CASE REPORT

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

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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-hyperammonamia-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 posttransplant 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.

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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 ornithine, 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

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albumin and clotting were normal. Urine copper and zinc levels were compatible with good adherence; hence, treatment was not escalated. At 6.5 years, he sustained a viral illness precipitating an episode of a metabolic crisis with decompensation of liver functions (Table 1). He recovered from metabolic crisis within 10 days. However, transaminases were persistently elevated up to a lesser degree (Table 1). USS showed a coarse liver with a new-onset splenomegaly (Table 1). A liver biopsy was performed at this stage showed cirrhosis.

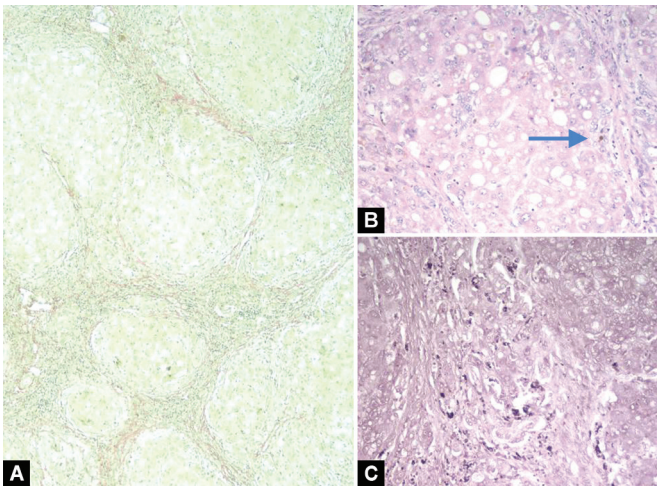
Two weeks later, he presented with acute-on-chronic liver failure (ACLF) which could not be rescued with medical management. Thus, he underwent an LTx. Sepsis was postulated as a possible trigger for this presentation although the blood culture was negative. Liver explant showed cirrhosis, moderate macrovesicular steatosis, and abundant copper-associated protein. There was also significant cholestasis including plugs of bile in biliary ductules as seen in sepsis. Histological features described in HHH, focal glycogenosis, and microvesicular steatosis were not identifiable at this stage, but multifactorial damage contributing to fibrosis is likely (Fig. 1).

Following LTx, good graft function and normal ammonia were noted, and the child was transferred to low dependency care on day 3. Antibiotics, antifungal medicines, and immunosuppressive drugs were commenced as per standard LTx protocol.

Though he was stable initially, irritability was noted on day 4 postoperatively. This progressed to severe encephalopathy requiring ventilation on day 6. Graft function, ammonia, and magnetic resonance imaging (MRI) brain were normal. Hepatic vasculature was patent, and no viremia was detected. EEG showed severe encephalopathy. Clinical condition deteriorated with encephalopathy and respiratory failure. He developed pulmonary hemorrhage, multiorgan dysfunction and died on day 23. Posttransplant biopsies performed showed cholestasis with ductular bile plugging in keeping with sepsis with no evidence of rejection. A sepsis-driven process was postulated for this unexpected deterioration although a definitive organism was not identified.

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



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

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 Spleen 8 cm			Coarse liver new-onset splenomegaly Spleen 12.1 cm		Coarse liver, splenomegaly, ascites
Histology							Cirrhosis		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

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 cholestatic 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.[7]

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.

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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.

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