was commenced on medical treatment for both the metabolic diseases since early life, his liver disease was rapidly progressive requiring a liver transplant (LTx) at 6-years. He died in the post-transplant period possibly due to sepsis and hidden metabolic consequences.

Conclusion: This case highlights that co-occurrence of WD and HHH syndrome would cause progressive liver disease despite medical treatment. Hence, the close clinical follow-up and early LTx would be warranted.

Keywords: Child, HHH syndrome, Liver disease, Liver transplant, Wilson’s disease.

BACKGROUND
Wilson’s disease (WD) is a disorder of copper metabolism due to mutations in ATP7B.1,2 Hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome is a urea cycle disorder caused by mutations in SLC25A15.3,4 Both disorders affect the liver and brain predominantly.2,5 Being individually rare disorders, the clinical implications of their coexistence have not yet been documented. We report on a child with WD and HHH syndrome who developed unusual, rapid progression of liver disease despite being on medical treatment for both conditions, eventually requiring a liver transplant (LTx).

CASE DESCRIPTION
A child of British-Asian ethnicity was screened for WD in infancy as parents were heterozygotes. He was homozygous for the familial c.1746dupA [p.Glu583fs] mutation in exon 5 of ATP7B confirming WD. Thereafter, transaminases were monitored and noted to be raised at 6 months of age (Table 1). Zinc was commenced and a good response was observed. Developmental delay was noted at 18 months which was unexplainable by well-controlled WD. At 3 years, he developed seizures and investigations revealed hyperammonemia, raised urinary ornitine, orotic acid, and homocitrulline. Genetics showed homozygosity for a c.208_209delGCinsTT [p.Ala70Leu] microrearrangement in exon 2 of SLC25A15, confirming HHH syndrome. Protein restriction and citrulline were commenced for HHH syndrome which resulted in an improvement in development and seizures. At 5 years, he developed raised transaminases (Table 1) and concomitant ultrasonography (USS) showed heterogeneous liver with no splenomegaly. Serum transaminases were monitored and concomitant ultrasonography confirmed hepatic involvement.

Case description:

A child of British-Asian ethnicity was screened for WD in infancy as parents were heterozygotes. He was homozygous for the familial c.1746dupA [p.Glu583fs] mutation in exon 5 of ATP7B confirming WD. Thereafter, transaminases were monitored and noted to be raised at 6 months of age (Table 1). Zinc was commenced and a good response was observed. Developmental delay was noted at 18 months which was unexplainable by well-controlled WD. At 3 years, he developed seizures and investigations revealed hyperammonemia, raised urinary ornitine, orotic acid, and homocitrulline. Genetics showed homozygosity for a c.208_209delGCinsTT [p.Ala70Leu] microrearrangement in exon 2 of SLC25A15, confirming HHH syndrome. Protein restriction and citrulline were commenced for HHH syndrome which resulted in an improvement in development and seizures. At 5 years, he developed raised transaminases (Table 1) and concomitant ultrasonography (USS) showed heterogeneous liver with no splenomegaly. Serum transaminases were monitored and concomitant ultrasonography confirmed hepatic involvement.

Conflict of interest: None

How to cite this article: Fernando M, Vijay S, Santra S, et al. Wilson’s Disease and Hyperornithinemia-hyperammonemia-homocitrullinuria Syndrome in a Child: A Case Report with Lessons Learned! Euroasian J Hepato-Gastroenterol 2021;11(2):100–102.

Source of support: Nil

© The Author(s), 2021 Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by-nc/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (https://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.
Wilson’s Disease and Hyperornithinemia-hyperammonemia-homocitrullinuria Syndrome

**Discussion and Conclusion**

We report on a child with WD and HHH syndrome who developed the progressive liver disease while being treated for both diseases. ACLF is defined as a rapidly progressive liver disease with organ failure in a setting of preexisting liver disease and might cause mortality without LTx.\(^2\)\(^,\)\(^6\) This child presented with ACLF at 6.5 years and eventually required LTx. He succumbed in the posttransplant period possibly due to the continuing effects of sepsis which triggered ACLF pretransplant. The presence of established cirrhosis on liver biopsy indicated that liver disease had been progressive despite the treatment for both diseases. Furthermore, the WD-related changes that were present in

| Table 1: Trends of results and interpretation |
|---------------------------------------------|
| **Age** | Results | 6 months | 2 years | 3 years | 4 years | 4.5 years | 5 years | 6.5 years Dec 13, 2012 | 6.5 years Dec 24, 2012 | 6.5 years Jan 03, 2013 |
|--------|---------|-----------|---------|--------|---------|---------|--------|---------------------|---------------------|---------------------|
| AST, IU/L     | 55      | 30        | 50      | 32     | 80      | 195     |        | 470                 | 220                 | 2232                |
| ALT, IU/L     | 45      | 25        | 45      | 30     | 55      | 186     |        | 443                 | 147                 | 464                 |
| PT, seconds   | 11      | 11        | 11      | 12     | 12      | 12      |        | 22                  | 13                  | 47                  |
| Albumin, g/L  | 39      | 40        | 40      | 39     | 39      | 40      |        | 39                  | 37                  | 22                  |
| TSBR/DSBR, µmol/L | 12/0  | —         | —       | —      | —       | —       |        | 20/3                | 15/3                | 621/478             |
| Ammonia, µmol/L | —      | —         | 190     | 45     | 50      | 50      |        | 240                 | 65                  | 226                 |
| USS           | Normal  | Normal    | Heterogeneous liver | Coarse liver new-onset splenomegaly | Coarse liver, splenomegaly, ascites |
| Histology     |         |           | Spleen 8 cm | Spleen 12.1 cm | Cirrhosis (explant) |
| Remarks       | Diagnosis of WD | Stable blood tests | HHH syndrome diagnosed | Both WD and HHH syndrome treated | Viral illness | Clotting; ammonia improved; transaminases not completely settled | Liver transplant |

**Figs 1A to C:** Explant liver: (A) Hematoxylin-van Gieson original magnification × 20 showing the nodular architecture of cirrhosis; (B) Hematoxylin and eosin original magnification × 200 steatosis and bile stasis including a ductular bile plug (arrow); (C) Orcein stain × 200, granules of copper-associated protein
his biopsy are usually seen in older age with WD. This indicates the
disease progression had been unusually rapid, possibly raising the
contribution from the coexistent metabolic disease.

The next discussion point would be regarding the dominant
metabolic condition which would have caused more liver injury.
Considering the clinical course, biochemistry, histology, and MRI
brain results, it is implied that WD had been dominant over HHH
syndrome. Milder phenotype of HHH syndrome is supported by
the age and the nature of the first presentation, improvement in
development with treatment, and the absence of changes of HHH
syndrome in the MRI brain. Liver histology was more of WD as it was
cholestasis with copper staining rather than showing microvesicular
steatosis, glycogen deposition, and vacuolation of hepatocytes
which would favor HHH syndrome.2,3

Lessons Learned!
We would like to highlight the lessons learned with possible
mechanisms of causation to improve future outcomes if faced with
a similar situation.

Firstly, the transaminitis at 5 years could have been a point which
warranted escalation of treatment for WD (addition of penicillamine/
trientine). However, the disease progression cannot solely be
attributed to WD. As a second mechanism, the modifier genes and
high mutational load caused by two metabolic diseases might have
contributed to the unusual progression of the liver disease.2

Secondly, it is not surprising that albumin and clotting were
stable till the ACLF and did not reflect end-stage liver disease. This
indicates that total reliance on biochemistry in similar situations is
questionable. Thus, liver histology should have been considered
when transaminases were raised at 5 years.

Finally, evaluating the posttransplant course, encephalopathy is
unlikely due to WD or HHH as LTx would have cured both conditions.
This is further supported by normal ammonia. The child had
irritability since the early posttransplant period which was apparent
once the sedatives were weaned. Thus, we postulate that worsening
clinical picture and encephalopathy must have been due to the
continuing effects of sepsis originating from the pretransplant
period, which was exacerbated with immunosuppression.

Considering the above, we would recommend a careful and
early assessment for liver transplantation in sepsis-triggered ACLF
as it may result in an unfavorable prognosis similar to adults.6
Furthermore, the progression of liver disease deems to be rapid
when two metabolic diseases are coexistent.

Availability of Data and Materials
This case report contains clinical data from the electronic
medical record in the Birmingham Children’s Hospital. Additional
information is available from the corresponding author on
reasonable request from the editor.

Acknowledgments
Authors would like to thank all the staff in Liver Unit and Department
of Inherited Metabolic Disorders in Birmingham Women’s and
Children’s NHS Foundation Trust for their contribution in the
management of this patient.

Authors Contributions
MF and GLG collected the patient’s data and performed the initial
draft of the case report. SV and SS contributed from the metabolic
expertise and went through the manuscript. MAP assisted in
biochemical diagnosis and contributed to the final draft of the
manuscript. RB was responsible for histological diagnosis and
providing the figure with the figure legend. RB contributed to the
main text of the manuscript as well. AR managed the child locally
as shared care and contributed to the final draft of the manuscript.

Orcid
Meranti Fernando @ https://orcid.org/0000-0001-7162-3748

References
1. Socha P, Janczyk W, Dhawan A, et al. Wilson’s disease in children:
a position paper by the Hepatology Committee of the European
Society for Paediatric Gastroenterology, Hepatology and Nutrition.
J Pediatr Gastroenterol Nutr 2018;66(2):334–344. DOI: 10.1097/
MPG.0000000000001787.
2. Fernando M, van Mourik I, Wassmer E, et al. Wilson disease in children
and adolescents. Arch Dis Child 2020;105(5):499–505. DOI: 10.1136/
archdischil-2018-315705.
3. Martinelli D, Diodato S, Ponzi E, et al. The hyperornithinemia-
hyperammonemia-homocitrullinuria syndrome. Orphanet J Rare
Dis 2015;10:29. DOI: 10.1186/s13023-015-0242-9.
4. Ranucci G, Rigoldi M, Cotugno G, et al. Chronic liver involvement in
urea cycle disorders. J Inherit Metab Dis 2019;42(6):1118–1127. DOI:
10.1002/jimd.12144.
5. Fecarotta S, Parenti G, Vajro P, et al. HHH syndrome (hyperornithinaemia,
hyperammonaemia, homocitrullinuria), with fulminant hepatitis-like
presentation. J Inherit Metab Dis 2006;29(1):186–189. DOI: 10.1007/
s10545-006-0120-7.
6. Arroyo V, Moreau R, Jalan R. Acute-on-chronic liver failure. N Engl J
Med 2020;382(22):2137–2145. DOI: 10.1056/NEJMr1914900.
7. Mira V, Boles RG. Liver failure with coagulopathy, hyperammonemia
and cyclic vomiting in a toddler revealed to have combined
heterozygosity for genes involved with ornithine transcarbamylase
deficiency and Wilson disease. JIMD Rep 2012;3:1–3. DOI:
10.1007/8904_2011_70.