Wilson disease presenting as acute haemolytic anaemia in a Sri Lankan child

***Janith Chandrakumara[1], Chanaka Rathnayake[2], Oshanie Muthukumarana[2], Givani Amarakoon[1], Meranthi Fernando[3]**

Sri Lanka Journal of Child Health, 2022; **51**(3): 481-483
DOI: http://dx.doi.org/10.4038/sljch.v51i3.10263
(Key words: Wilson disease, Haemolysis, Anaemia, Sri Lanka, Child)

Introduction

Wilson disease (WD) is a rare, inherited disorder of copper metabolism causing copper toxicosis in multiple organs[1]. It is recessively inherited, and the mutations lie in the ATP7B gene[1-3]. The estimated prevalence is 1:5000 to 1:30,000 births worldwide[3]. The disease exhibits marked geographical and ethnic variation of genotype and phenotype[2]. The diagnosis is traditionally established by Wilson's diagnostic score (WDS) and mutational analysis confirms the diagnosis[1,3]. Early detection facilitates treatment with copper chelators[1]. End-stage liver disease and medically refractory acute liver failure (ALF) warrant immediate liver transplantation[1]. The lag time for diagnosis of WD is high due to a lack of awareness of uncommon presentations of the disease[1] and the unavailability of diagnostic facilities. Published literature on WD in children from Sri Lanka is sparse. We report a child with WD who first presented with acute haemolysis, which is an overlooked presentation of WD.

Case report

An eight-year-old, previously healthy girl, was admitted to Teaching Hospital Anuradhapura, with a 2 day history of lethargy. Her parents were non-consanguineous, and there was no family history of liver disease. She was severely pale and icteric on admission. Abdominal examination revealed hepatomegaly of 1 cm, a just palpable spleen and free fluid.

[1]*Rajarata University of Sri Lanka,* [2]*Postgraduate Institute of Medicine, University of Colombo, Sri Lanka,* [3]*University of Kelaniya, Sri Lanka*
**Correspondence:* janith@med.rjt.ac.lk
https://orcid.org/0000-0002-1292-2892
(Received on 19 September 2021: Accepted after revision on 19 November 2021)
The authors declare that there are no conflicts of interest
Personal funding was used for the project.

Haemoglobin was 5.5g/dl with the mean corpuscular volume (MCV) 91.6fL, mean corpuscular haemoglobin (MCH) 29.1pg and the mean corpuscular haemoglobin concentration (MCHC) 31.7g/dL, all within normal ranges. Blood picture showed normochromic normocytic anaemia with nucleated cells and spherocytes suggestive of haemolysis. Reticulocyte count was 23% and the direct antibody test was negative. Urine for haemoglobin was negative. Liver functions showed a total bilirubin level of 573 micromol/L with a direct bilirubin level of 264 micromol/L (46%). Serum aspartate transaminase (AST) was 111 IU /L [normal range (NR): 10-35 IU /L) and serum alanine transaminase (ALT) was 16 IU/L (NR: 13-40 IU /L). Alkaline phosphatase (ALP) was 26 IU /L (NR: 24-147 IU /L) and gamma-glutamyl transferase (GGT) was 37 IU/L (NR: 0-30 IU/L). Serum albumin level was 28.7 g/L (NR: 35-52 g/L), and the international normalized ratio (INR) was 2.51.

Ultrasonography of the abdomen showed altered liver echogenicity with moderate ascites. Portal vein Doppler did not show evidence of portal hypertension. Kayser–Fleischer (K-F) rings were noted on ophthalmological assessment. Caeruloplasmin level was 18.6 mg/dL (NR: 20-40 mg/dL) with a normal C-reactive protein (CRP) level. She fulfilled a WDS of 3 initially (Table 1). Haemolysis could not be used for the diagnostic score as the facilities to get serum copper were unavailable in-house.

She was initially managed with two blood transfusions. Copper chelation with penicillamine for WD was commenced simultaneously. Her liver functions were normalized within 2 weeks. Genetic results showed that she is compound heterozygous for c.3182G>A p.(Gly1061Glu) and c.3008C>T p.(Ala1003Val) mutations. On routine psychiatric assessment, she was reported to be having anxiety and low mood. Magnetic resonance imaging (MRI) of the brain showed hyper-intensity in basal ganglia. Renal tubular functions were normal.

Table 1: ***Wilson diagnostic score of the patient (bold italics) in the first week of presentation***

Diagnostic score for Wilson disease				
Score	-1	0	1	2
Kayser–Fleischer rings				***Present***
Neuropsychiatric symptoms or MRI brain findings		Absent		
Coombs negative haemolytic anaemia + high serum copper		Absent	Present	
Urinary copper		Normal	1-2 upper limit normal	2 upper limit normal (ULN) but >5 ULN following penicillamine challenge
Liver copper quantitative	Normal		< 250 mcg/g	>250 mcg/g
Rhodanine positive hepatocytes		Absent	Present	
Serum caeruloplasmin		>0.2 g/L	***0.1 – 0.2 g/L***	<0.1g/L
Disease causing mutations	None	One		Two
Interpretation of the score: (0-1) – unlikely; ***(2-3) – probable***; (4 or more)- highly likely				

Discussion

Defective copper transport causing accumulation of copper in multiple organs is responsible for disease manifestations in WD[1]. The most common presentations are hepatic in children and neurological in adults. Though haemolysis is a known presentation of WD, it is uncommon[3,4]. It is theorized that copper itself or copper-induced superoxide radicals can lead to haemolysis[4,5]. Another theory is that copper triggers sphingomyelinase activation, leading to the release of ceramide in the red blood cell (RBC) membrane resulting in haemolysis[5].

Walshe JM, *et al*[4] reviewed 22 cases of WD presenting with haemolysis and reported that the delay in diagnosis ranged from 1 month to 8 years. In some cases, the anaemia in WD was intermittent and resolved with symptomatic management, which could have contributed to this delay[1,4]. In this child, the diagnosis was considered on the second day of admission, and the copper chelators were commenced on the following day based on WDS. Haemoglobin concentration ranged from 4 - 8.9g/dL in the cohort described by Walshe JM, *et al*[4], whereas in this child it was 5.5 g/dL. The haemolysis is suggested to be extravascular in WD as neither patients described in literature nor the patient we describe had haemoglobinuria[4].

p. Arg778Leu is the most reported mutation reported in Asia, and it is often homozygous[2]. In the child we report, she was compound heterozygous, having two different mutations.

We highlight that acute haemolytic anaemia or chronic intermittent haemolytic anaemia can be the first presentation of WD. Early diagnosis and timely copper chelation improve long-term outcomes by avoiding or delaying the need for liver transplantation. WDS is helpful for the diagnosis and facilitates timely chelation. The diagnosis should be confirmed genetically as this helps understanding genotype-phenotype correlation.

Acknowledgments

We thank the healthcare staff of the university paediatric units of the Teaching Hospital, Anuradhapura, and Colombo North Teaching Hospital.

References

1. Fernando M, van Mourik I, Wassmer E, Kelly D. Wilson disease in children and adolescents. *Archives of Disease in Childhood* 2020; **105**(5): 499-505. https://doi.org/10.1136/archdischild-2018-315705 PMid: 31974298

2. Gomes A, Dedoussis GV. Geographic distribution of ATP7B mutations in Wilson disease. *Annals of Human Biology* 2016; **43**(1): 1-8. https://doi.org/10.3109/03014460.2015.1051492 PMid: 26207595

3. Ye XN, Mao LP, Lou YJ, Tong HY. Haemolytic anaemia as first presentation of Wilson's disease with uncommon ATP7B mutation. *International Journal of Clinical and Experimental Medicine* 2015; **8**(3): 4708-11.

4. Walshe JM. The acute haemolytic syndrome in Wilson's disease--a review of 22 patients. *Quarterly Journal of Medicine* 2013; **106**(11): 1003-8. https://doi.org/10.1093/qjmed/hct137 PMid: 23842488

5. Attri S, Sharma N, Jahagirdar S, Thapa BR, Prasad R. Erythrocyte metabolism and antioxidant status of patients with Wilson disease with haemolytic anaemia. *Pediatric Research* 2006; **59**(4 Pt 1): 593-7. https://doi.org/10.1203/01.pdr.0000203098.77573.39
PMid:16549536