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Case Report

Evaluation of oxidative events and copper accumulatıon in oral tissues of patients wıth Wilson's disease: three case report

Mustafa Ozturk[1], Ezgi Karacelebi[1], Kahraman Gungor[2], Sule Coskun[3], Esma Boysan[4]

[1]Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Gazi University, Ankara, Turkey; [2]Department of Oral and Dentomaxillofacial Radiology, Faculty of Dentistry, Gazi University, Ankara, Turkey; [3]Department of Biology, Faculty of Science and Literature, Gazi University, Ankara, Turkey; [4]Department of Oral and Maxillofacial Surgery, Antera Dental Clinic, Antalya, Turkey

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Abstract: Wilson's disease (WD), also known as hepatolenticular degeneration, was first described in 1912 by Kinnear Wilson. It is an autosomal recessive disorder caused by mutations in the ATP7B gene, a membrane-bound copper transporting ATPase. The disorder is caused by impairment of the copper transporting ATPase, ATP7B, in the liver, which disturbs copper transport, excretion into the bile, and incorporation into apoceruloplasmin. WD is an inherited copper metabolism disorder with pathological copper accumulation in many tissues, but especially in brain and liver. We conducted this study because copper accumulation in oral tissues in patients with WD have not been studied before. We think that copper accumulation and differences of oxidative events in oral tissues can cause tendency to periodontal diseases.

Keywords: Wilson's disease, hepatolenticular degeneration, copper, penicillamine

Introduction

When normal dietary consumption and absorption of copper exceed the metabolic need, the normal copper level in blood is preserved by the biliary excretion of copper. WD is an inherited disorder in which defective biliary excretion of copper leads to its accumulation, particularly in liver and brain. The reason of WD is the mutations of the ATP7B gene on chromosome 13 [1]. This gene, *ATP7B*, encodes a metal-transporting P-type adenosine triphosphatase (ATPase), which is generated in hepatocytes and functions in the transmembrane transport of copper within hepatocytes. Absence or reduced function of ATP7B protein leads to decreased hepatocellular excretion of copper into bile. This results in hepatic copper accumulation and injury. Eventually, copper is released into the bloodstream and deposited in other organs, notably the brain, kidneys, and cornea [2].

Onset of WD 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 Even in asymptomatic cases, the specific treatment should begin as soon as the diagnosis is established. The objective of therapy is to remove copper from the tissues and to prevent its reaccumulation [3]. The therapeutic strategies for WD include low fat diet, D-Penicillamine (PCA), trientine, ammonium tetrathiomolybdate and zinc [1, 4].

Here; we present three patients with WD applied to Faculty of Dentistry, Gazi University because of toothache. Dental problems of these three patients with WD were treated. In the samples taken from the patients, copper accumulations and diffrerences of oxidative events in oral tissues were determined.

Case report

A female and two male patients, who was diagnosed with WD, presented to the oral and maxillofacial department of the Gazi University of Ankara in Turkey, complaining of toothache. The

Table 1. Cu, NOx, plasma MDA and RSH levels, MPO activity in blood, gingiva and tooth of patients with WD

Patient	Gingiva		Tooth	Blood			
	Cu (μg/tissue)	NOx (μmol/gr)	Cu (μg/tissue)	NOx (μmol/ml)	MDA (nmol/ml)	RSH (nmol/ml)	MPO activity (U/gr)
1	0.57	1029.56	19.8	75.54	6.4	330.00	2.00
2	0.97	940.98	28.9	96.00	4.7	197.02	2.08
3	0.69	642.2	23.4	89.88	3.2	205.00	2.15

average age of the patients in the study is twenty-one. All patients were using PCA. After we examined the patients, we decided to remove the teeth causing pain. Patients were informed about the procedure and they approved it. Because of the fact that copper accumulated in the brain of one of the patients, his behavioral disorders were clinically observed, and neurodegeneration formed. In the other two patients were copper accumulation was identified in the liver. All patients were consulted to neurologist, haematologist and internal specialist. In preoperative term, fresh blood plasma was injected by their doctors and then blood samples were taken. After a tooth extraction, samples were taken from the tooth and surrounding gingiva of the tooth. Serum nitric oxide (NOx), total sulfhyryl groups (RSH), malondialdehyde (MDA), myeloperoxidase (MPO) and MPO activity were evaluated in blood samples by biochemists. Serum and tissue concentrations of copper were measured by philips model PU-9200.

The tissue samples were evaluated according to the method of Falchuk and his friends [5]. The nitrat levels of the plasma were spectrophotometrically identified. The nitrate reduction with vitrine VaCl3 was selected as a baseline [6]. The vitrine levels were estimated with Griess reaction [7]. The level of plasma MDA and RSH were evaluated with spectrophotometric methods [8].

Results

We identified accumulation of copper in samples which were taken from the patients. Copper and quantity of serum NOx, in tooth and surronding tooth tissue of all patients are showed in **Table 1**.

Discussion

WD is an autosomal recessive disorder of the copper metobolism. Up to this time the researcheres have reported ATP7B gene mutations cause excessive copper accumulation in numoreus tissues, particularly in liver, brain and cornea, but pathological copper accummulation in any oral tissues hasn't been reported [1, 3]. In this study, we determined excessive copper accumulation in gingiva and tooth of all three patients with WD. We think that copper accumulation in oral tissues can cause tendency to periodontal diseases.

Changes in the oxidative events occur as a result of the degenerate copper metabolism in the patients with WD. NOx is an important molocule which has a role on both physiologic and pathological processes. It is alleged that lipid peroxidation increases with the existence of NOx. A lot of biopolymer in the organism is affected as a result of increased oxidative damage, but the most delicate and sensitive ones are lipids. In this study, MDA levels were examined on the serum samples as the indication of lipid peroxidation. Free radicals that are harmful and come out of various reasons in the organism are removed with the help of enzymatic and nonenzymatic antioxidants in the body. The state of antioxidant capacity on the patients with WD has been tried to be shown with RHS level [9].

When WD patients' MDA and NOx values are compared with the healthy people's serum values; it is seen that both parameters increased. These results have shown that in these patients increased oksidative damage is seen because of the changing copper metobolism. NOx levels are determined to be similar in gum samples.

Dentists' attitudes towards the patients with WD is very considerable during the treatment because of the effects of the copper accumulating on the organs as a result of this disease and the side effects of the preferred medicines for WD. Especially the copper accumulating in liver, free radical reactions and lipid peroxida-

tion cause induce mitochondrial damage. Excessive copper coming out of hepatocyte necrosis results in hepatosit damage, inflammation and fibrogenesis. Consequently, liver damage, steatozis, inflammation, cirrhosis and sometimes liver failure may occur [10]. Damage in the liver may result in clotting defects. For this reason, WD patients' risk of bleeding is important for the dentist during the surgical operation in oral and maxillofacial region.

Management of WD consists of Copper chelating agents, such as PCA, trientine hydrochloride, and copper absorbtion blockers such as zinc salts, are effective and have modified the prognosis WD. PCA used against WD and excessive metal intoxication is based on immunosuppression by inhibiting T-lenfosits, mechanism of action and it inhibits antibody synthesis. The side effects of this medicine are seen frequently [1, 3]. During dental treatments the dentists should determine treatment process considering the state of these patients who are more prone to infection, because a side effect such as leukopenia may occur as a result of immunosuppression of PCA.

Copper accumulation in oral tissues in patients with WD have not been studied before [2, 3]. This study has showed that patients with WD also have copper accumulation in their oral tissues excluding the intese copper accumulation in their livers, brains and organs like eyes. As a result, wide ranging studies with control groups are needed to support the derived data and identify if the copper accumulation in oral tissues has caused adverse effects.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Ezgi Karacelebi, Gazi University, Faculty of Dentistry, Department of Oral and Maxillofacial Surgery, Ankara, Turkey. Tel: +903122034142; Fax: +903122239226; E-mail: dtkaracelebi@gmail.com

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