Dental considerations in the patient with Wilson’s disease

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Wilson’s disease was described by Wilson in 1912. It is an autosomal recessive disorder caused by mutations in the ATP7B gene, a membrane-bound copper transporting ATPase. The deficiency of ATP7B protein impairs the biliary copper excretion, resulting in positive copper balance, hepatic copper accumulation, and copper toxicity from oxidant damage. The disease is a form of copper poisoning caused by a defect in the transport of copper that renders the patient unable to handle trace amounts of copper normally present in the diet and hence the clinical manifestations are those typically caused by copper toxicity and primarily involve the liver and the brain. Because effective treatment is available, it is important to make an early diagnosis. In this article, a review of clinical aspects of Wilson’s disease, and its impact on dental management and dental considerations are discussed. (Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;111:20-23)

Wilson’s disease was described by Kinnier Wilson in 1912, who named it “hepatolenticular degeneration.” This is a rare but important condition in which the total body copper is increased, with deposition of excess copper in several organs, consequently leading to organ damage.1,2 Copper is an integral part of numerous enzyme systems, including amine oxidases, ferroxidase (ceruloplasmin), cytochrome-c oxidase, superoxide dismutase, and dopamine hydroxylase. It plays a role in iron metabolism, melanin synthesis, and central nervous system function; synthesis and cross linking of elastic and collagen; and the scavenging of superoxide radicals. Copper is absorbed in the proximal small intestine and about 90% of circulating copper is bound to ceruloplasmin. The body contains 50 to 120 mg of copper and higher concentrations are found in liver, brain, heart, spleen, kidney, and blood. An average diet provides a substantial amount of copper, typically 2 to 5 mg/d; the recommended intake is 0.9 mg/d. Copper is primarily excreted in the feces and in smaller amounts in urine.3,4 Excessive accumulation of copper in the tissues will give rise to various signs and symptoms.

EPIDEMIOLOGY, ETIOLOGY, AND PATHOGENESIS

Wilson’s disease is relatively rare. Its prevalence is estimated at 30 per 1 million standard population with pockets of higher prevalence in Northern India and Sicily.1,5 It is a familial disorder occurring in an autosomal recessive pattern. Only homozygous autosomes produce symptoms. The gene responsible is on chromosome 13, and has been designated as adenosine triphosphatase (ATP7B), with multiple genome muta-
ATP7B is a membrane-bound copper-transporting ATPase. The deficiency of ATP7B protein impairs biliary copper excretion, resulting in positive copper balance, hepatic copper accumulation, and copper toxicity from oxidant damage. Excess hepatic copper is initially bound to metallothionein, but as this storage capacity exceeds, liver damage begins as early as 3 years of age. Defective copper incorporation into apoceruloplasmin leads to excess catabolism and low blood levels of ceruloplasmin. Serum copper levels are usually lower than normal because of low blood ceruloplasmin, which normally binds more than 90% of serum copper. As the disease progresses, nonceruloplasmin serum copper (“free” copper) levels increase, resulting in copper build up in other parts of the body, such as the brain, leading to neurologic and psychiatric disease.

CLINICAL PRESENTATION
Onset of Wilson’s disease as early as 4 years of age and as late as the fifth decade of life has been reported. It occurs equally in males and females. As copper initially accumulates in the liver, patients with hepatic symptoms are younger than those with extrahepatic symptoms. The first manifestation of nervous system involvement is usually a decline in intellectual function. Deterioration in schoolwork is a frequent early sign. Patients have difficulty focusing on tasks, but cognition is not usually grossly impaired. The patient may later become depressed and withdrawn and exhibit some slowness of movement, loss of facial expression, and slurring of speech. A tendency to keep the mouth open constantly is often noted. Patients who first have symptoms in childhood tend to have dystonic and athetoid features, whereas those who first have symptoms after childhood have dysarthria and a tremor of the hands. Muscular rigidity and bradykinesia may then develop, leading to a clinical picture resembling that of Parkinson’s disease; Wilson’s disease is an important cause of juvenile Parkinsonism. The Kayser–Fleischer ring, a golden-brown ring of pigmentation at the outer margin of the cornea (Fig. 1), is almost always present in patients with neurologic manifestation.

DIAGNOSIS
Wilson’s disease should be considered in any individual with liver abnormalities of uncertain cause and those with new-onset movement disorders. The Kayser–Fleischer ring is the most important single clinical clue to the diagnosis and it can be seen in most patients presenting in or after adolescence. Liver biopsy quantitative copper concentrations (more than 250 μg/g of dry liver) remain the best biochemical evidence of Wilson’s disease. A low ceruloplasmin (normal laboratory range 0.2 to 0.5 g/L), and 24-hour high urinary copper excretion (more than 100 μg/24 h) are the best laboratory clues to the diagnosis and treatment of Wilson’s disease. If neurologic signs and symptoms are present, then computed tomography (CT) scan or magnetic resonance imaging (MRI) is recommended. Family screening of first-degree relatives must be undertaken. Whenever possible, genetic study should be carried out to confirm the diagnosis, especially in patients with indeterminate clinical and biochemical features. Infants should not be tested until after 1 year of age because ceruloplasmin levels are normally low in the first year.

MEDICAL MANAGEMENT
Even in asymptomatic cases, the specific treatment should begin as soon as the diagnosis is established. The goal of therapy is to remove copper from the tissues and to prevent its reaccumulation. Prognosis is excellent provided treatment is started before there is irreversible damage.

Restriction of dietary copper
Shellfish, organ meats, legumes, chocolate, nuts, dried fruits, mushrooms, and areca nuts should be avoided. A substantial amount of copper is released from areca nut products. Antioxidants like Oxigard (Glenmark Pharmaceuticals Ltd., Mumbai, India) and Oxiban (Medley Pharmaceuticals Ltd., Mumbai, India) contain copper sulfate as one of the constituents, hence their consumption should be avoided.

Copper removal
Copper removal can be achieved with a chelating agent, such as penicillamine, but it does not play a
major role in treatment because of its toxicity. If the patient has only hepatic involvement and there is no evidence of decompensation, zinc, 50 mg 3 times a day, is recommended. Zinc decreases copper absorption from the small intestine and also promotes fecal copper excretion. If there is mild to moderate hepatic decompensation, trientine 500 mg twice daily and zinc can be advised. The trientine treatment requires monitoring because of the potential for narrow suppression and proteinuria. Complete blood counts, standard biochemical profiles, and urinalysis should be performed at weekly intervals for a month, followed by 2-week intervals for 2 to 3 months, then at monthly intervals for 3 to 4 months, and at 4- to 6-month intervals thereafter. Zinc alone has been advocated for presymptomatic and asymptomatic patients. There is a need for a lifelong follow-up by a specialist unit to monitor the clinical progress. 

**DENTAL MANAGEMENT IN THE PATIENT WITH WILSON’S DISEASE**

In general, one third of the patients with Wilson’s disease have liver disease, one third have neurological impairment, and one third have both. 

**Management of patients presenting in acute stage**

In Wilson’s disease, copper initially accumulates in the liver; therefore, patients presenting in the acute stage show liver involvement and are of significant interest to the dentist because the liver plays a vital role in metabolic functions, synthesis of coagulation factors, and drug metabolism. Hence, it is important to suspect and inquire about any bleeding tendency. Laboratory evaluation before any surgical or periodontal procedures should be directed at bleeding parameters. Various tests, such as complete blood counts, coagulation studies, liver function tests, and kidney function tests, should be carried out before general anaesthesia or surgery. Most of the amide local anesthetics used in dental practice undergo biotransformation in the liver. Agents, such as sedatives and general anesthetics, are potentially dangerous in liver disease mainly because of impairment of detoxification. Therefore, less hepatotoxic agents, e.g., enflurane, sevoflurane, can be used. Severe bleeding can occur after dental extractions in patients with chronic liver disease. If surgery is required in such patients, discussion with the physician is necessary. A perioperative infusion of fresh frozen plasma is often required and intravenous injection of vitamin K corrects the problem. The drugs metabolized by the liver, e.g., fluconazole and paracetamol, should be used in decreased dosage, as at higher doses these drugs are hepatotoxic. Erythromycin, miconazole, metronidazole, nonsteroidal anti-inflammatory drugs, and tetracycline are avoided if possible and consequently consulted with the patient’s physician.

Patients presenting in the acute stage may show neurological impairment along with liver involvement and may simultaneously present with tremors, choreoathetosis, dystonia, parkinsonism, and dementia. Orthostatic hypotension and rigidity are common in these patients. To reduce the likelihood of a fall from the dental chair, the patient should be assisted to and from the dental chair. Because of dysphasia and an altered gag reflex, the patient must be treated in the upright position. Special precautions must be taken to avoid the aspiration of water or materials used during dental procedures. At the end of each appointment, the chair should be inclined slowly to allow for reequilibration. Patients having a clinical picture resembling that of Parkinson’s disease have excess salivation, which can cause difficulty in visibility, leading to problems not only in administering anesthesia but also in providing the treatment. In addition, anxiety in these patients can increase both the tremor and the degree of muscle rigidity. The antimuscarinic antiparkinsonian drugs reduce the salivation and degree of tremor but can produce taste disturbances and dry mouth, which might increase caries incidence. The consequent root caries and recurrent decay must be diligently treated. Patients also often have difficulty in maintaining their dentition because of their physical disability. For all these reasons, frequent recalls may be necessary after the dental treatment is over. Drug interactions of concern to dentistry like epinephrine vasoconstrictors should be used with caution and the dose should be limited. Erythromycin should not be given to patients taking the dopamine agonist, pramipexole. The clinician should be aware that antiparkinsonian drugs can be central nervous system depressants, and the sedative prescribed for dental treatment can have an additive effect.

**Management of patients presenting in chronic (maintenance) stage**

If the related laboratory findings of the patient are within normal limits, dental treatment can be safely delivered in consultation with the patient’s physician. Wilson’s disease is a form of copper poisoning and therefore the role of the dentist is to minimize the use of copper containing dental materials and medicines. In these patients there is impaired healing and if the treatment involves use of orthodontic appliances, removable appliances should be preferred to fixed; the reason being that the fixed appliances are fast acting and exert more pressure, causing fast resorption. Use of nickel-titanium (Ni-Ti) wires should be especially avoided.
because although in traces, one of the components of these wires is copper.\textsuperscript{18}

**CONCLUSION**

With the advancement in modern oral medicine, medically compromised patients tend to visit the dental clinic for their dental problems. It is necessary to recognize such medical deviation before taking any treatment decisions. The knowledge of the clinical presentations and the treatment of Wilson’s disease are of utmost importance for the safe delivery of dental care. A thorough history usually alerts the clinician to the various potential problems encountered in Wilson’s disease.

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