JCBPS; Section B; February 2018 – April 2018, Vol. 8, No. 2; 301-309, E- ISSN: 2249 –1929

[DOI: 10.24214/jcbps.B.8.2.30109.]

Journal of Chemical, Biological and Physical Sciences

An International Peer Review E-3 Journal of Sciences

*Available online at*www.jcbsc.org

Section B: Biological Sciences

CODEN (USA): JCBPAT Research Article

Complex treatment in patient with Wilson's disease

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Received: 11 January 2018**; Revised:** 26 January, 2018; **Accepted:** 03 February 2018

Abstract: Wilson's disease is an autosomal recessive disorder, caused by a mutation in the ATP 7B gene, it is a membrane-bound copper-transporting ATPase. The distorted copper excretion increases its serum concentration and leads to an accumulation within the body. Multi-organ manifestations are observed from the liver, the nervous system, kidneys, eyes and heart.

Case report: We present a patient at the age of 46, with Wilson's disease, she visited the clinical halls of FDM-Plovdiv, requiring complex treatment for the recovery of the chewing apparatus. A treatment plan was drawn up after diagnosis, including tooth extraction under local anesthesia, whereas she underwent a CBC and biochemistry with an INR test, due to the rest of hemorrhage in these patients. Material for a histological test was sampled during the extraction, aimed at establishing the presence of copper in

the mucous membrane and bone. Recovery of speech, function and aesthetics was performed with detachable and fixed denture constructions that contain no copper. The disease is incredibly rare, approximately 1 in 40 000, with serious damage to the liver and the nervous system, which requires an in-depth analysis and discussion of the treatment plan, for its realization, as well as not allowing any complications during its implementation.

Keywords: morbus Wilson, INR, Kayser–Fleischer ring, complex treatment

INTRODUCTION

Wilson's disease was first described by Dr. Samuel Alexander Kinnier Wilson, a British neurologist, in 1912, he names it "hepatolenticular degeneration"[1-3]. It is an autosomal recessive disorder, caused by a mutation in the ATP 7B gene, it is a membrane-bound copper-transporting ATPase. The distorted copper excretion increases its serum concentration and leads to an accumulation within the body. Multi-organ manifestations are observed from the liver, the nervous system, kidneys, eyes and heart. The copper ion is an integral part of many enzyme systems, including aminooxidans, ferooxidans (ceruloplasmin), cytochrome-C oxidase, superoxide dismutase and dopaminehydroxylase. It is absorbed in the proximal departments of the small intestine and about 90% of the circulating copper connects to ceruloplasmin. It plays the important role in iron metabolism, melanin synthesis and the functions of the central nervous system, the synthesis and the cross-linking of elastin and collagen, the removal of free radicals. The body contains between 50 and 120 mg of copper, while a higher concentrations are found within the liver, the brain, heart, spleen, kidneys and blood. It is excreted with the faeces and, in a smaller degree, in urine. The increased accumulation of copper in the organism leads to a series of symptoms and damage[4].

Wilson's disease is a very rare condition with a frequency of 1 per 30,000 – 40,000 people with a higher frequency in Northern India and Sicily. It is an inherited autosomal recessive disorder. Only homozygous patients exhibit the symptoms of the disease. The gene responsible for the synthesis of adenosine triphosphate (ATP7B) is located in the 13th chromosome, whereas multiple genomic mutations being noted. ATP7B is a membrane-bound copper-transporting ATPase. The lack of this enzyme disrupts the biliary excretion of copper, which is manifested with the positive balance and accumulation in the liver, which to toxicity from damage to the oxidases. The disruption of the copper incorporation in apoceruloplasmin leads to an increased catabolism and a lower level of ceruloplasmin in the blood[1].

The serum levels of copper are usually lower than normal, because the ceruloplasmin is decreased, due to it connecting to more than 90% of the serum copper. With the progression of the disease, the free (unconnected with ceruloplasmin) copper is increased in the blood, as a result an accumulation begins in other organs such as the brain, which leads to neurological and psychological changes.

The onset of the disease is in early childhood, at that point symptoms can be observed in the liver. The first manifestations of effects on the nervous system being an intellectual deficit. The concentration in school is reduced, patients are depressed due to the slower speech and the uncoordinated hand movements. The muscular rigidity and bradykinesia lead to a development of a clinical picture resembling a juvenile Parkinsonism. The rest of the clinical changes happen occur around the 5th decade of life. In the brain, the toxicological damage mainly affects the base ganglia, and the putamen, which shows an atrophy and even a cavitation. Almost all patients with neurological symptoms develop eye

lesions, called the Kayser–Fleischer ring, which represents a green to brown deposits of copper in the membrane of the Descemet in the corneal lymph. Sulphur-copper deposits are formed, which in turn create invisible copper deposits[5,6]. Wilson's disease must be suspected in all patients with an undetermined liver disease, especially at age under 35. An increase in aminotransferases and bilirubin is observed, as well as a reduction in total protein. A low serum concentration of ceruloplasmin is typical (normal laboratory range is 0.2 to 0.5 g/L) and an increase excretion of copper in the urine (more than 100 micrograms per 24 hr). Liver biopsy showing quantitative copper concentration (more than 250 micrograms per gram of dry liver) remain the best biochemical evidnce of Wilson`s disease. If neurolgic signs and symptoms are present, then a computer tomography (CT) scan or a magnetic resonance imaging (MRI) are recommended. Whenever possible, a genetic study should be carried out to confirm the diagnosis[7,8].

CASE REPORT

We present a 46-year-old woman at apparent age much older than the actual one.

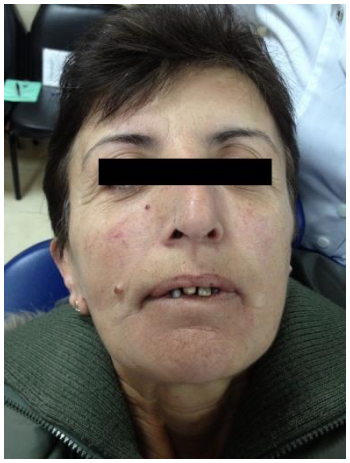

Figure 1: Extra oral examination

In terms of medical history, the patient mentions the Wilson's disease, which is confirmed in June of 2015, when treatment with Cuprenil began. Complaints began in 2000 with the manifestation of a tremor of the head, weakness during walking and staggering. A CAT of the head was performed with data for an ischemic zone in the left-brain cerebellum at the level of the putamen, which is accepted with a diagnosis of ischemic stroke with a right side hemiparesis. In 2002, as a result of a MRI test a bilateral necrosis of the basal, mesencephalic and cerebral cores was discovered. Due to the progressing discoordination syndrome and the hemiparesis, as well as the new onset of swallowing disruption, especially with hard food, changes in speech, apathy, bedridden, hepatosplenomegaly, the patient underwent an examination on the exchange of copper and the diagnosis of Wilson disease was confirmed. An asthenic habitus, kyphoscoliosis of the thoracic lumber section were established from the general condition. The woman is bradypsychic with dysarthria, her speech is saccadic, at times broken. Resting tremor of the upper limbs was discovered, manifested stronger in the right hand with a contracture in the right

metacarpophalangeal joints, rigid, increased tonus of the four limbs, manifested stronger in the right side. Spastic-ataxic gait. The typical Kayser-Fleisher ring is observed. **(Fig.2)**

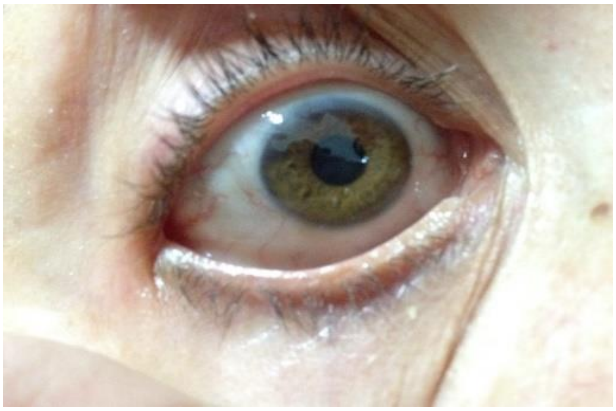

Figure 2: Kayzer-Fleischer ring

A focal form of hepatic parenchyma was discovered after a control echography examination, as well as from the performed MRI. From the performed contrast-enhanced echography it was discovered that there is no data for neoplastic focal lesions. A liver biopsy, under a echographic control, was performed for a histological examination. A fibrogastroscopy was performed with data on esophageal varices, group I, portal gastropathy, epithelial duodenal ulcer.

A partially untoothed upper and lower jaws were discovered from the local intraoral status, as well as deeply deposited tartar, chronic generalized II-III-degree periodontitis. A lack in pigmentation on the gingivitis, the tongue is unfurred. Extensive carious lesions of the molars and large obturations with secondary caries on the frontal teeth. The obturations are marginally colored.

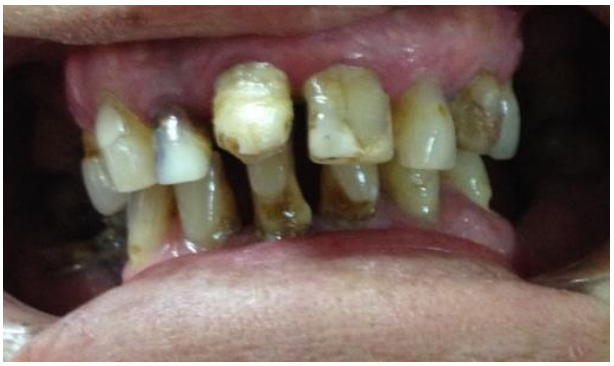

Figure 3: Intraoral examination

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. Teeth 18, 48, 47, 41, 42, 28, 38 that were 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, as well as stitches were placed in order to reduce the bleeding.

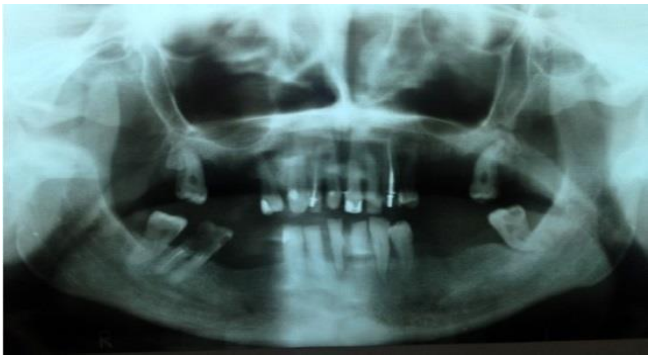

Figure 4: Orthopantomography

MATERIALS AND METHODS

Complex treatment began with a stepwise extraction of teeth 18, 48, 47, 41, 42, 28, 38. Local anesthesia from the amide group was used due to the liver damage – articaine, containing the thiophene ring, which has two ways of elimination – through the liver and the plasma, thus the toxic effect of their cumulation is diminished.

Figure 5: Application of terminal anesthesia with Septanest 1: 200,000 for the extraction of tooth 18

Reduced production of coagulation factors required the examination of the prothrombin time and INR. Local hemostatic agents were applied – sterile gelatin sponge, as well as a surgical handling of the extraction wounds – suture. A histological examination of the mucous membrane and bone was performed. The materials were fixated in 10% formalin, processed under a routine paraffin method and stained with hematoxylin eosin. To prove the presence of copper, a staining with rubeanic acid was performed. The morphological analysis of the gingival samples showed a presence of hyperplasia of multilayer flat epithelium. Significant chronic inflammatory infiltration, haemorrhage and edema were observed in the sub-epithelial connective tissue. (**Fig. 7A**) Among the inflammatory infiltration, a number of osteoclast-like giant multi-core cells (**Fig. 7B)** and macrophages with the presence of brownish granules in the cytoplasm stand out. **(Fig. 7C)** When applying rubeanic acid to prove the presence of

copper in the granules, they are colored in a black-green color, while the other tissue is colored in pink, which corresponds to a histochemical constellation of copper (**Fig. 6**). The morphological assessment of the condition of the alveolar bone shows moderate reduction in bone mineral. (**Fig. 7D**) Huster et al and Tovaru et al make similar descriptions in the cases they observed[7,8].

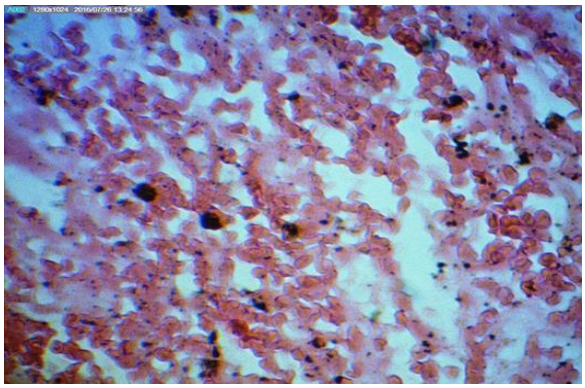

Figure 6: Staining with rubeanic acid

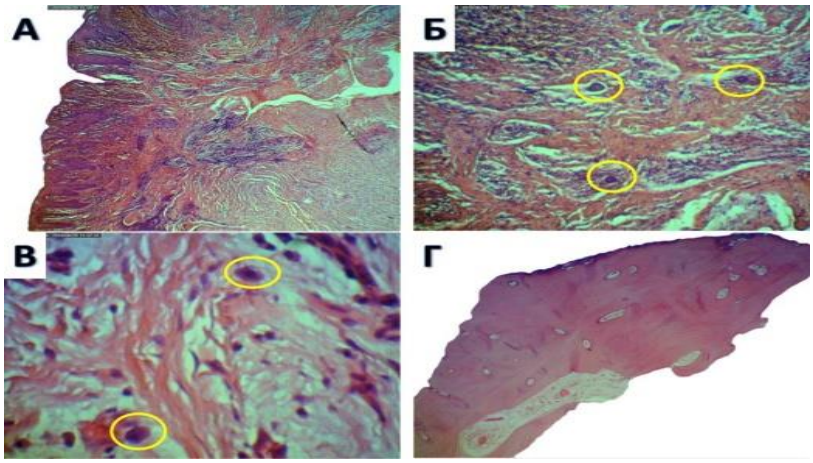

Figure 7: A. Material of gingival mucosa with hyperplasia of multilayer flat epithelium and presence of inflammation and haemorrhage in subepithelial connective tissue (HE, X40), **B**. The average inflammatory infiltrate is found in osteoclast-like giant multi-core cells (yellow circles) (HE, X100**). C.** Subanginal macrophages with the presence of brownish granules in the cytoplasm (HEX200). **D.** Bone material with moderate bone mineral reduction (HE, X40).

The second stage of the complex treatment included treatment of the present carious lesions and restoration of the detachable and fixed constructions that restore the speech and chewing functions as well as aesthetics. The metal elements were produced from alloys that contain no copper. A temporary and permanent constructions were produced that cover the frontal section of the upper jaw.

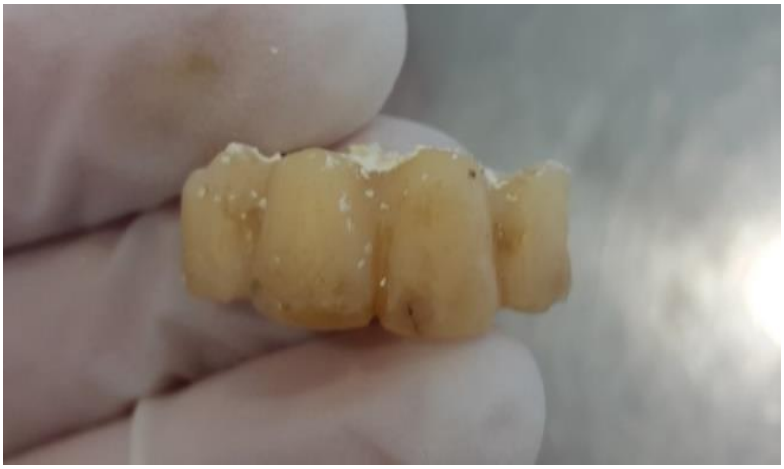

Figure 8: Temporary construction in upper jaw

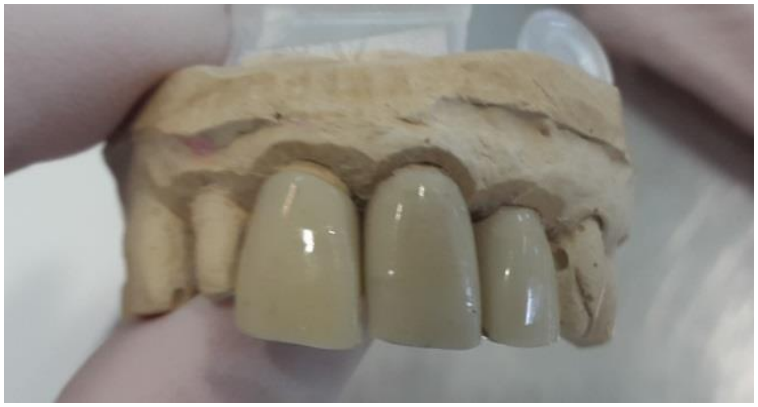

Figure 9: Permanent construction in upper jaw

After the final cementing of the construction to the upper jaw a fixed denture was produced, that covered the frontal section of the lower jaw.

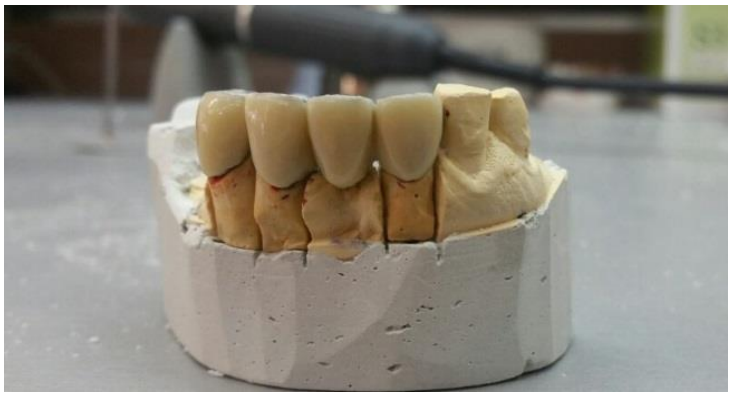

Figure10: Permanent construction in lower jaw

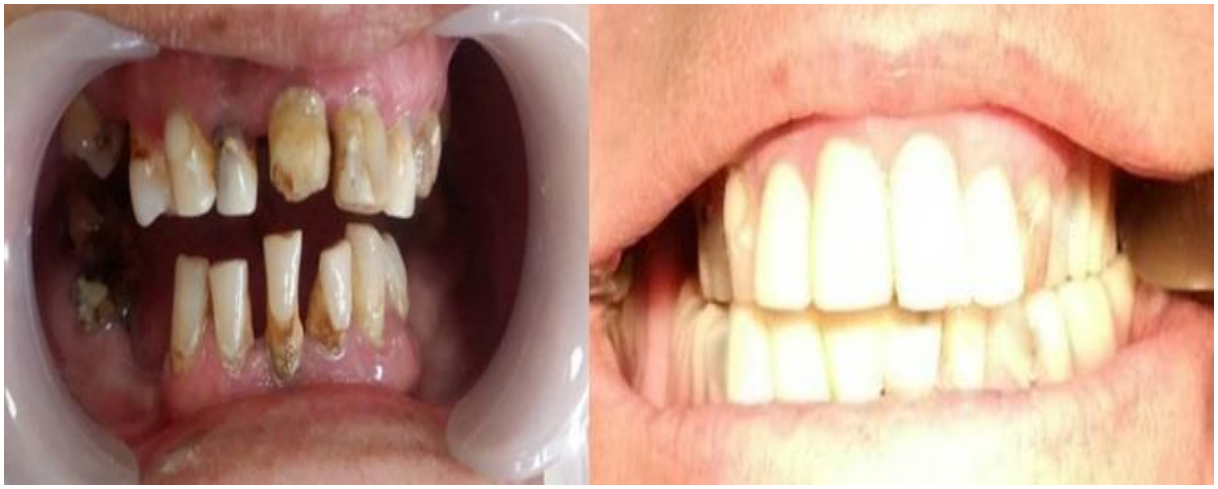

Figure 11: Before and after the complex treatment

CONCLUSION

The disease is extremely rare, approximately 1 case in every 40,000 people, with serious damage to the liver and the nervous systems, which requires an in-depth analysis and discussion, in the clinic as well as in the paraclinical situation with the aim of overcoming the complications and reaching the desired result[9,10].

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Online publication Date: 31.01.2018