Wilson’s disease: A Clinical autopsy case report with review of literature

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Abstract

Wilson’s disease is an autosomal recessive disease resulting in defective copper metabolism, which is usually seen in young adults, predominantly affecting liver and brain. Although it is not uncommon in India, variation in epidemiology, clinical presentation and course are reported. However, community-based incidence and prevalence rates are not available in India and incidences are limited to hospital based reports. Most often, the diagnosis is delayed. We present a clinical autopsy case in a 39 year-old female who had presented with clinical symptoms at 18 years of age. The duration of illness was 21 years. Patient’s parent had consanguineous marriage and the younger sibling had died at 5 years of age with similar complaints.

Key words: Clinical autopsy, Wilson’s disease, autopsy, autosomal recessive disease

INTRODUCTION

Wilson’s disease (WD) is an autosomal recessive disease involving brain and liver secondary to altered copper metabolism. About 47% and 55% of cases reported have positive family history and consanguinity, respectively.[1] The symptoms are nonspecific and the disease may present as hepatic disease or progressive neurological disorder (hepatic dysfunction being less apparent or occasionally absent) or as psychiatric illness with liver disease. The liver disease may be asymptomatic, with only biochemical abnormalities of cirrhosis.[2,3] A patient (5-40 years old) presenting with liver disease, with a decrease in serum ceruloplasmin and detectable Kayser–Fleisher (KF) rings are generally regarded as having classic WD.[3] Delay in diagnosis of WD is observed across all the health care levels.[4]

CASE REPORT

A 39-year-old female patient presented with pain in abdomen and fever (intermittent and low grade) since 5 days. Patient had vomited 500 ml of black colored vomitus 3 times and was bleeding per vagina on the 1st day of admission. There was no history of melena or altered sensorium. On examination, patient was conscious, oriented, had pallor, icterus, periorbital puffiness, pedal edema and anasarca. Per-abdomen examination showed distension of abdomen with shifting dullness and spleen was palpable. Cardiovascular, respiratory, musculoskeletal system and skin were normal. No focal neurological deficits were observed. KF rings were present in both eyes. Past history revealed that patient had vomiting, melena, per-vaginal bleeding, pain in abdomen and hepatosplenomegaly when she was 18 years old, with recurrence of these symptoms 2 years later when the case was diagnosed as cirrhosis. A year later when similar episode recurred, endoscopic examination showed esophageal varices; with liver biopsy and biochemical investigations a diagnosis of WD was made. At 22 years of age, patient had similar clinical presentation and penicillamine was advised, however this treatment was discontinued by the patient after a few months due to financial constraints. Subsequently, patient had repeated episodes once in every 2-3 years with additional symptoms of insomnia and muscle spasm developing at 27 years of age. Family history revealed that parent of the patient had consanguineous marriage. The youngest sister of the patient had died with similar complaints at 5 years of age [Figure 1]. Significant clinical investigations observed at admission are presented in Table 1. Endoscopy showed Grade III esophageal varices. A diagnosis of WD with cirrhosis of liver, portal hypertension and chronic anemia was made. Patient died on 5th day of admission after repeated bouts of vomiting blood.
Consent for full body autopsy was taken from the family members. The salient features of autopsy were as follows. Brain weighed 1070 g [Figure 2] and microscopy from sections of different parts of brain and cervical spine was normal. Right and left lungs weighed 360 and 410 g, respectively and showed features of pulmonary edema. Heart weighed 300 g, grossly, and microscopically was normal. Liver and gall bladder weighed 850 g. External surface of liver showed micro and macronodular areas, cut surface was nodular [Figure 3] and microscopy showed features of cirrhosis [Figure 4]. Spleen weighed 600 g, firm in consistency, cut surface showed foci of infarct and fibrosis [Figure 5] and microscopy showed features of congestion, Gamma Gandy bodies, and areas of fibrosis, infarction and calcification [Figure 6]. Esophagus showed multiple dilated and congested blood vessels in lamina propria and submucosa [Figure 7]. Stomach wall was dilated, thinned out [Figure 8] and mucosa showed atrophic changes. Small and large intestine was grossly normal. Right kidney measured 11 cm × 6 cm × 3 cm and cut section showed cortico-medullary differentiation. Left kidney measured 5 cm × 3 cm × 1 cm, cut section showed thinning of cortex [Figure 9]. Microscopically, right kidney showed features of acute tubular necrosis and left kidney chronic pyelonephritis. Liver biopsy block was subjected to copper staining with rhodamine stain, which showed patchy positivity in hepatocytes in cirrhotic nodules and focally in Kupffer cells [Figure 4]. Autopsy diagnosis of hepatic form-WD was made.

**DISCUSSION**

In 1968, first case of WD was reported in India.[2,3] WD is an autosomal recessive disease having inborn error of copper metabolism and potentially curable disease if recognized and treated early.[2] The chance of sibling and offspring being a homozygote and developing clinical disease is 25% and 0.5%, respectively.[8] In the present case, the youngest sister of the patient had died with similar complaints.

Worldwide the average prevalence is about 30 individuals per million populations.[3-5] A variable prevalence rate is observed geographically that is, 12-29/million in Europe, 33-68/million in Japan and 38-68/million in Asian countries other than India. The higher incidence rate in Asians is attributed to consanguinity. In India, the prevalence rate is not performed.

| Parameter                          | Value (normal range) |
|------------------------------------|-----------------------|
| Hemoglobin                         | 7.0 g/dl              |
| Platelets                          | 16,000/cu mm          |
| Total leukocyte count              | 3500/cu mm            |
| Differential leukocytes count       |                       |
| Prothrombin/partial thromboplastin time | 16 s                  |
| Peripheral blood smear             | Microcytic hypochromic anemia with ovalocytes and polychromatophilic cells |
| Blood group                        | AB positive           |
| Total bilirubin                    | 1.6 mg/dl             |
| Lactate dehydrogenase              | 365 U/L               |
| Blood urea                         | 74 mg/dl              |
| Serum creatinine                   | 1.1 mg/dl             |
| Serum total protein                | 4.6 g/dl              |
| Serum albumin                      | 2.1 g/dl              |
because of paucity of studies; however it is relatively common in South India because of more consanguineous marriage (55%). Recorded community based incidence and prevalence are not available in India (many are hospital based reports), although variation in epidemiology, clinical presentation and course are reported.\textsuperscript{[1,2,4]}

Figure 4: Microphotograph of liver showing hepatocytes in nodules (single arrow) with thick fibrous bands (H and E, x100). Inset shows patchy copper staining (double arrow) in liver (Rhodamine x100)

Figure 5: Gross photograph of spleen, cut section showing features of congestion

Figure 6: Microphotograph of spleen showing Gamma Gandy bodies (H and E, x100)

Figure 7: Microphotograph of esophagus showing dilated blood vessels in lamina propria (H and E, x400)

Figure 8: Gross photograph of stomach showing dilated stomach with wall thinned out

Figure 9: Gross photograph of right and left kidney showing shrunken left kidney
In WD, the defect is in copper transport by hepatic lysosomes caused by impaired function of metal transporting P-type adenosine triphosphatase (ATPase) expressed in hepatocyte, encoded by ATP7B gene, located on chromosome 13q14. Decreased or nonfunction of ATP7B protein causes decreased hepatocellular excretion of copper into bile giving rise to excess hepatic copper accumulation and cell injury. There is also failure of copper binding to ceruloplasmin. Hence, hepatic synthesis and secretion of ceruloplasmin protein without copper gives rise to apoceruloplasmin, which has decreased half-life compared with ceruloplasmin resulting in decreased serum ceruloplasmin in WD. Abnormal accumulation of copper in hepatocytes spill into circulation, increase copper content in blood and get deposited in various organs such as brain, kidney, cornea and skeletal system. Until now >400 mutations in the gene have been documented. In India, cases are mainly reported from Chandigarh, Kolkata and Vellore. Until date, a total of 51 mutations of ATP7B are documented in India, of which C813A is the most common mutation. However, no single predominant mutation is observed in Indian population unlike in other countries indicating the genetic heterogeneity. In European population, 60% cases show PH1069Q, while in Chinese population PR778 L is seen in 45% cases.[1-3] In the present case, genetic study was not done.

The toxicity in WD is due to excess deposition of copper in brain and liver. The progression of hepatic insufficiency in the absence of further copper toxicity are also reported, however its mechanism remains unclear. The widespread deposition of copper throughout the grey matter of the brain gives rise to generalized atrophic changes and ventricular dilatation. Copper toxicity causes cellular alterations; causing 50 fold decrease in dopamine concentration in the caudate nucleus and 30 fold decrease in the putamen affecting striate-nigral and striate-palladial pathways resulting in Parkinsonism. Renal manifestations are due to primary or secondary toxicity from copper. The copper induced activation of the nor-adrenaline synthesizing enzyme, dopamine beta-hydroxylase explains some of the psychiatric symptoms observed. Accumulation of protein bound copper in tissues become noxious, as some of the reactions of oxidative stress are catalyzed by free copper, facilitating the release of oxygen free radicals. Pro and antiinflammatory cytokines such as interleukin-2 (IL-2), IL-4, IL-6, interferon-gamma and tumor necrosis factor-alpha are significantly elevated in WD, however the role of these cytokines as cause or effect of the disease is not ascertained.[1,2]

Majority of cases present between 5 and 35 years of age, although WD is reported in 3 and >80 years old patients. Neurological manifestations typically present later than liver disease. The mean age of presentation is 15 ± 0.8 years (ranges between 8 and 23 years).[1,3,7] In a study at NIMHANS, Bangalore, the mean age of onset of symptoms was 13.5 years (range: 3-44 years), the mean age at presentation was 15.6 years (range: 3-45 years) and the mean delay at diagnosis was 2.0 years (0.08-30 years).[1,4] In the present case, the age of index case at onset of symptoms was 18 years, age at first presentation was 20 years and delay in diagnosis was 3 years.

The mean duration of symptoms reported is 462.5 ± 530.5 days (ranges from 30 to 1460 days). Hepatic form has shorter duration of illness. Mean total duration of illness, that is, time between the onset of first symptom related to WD as jaundice, behavioral changes and movement disorders to the time of death is 1377.1 ± 1568.7 days (ranges from 60 to 3980 days).[1] In the present case, the total duration of illness was 21 years. The WD is seen in three forms; hepatic only, neurological only and mixed forms. The disease has clinical heterogeneity. The early manifestation are generally hepatic or neurological (40% each), while the remainders present with psychiatric, hematological, renal or osteochondrotic manifestation. The hepatic form of the disease is more commonly seen in children and young adults than older adults.[2,4] The liver disease is highly variable, ranging from asymptomatic with only biochemical abnormality to acute liver failure. WD constitutes about 6-12% of all acute liver disease cases. The liver disease may precede neurological manifestation by 10 years. Neuromuscular features are also reported. The cardiac manifestations are; arrhythmias, cardiomegaly, autonomic dysfunction and cardiac death. KF rings are reported in 44-62% of mainly hepatic disease, invariably seen in majority (95%) of cases of neurological presentation. In children KF rings are usually absent. However KF rings are not specific for WD, as it can be seen in chronic cholestatic diseases. Sun flower cataract is found in WD.[3,7,8] The acute episodes of coomb’s hemolytic anemia are reported in WD. Other manifestations are osteoarthritis, hypoparathyroidism, pancreatitis, infertility, and repeated abortions.[9,10] In the present case, the index case presented as hepatic form of WD with cirrhosis and its complication. KF rings were present. Insomnia and muscle spasm was present in late stage of the disease.

The investigations in WD are biochemical parameters, immunological markers, magnetic resonance imaging, neuropathological study and genetic analysis. Delay in diagnosis is mainly due to diagnostic errors. Biochemical evidence of hepatic dysfunction is defined by the presence of at least one of the following: Serum bilirubin ≥2 mg/dl, aspartate aminotransferase/alanine transaminase >100 IU/L, serum protein <5.5 g/dl and serum albumin <3.0 g/dl. Serum ceruloplasmin and uric acid are decreased; serum nonceruloplasmin bound copper and 24 h urinary copper excretion are usually increased. Combinations of biochemical tests reflecting disturbed copper metabolism is required for diagnosis than single test. Special stains like rhodamine, orcein or more sensitive Timms sulfur stain in liver biopsy reveal only lysosomal copper stores and it is positive only in 10% cases of WD. Hence hepatic parenchymal copper concentration of...
>250 μg/g of dry weight is the better biochemical evidence of hepatic copper overload than histochemical evaluation. Renal dysfunction is due to sepsis. Bone X-ray shows features of osteoporosis and fracture. Radiologically, basal ganglion, thalamus and cerebral hemisphere show hypodensity. Molecular diagnostic studies for disease specific ATP7B mutations on chromosome 13 can be detected in patients/first degree relatives and can be used for prenatal diagnosis. However genetic diagnosis is expensive. Grossly, brain shows cortical atrophy, especially frontal atrophy, atrophy of caudate/brain stem/crebrum, cystic changes in lentiform nucleus, putaminal softening, cavitation in white matter and ventricular dilatation. Cavitative lesion increases with duration of disease. Lenticular involvement is not universal as believed. Microscopic features are; reactive astrocytes, Alzheimer type II astrocytes, demyelination, Alzheimer type I astrocytes, decreased oligodendroglia, no inflammation/sparse histiocytes and pontine myelinolysis. Opalski cells in white matter are characteristics, also rarely seen in grey matter. Liver shows features of hepatitis, micro/macronodular cirrhosis and copper can be demonstrated in hepatocytes and Kupffer cells. The liver tissue may stain negative in early stages of the disease because of significant variation in the distribution of the metal. Spleen shows features of chronic venous congestion suggesting portal hypertension. Kidney shows features of focal tubular necrosis with protein cast. Urolithiasis, hydronephrosis (Wilson’s nephropathy) and bronchopneumonia are also reported. Autopsy features are heterogeneous and depends on variability of clinical presentation, severity, duration, compliance with decoppering treatment and cause of death of the disease.[1-4,7] The clinical diagnostic criteria of WD is KF rings in cornea confirmed by slit lamp, decreased serum ceruloplasmin, cupriuresis and hepatic pathology with copper deposition proved by special stains for copper.[9] In the present case, the index case had raised serum total bilirubin, liver tissue showed features of cirrhosis with copper deposits, spleen had congestive changes, right kidney showed acute tubular necrosis and left chronic pyelonephritis. The brain showed atrophic changes.

The incorrect diagnoses of WD are diverse and form the differential diagnosis. They are flat feet, myxedema, myasthenia gravis, encephalitis, multiple sclerosis, Parkinson’s disease, schizophrenia, depression, anxiety state, acute/chronic hepatitis/cirrhosis of any cause, etc.[6,9,3] WD is potentially treatable disease, however fatal if left untreated. The mean duration of therapy reported is 871.5 ± 1512.5 days (ranges from 0 to 3920 days).[11] There is always delay in diagnosis and start of treatment which is attributed to underestimation and lack of awareness, laboratory errors, evaluation of KF rings, absence of family history, lack of awareness about long term treatment, nonavailability of drugs in peripheral areas, cost of drugs, improper counseling of patients regarding the disease and the need for treatment. In the present case, treatment was taken only for a short duration due to financial constraints.

The screening tests in suspected cases are examination for KF rings, ultrasound examination of liver, serum copper/ ceruloplasmin and 24 h urine copper especially in asymptomatic sibs of index cases.[6] Early molecular genetic and biochemical studies can be done to confirm diagnosis. Natural course of the neurological form of WD with limited liver disease may progress rather slowly extending over a period of 20 years and has better life expectancy.[7] Untreated, the disease progress inexorably resulting in extrapyramidal disease and patient in bed ridden status. British anti-Lewisite and D-Pencillamine are likely therapeutics and orthotopic liver transplantation is lifesaving.[2-8] Hepatocellular carcinoma and cholangiocarcinoma complicating WD are also reported.[9] Since last century increased awareness, improved diagnostic facilities has resulted in early diagnosis in presymptomatic phase, distinction from mimics and with aggressive effective therapeutic approaches has decreased mortality and morbidity.[9]

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