WILSON'S DISEASE - A CASE REPORT WITH CURRENT STATUS AND MANAGEMENT

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Wilson's disease (WD) is an autosomal recessive inherited disorder of copper metabolism. The condition is characterized by excessive deposition of copper in the liver, brain, and other tissues. The worldwide incidence rate is 10-30 million cases per year. The diagnosis is made by measuring serum ceruloplasmin, urinary copper excretion, and hepatic copper content, as well as the detection of Kayser-Fleischer rings. The mainstay of therapy is copper chelators like D-Pencillamine and Trientine for reduction in body copper to sub-toxic levels. This case report tries to give an insight into the clinical features, diagnosis and management of WD with special emphasis on the dental management that may be taken during the treatment of the same.

Key words: Wilson's disease, D-pencillamine, Aplastic anemia, gingival bleeding

INTRODUCTION

Wilson's disease (WD) is an autosomal recessive inherited disorder of copper metabolism. The condition is characterized by excessive deposition of copper in the liver, brain, and other tissues. The major physiologic aberration is excessive absorption of copper from the small intestine and decreased excretion of copper by the liver.[1] The worldwide incidence rate is 10-30 million cases per year, with increased rates in areas of consanguinity. Disease affects approximately one in 30,000 people worldwide. WD is now one of the leading liver diseases in children in India. [2]

Intestinal copper absorption and transport into hepatocytes is intact in WD. But, the processes of incorporation of copper into ceruloplasmin and excretion of excess copper into bile are impaired. The transport of copper by the copper-transporting P-type ATPase is defective in WD secondary to one of several mutations in the *ATP7B* gene. Initially, the excess copper is stored in the liver and causes damage to the hepatocytes. Eventually, as liver copper levels increase, it is released into the circulation and deposited in other organs.

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Copper begins to accumulate immediately after birth. Excess copper attacks the liver or brain, resulting in hepatitis, psychiatric, or neurologic symptoms. The symptoms usually appear in late adolescence. Patients may have jaundice, abdominal swelling, vomiting of blood, and abdominal pain. They may have tremors and difficulty walking, talking and swallowing. They may develop all degrees of mental illness including homicidal or suicidal behavior, depression, and aggression. Women may have menstrual irregularities, absent periods, infertility, or multiple miscarriages. No matter how the disease begins, it is always fatal if it is not diagnosed and treated.

The tests can diagnose the disease in both symptomatic patients and people who show no signs of the disease. These tests can include:

- Ophthalmologic slit lamp examination for Kayser-Fleischer rings
- Serum ceruloplasmin test
- 24-hour urine copper test
- Liver biopsy for histology and histochemistry and copper quantification
- Genetic testing, haplotype analysis for siblings and mutation analysis.

WD is a very treatable condition. With proper therapy, disease progress can be halted and oftentimes symptoms can be improved. Treatment is

aimed at removing excess accumulated copper and preventing its reaccumulation. The mainstay of therapy is copper chelators like D-Pencillamine, and Trientine for reduction of copper to sub-toxic levels in the body. D-Pencillamine binds to copper and forms a stable compound that is then released in urine. But chronic usage of this drug depletes pyridoxine or Vitamin B_6 from the body and other side effects range from minor disturbances to severe or life threatening complications, such as aplastic anemia, immune complex nephritis, systemic lupus erythematosus or worsening of neurological symptoms.[3]

This case report tries to give an insight into the clinical features, diagnosis, and management of WD with due emphasis on the distinctive considerations during dental management of the same.

CASE REPORT

A female patient, aged 21 years was referred from the Department of Neurology, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, India to the Department of Periodontics, Government Dental College & Research Institute, Bangalore, India (June 2005) for the evaluation of bleeding gums.

Medical history revealed that she was previously healthy, right-handed female leading a normal life. Suddenly, on a fateful day (Jan 2004), she awoke that morning with drooling and mumbling for several minutes, with her eyes fixed to one side associated with abrupt onset of focal neurologic signs involving her right side. The right arm and leg had abnormal posturing, followed by hemiparesis. Electroencephalogram revealed mild generalized slowing with occasional sharp discharges. A second identical episode 5 months later (June 2004) occurred (with milder hemiparesis, but lasting 12 hours), and the patient was put on antiepileptic medication (phenytoin sodium 100mg, twice daily). Further, her parents observed a change in her speech (more rapid, minimally audible, with poor articulation), increased fidgetiness, altered handwriting, and clumsiness over the intervening for five months.

An extensive evaluation for vascular and nonvascular etiologies of possible stroke was unrevealing. After the second presentation with hemiparesis, choreiform movements and abnormal facies were observed.

At that point, additional diagnostic testing indicated a low ceruloplasmin, a low serum copper, normal hepatic transaminase, and an elevated 24-hour urine copper, all highly suggestive of WD. (Table 1)

Table 1

	Normal Value	In Patient
Serum Ceruloplasmin	18-35 mg/dL	2 mg/dL
Serum Copper	75-160 ì g/dL	14 ì g/dL
Serum Glutamate Pyruvate Transaminase	5-40 IU/L	36 IU/L
Urine Copper	20-53 ì g/ 24 hours	131 ì g/ 24 hours

Ophthalmologic examination confirmed Kayser-Fleisher rings, which are golden or greenish, brown rings around the cornea of the eyes due to copper deposition.[4] (Fig 1)

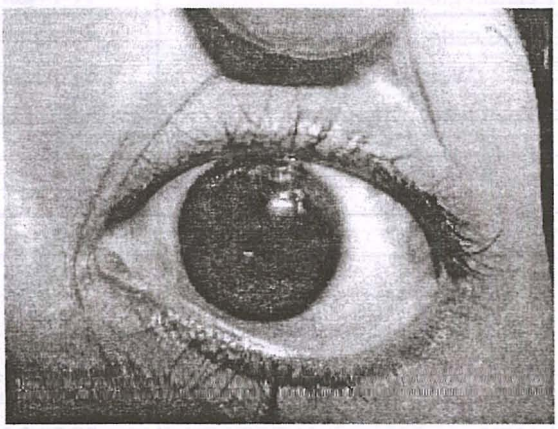


Figure 1: Kayser-Fleisher rings, which are golden or greenish, brown rings around the cornea.

Based on these findings, a diagnosis of WD was arrived at and anticopper therapy in the form of D-Pencillamine (250 mg, twice daily) was advised (June 2004).

She returned to the clinical research center (NIMHANS) for a follow-up examination one year after the initial anticopper therapy in May 2005. She had significant improvement in her clinical symptoms; her speech was less dysarthric, her choreic movement had subsided and was able to ambulate on her own and resume oral feedings.

After one year anticopper therapy, her parents noticed that there were bleeding gums while brushing for the first time, which prompted them to seek medical attention. On intra-oral examination her periodontal findings were as follows: oral hygiene index simplified[12] (2.2); modified gingival index score[5] (1.8), and modified sulcus bleeding index (mSBI) score[6] of 2.2. This showed that the bleeding from gingiva on probing may be due to the local factors present in lieu of her physical inability to maintain oral hygiene or to some other variable, probably leading to gingival bleeding.[7] An orthopantomograph was advised as an initial diagnostic radiograph, which revealed generalized crestal bone loss but specially in the maxillary and mandibular anterior teeth region, widened periodontal ligament space around teeth # 17, 16, 12, 11, 21, 31, 41, 42, 43. (Fig. 2) Hematological investigations are shown in Table 2. Aplastic anemia (notably thrombocytopenia) was evident from the patient's blood picture, which could be attributed to chronic use of D-Penicillamine.[8]

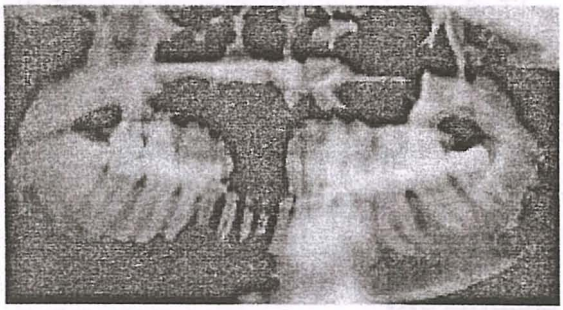


Figure 2: Orthopantomograph showing minimal crestal bone loss in the right and left posterior teeth region, normal periodontal ligament space, unaltered trabecular pattern, intact lamina dura and normal alveolar bone height in other areas

TABLE 2

	Normal Value (in Female)	In Patient
Haemoglobin	11-14 gm%	11.2 gm%
RBC count	4.5 ± 1 million/cmm	3.48 million/cmm
ESR (Westergren's)	0-7 mm/hr	32 mm/hr
Total leukocyte Count	4,000-11,000/cmm	6,300/cmm
Differential count Neutrophil	40-75%	70%
Lymphocyte	20-45%	25%
Eosinophil	1-8%	4%
Monocyte	2-10%	1%
Basophils	0-1%	0%
PCV	36-47%	32%
MCV	86 ± 10 cubic microns	92.1 cubic microns
MCH	29.5 ± 2.5	32%
MCHC	33 ± 2 picogram	34.9 picogram
Platelet count	1.5-4.5 lakh/cmm	1.04 lakh/cmm

With consent from the patient's physician, a thorough scaling and root planing was performed as a prophylactic measure and strict oral hygiene instructions were given both to the patient and her parents along with chlorhexidine mouth rinse 0.12% twice daily. During the patient's next visit, after 1 month gingival bleeding was evident but was substantially reduced as indicated by the mSBI scores (2.2 to 0.8). (Fig 3 & 4) After 6 months she returned with excellent soft tissue profile. (Fig 5) There was a fractured incisal edge of # 11 which was later on restored with tooth colored restorative material.

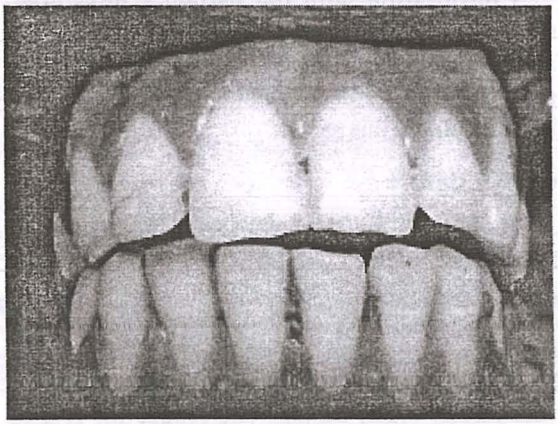


Figure 3: Initial clinical presentation of the case showing poor oral hygiene maintenance.

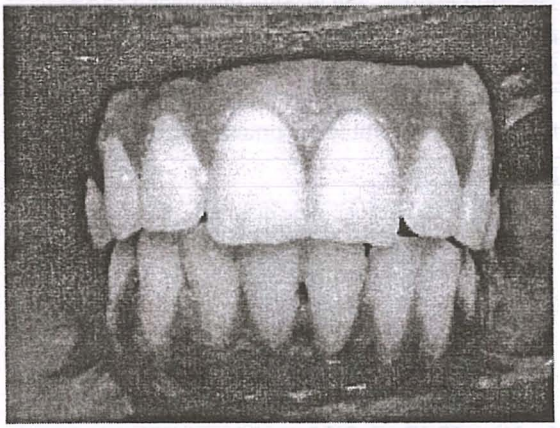


Figure 4: Clinical photograph after treatment (1 month) with supragingival scaling.

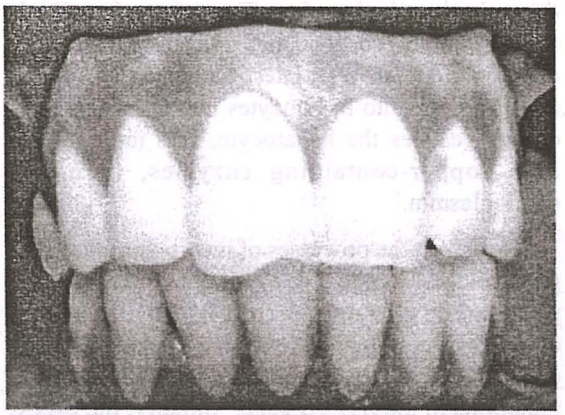


Figure 5: Clinical photograph after treatment (6 month) with supragingival scaling.

The important modifications recommended to be considered while treating patients with WD includes:

1. Behavioral problems: These patients show behavioral problems (highly uncooperative, nagging etc) necessitating the presence of attendants during their treatment.
2. Chair position/ patient positioning: Normal semi-reclined position is not advisable for these patients as they lack proper reflexes and have limited control over their musculature, particularly their pharyngeal musculature. Therefore, keeping the patient in an upright position will be helpful in preventing the seepage of fluids into the oropharynx. The use of high vacuum suction is highly recommended.
3. Use of mouth props: Mouth props may be helpful in assisting the patient in keeping the mouth open during the course of treatment and also aids proper instrumentation.
4. Oral hygiene maintenance: Strict plaque control regimen including an adjunctive prophylactic 0.12 % chlorhexidine gluconate oral rinse is indicated in such cases.

DISCUSSION

Copper is an important component of several metabolic enzymes, including lysyl oxidase, cytochrome c oxidase, superoxide dismutase, and

dopamine beta-hydroxylase. The estimated total body copper content is 50-100 mg, with an average intake of 1-2 mg/day. In WD, intestinal copper absorption and transport into hepatocytes is unaffected. After copper reaches the hepatocyte, it is incorporated into copper-containing enzymes, including ceruloplasmin.[3]

However, the processes of incorporation of copper into ceruloplasmin and excretion of excess copper into bile are impaired in WD. The transport of copper by the copper-transporting P-type ATPase is defective in WD secondary to one of the several mutations in the *ATP7B* gene.[9] Initially; the excess copper is stored in the liver and causes damage to the hepatocytes. Eventually, as liver copper levels increase, it is released into the circulation and deposited in other organs, particularly the basal ganglia of brain, cornea of eyes (Kayser- Fleischer rings) and kidneys. Thus, WD is also known as hepatolenticular degeneration.

All patients with WD, symptomatic or asymptomatic, require treatment. Therapy can be divided into two phases. In the initial phase, efforts are directed towards bringing toxic copper levels back to the normal range. A copper-poor diet and ingestion of zinc sulfide with each meal reduce copper absorption from the intestine. Till date, D-pencillamine is the drug of choice, which acts as a copper chelator that increases its urinary excretion. Unfortunately, adverse reactions of this drug, including worsening of neurological symptoms, aplastic anemia leading to bleeding tendencies, etc are seen in about 25 per cent of the patients.[10] It is important from the clinical point of view to get thorough blood investigations along with physician's consent before starting treatment procedures to avoid any intra or post- operative complications.

In the present case, spontaneous bleeding from the gingiva may be presumed to be caused by the inflammation associated with local factors secondary to the D-pencillamine-induced aplasic anemia.

Recently, many neurologists advocate initial therapy with ammonium tetrathiomolybdate in the management of WD. This molecule is known to form a tripartite complex with copper and protein, blocking copper absorption from the intestine, and thus renders blood copper less toxic.[11] Latest FDA-approved drug is zinc acetate. Zinc acts by blocking the absorption of copper in the intestinal tract. This action both depletes accumulated copper and prevents its reaccumulation.

In subsequent phase of therapy normal serum copper level is maintained by oral administration of zinc acetate, which appears to be the treatment of choice after the initial goals are accomplished.[11]

Consultation with the patient's physician, tetrathiomolybdate is now being considered for usage to avoid the various neurological complications and bleeding tendencies due to the use of D-Pencillamine in this patient.

CONCLUSION

In view of the given incidence of WD in general population, it is not very rare to come across these patients in routine clinical practice. Hence, it is essential to consider WD in patients with unexplained hepatic, neurological, and psychiatric dysfunction, because, appropriate early medical treatment can prevent further organ damage and reduce the risk of permanent damage to the liver and brain. The dental surgeon is expected to be capable of diagnosing the disease based on the clinical presentation, medical and drug history, and be able to manage and predict any complication like bleeding tendencies that he may encounter during the management of these patients. In this context the above mentioned recommendations can be helpful to the practicing dental surgeon.

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