Wilson's Disease: Analysis of 10 Cases and The Need for Liver Transplantation

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Summary: *Though not so common, Wilson's Disease (WD) is an important cause of the end stage liver disease in Türkiye. It was diagnosed eight hundred and thirty-two patients diagnosed to be cirrhotic in the last fourteen years in the Hacettepe University Hospital, Ankara, and ten of them were proven to be suffering from WD. These ten patients were followed-up and treated appropriately, but because of intractable cirrhotic complications, liver transplantation had to be performed in three of them.*

Key Words Wilson's Disease (WD), Extra Pyramidal System (EPS), Liver Transplantation

Once it was thought that, ceruloplasmin deficiency was responsible for the WD. However, now, an unknown defect in the biliary excretion of copper (probably a lysosomal defect) seems to be the cause of the disease. As a result of this, copper starts to accumulate in tissues, especially in the liver, brain, kidneys, and cornea. After a certain period of time, the patients with WD have difficult time, struggling with cirrhosis, Fanconi syndrome, non immune hemolytic anemia and Extra pyramidal System (EPS) dysfunction etc. In this article, we tried to explain the course of the disease in 10 Turkish patients with WD, and would like to stress on the fact that, with good therapy and follow up, WD is not so scaring.

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MATERIAL and METHOD

In the last fourteen years, 832 cirrhotic patients were diagnosed and treated in the Hacettepe University Hospital, Ankara-Türkiye 10 of them were proven to be patients with WD (with serology, liver biopsy, signs and symptoms, Kayser-Fleischer rings etc.). These ten patients with WD were followed in our out-patient's clinics, at least with three months intervals, and were hospitalized whenever needed (ex.for liver biopsy, hepatic coma, seizures, variceal bleeding). D-penicillamine (1-1.5 gr./day in 4 divided doses, i.e. before meals and at bed time), and for one patient we tried triethyl tetramine (triene). Along the course of the disease, sometimes we had to use antiepileptics, neuroleptics, diuretics too.

We worked in coordination with neurologists, who examined and followed the WD patients for EPS dysfunction; with ophtalmologists, who tried to determine the presence of the Kayser-Fleischer rings using slit-lamp examination; and with the psychiatrists who examined and followed the patients for psychiatric signs and symptoms.

Routine labaratory tests were performed for every patient (i.e. complete blood count, peripheric blood smear, urine analysis, erythrocyte sedimentation rate, liver and kidney function tests). Also, we performed tests for infectious hepatitis, serum ceruloplasmin, serum and urinary copper levels, anti-

mitochondrial and anti-smooth muscle antibodies.

For the anemic patients, we performed direct and indirect Coomb's tests and determined the serum haptoglobulin level, serum direct and indirect bilirubin, LDH levels in addition to the tests mentioned before. Liver biopsy was taken from all of the patients with WD (to take the liver biopsy the patients with WD were hospitalized and if the prothrombin time was above normal we infused plasma to normalise the prothrombin time and then performed liver biopsy). The biopsy specimens were examined for copper content and morphology too.

Esophagography, and if needed, gastroesophageal endoscopy were performed too, to grade the esophageal varices and to perform sclerotherapy.

At the first application, the patients were divided into two categories. Those applying with neurologic signs and symptoms or those with signs and symptoms attributable to hepatic involvement.

RESULTS

A t the first application, the chief complaint of the patients were either icterus (patients no. 1,2,5 and 8) or complaints attributable to EPS involvement (patients no. 4,6,7,9 and 10) or both (patient no. 3). The patients in the icteric group were found to have high bilirubin levels. Both the direct and indirect bilirubin levels were 5.4 and 2.8 mg/dl respectively. The serum levels of the transaminases reached only 2-3 times the normal value as the disease progressed. The total serum protein and albumin levels were low (the mean values being 6 and 1.9 mg/dl. respectively). The prothrombin time was elevated in all of patients, but it was only minimally so in the ones who applied with dysarthria, mask face i.e. EPS involvement.

Kayser-Fleisher rings were present in the corneas of all the patients. The serum ceruloplasmin level was low in all of the cases and the serological tests for infectious causes of hepatitis were always negative. None of the patients had anti-mitochondrial or anti-smooth muscle antibodies, but 24 hours urinary copper was always high. The mean values for serum ceruloplasmin and 24 hours urinary copper levels were 12 mg/dl and 184 microgram/ respectively.

Out of the 4 icteric patients, 3 had esophageal varices of grade 3 or 4 and 2 of them bleeded. These two were hospitalized and using Sangstaken-Blackmoore tubes, endoscopic sclerotherapy and blood transfusions they were treated. However, these two patients after being followed for 2 and 11 years had to undergo liver transplantation in the end.

Two patients who admitted because of yellow skin and sclera, developed EPS involvement one after 2 years and the other after 11 years. Only two patients were hospitalized because of hepatic coma, and their chief complaint was yellow skin and sclera on the first application. These two (one having EPS involvement too) had all signs of the cirrhosis i.e ascites, esophageal varices, edema, spider angiomata etc., and thus we had to use the appropriate therapy for them.

One patient, patient number 3, was complaining of both icterus and dysarthria on the first application. He was a young male who suffered from very severe course and he developed esophageal varices of third degree, ascites, general edema, psychiatric symptoms, and his prothrombine time was once 23 when he bleeded, requiring 5 units of blood transfusion for 48 hours, in that period he was in hepatic coma too. He had renal involvement (with a proteinuria of 0.5gr/day) and a positive family history too. Finally, 10 years after the first application, he had a liver transplan-

Table I: Shows age and sex distrubition, and first clinical presentation

PATIENT No.	AGE (yrs.)	SEX	CHIEF COMPLAINTS	FOLLOW UP (yrs.)	HEPATIC TRANSPL.
1	36	F	Icterus	3	yes
2	11	M	Icterus	14	no
3	22	M	Icterus-EPS involvement	10	yes
4	15	F	EPS involvement	7	no
5	8	F	Icterus	11	yes
	37	F	EPS involvement	9	no
7	13	M	EPS involvement	14	no
8	11	F	Icterus	14	no
9	32	M	EPS involvement	9	no
10	4	M	EPS involvement	22	no

tation. He is in good healt.

Patient number 5. (icteric at the first application) was the only patient with WD who had hemolytic anemia. The hemolysis was proven to be Coomb's negative, and this girl, after hepatic transplantation is now free of any symptoms.

Five patients (patients no. 4,6,7,9 and 10) had EPS involvement on the first application. Besides copper free diet and D-penicillamine, they were also given neuroleptics too. With these drugs, only one of them is having a difficult time who was hospitalized ten times in fourteen years, because of focal motor epilepsy. None of these five patients had problems due to decreased hepatic reserve.

The patients were from 4 to 37 years old on the first application and the follow up-period was ten years on average. As for the family history, three of the patients had WD in the first degree relatives. On the other hand, another three had first degree relatives who died of cirrhosis of unknown cause.

Liver transplantation had to be performed for three patients in our study (patients no. 1,3 and 5). Two of them are in good condition one year after the transplantation, but patient no. 1 died due to a post-transplantation complication.

DISCUSSION

In the last fourteen years, we diagnosed and treated patients with WD in Hacettepe University Hospital, Ankara. In all of them the serum ceruloplasmin levels were low, twenty-four hours urinary copper excretions were high, their liver biopsies revealed copper deposition with cirrhotic changes and they all had Kayser-Fleischer rings.

Our hospital, Hacettepe University Hospital, is the reference hospital of the Central Anatolia (a region where about fifteen million persons live), and if we think about the small number of patients with WD diagnosed in the last fourteen years, we can easily see that it

Table II: Shows family history and main complication of ten Wilson's Diseas

PATIENT NO.	FAMILY HISTORY	HEPATIC COMA	ESOPHAGEAL VARICES	GIT BLEEDING
1	Negative	yes	grade 4	yes
2	Brother died of cirrhosis	no	negative	no
	Sister WD	yes	grade 3	yes
4	Brother WD	no	negative	no
5	Negative	no	grade 4	yes
	Negative	no	negative	no
	2 brothers died of cirrhosis	no	negative	no
	Negative	no	negative	no
9	Sister died of GIT bleeding	no	negative	no
	2 brothers WD	no	negative	no

can not represent the real incidence of the disease in Turkiye. When we asked the ten patients with WD about their first degree relatives, we discovered that six of them had first degree relatives diagnosed to be either patients with WD or cirrhotic. Because of this we started to perform a screening program for the families or cirrhotic patients and its results will be presented in another article.

It was used drugs, namely D-penicillamine, triethyl tetramine (triene) and zinc salts. First two drugs chelating agents and act by increasing the urinary excretion of free copper (increased cupriuresis). On the oher hand, zinc salts limits the absorption of copper through the gastrointestinal tract.

D-penicillamine, though the first drug available for the WD, is still the most used one. In our series we used it 250 mg four times daily, 30 min before meals and at bed time for all the patients with WD and we did not come across any of its side effects (fever, urticaria, rash, nephrotoxicity, thrombocytopenia, leukopenia, SLE like syndrome etc). Since D-penicillamine has an antipyridoxine effect in animals, additionly 25 mg/day of vitamine B6 was also given to the patients taking D-penicillamine.

From time to time we used zinc salts when symptoms seem to go out of control, but for most of the time, D-penicillamine was effective enough to control the disease.

In one particular patient, we had to use triene because he insisted on taking drug very much. However, as a result of severe neurological side effects we had to stop it and after reconstituting the D-penicillamine therapy he was fine again.

The main defect in WD is most probably in the liver. More specifically, in the biliary system, so that copper excretion can not occur properly. This brings into mind a question what happens if we remove the defective liver and transplant a healty one? In our study, liver transplantation was performed for three patients, because of intractable hepatic problems i.e hepatic coma and variceal bleeding 2 of these 3 are still alive one year after the transplantation without being treated for the WD.

Liver transplantation will be for sure the mighty solution for the WD in the future. But for the time being, we recommend it for the intractable cases only, because we see that many patients are doing well with the anti WD drugs, and yet another reason is that, transplantation carries its risks too much to perform it as the treatment of choice for the WD patients.

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