International Journal of Contemporary Pediatrics
Ranjan S et al. Int J Contemp Pediatr. 2016 Nov;3(4):1466-1468
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: http://dx.doi.org/10.18203/2349-3291.ijcp20163702

Case Report

Varied and atypical presentation of Wilson disease in a family: report of 3 cases in siblings

Shilpi Ranjan[1], Kumar Saurabh[2]*

[1]Department of Community Medicine, Government Medical College, Bettiah, Bihar, India
[2]Department of Pediatrics, Government Medical College, Bettiah, Bihar, India

Received: 15 August 2016
Accepted: 24 September 2016

***Correspondence:**
Dr. Saurabh Kumar,
E-mail: dr_saurabh_life@yahoo.com

ABSTRACT

Study reports a series of three cases of atypical presentation of Wilson disease from a family. First sibling presented with isolated neurological manifestation without hepatic involvement and responded well with low dose penicillamine and zinc. Second sibling had history of recurrent long bone fractures along with hepatitis who also responded well with zinc therapy. Third sibling who was presymptomatic turns up into symptomatic state even after appropriate zinc prophylaxis.

Keywords: Wilson disease, Penicillamine, Zinc

INTRODUCTION

Wilson disease is an autosomal recessive disease caused by mutations in the ATP7B gene resulting in a defect of copper transport. The final step in the pathogenesis of Wilson disease is excessive copper deposition in various organs leading to free radical damage.[1] We are presenting a case series of 3 siblings who presented with different and atypical manifestations of Wilson disease at different points of time.

CASE REPORT

Case 1: First sibling 9 years old boy, a product of consanguineous marriage presented with dysarthria, drooling of saliva, difficulty in walking and poor school performance for last one year. There was no history of jaundice, seizure, ascites or bleeding from any site. Neurological examination revealed dysarthria, bilateral ptosis, abnormal gait, hypertonia, brisk deep tendon reflexes, up going plantars and tremor of hands. Complete blood count (CBC), liver function tests (LFT), kidney function test (KFT) and coagulation profile were all within normal limits. Magnetic resonance imaging (MRI) of brain showed hyperintense signal changes in lenticular nucleus. On slit lamp examination Kayscer-Fleischer ring was noted in both eyes. Serum ceruloplasmin level was 6 mg/dl, 24 hours urinary copper levels was 269 µg. Penicillamine (low dose) and zinc was started as Triantene was not affordable and patient showed a marked improvement in neurological status in subsequent follow up.

Case 2: Second sibling 6 years girl presented with a history of multiple long bones fracture over a period of last 8 months. There was a past history of jaundice at 4 years of age which resolved spontaneously. Neurological and other systemic examination was normal except for hepatomegaly. CBC and KFT were normal however LFT was deranged with a serum billirubin of 0.7 mg/dl, AST of 234 mg/dl, ALT of 449 mg/dl and ALP of 511 mg/dl. Ultrasonography of abdomen revealed enlarged liver with altered echotexture. Serum ceruloplasmin was 11 mg/dl and 24 hours urinary copper was 332µg. Treatment with penicillamine and zinc lead to marked improvement in LFT and no new fracture noted thereafter.

Case 3: Third sibling 4 years old girl was clinically and biochemically asymptomatic during this period. Her serum ceruloplasmin was 24mg/ dl and 24 hours urinary copper was 244µg. Ultrasonography of abdomen was normal. She was prescribed with low copper diet and zinc (25 mg thrice a day orally, one hour before meal) as a prophylaxis for WD but after 1.5 year patient presented with jaundice in spite of good compliance of drug. On physical examination icterus, hepatosplenomegaly and wrist widening was noted. LFT was abnormal with a serum billirubin-6.8 mg/dl (total), AST-612 mg/dl, ALT-557 mg/dl and ALP- 923 mg/dl. 24 hours urinary copper was 303µg and Ultrasonography of abdomen showed hepatosplenomegaly with coarse echotexture. Findings in X-ray wrist were consistent with rickets. Later on penicillamine was started along with zinc resulting in control of symptoms and improvement in biochemical profile.

DISCUSSION

After 100 years since the recognition of wilson's disease as hepatolenticular degeneration, last century has witnessed several changes mainly increased awareness, recognition of atypical presentation and aggressive treatment strategy leading to reduced morbidity and mortality. Though in a classic case of Wilson disease of pediatric age group hepatic involvement occurs early in the course but it may go unnoticed, even sometimes it may not be the first presenting symptom.[1] Hepatic involvement in wilson's disease may range from subclinical liver disease to acute fulminant hepatitis.[1,2]

Among neurological manifestations of WD dysarthria and tremors of hands seem to be a sensitive and most common early symptom well noted by parents as in our case.[3,4] Other neurological manifestation of WD in juvenile age group include personality changes, drooling of saliva, dysphagia, dystonia, clumsiness of hands, abnormal gait and fall at work in school.[4]

Atypical and rare presentation of WD include polyarthritis, hemolytic anemia with jaundice, fractures, rickets, renal stones and gall stones cardiomyopathy, dysrhythmias, pancreatitis, hypoparathyroidism.[1-3]

Multiple and recurrent long bone fractures is a known complication of Wilson disease but rarely reported as presenting symptom. However Taly et al. has mentioned an incidence of 3.4% fractures in his study of 282 patients.[5]

In this case series of three siblings the presentation of Wilson's disease has many atypical features. First sibling presented with isolated neurological manifestation without hepatic involvement at 9 years of age. Second sibling had history of multiple fractures of long bone without involvement of hepatic or neurological features. Rickets is also a rare presentation of WD but it is well described in literature. Furthermore progression of pre-symptomatic to symptomatic state of Wilson's disease in third sibling in spite of prophylactic zinc therapy is very unusual and rarely described in literature.[6]

MRI findings in our case were consistent with WD. MRI findings of WD include atrophy of cerebrum, cerebellum, brain stem, signal abnormalities in putamen, caudate, thalamus, midbrain and pons.[7] Presence of central pontine myelinolysis like changes and midbrain tectal plate signal changes in MRI are the specific features that distinguishes WD from other movement disorders.[8]

Pharmacological therapeutic options include penicillamine, zinc acetate, triantene and aluminium tetrathiomolybdate. A combination of chelator (penicillamine or triantene) and zinc is the most recommended and easily available treatment option for initial hepatic decompensation. As the disease is close to 100% penetrant, all presymptomatic patients should be treated prophylactically with zinc. However tetrathiomolybdate is emerging as the drug of choice for initial neurological manifestations because of preservation of neurological function. As tetrathiomolybdate is commercially unavailable so zinc therapy is recommended.[2,9]

This case series shows that phenotypic variability of WD was very high and even different patients with same genetic makeup (siblings) of a family may present with its diverse manifestations.

CONCLUSION

In recent years WD has been seen with more atypical and rare forms so a high index of suspicion is needed to detect WD in these forms specially if they are familial, because it is a potentially curable disease if identified and treated early. Failure of zinc prophylaxis, though rare is a concern.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Ranjan S, Saurabh K. Varied and atypical presentation of Wilson disease in a family: report of 3 cases in siblings. Int J Contemp Pediatr 2016;3:1466-8.