Wilson’s disease (WD) is an autosomal recessive disorder of copper metabolism and regulation in the body, which presents with varied clinical symptoms commonly referable to hepatology (cirrhosis), neurology (dyskinesia and movement disorders), and psychiatry (abnormal behavior). The other systems, which may be involved, are endocrine (hypoparathyroidism), musculoskeletal (osteomalacia) and the genito-reproductive system (miscarriages and still births). We present a case, which was diagnosed as WD during evaluation of primary infertility and subsequently conceived after therapy with zinc.

**Key words:** Infertility, Wilson’s disease, pregnancy

**INTRODUCTION**

Wilson’s disease (WD) results from improper copper metabolism and is commonly characterized by progressive hepatic and neurological dysfunction. The disease was first described as a syndrome by Kinnier Wilson in 1912.[1] The disease results from a dysfunctional ATP7B gene resulting in decreased copper excretion and progressive accumulation in the body. Most common manifestations of the disease are due to the involvement of the liver[2] (transaminitis, acute liver failure, and cirrhosis), and the brain[3] (tremor, chorea, gait disturbances, dysarthria, depression, neuroses, and psychosis), but as the manifestations of the disease are varied there may be symptoms referable to other systems. Other lesser common manifestations include ophthalmic (Kayser–Fleischer [KF] rings, sunflower cataracts), bone and periarticular structures (osteomalacia, osteoporosis, and azure lunulae of the fingernails) and cardiac (myocardial copper accumulation, cardiomyopathy, and arrhythmias).[4] Some rare manifestations include hypoparathyroidism, infertility,[4] repeated miscarriages[5] and renal abnormalities (aminoaciduria and nephro-calcinosis).[6] We present a lady, with primary infertility, which was detected to have a nodular cirrhotic liver on laparoscopy. Subsequent evaluation revealed WD and she conceived with therapy with zinc.

**CASE REPORT**

A 23-year-old female, married for 5 years, had presented to our center for inability to conceive. She had been evaluated at another hospital where ovulation induction was unsuccessful. The husband’s semen analysis was normal. There was no other significant history. On examination, her vitals were stable and the systemic examination was normal. The hemogram was normal and the metabolic parameters revealed slightly elevated aspartate transaminase (56 IU/L, reference range: 5-40 IU/L) and alanine transaminases (68 IU/L, reference range: 7-56 IU/L). She was taken up for laparo-hysteroscopy, which revealed normal uterus, tubes, ovaries, and an intact tubo-ovarian relationship without any evidence of endometriosis/adhesions. Laparoscopic chromo-perturbation demonstrated bilateral spill indicating patent fallopian tubes. She was noted to have nodular cirrhotic liver and was referred for cirrhotic liver to our center. She denied any history of jaundice, hematemesis, melena, abdominal distension, oliguria, altered sensorium, palpable lump, or pain abdomen. Ultrasonography of abdomen showed a liver with coarse echotexture with surface nodularity. The spleen was 9.6 cm. There was no ascites or collaterals. Blood flow along the spleno-portal axis was normal. Upper gastro-intestinal endoscopy showed portal hypertensive gastropathy at the fundus, but no varices, ulcers, growth, or stricture. Twenty four hours urinary copper (30 mcg/day, reference range < 40 mcg/day) and serum copper (90.6 mcg/dl, reference range: 70-140 mcg/dl) were normal, but the serum ceruloplasmin (7.3 mg/dl, reference range: 20-40 mg/dl) was low. Psychological test reporting did not show any cognitive deficit. Anti-nuclear antibody was negative and ferritin levels were normal. Magnetic resonance imaging brain...
was normal. A liver biopsy was done [Figure 1], which confirmed cirrhosis and the histological findings were consistent with diagnosis of WD. She was counseled for sibling evaluation when she revealed her brother's illness in 1995, which started with tremors of tongue, slurring of speech and a change in handwriting. Perusal of his documents showed him to be having KF ring and a sunflower cataract and confirmed him as a case of WD. She was started on zinc sulfate for WD and followed-up. Over the next 6 months, the tranaminases normalized and she finally conceived.

DISCUSSION

Wilson’s disease is genetic disorder characterized by Mendelian autosomal recessive inheritance. It affects between one in 30,000 and one in 100,000 individuals.[5] The disease is characterized by a genetic defect in ATP7B gene. ATP7B gene has dual synthetic and excretory function. It causes transportation of copper into the Golgi compartment, incorporation into ceruloplasmin and excretion of excess stores into the bile. Defective ATP7B function results in decreased excretion and progressive accumulation of copper in various organs of the body, which results in hepatic and neurological dysfunction. WD also affects a number of other organ systems, but less commonly when compared to the liver and the brain. Furthermore, the liver may be affected in various ways, which include asymptomatic quiescent disease, acute hepatitis, acute liver failure, asymptomatic cirrhosis and decompensated cirrhosis. The disease is easily diagnosed in proper clinical settings, but becomes increasingly difficult to suspect if it present otherwise.

Menstrual irregularities, repeated abortions and miscarriages are common obstetrical and gynecological complication of WD, but procreation disability and infertility has not been very commonly described in WD.[5,7] Our patient had presented primarily with infertility and did not have any symptoms or signs attributable to dysfunction of the liver or the brain. She was incidentally detected to have a nodular liver and subsequently diagnosed to have WD. There have been reports of successful therapy of WD and conception following treatment.[8] We treated our patient and the patient conceived as a result of successful therapy.

The treatment of WD involves a number of drugs and the choice becomes important point to remember, especially in women of child bearing age. Chelating agents bind excess copper. The various chelating agents recommended for treatment of WD are ammonium tetrathiomolybdate (as an initial treatment for patients who present with neurologic or psychiatric manifestations), penicillamine (a drug of choice before newer regimens were available and always to be used with pyridoxine as it causes pyridoxine deficiency), trientine (an oral chelator used to induce cupruresis especially in penicillamine intolerant patients or if the initially presentation is hepatic) and dimercaprol (for refractory cases of WD). The side-effects of the drugs and the teratogenic effects of the therapy should be borne in mind. Zinc at very high doses is associated with preterm deliveries and stillbirths especially if used in the third trimester. Penicillamine on the other hand is not preferred in pregnancy due to interaction with pyridoxine metabolism[6] and potential teratogenicity. Breast feeding women should not take penicillamine. The data about the other drugs used to treat WD is limited in relation to pregnancy, child birth and breast feeding.

CONCLUSION

Wilson’s disease is a rare cause of infertility and may coexist with an asymptomatic liver involvement and should be investigated for in a woman with cirrhosis and infertility. It is also useful to remember that the treatment of women of child bearing age should be planned after giving due cognition to the teratogenicity of the agents available.

REFERENCES


Figure 1: Classical features of Wilson’s disease in the form of steatosis and portal inflammation with glycogenated nuclei (a), spotty necrosis (b), bile ductular proliferation (c), and irregular nodularity (d) indicating cirrhosis

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