SURGICAL TREATMENT IN PATIENTS WITH WILSON’S DISEASE

Radka Cholakova¹, Martin Drangov¹, Kremena Markova², Viktoria Zidarova³, Martina Avramova³
1) Department of Oral Surgery, Faculty of Dental Medicine, Medical University – Plovdiv, Bulgaria
2) Department of Operative dentistry and Endodontics, Faculty of Dental Medicine, Medical University – Plovdiv, Bulgaria
3) Student, Faculty of Dental Medicine, Medical University – Plovdiv, Bulgaria

INTRODUCTION:
Wilson’s disease was first described in 1912 by Dr. Samuel Alexander Kinnier Wilson, a British neurologist, who called the condition ‘hepatolenticular degeneration’ [1, 2, 3]. It is an autosomal recessive disorder due to mutation in ATB 7B gene, which is a membrane-bound copper-transporting ATPase. The impaired excretion of copper results in an increase in serum levels and accumulation of copper in the body. Various clinical signs can be observed in liver, nervous system, kidneys, eyes, heart. There are also changes in blood chemistry.

Objective: A forty-six-year-old female patient presents with Wilson’s disease in the treatment rooms at the Faculty of Dentistry in Plovdiv. She needs complete dental care. She has also had an ischaemic stroke.

Methods and results: As the treatment plan started with extraction of teeth under local anaesthesia, a complete blood count and INR test were performed. Oral mucosa and bone were obtained by biopsy for evidence of pigments in these tissues. The biopsy results showed accumulation of copper in them as well.

Conclusion: It’s a rare disorder, approximately 1 in 30 000-40 000 from the population with a higher incidence in North India and Sicily. It is a hereditary form of an autosomal recessive disorder. Only homozygous patients manifest the symptoms of the disease. The gene responsible for the synthesis of ATP (ATP 7B) is in chromosome 13 where multiple genomic mutations can be observed. ATP 7B is a membrane-bound copper-transporting ATP-ase. The absence of this enzyme leads to impaired biliary excretion of copper, which is manifested by higher levels and accumulation in the liver. It all ends up in toxicity due to the impaired oxidases. The impaired copper incorporation in the apoceruloplasmin results in increased catabolism and low levels of ceruloplasmin in blood [1].

The levels of copper in serum are usually lower compared to normal ones, because the ceruloplasmin, which normally binds more than 90% of the copper in serum, decreases. As the disease advances the free (not bound to ceruloplasmin) copper increases in blood. As a result, copper accumulates in other tissues like brain, which leads to neurologic and mental changes.

The disease starts in early childhood when liver symptoms appear. The first signs of affecting the nervous system occur with intellectual disability. The concentration at school decreases, patients feel depressed by the delayed speech and uncoordinated movement of arms and/or hands. Muscle rigidity and bradykinesia lead to clinical characteristics typical of juvenile Parkinsonism. The rest of the clinical changes appear at about the fifth decade. The presenting symptoms are parkinsonism, which leads to a number of symptoms and disorders [4].

Wilson’s disease is a rare disease, it occurs in 1 per 30 000-40 000 from the population with a higher incidence in North India and Sicily. It is a hereditary form of an autosomal recessive disorder. Only homozygous patients manifest the symptoms of the disease. The gene responsible for the synthesis of ATP (ATP 7B) is in chromosome 13 where multiple genomic mutations can be observed. ATP 7B is a membrane-bound copper-transporting ATPase. The absence of this enzyme leads to impaired biliary excretion of copper, which is manifested by higher levels and accumulation in the liver. It all ends up in toxicity due to the impaired oxidases. The impaired copper incorporation in the apoceruloplasmin results in increased catabolism and low levels of ceruloplasmin in blood [1].

The levels of copper in serum are usually lower compared to normal ones, because the ceruloplasmin, which normally binds more than 90% of the copper in serum, decreases. As the disease advances the free (not bound to ceruloplasmin) copper increases in blood. As a result, copper accumulates in other tissues like brain, which leads to neurologic and mental changes.

The disease starts in early childhood when liver symptoms appear. The first signs of affecting the nervous system occur with intellectual disability. The concentration at school decreases, patients feel depressed by the delayed speech and uncoordinated movement of arms and/or hands. Muscle rigidity and bradykinesia lead to clinical characteristics typical of juvenile Parkinsonism. The rest of the clinical changes appear at about the fifth decade. The presence of golden-brown pigmentation of the peripheral corneal stroma, called Keyser-Fleischer ring is observed when the nervous systems is affected and there are neurologic symptoms.

CASE REPORT:
We are presenting a woman at visible age that does not correspond to the real forty-six years (Fig.1.). She has...
been directed to the Department of Oral Surgery for planned extraction of teeth and improvement of oral health. The patient has a history of Wilson’s disease, which was confirmed in June of 2015 and then Cuprenil therapy was initiated. The complaints started in the year 2000 with evidence of tremor of head, leg weakness, walking difficulty and staggering. Head CT was performed and it indicated ischemia in the left hemisphere near the putamen, then the patient was diagnosed with ischemic stroke with right-sided hemiparesis and hospitalised. In 2002, MRI scan indicated both-sided necrosis in basal, mesencephalic and cerebellar nuclei. A test of copper metabolism was carried out due to the progressive syndrome of incoordination and hemiparesis as well as new signs of having difficulty swallowing solid food in particular, changes in speech, apathy, becoming recumbent, hepatosplenomegaly. The diagnosis Wilson’s disease was later confirmed. A follow-up ultrasonographic evaluation indicated focal formation in liver parenchyma, which was confirmed by the MRI scan. The contrast-enhanced ultrasound did not show any evidence of neoplastic nodular lesions. A tissue sample was taken by liver biopsy for the purpose of histologic examination under sonographic control. Fibrogastroscopy was carried out and indicated esophageal varices grade 1, portal gastropathy, epitelised duodenal ulcer. The patient’s general status indicated asthenic habitus, kyphoscoliosis in thoracic and lumbar portion. The patient is bradypsychic with dysarthria, her speech is saccadic, broken from time to time. Postural and resting tremor in the upper limbs, aggravated in right hand with a contracture in metacarpophalangeal joints, high muscle tone and stiffness, especially on the right side. Spastic-ataxic gait.

Following a consultation with an ophthalmologist, fine paralimbic deposits of copper were found oriented towards 6 and 12 o’clock on both eyes – Kayser-Fleischer’s ring (Fig. 2.).

**Fig. 1. Extraoral status**

The intraoral exam showed partially edentulous maxilla and mandible, large deposits of tartar settled on the remaining teeth, generalised moderate and advanced chronic periodontitis (Fig. 3.). There was no pigmentation found on the gingiva, the tongue wasn’t furred. Large carious lesions in molars and large restorations with secondary caries on front teeth were evident. The restorations had marginal discoloration.

**Fig. 2. Kayser-Fleischer’s ring**

**Fig. 3. Intraoral status**

Here are the patient’s laboratory values: Westergren (ESR) – 124; Neutrophils Sg - 70.3; Eosinophils EOS – 1.3; Basophils BASO – 0.01; Monocytes MONO – 6.3; Lymphocytes LYMPH – 19.7; Hemoglobin HGB – 117; Erythrocytes RBC – 3.97; Hematocrit HCT – 0.369; Mean cell volume MCV – 92.8; Index MCH – 29.4; Index MCHC – 316.0; Leukocytes WBC – 4.24; Platelets PLT – 109.0; Activated Partial Thromboplastin Time APTT – 31.7; Fibrinogen Fbg – 2.39; Prothrombin time, % - 59.8; Prothrombin time, sec – 13.6; Prothrombin time, INR – 1.22; SGPT ALT – 12.0; Albumin ALB – 29.0; Al-
kaline phosphatase ALP 65,0; Amylase AMYL – 1101,0; SGOT ASO 39,0; Gamma-glutamyl transferase GGT – 181,0; Glucose GLUC – 5,0; Conjugated bilirubin BIL – 5,8; Iron IRON – 18,0; Potassium K – 3,2; Creatinine – serum CREA – 70,0; LDH LDH – 359,0; Sodium Na – 140,0; Total protein test TPROT – 61,0; Total bilirubin T BIL – 123,8; Uric acid UR AC – 92,0; C-reactive protein CRP – 12,0; Urea – serum UREA – 3,8; Chloride Cl – 98,0; Cholesterol CHOL – 3,4; Cholinesterase CHE – 2170,0;

Immunoglobulin G IgG – 17,7; Immunoglobulin A IgA – 1,5; Immunoglobulin M IgM – 1,65; Alphafetoprotein AFP – 8,56; Ceruloplasmin CERULO – 0,02 L; Copper in serum – 6,7.

There were no abnormalities found in the patient’s urine.

The OPG (Fig.4) showed evidence of generalized moderate and advanced periodontitis with vertical bone loss in teeth 28, 38, 41. Chronic periapical periodontitis was evident in tooth 12.

**Fig. 4.** Orthopantomography

The medical tests and examination showed that the patient’s main disease is moderate, which allows tooth extraction to be carried out avoiding the chance of high risk. Anesthetic with low concentration of adrenaline was used considering the recent history of ischemic stroke – Septanest 1:200 000. Teeth 18, 48, 47, 41, 42, 28, 38 diagnosed with chronic moderate and advanced periodontitis were extracted. A large bone wound opened following the extraction of teeth 48 and 47, and a collagen sponge and stitches were placed in order to reduce bleeding. Tooth 38 had root dilaceration, which required creating mucoperiosteal flap. During that intervention tissue samples from the gingiva and bone were taken for histologic examination for finding pigments. The wound healed by first intention. The patient came at a follow-up visit the next day and hematoma was found on the cheek. Vitamin C and cold compression therapy were prescribed and the patient’s condition improved.

**DISCUSSION:**

The low levels of ceruloplasmin (0.02 g/L) are striking. The genetic mutation in ATB 7B gene is followed by impaired synthesis of that protein, which has shortened half-life in plasma and low concentration in serum. The lower concentration of cholinesterase indicates an advanced liver disease. The concentration of that enzyme is a good indicator for the synthetic capacity of the liver. Although it does not give further information about the type of disease, high levels of gamma-glutamyl transferase (GGT) indicate a microsomal infection in the hepatic parenchymal cells. Copper accumulates mainly in the liver in patients with Wilson’s disease, which disturbs its metabolic function, blood clotting coagulation protein synthesis and drug metabolism. Using local anesthetics should be carefully considered beforehand and the amide-type local anesthetic group should be of choice [1]. They are metabolised in the liver by cytochrome P 450. The modern anesthetics like articain (containing thiophene ring) have two routes of excretion – via liver and plasma. The toxicity of their accumulation is less that way. The impaired nervous system requires the use of anesthetics with lower concentration of adrenaline.

It is well-known that patients with Wilson’s disease develop bone changes like osteoporosis, they are susceptible to spontaneous fractures and also have large areas of sclerosis and demineralisation of upper and lower jaw [2, 5].

The reduced synthesis of coagulation factors leads to predisposition for hemorrhage in bone wounds. That’s way, prothrombine time and INR must be checked before tooth extraction. Preoperative preparation with fresh frozen plasma (FFP) or intravenous vitamin K should be performed, if necessary. It is a good idea to place topical hemostatic agents as well as suturing a wound in order to aid hemostasis and healing. Treating patients with penicilamine can disturb the binding between tropocollagen and separate newly-formed molecules. That’s way, a lower dose of penicilamine is recommended prior to surgery, so that collagen formation can increase and healing process come [6].

The use of antibiotics should be considered carefully according to their metabolism via liver – antibiotics of choice are those that do not have hematotoxicity. Macrolides and macrolide-like antibiotics, tetracylines and nonsteroidal anti-inflammatory drugs, except paracetamol, are avoided.

**CONCLUSION:**

Surgical treatment in such patients has a high risk due to the possibility of hemorrhage as well as toxic signs after using an anesthetic. Further consultation concerning patient’s general health and preoperative preparation is highly recommended, if necessary.
REFERENCES:


DOI: https://doi.org/10.5272/jimab.2017231.1447

Received: 03/11/2016; Published online: 03/02/2017

Correspondence to:
Dr. Radka Cholakova,
Department of Oral Surgery, Faculty of Dental Medicine, Medical University – Plovdiv, Bulgaria;
E-mail: r_cholakova1978@abv.bg