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Wilson's Disease, A Screening Necessity among Siblings: A Case Series Reported from Northern India

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ABSTRACT

Wilson disease is a rare genetic condition causing pathologic deposition of copper in the liver, brain, cornea, kidney, and cardiac muscles. Here we present a series of cases among siblings with different presentation of symptoms among them. These symptoms varied among siblings from asymptomatic with laboratory finding of Wilson's disease to involving liver, neurological squeal to even death. These presentations can be taken as different phenotypic expression of same genetic mutation among siblings. Hence, screening of siblings is most important among diagnosed cases of Wilson's disease.

Key words: Wilson's disease, Siblings, K-F rings, Ceruloplasmin

INTRODUCTION

Wilson's disease (WD) is an autosomal recessive disease involving a defect of copper transport by the hepatic lysosomes. It leads to excess copper deposition in the liver, the brain, the kidneys and the skeletal system, affecting most commonly children or young adults and running an invariably fatal course if not adequately treated by de-coppering therapy. The last century has witnessed several changes, notable among these are: Increased awareness, improved diagnostic facilities leading to earlier recognition even in the pre-symptomatic phase, clear distinction from its mimics, aggressive therapeutic approaches owing to availability of effective treatment and an overall reduction in the morbidity and mortality. It is widely acknowledged that the disease is not as rare as once believed. Sir SAK Wilson published his landmark article in 1912, but it was only in 1968 that the first patient of WD was reported from our country.

Siblings Pair – 1:

The first pair of sibling was 8-year-old symptomatic female child and her 10-year-old brother. She presented with history of fever for 1 month along with abdominal distension followed by jaundice for period of 15 days. She was a fully immunized child for her age along with normal development.

On examination she was found to have normal systemic examination except abdominal distension and increases liver span. Liver was firm with sharp margins to palpate. The blood, biochemical parameters and radiological investigations were as shown in the table-1. Based upon above features and investigation possibility of liver disease secondary to Wilson was kept. Blood biochemistry shows deranged liver functions, decreased Ceruloplasmin and increased 24-hour urinary copper. Work up for autoimmune and infectious hepatitis was negative. Eye examination was normal. Patient was started on d-penicillamine, and urinary copper investigations were repeated

which are suggestive of diagnosis. She was managed conservatively and discharged upon improvement with d-penicillamine and during follow-ups zinc was added to treatment.

Her sibling who was asymptomatic was also screened and was found to have low Ceruloplasmin levels so started prophylactically on zinc (investigations in table 1). Both the children were kept on follow up and are doing well currently.

Siblings Pair – 2:

The second pair of siblings was of a 9-year-old symptomatic male child and his asymptomatic younger brother. This male child was admitted to our hospital with complaint of peri-orbital puffiness with associated abdominal pain. Parents gave prior history of multiple episodes of jaundice.

Initial Workup revealed (table-1) deranged liver function tests. Further investigation was done for causes of chronic hepatitis which revealed Wilson's disease. He was started on d-penicillamine and after 7 months of treatment child show abnormal behavior and abnormal body posturing of hand and feet. Abnormal behavior includes the decreased interest in surroundings, staring at object for long time and poor performance in studies. Abnormal of posture of hand and feet (fig-1) along with impaired sleeping and involuntary repetitive limb movements were present. Speech abnormalities also developed in due course. There was impaired gag reflex on cranial nerve examination. Tandem walking was impaired along with loss of coordination. KF rings were also present. MR imaging (fig-2) showed- T-2/Flair hyper intensity in bilateral Lentiform/caudate nucleus, hyper intensity in Tegmentum and substantia niagra with sparing of red nucleus.

Child was managed conservatively and his sibling was screened for Wilson's disease and came out to be having low Ceruloplasmin levels and high copper level in urine. He was started prophylactically on Zinc.

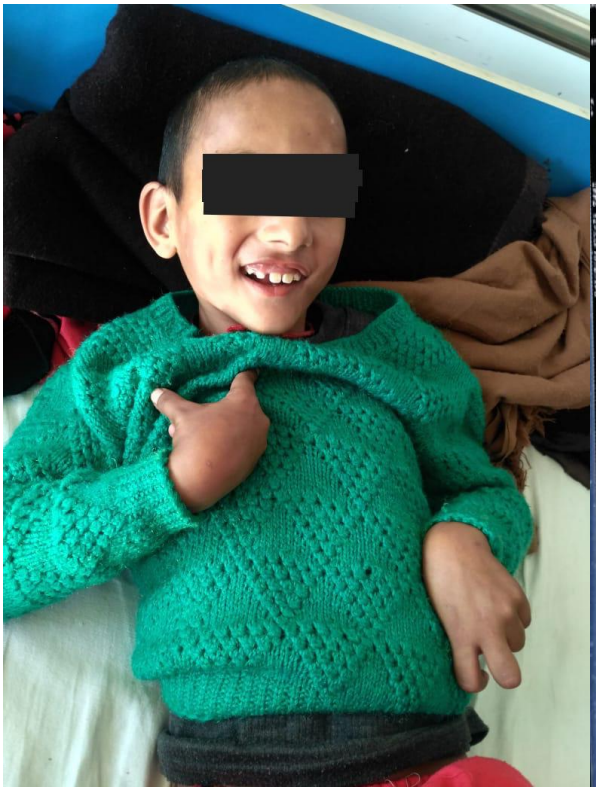

Fig-1

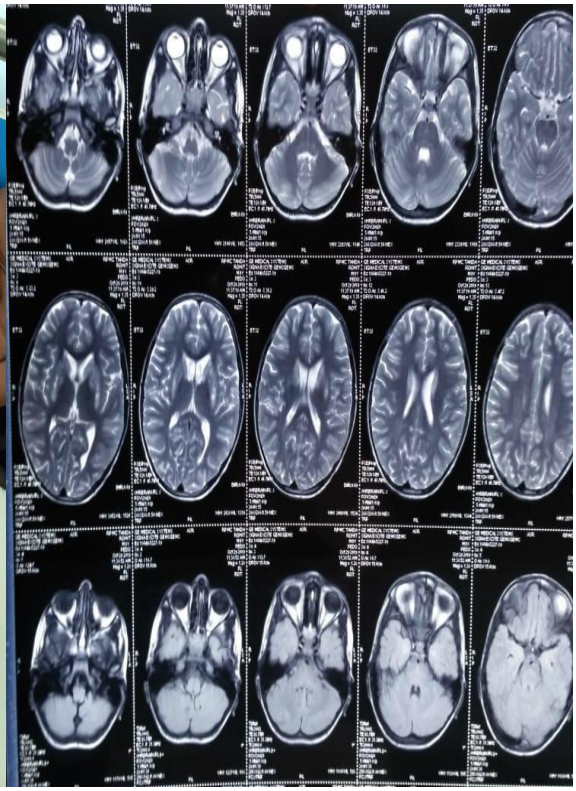

Fig-2

Table: 1

	Siblings pair-1		**Siblings pair-2**		**Case-3**
Investigation	Symptomatic	Asymptomatic	Symptomatic	Asymptomatic	Symptomatic
Hb	12.9	13.1	11.9	12.1	10.2
TLC	14000	9000	5420	6700	8090
Platelets	1.88	2.10	1.29	1.80	0.95
TSB	2.03	1.01	3.00	0.90	8.1
Direct Bilirubin	0.95	0.25	1.5	0.4	3.1
SGOT/SGPT	31/13	20/21	100/102	34/32	756/703
PT (sec)	14	16	14	14	>60
INR	1.02	1.01	1.03	1.00	2.66
TSP	5.2	5.9	4.6	5.1	7.5
BUN/CREAT	21/0.6	18/0.8	20/0.9	18/0.9	9/0.85
24 hr. urinary copper	194.76 mcg/l	180 mcg/l	236.36 mcg/l	899 mcg/l	2001.29 mcg/l
ANA	Positive	Negative	Negative	Negative	Negative
Anti-LKM, Anti Sm, Anti-MT	Negative	Negative	Negative	Negative	Negative
Usg abdomen	HSM* with mild ascites	Normal	Normal	Normal	Cholelithiasis, fatty liver, Ascites
Fibroscan	Cirrhosis	Normal	Normal	Normal	Cirrhosis
K-F rings	Present	Absent	Present	Present	Present
Serum Cerruloplasmin	<0.10	<0.10	<0.10	0.12	<0.10
HBsAg	Non-Reactive	Non-Reactive	Non-Reactive	Non-Reactive	Non-Reactive
HCV	Non-Reactive	Non-Reactive	Non-Reactive	Non-Reactive	Non-Reactive

*HSM – Hepatosplenomegaly.

CASE – 3:

The third case was of a 17-year-old male who presented with yellowish discoloration of eyes for one week along with swelling face. There was no history of previous hospitalization or similar complaints. Child was immunized for age and developmentally normal. On examination child was icteric along with palpable Liver (firm consistency with sharp margins) and spleen. Child had developed ascites and on auscultation there was presence of short systolic murmur over tricuspid region. Depending upon history and clinical examination a possibility of chronic liver disease was kept and Child was investigated and it came out to be Wilson's disease after blood and biochemical work up. Child had low Ceruloplasmin levels and high urinary copper excretion along with KF rings. Patient was started on Zinc and d-penicillamine. His well-being improved but later on he again went into decompensation and died. This patient did not have any sibling.

DISCUSSION

Wilson disease (hepatolenticular degeneration) results from a defect in hepatocellular copper transport, leading to the accumulation of copper in the liver and other tissues, including the brain. Over time, the damage from the accumulation of copper results in the hepatic, neurologic, and psychiatric manifestations of Wilson disease. Wilson disease is found worldwide, with an estimated prevalence of 1 case per 30,000 - 50000 live births in most populations[1] and 1 in 10000 in Chinese and Japanese population[2,3]. Diagnosis is mainly based upon the clinical manifestations, biochemical levels of copper and elevated urinary copper content. In early stages of disease typical symptoms are not there so genetic detection is an important tool for diagnosis[4,5,6]. Wilson's disease is caused by mutation in P-type *ATP7B* gene located on chromosome 13q14.3. Wilsons's disease has high mortality and disability rate[7]. However, it is one of the treatable hereditary diseases if detected in early stage[7]. Irreversible injuries can be prevented by diagnosing it in early stage[8]. Family members of patients are at different risk at different stages hence it is essential to screen family members for Wilson's disease[7]. There can be various screening like biochemical or genetic. There were families reported in which there were no symptoms but biochemical abnormalities have been detected in first degree relatives and siblings[7]. Similar observation gave been

made in our series of cases where siblings showed biochemical abnormalities without symptoms. As per American Association for study of Liver Disease[9] and European Association for study of liver[5], it is recommended to screen first degree relatives and siblings.

Wilson's disease not only occur in siblings (25%) and offspring's (0.5%), but also occur in previous generations (0.5%)[10]. Wilson's disease also shows different symptoms or fairly asymptomatic and phenotypes often differ among same genotype within a single family[11]. Screening based upon the symptoms and biochemical parameters is easy, but due to different symptoms and ambiguous biochemical reports its difficult also[12]. Thus, there can be misdiagnosis. Clinician must use appropriate method and his clinical experience for screening family members. Ceruloplasmin levels can be in normal range in Wilson's disease with pregnancy, OCP intake, Infections and hepatitis[13]. A pre-symptomatic gene analysis is recommended for diagnosis[5]. It avoids the need for continuous testing and appropriate therapy can be initiated early. Although cost of detecting is very expensive. As in our cases, due to poor financial status of families we weren't be able to perform mutational gene analysis of siblings. But screening them for symptoms, thorough clinical examination, Ceruloplasmin levels and blood and urine copper biochemistry is good and cost effective. By using these basic tools, we can easily screen families of Wilson's disease patients and can initiate appropriate treatment to prevent irreversible injury.

CONCLUSION

There can be paradigm of presentation in Wilson's disease among families raging from asymptomatic to full blown neurological and hepatic decompensation. The incidence of disease among siblings is as high as 25%. Hence, screening of sibling along with other family members should always be done using appropriate method. Genetic testing if available should be conducted. Early initiation of therapy is the key to treat this hereditary illness.

Declaration of patient consent:

The authors certify that they have obtained all appropriate consent forms, in which the patient's parents have given their consent for their images and other clinical information to be reported in journal. The patient's parents understand the name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

Conflict of interest: Nil

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