

Case Report

Wilson disease: early screening for better living

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ABSTRACT

Autosomal recessive diseases are more common among consanguineous marriages noted particularly in southern parts of India. There is a gradual increase in the genome wide homogeneity with the increasing levels of consanguinity. Here we are reporting a case series of such an autosomal recessive condition, namely Wilson Disease (WD), where three children were affected with the disease, who were born out of consanguineous marriages. The first case presented with neuropsychiatric manifestations, the second case and third cases were diagnosed through screening of family members leading to earlier identification of the disease. In these cases consanguinity has been emphasised as the major predisposing factor leading to their manifestations. This case series highlights the importance of screening the other family members of the index case. Conditions such as Wilson disease have an excellent prognosis if pharmacotherapy is initiated appropriately.

Keywords: Consanguinity, Screening, Wilson disease

INTRODUCTION

Wilson Disease (WD), also known as hepatolenticular degeneration is an autosomal recessive disorder caused by the mutations in ATP7B gene which leads to impaired cellular copper transport resulting in excessive accumulation of copper in several organs, most notably the liver, brain and cornea.¹ Clinical presentation of WD ranges from silent carrier to liver failure and irreversible brain damage, leading to death.

CASE REPORT

Case 1

The 11-year-old developmentally normal female child, born to a third-degree consanguineous couple brought with history of gait disturbances for 6 months in the form

of swaying on both sides which was gradually progressive in nature. Child also had history of drooling of saliva, slurring of speech and decreased scholastic performance. Her hand writing deteriorated over the past few months and she was noticed to have emotional lability by her parents. There is no history of involuntary movements, seizures, weakness of limbs and paresthesias. No history suggestive of cranial nerve involvement or visual disturbances. She had a past history of jaundice on two occasions for which native treatment was taken. She never had any history of hematemesis. On examination, child was alert, conscious and oriented. Except for dysarthria, rest of the CNS examination was normal. Child had hepatosplenomegaly on abdominal examination.

Slit lamp examination showed bilateral KF rings. USG abdomen showed coarse liver (with surface irregularities

and altered echoes) and splenomegaly. USG Doppler showed Portal Vein (PV) diameter of 10mm at porta-hepatis. UGI endoscopy showed grade II esophageal varices. On further evaluation (Table 1) the child was

diagnosed to have NEURO WILSON DISEASE and started on D-Penicillamine and pyridoxine following which her symptoms improved.

Table 1: Laboratory investigations.

Parameters	Case No 1	Case No 2	Case No 3
S. ceruloplasmin	<3mg/dl	4.44mg/dl	19.92mg/dl
24hr urinary copper excretion	217mcg/24hrs	109mcg/24hrs	181.73/24hrs
KF ring	Present	Absent	Absent
AST/ALT	53/43	348/401	32/22
Alkaline phosphate	429/90	747	284
GGT	90	25	11
PT/ INR	60/5.5	20.1/1.57	Initial-14/1.03; Later-60/5.5
T. bilirubin/direct bilirubin	0.16/0.1	0.73/0.22	0.68/0.32
Nazer's index	4	7	4

Case 2

The 8-year-old developmentally normal female child, younger sibling of case no 1 was screened for WD during which she was found to have mild fatty liver and splenomegaly with a PV diameter of 9mm without collaterals. UGI endoscopy was done which was found to be normal. Based on the rest of the investigations (table no 1), child diagnosed to have Asymptomatic Wilson disease for which she was started on D-Penicillamine and Pyridoxine.

Case 3

The 11-year-old developmentally normal male child, paternal cousin of case no. 1, born to a second degree consanguineous marriage was also screened for WD and found to have low serum ceruloplasmin, for which child was started on zinc therapy prophylactically. 6months later, he developed symptoms in the form of upper gastrointestinal bleed following which he was started on D-Penicillamine and pyridoxine.

DISCUSSION

While the worldwide prevalence of Wilson Disease (WD) is 1 in 30,000, the carrier frequency is as high as 1 in 90 persons.² The mortality and morbidity has been reduced in the past few decades due to the increased awareness, recognition and aggressive management.

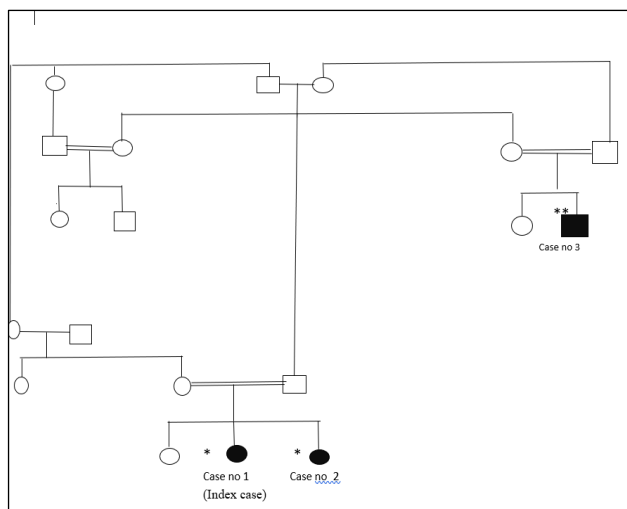
A classic case of WD in pediatrics usually presents with hepatic involvement which may be missed or it may not be the only initial symptom.³ By 10 years of age, 83% will present with hepatic manifestations and 17% with neuropsychiatric manifestations; between 10 and 18 years, 52% present with hepatic and 48% with neuropsychiatric symptoms. After the age of 18 years,

75% patients present with neuropsychiatric features and 25% patients develop liver disease.⁴ The variability in the age of onset of WD probably reflects differences in mutations and penetrance, extragenic factors, and environmental influences including diet.⁵

Hepatic presentation varies from subclinical stage where elevated transaminases may be an incidental finding to acute fulminant liver disease. Most of the patients present initially with jaundice (50%) as seen in our case no 1, which was not investigated further due to low index of suspicion which indicates the importance of screening.¹ In an analysis of 100 cases from Bangladesh, 69% patients presented only with hepatic manifestations, 6% only with neurological features and 14% manifested with both hepatic and neurological disease. The age of onset of hepatic WD was between 5 to 10 years and that of neurological was after 10 years.⁶

Among neurological manifestations, dystonia, dysarthria and cognitive decline are the most common manifestations.⁷ In particular, WD should be considered in children with liver abnormalities with uncertain etiology, especially in those presenting with liver disease accompanied by neurologic and psychiatric symptoms. A study by Ala A et al reported that WD can present as late as eighth decade of life which highlights the wide range of phenotypical expression for the disease.⁸

Our study included three large families which spanned three generations that included 19 members and three consanguineous marriages were noticed among them. Out of these, three children were diagnosed to have WD. Extensive pedigree was obtained for all the families (Figure 1). This indicates inbreeding as one of the important factors that contribute to the prevalence of the disease. The result of this is limited genetic heterogeneity among them as they would share common genetic factors.



*Case no 1 (Index case) and Case no 2 are siblings. **Case no 3 is a paternal cousin of case no 1 and 2.

Figure 1: A large family of 19 members with three consanguineous marriages. Out of these, three children were diagnosed to have Wilson disease.

The practice of marriage among cross cousins and closed relatives is comparatively high in southern India. According to the National Family Health Survey (2018), Tamilnadu and Lakshadweep stood first with 33% consanguineous marriages, followed by Andhra Pradesh and Telangana with 32% and 30% respectively.

Inbreeding is most common in the traditional rural communities. Occurrence of identical homozygous mutations within family members reflect the genetic inbreeding in the population. A study reported a greater prevalence of adverse pregnancy outcome among consanguineously married couple compared to non-consanguineous marriages.⁹ A study by Mehrjoo et al, reported that with the increasing levels of endogamy and consanguinity, there is a gradual increase in the genome wide homozygosity.¹⁰ Subsequently in the resulting offspring there would be expression of these recessive genes inherited from the common ancestors.

It is essential to screen siblings of a newly diagnosed WD because the chance of being a homozygote and developing clinical disease is 25%.¹¹ Assessment should include physical examination, serum ceruloplasmin, 24hour urinary copper excretion, slit lamp examination for KF ring and liver function tests. Patients were diagnosed to have WD 4 years earlier by family screening which prevents liver and/or neurological disease.¹²

Gold standard therapy for WD is D-Penicillamine. Pyridoxine should be supplemented to prevent the side effects caused by penicillamine.¹³ Zinc is the recommended drug for presymptomatic patients but progression of symptoms while on prophylactic zinc therapy as seen in case no 3 indicates the inadequacy of

zinc alone for prophylaxis. However, zinc still remains the drug of choice for the initial treatment of presymptomatic children and there should be regular clinical and biochemical follow up of such cases.¹⁴

CONCLUSION

The early and accurate diagnosis is essential as the initiation of oral chelating agents can prevent the development of hepatic and neurologic symptoms and improve the quality of life.

It is very critical to educate and counsel families of WD not only about the disease but also about the inheritance and the consequence of consanguineous marriage.

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