MODERN ASPECTS OF PATHOGENETIC TREATMENT WITH ZINC SALTS OF PATIENTS WITH WILSON'S DISEASE IN UKRAINE

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Abstract: The aim – to study the effectiveness of zinc salts in the treatment of patients with neurological forms of Wilson's disease (WD).

Materials and methods. The analysis of the treatment results of 128 patients with hepatocerebral degeneration (71 men and 57 women) in the State Institution "Institute of Neurology, Psychiatry and Narcology of the National Academy of Medical Sciences of Ukraine" was carried out. At the time of hospitalization, the age of patients ranged from 5 to 55 years, an average of 27.3 years, and at the time of debut of the disease – from 1 year to 40 years, an average of 21.3 years. 33 patients underwent monotherapy with zinc salts, 63 – combined therapy with small doses of penicillamine and zinc salts, 32 – monotherapy with penicillamine.

Results. Because of the treatment, 67.1 % of patients showed an improvement in neuropsychiatric status: speech improved significantly, tremor of the extremities and the amplitude of hyperkinesis decreased, muscle tone decreased, and cognitive functions improved. According to the international two-level rating scale (UWDRS), the total pathology index decreased by 21 points. Zinc salts are effective and low-toxic and can be the drug of choice in the treatment of patients with hepatocerebral degeneration in the pre-symptomatic stage of the disease, as well as at the stage of maintenance treatment, both as monotherapy and in combination with penicillamine. However, zinc salts and penicillamine are not enough for the treatment and rehabilitation of patients with hepatocerebral degeneration. Therefore, taking into account the clinical picture and the data of additional research methods, it is necessary to conduct courses of symptomatic treatment at least 1–2 times a year.

Conclusions. Thus, it can be noted that zinc salts are very effective and low toxic, and, therefore, can be the drug of choice in the treatment of patients with HCD in the pre-symptomatic stage of the disease, as well as at the stage of maintenance therapy as a single drug, and in combination with penicillamine or other chelate drugs.

Keywords: hepatocerebral degeneration, Wilson's disease, clinical and neurological symptoms, treatment, zinc salts, penicillamine, trientine, tetrathiomolybdate.

1. Introduction

Hepatocerebral degeneration (HCD), or Wilson's disease (WD), is a severe chronic progressive disease with a genetically impaired metabolic disorder of copper. The ATP7B gene, located on the long arm of the 13th chromosome and encoding the P-type ATPase transmembrane protein, is responsible for the development of HCD. Thanks to this, the copper molecule is integrated into apo-ceruloplasmin and excess copper is released into the bile. As a result of a mutation of the mentioned gene, the excretion of copper with bile is disrupted, the copper depots in hepatocytes are overloaded and excess copper enters the blood, followed by its deposition in target organs, especially in the subcortical structures of the brain [1, 2].

HCD is one of the few hereditary diseases that can be treated. In this disease, the main measures are aimed at limiting the intake of copper in the body and its accelerated elimination to prevent the accumulation and deposition of free toxic copper in the liver, brain and kidneys. Currently, there is no consensus on the choice of therapeutic target and therapeutic drug. To date, only two pathogenetic therapy drugs have been registered in Ukraine: penicillamine and zinc salts, while other alternative pathogenetic therapy drugs like the chelator Trientine and Tetrathiomolybdate, unfortunately, are still not officially registered [3].

In 1956, J. M. Walshe proposed penicillamine as a chelate agent for removing copper from the body [4]. To date, the world has accumulated extensive experience in the treatment of HCD with this drug. Despite its high efficiency, its use is often accompanied by severe complications [5, 6].

U. Merle et al. conducted a retrospective analysis of treatment results from 2000 to 2005 of 163 patients with Wilson's disease. 137 (84.1 %) cases were classified as symptomatic, 26 (15.9 %) as asymptomatic, in the latter case, the diagnosis was made using family screening. Hepatic symptoms were noted in 58.9 % of patients, and neurological disorders prevailed in 33.7 %. 138 patients were treated with D-penicillamine, 9 with trientine, 13 with zinc salts. Three patients underwent a liver transplant. In most patients, the authors noted adverse pathological effects. These were predominantly patients who were treated with D-penicillamine. In this group, severe side effects were reported in more than 30 % of patients. In this regard, according to the authors, D-penicillamine should not be a drug that is preferred over zinc salts in the treatment of patients with neurological symptoms [6]. Due to the fact that the chelate drug penicillamine often causes complications, especially at the beginning of treatment, it was necessary to find other, less toxic drugs for the treatment of HCD.

In 1961, G. Schouwink proposed the use of a low-toxic drug such as zinc salts for the treatment of HCD [7, 8]. The extremely low toxicity of zinc is evidenced by the fact that for more than 100 years its salts have been used as antiepileptic drugs. The mechanism of the therapeutic effect of zinc is that zinc stimulates the production of a metallothionine protein (endogenous chelating agent), which binds copper in enterocytes of the small intestine and liver hepatocytes and reduces its output into the portal circulation. Thus, copper ingested with food and bound by metallothionine in the intestine is not absorbed and excreted from the body with feces [9]. Recently, the number of studies on the effectiveness of the use of zinc preparations for the treatment of HCD has increased. The successful use of zinc preparations as a preventive therapy in presymptomatic patients, supporting therapy after a course of chelation with penicillamine, as well as for the initial treatment of the neurological stage of the disease, is indicated by the results obtained by many authors [10, 11].

H. H. Franciska et al. on the basis of prolonged follow-up history (from 2 to 30 years, on average – 14 years) of zinc salt monotherapy in 17 patients with Wilson's disease, came to the conclusion that such therapy is preferable for presymptomatic patients and patients with exclusively neurological manifestations of the disease. For patients with exclusively hepatic manifestations or with a combination of them with neurological and hepatic manifestations, treatment with zinc salts can be prescribed only if the liver has no severe damage [12].

Hong Chang et al. monitored 89 children with Wilson's disease between 1990 and 2008. Of these, 65 patients underwent

combination therapy with small doses of D-penicillamine and large doses of zinc sulfate. In most (89.2 %) patients, the course of the disease was stable or with improvement. Complications were observed only in 10.8 %. Three (4.6 %) patients died. Four (6.2 %) patients underwent a liver transplant. Based on the literature and their own experience, the authors believe that combination therapy with zinc salts and D-penicillamine deserves wider use due to its effectiveness, safety and availability [13].

There is no consensus on the advantages and disadvantages of zinc preparations compared to penicillamine.

K. M. Weiss et al. after analyzing the results of treatment of 288 patients with HCD, found that the frequency of discontinuation of treatment with zinc preparations due to inefficiency and complications was higher than with penicillamine. The authors also noted that combination therapy with penicillamine and zinc preparations is associated with a high incidence of adverse outcomes. Indicators such as liver transplantation and death of patients were higher in the group receiving zinc monotherapy. According to the authors, zinc mono- and combination therapy are the method of choice in the treatment of asymptomatic patients and patients with neurological forms of the disease. In these patients, liver function should be periodically monitored. Patients with an abdominal hepatic form are preferable to prescribe chelators such as penicillamine [14].

According to T. U. Hoogenraad, it is necessary to change the paradigm of treatment for HCD. Zinc preparations should be preferred in the treatment of this disease. He substantiates this provision by the fact that the pathogenesis of disease symptoms is caused not by the amount of deposited copper, but by the level of circulating free toxic copper. Therefore, according to the author, the aim of treatment should not be the excretion of copper in the urine, but the normalization of the level of free toxic copper. He regards the accumulation of copper in tissues as a sign of detoxification of free copper in the liver by metallothionein [15].

The aim of the work – to study the effectiveness of zinc salts in the treatment of patients with neurological forms of hepatocerebral degeneration.

2. Materials and methods

From 1992 to 2019 128 patients with Wilson's disease were examined and treated at the clinic of the State Institution "Institute of Neurology, Psychiatry and Narcology of the National Academy of Medical Sciences of Ukraine". Of these, 36 people were observed in dynamics from one to three years. The diagnosis was made or confirmed based on a decrease in serum ceruloplasmin less than 20 mg/dl and an increase in urinary copper excretion of more than 100 μg/day, as well as the presence of Kaiser – Fleisher rings. In some patients, a genetic confirmation of the diagnosis was carried out, and neurological symptoms that were relatively specific for WD were taken into account, such as tremor in the form of a "heartbeat" and facial expressions in the form of a pseudo-smile (risus sardonicus).

The Committee on Ethics and Deontology at the State Institution "Institute of Neurology, Psychiatry and Narcology of the National Academy of Medical Sciences of Ukraine" approved the work that was carried out in accordance with the Code of Ethics of the World Medical Association (Helsinki Declaration). All study participants signed informed consent.

Of all 128 patients with WD, 71 were men, 57 women. For the period of hospitalization in the clinic, the age of the patients was in the range of 5–55 years, on average – 27.3±5.6 years. The age of patients at the time of the onset of the disease was 1 year – 40 years, on average – 21.3±3.2 years.

The time from the onset of the first symptoms of the disease to the final diagnosis of WD, and, therefore, to the start of etiopathogenetic therapy, averaged 2.5 years and ranged from 0–7 years. Depending on the clinical manifestations, patients were treated in various profiles of medical institutions with different diagnoses. The initial diagnosis of WD was determined in less than half of patients (47 people). In some patients, before the diagnosis of WD was established, the diagnosis changed 3–4 times over several years.

In addition to the control of copper metabolism, the patient was performed MRI and MP spectroscopy of the brain and spiral computed tomography of the abdominal organs in the clinic of the institute. With the help of ultrasound, hemodynamics of the brain and liver were studied. The functional state of the liver was evaluated using indicators such as total bilirubin (direct, indirect), alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, alkaline phosphatase (ALP) and gamma-glutamyl transpeptidase (GGT).

For an objective assessment of the patients' condition and the dynamics of their neuropsychiatric status during treatment, the Unified Wilson's Disease Rating Scale (UWDRS) was used, which allows us to evaluate the multisystem manifestations of WD disease. The first level assesses general disorders in four areas: liver, motor system, cognitive system and behaviour, as well as the musculoskeletal system. The second level evaluates neuropsychiatric dysfunctions; it has 14 points with a total pathology score of 56 units [16].

3. Results

Of all 128 patients with HCD observed in the institute's clinic, 33 patients received monotherapy with zinc alone. For 11 out of 33 patients, zinc monotherapy was prescribed due to intolerance to the chelator penicillamine. The dosage of the zinc preparation was 124 mg per tablet, taking 1–2 tablets 2–3 times a day 15–20 minutes before meals. Six patients received zinc salt monotherapy because they were heterozygous siblings of patients and did not have a pronounced clinical picture of the disease. The dosage of zinc salts was 1 tablet, 3 times a day. 16 patients received maintenance monotherapy with zinc salts of 1 tablet 3 times a day after treatment with cuprenyl by this patient.

63 patients underwent combination therapy with small doses of the penicillamine chelator and zinc salts (penicillamine 250 mg in tablets, 1 tablet 2 times a day 1.5–2 hours after meals, zinc salts 1 tablet 3 times a day for 15–20 minutes before meals).

Analysis of the effectiveness of the treatment showed that 67.1 % of patients had an improvement in the psychoneurological status: speech improved significantly, tremor of the extremities and the amplitude of hyperkinesis decreased, tension of muscle tone decreased, and cognitive functions improved. According to the international two-level scale, the total pathology index decreased by 21 points.

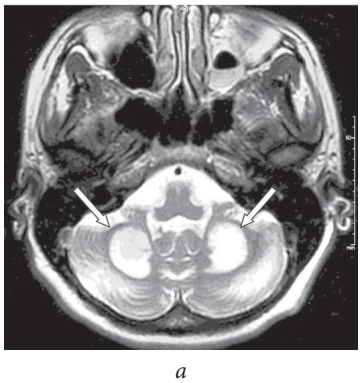
Our clinical case can serve as an illustration of the effectiveness of monotherapy for patients with HCD zinc salts.

Patient C, 30 years old, now complains of moderate weakness throughout the body, joint pain, periodic cramps in the legs and fingers, constipation.

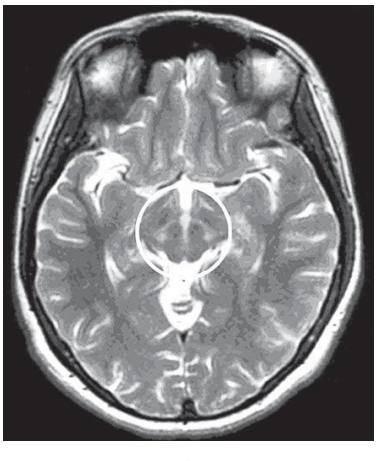
From the anamnesis, it is known that in 2000, for no apparent reason, the body temperature rose to 40° and a diagnosis was made: chronic pyelonephritis. In 2006, handwriting imperceptibly worsened, tremors appeared, speech worsened, shakiness appeared while walking, convulsive laughter joined, and increased irritability appeared. He was diagnosed with Parkinson's disease. In 2007, Kaiser-Fleischer rings were discovered and Wilson's disease was diagnosed. A chelator penicillamine

at a dose of 250 mg was prescribed per day (1 tablet). On the third day of taking penicillamine in a patient, the temperature rose to 40°. While taking penicillamine, the patient's condition worsened dramatically: the patient stopped walking, large-amplitude hyperkinesis of the upper extremities appeared, translational-rotational movements of the head, there was severe salivation, the sense of smell disappeared, and speech was sharply disturbed. In this regard, penicillamine was cancelled and monotherapy was prescribed with zinc salts of 1 tablet 4 times a day. Only after 1.5 years of zinc treatment, the neuropsychiatric status of the patient returned to baseline before taking penicillamine.

Currently, there is a slight lack of productivity of cognitive functions by the organic type. Muscle tone in the upper and lower extremities is increased in plastic type. Performs coordinating tests with elements of easy intention. In the Romberg position, slight shakiness. On both sides, there are Kaiser-Fleischer rings. Long-term monotherapy with a zinc preparation not only stabilized the patient's neuropsychiatric status, but also significantly improved the brain MRI picture. In 2008, 8 years after the onset of the disease, the patient underwent an MRI of the brain. On MRI tomograms, a bilateral pathological increase in the MR signal from subcortical structures and dentate nuclei of the cerebellar hemispheres was detected (**Fig. 1, *a***), as well as an increase in the signal from the midbrain as a "panda head" (**Fig. 1, *b***). In 2011, MR imaging of brain tomograms showed significant positive dynamics (**Fig. 2, *a*, *b***). Ultrasound: endothelial dysfunction 7.5 % (norm>10 %), diffuse changes in the liver, enlarged spleen, bilateral diffuse changes in the pyramidal parts of the renal parenchyma.

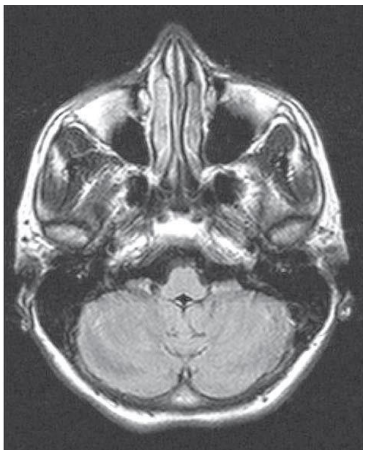


a

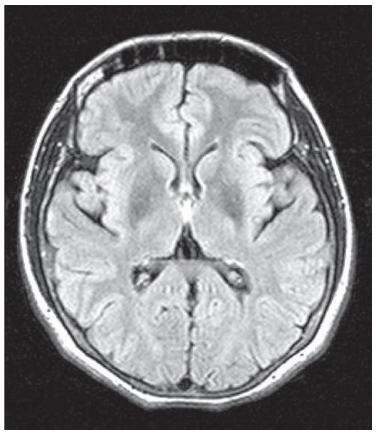


b

Fig. 1. Brain MRI: T2-weighted images: *a* – an increase in the MR signal from the dentate nuclei of the cerebellar hemispheres; *b* – from the midbrain according to the type of "panda head"



a



b

Fig. 2. MRI of the brain after 3 years: *a* – the absence of a pathological increase in the MR signal from the cerebellar hemispheres and from the subcortical structures; *b* – small focus of gliosis in the right cerebellar hemisphere

Analysis:

– ceruloplasmin 0.044 units (Norm: 0.200–0,600 units);

– copper in the blood 6.9 μmol/l (Norm: 13.4–24.4 μmol/l);

– daily urinary copper excretion of 64.8 mcg/24h (Norm≤ ≤60 mcg/24h);

– creatine 109 μmol/L (Norm: 53–97 μmol/l);

– ALT and AST are within normal limits.

As can be seen from this example, the patient gave a pathological reaction to treatment with cuprenyl with a pronounced and persistent neurological deficit. With the help of monotherapy with zinc salts, it was possible within 1.5 years to return the neurological status to the initial one, which was before taking cuprenyl. It should also be noted that with the help of zinc monotherapy it was possible not only to stabilize the dysfunction of the nervous system, but also to achieve a relative clinical and neurological recovery. However, according to ultrasound, structural pathological changes in the liver and kidneys remain, although there is a positive trend compared with previous data two years ago.

In this example, there is another question: "why did the patient give such a violent temperature and neurological reaction to the short-term administration of a relatively small dose of penicillamine (1 tablet)"? Most likely, this condition is caused primarily by the toxic effect of penicillamine itself, as well as by the large release of free toxic copper deposited in target organs into the bloodstream caused by it. These two toxic factors were

superimposed on the patient's initial kidney damage. After all, she had the onset of HCD at the age of 18 in 2000 was chronic pyelonephritis. This is also indicated by ultrasound data, where bilateral diffuse changes in the pyramidal sections of the renal parenchyma are noted. Another author [3] notes the influence of the initial pathology of the kidneys on the development of renal complications in the treatment of penicillin with patients with HCD in his extensive work [3].

4. Discussion and conclusions

Thus, it can be noted that zinc salts are very effective and low-toxic, and, therefore, can be the drug of choice in the treatment of patients with HCD in the pre-symptomatic stage of the disease, as well as at the stage of maintenance therapy, both as a single drug and in combination with penicillamine [17–19]. Given that the treatment of these patients lasts a lifetime, the fact that zinc preparations are several times cheaper than penicillamine and other chelating drugs is of great importance.

At the same time, it is necessary to take into account the fact that chelating preparations and zinc salts are aimed only at triggering pathogenetic mechanisms – normalization of copper metabolism in the body and cannot solve all the problems of the rehabilitation treatment of patients with HCD. The clinical picture of HCD is characterized by a large polymorphism in relation to both somatic and neurological manifestations, which is due to a cascade of metabolic disorders. In these patients, important life support systems are involved in the process. Therefore, depending on the clinical manifestations and the data of additional research methods, patients also need symptomatic course treatment 1–2 times a year.

Conflict of interests

There is no conflict of interests.

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