A Case Report of Wilson Disease with Neurological Features (Extra Pyramidal Symptoms) & Psychiatric Disorders (Mood & Behavioral)

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Abstract

Wilson disease is a genetic disorder with an autosomal recessive pattern of inheritance. It is due to an error of copper metabolism with the major presentations of changes in liver, Central nervous system, Eye and occasionally other organs.

ATP7B is the gene product of the Wilson disease gene located on chromosome 13 and resides in hepatocytes transporting copper into the secretory pathway for incorporation.

The disease can be early seen in childhood or early adolescences, and the prevalence for the hepatic and nervous features are equal.

The neurotic features of Wilson disease reflect the morbidity of caudal nucleus, putamen, cerebral cortex and cerebellum. Neurological signs include tremor, chorea like movements, spasticity, akinetic, dysarthria, dysphagia, abnormal body posture and ataxia. Psychiatric disorders accompany the disease are Dementia, Affective disorder, behavioral, Personality changes and rarely psychosis.

Laboratory exams conclude the determination of copper level in 24 hour collected urine and blood serum, Ceruloplasmin level, biopsy of the liver and brain imaging.

In case of neurotic disorders, one should keep in mind the differential diagnosis with multiple sclerosis and Huntington. The treatment is supportive and the best way is to clear the copper from the body is still controversial, but a copper level absorber from the body tissues is used these days. Early treatment will partially or completely help with cure of the disease. On the other hand the disease will progress and is fatal. Liver transplantation is necessary in cases of liver failure.

The asymptomatic patients of Wilson disease should undergo evaluation for Wilson disease. We hereby report a case of Wilson disease that was found in a 19 year old boy in Ali Abad teaching hospital department of neuropsychiatry back in February 2019.

The clinical features found were extra pyramidal, dystonia, Kyser Fleischer rings in eyes and psychiatric (behavior and mood) disorders, and with the help and detection of copper and Ceruloplasmin levels in blood serum the diagnosis of Wilson was made in this boy.

We advised a copper level absorber (Penicillinium) and the cessation of copper. With these measures we found an improvement of the patient's condition in 4 months.

Key words: Wilson, Ceruloplasmin, copper, extra pyramidal, dystonia, Parkinson, tremor, Kyser-Fleischer ring, Pinicillamine & ATP7B.

Introduction

Wilson disease is a rare hereditary disorder of hidden autosomal (Chromosome 13) metabolism of copper which also called hepatolenticular degeneration[1,2,5,6,8,10.12.13.15.16.18]. For the first time this disease is demonstrated over twelve patients by a British neurologist, Dr. Wilson (Samuel Alexander Kinner Wilson 1878-1937) in 1912 [4,8] . Events of this disease is 1/30000 along the life, however recent researches reported 1/100000. Beginning of the diseases is much more between 10-20 years old. 40% of patients presents with neurological symptoms, 40% of patients presents with hepatic symptoms and 15-20% of patients presents with mental symptoms [1,3,4,8,9,10,11,12,14,15,18] .

However exact property of biochemical abnormality of Wilson disease is unknown, but it looks that pathogenesis of the diseases is including decrease of copper binding with its transient protein that's mean Ceruloplasmin. At the result excessive of free copper is entered to the circulatory system and subsequently sediments at the brain, liver, kidney, cornea and other tissues [1,3,12,13,15,16,17].

Pathophysiology of Wilson disease is toxicity of the copper and absorbed copper from food is connected with portal circulatory albumin and severely bowed for extraction of copper by liver cells and the combination of Ceruloplasmin is excreted in bile. Eventually liver cells' copper is used for necessity of the body metabolism. The transfer of copper from liver cells to the bile is through vesicular route which is dependent to the ATP7B activity (ATPase type B, copper transmitter) therefore, decrease and inactivity of that causes decrease of bile copper which is responsible for copper rally or sedimentation [1,3,6,7,8] . Toxic effect of copper is included production of free radicals, peroxidation of membrane fat and DNA and forbids protein synthesis and alteration of cellular antioxidant levels. In this disease first copper is stored in liver and when sediments more than the capacity of liver cells it causes cell injury and copper gets out from liver and sediments in the other tissues of the body (Prominently in brain, kidney, eye and bones). Ceruloplasmin (serum glycoprotein) is made in liver and works as a big transmitter of copper in serum. In more patients of Wilson disease blood Ceruloplasmin level is decreased due to decrease of synthesis in liver, but is has no main role in the pathogenesis of the disease. It is thought that copper has role in synthesis of Ceruloplasmin in golgi apparatus and during biosynthesis process that in transfer of copper must cross membrane of gulgi apparatus which is dependent to the ATP7B (in Wilson disease it is decreased or absent). Believes it, that decrease in combination of copper with Ceruloplasmin causes decrease circulatory level of this protein and the other hypothesis is that Ceruloplasmin deficiency in Wilson disease maybe inherited or genetic [2,3,4,7,11,14].

Neurological and psychiatric sign and symptoms of the disease are different according to the affected area of the brain including pseudo chorea (pseudo dance) limbs, face smiley, organ stiffness, lightning movements or a kinetic rigid syndrome like Parkinson, tremor (shaking situation or during rest), imbalance and dystonic syndrome motor inconsistency with neurological origin, abnormal spasticity condition (curved stature), dysarthria, dysphagia, migraine, sleeplessness and epilepsy also reported. Mental disorders derived from Wilson disease is specified

by personality changes (like aggressive and aggression attacks), despair, psychosis, loss of cognition (like dementia) [2,3,5,8,9,10,16,18]. In this case tendency to dystonic feature or Parkinson with hyper reflexia and responses to the sole footprint can be seen when the disease has begun before the age of 20 years. The most common eye signs are Kyser Fleischer rings which are bilaterally brown color corneal rings arising from sedimentation of copper at the descent membrane and only by a shed light check can be determined [3,7].

Liver damage leads to the chronic cirrhosis which may blend with splenomegaly, esophageal varices with bloody vomiting (hematemesis) or may complicated by severe liver insufficiency. Splenomegaly may cause hemolytic anemia and thrombocytopenia [2,4,7,8,9,11,14].

Investigations may represent abnormal liver function test, platelets test and amino acid urea due to tubular problem of the kidneys. Copper and Ceruloplasmin (α-2 glubolin which has connection of 90% circulatory copper) serum level is decreased and generally the amount of excreted copper in 24 hour urine increase. The liver biopsy represents the massive deposition of copper, biopsy also usually reveals cirrhosis. No laboratory testing alone can be identified for diagnosis. Brain CT scan and MRI may reveal atrophy or hypertrophy of brain cortex and basilar lymphnodes abnormality [3,4,6,7,8,10,16,17].

Treatment of Wilson disease patients is divided into four sections including nutrition (By reducing the consumption of copper containing foods), reducing the absorption of copper through the intestine, (by zinc and Tetrathiomolybdate), treatment for chelation increase and elimination (by Pinicillamine and Trientene) and liver transplantation [3,5,8,12,18]. Treatment should start as soon as possible and treatment should continue life time even after liver transplantation. The majority of the patients who have been treated early can expect a full or about to full recovery. Liver transplantation may be required in cases of hepatic impairment [3,8,12]. For discovering of asymptomatic Wilson disease sisters and brothers of affected people should undergo neurological examination and slit lump and Ceruloplasmin level [3]. Oyster snail, nuts, chocolate, mushroom, meat with a higher content of copper should not be consumed by the patients. Early treatment of the patients is along with full or partial recovery. Otherwise, it is a progressive disease that even fatal [3,4,8,11,14].

We also report here a case of Wilson disease at Aliabad Teaching Hospital of Kabul Medical University in February 2019, in a 19 years old body that manifestation of the disease started since four months started with clinical manifestation of extrapyramidal symptoms, dystonia and mental disorder (Mood and behavior Disorder). This case has been diagnosed based on neuropsychiatric clinical features, existence of kayser- Fleishcer rings at eyes and assessment of laboratory examinations (copper level and Ceruloplasmin). Treatment is continued with copper absorbent and advice on not getting copper bearing materials. After a few months follow up treatment, the patient's condition was relatively better.

Case report

Wilson disease is a rare hereditary disorder of hidden autosomal metabolism of copper due to its disorder and non-transfer in the body. Now we are reporting here a case of Wilson disease at the

Aliabad Teaching Hospital of Kabul medical university in February 2019, with a boy living in the second decade of life.

A 19 years old patient born from parents who have close affinity to each other presented to the hospital with four months history of tremor, limbs dystonia, sialorrhoea, dysarthria, bradykinesia and sometimes body akinesia due to muscle stiffness and dystonia and mental problems that, mental or psychiatric disorders includes bradyphrenia, lack of affection and less contact with family and friends, behavioral disorders, less and slow speaking and short answers to questions (poverty of thought) and sometimes no talking (Mute). Trembling or tremor first occurred or started in the right hand and then on the right foot and subsequently on left side first on the hand and then on the foot. Over time, this condition progressed and currently head shaking also started. The tremor first appeared during grief and fierce with less intense and as the disease progressed the tremor occurs during rest (Resting Tremor) and has relatively more intensity and the patient cannot do all their daily activities naturally so he was condemned to bed. At the same time, its psychiatric features indicate mood and behavior disorders.

Particular additions are not available in the family history and medical history of the patient and the patient has normal vital signs and fully conscious, but apparently it seems ill. Neurological examination represents extrapyramidal features (in the form of Parkinson or dystonia) including, severe tremor of four limbs with head shaking which is relatively more on the right side and increase during rest. Hypertonia of extremities and severity of deep reflexes also checked out. The inability to stand on straight position (orthostatic Position) is seen and it's only possible to stand up to the curved position (Bend forward) and walking problems are seen in Parkinson form that's mean Festination Gait (Walking is initially started with small steps and then slowly slowly sharpening). The patient's speech has uniform description (Monotonous) and has mask like face. (It appears younger than its real age). Meanwhile with Gallobolar tap (Tapping slowly between two eyebrows) Myerson's sign (Blinking several times with one tap) is also positive which shows basilar nucleus affliction. Dystonia of extremities are in the form of expansion and severe spasticity is present at four limbs and trunk and the patient has taken almost no mobility. The extremities muscle weakness strength varies between 1-3 degrees. Meanwhile, the muscular tone of all muscles of the body has risen due to muscle stiffness and dystonia and shows hypertonia. Of course all superficial reflexes of all extremities are normal but deep reflexes at upper and lower limbs are seen in stretched form. No pathology was fund in evaluation of sensory and cranial nerve pairs examinations. Psychological examination of the patient represents mood and behavior disorders that includes mental retardation, lack of interest and less contact with people around, less and slow taking and answering questions shortly and sometimes it takes a dumb mode (Mutt), also behavior disorders are seen in the form of emotional instability or incongruity affect (crying and inappropriate laughs) and aggressive. Other psychiatric examinations show no pathologic effect.

The patient has no history of liver problem and abdominal ultrasound did not confirm any pathological findings. By physical examination of the patient no pathological signs like palmar erythema, jaundice, breast enlargement, testicular atrophy, ascites and spider nevi are detected to

confirm and show liver impairment. Heart, lungs and abdomen were also found normal during physical examinations.

Ophthalmic examination of the patient indicates kyser-Fleischer rings which are very helpful in confirmation of diagnosis of Wilson disease.

In the laboratory examinations of this patient copper metabolism abnormality is that serum copper level is 88.96ug/L, Ceruloplasmin level is 0.12g/l and amount of copper in 24 hours urine is about 120ug/24h. Liver function tests was found a little higher than normal range which is described as bellow.

Serum total bilirubin = 1.8mg/dl (Direct bilirubin=0.5mg/dl & indirect bilirubin=1.3mg/dl), Gama GT=27IU/L, SGPT (ALT)=40IU/L, Alkaline phosphatase =115IU/L.

Brain CT-scan and MRI also shows no pathology.

This case of Wilson disease is diagnosed based on neuropsychiatric clinical manifestations, evaluation of laboratory examinations or tests and existence of Kyser-Fleischer rings at eyes by ophthalmic examination. Determination of copper concentration in biopsy of liver tissues is completely reliable test, but it is not pathognomonic because it may also be high in other liver diseases and copper level of liver tissue dry weight >3.1mmol/gr or 250mcg/gr is helpful for making diagnosis of Wilson diseases but unfortunately due to following reasons could not performed.

Because this operation is an offensive procedure, the inability to estimate copper in the liver dried tissue with hand held appliances in the country and dissatisfaction by family members of the patient.

This illness dose not has any specific treatment and the treatment is palliative. So a copper absorbent medication named penicillamine 250mg is used three times a day to precipitate excretion of sediment copper from body tissues, Propranolol 10mg three times a day to reduce tremor, Amantadine 100mg twice a day for Parkinson symptoms, Trihexiphenodyl 2mg three times a day for dystonia and Zinc acetate 150mg/day is used for competitive absorption of zinc instead of copper from intestine. Also for mood disorder Amitriptyline 25mg is used bed time. The patient was recommended to avoid fat and copper containing foods and also avoid using copper dishes.

As a result of this report, it is clear that after few months treatment follow up the patient returned to relatively normal condition and continues his normal activity as before and patient's family members were recommended to undergo all of their family members for neuropsychiatric and liver examination, evaluation of laboratory examination and ophthalmic examination for early detection of Wilson diseases.

Discussion

As previously mentioned, Wilson disease is a rare hereditary illness [1,2,5,6,8,10,12,13,15,16,18] disability and mortality can be prevented by early diagnosis of the disease. We found a case of Wilson disease at the Aliabad Teaching Hospital of Kabul medical university in February 2019, in a 19 years old boy born from parents who have close affinity to each other with clinical features of extra pyramidal symptoms and psychiatric features. This case is diagnosed based on

neuropsychiatric features, existence of Kyser- Fleischer rings at eyes and evaluation of laboratory tests which are compared with medical literatures as bellow:

In this case psychiatric features (Mood and behavior disorders) and neurological features (Dystonia and extrapyramidal manifestations) started before 19 years old that, according to the medical literatures the diseases starts in 2 and 3 decade of life that's mean it begins at the time of childhood and adolescence[8,9] so always in all patients between 3-45years old who presents with neurological, psychiatric and hepatic clinical features Wilson disease should be confirmed and rejected [3] . However, the onset of the disease was reported at the age of less than six years of age and after the age of fifty years. Also the onset of neuropsychiatric symptoms (in 18 years of age) in comparison with hepatic symptoms (in 14 years of age) appears late[5] and neurological symptoms are more likely in the form of basilar nucleus (Extrapyramidal symptoms) and motor symptoms [1,2,3,17] .

Psychological examination of the patient represents mood and behavior disorders that includes mental retardation, lack of interest and less contact with people around, less and slow taking and answering questions shortly and sometimes it takes a dumb mode (Mutt), also behavior disorders are seen in the form of emotional instability or incongruity affect (crying and inappropriate laughs) and aggressive. Other psychiatric examinations were found normal. Also these psychological disorders are similar to the disorders described in Taksande A and his colleague's report[16]. Also mood disorders (in 30-60% cases), behavioral disorders and destructions of cognition (<25% cases) and personality disorders are the most common psychiatric disorders of Wilson's disease, meanwhile mental and behavioral abnormalities are noticeable between 30-100% of patients and occurs like early onset symptoms in 2/3 patients. Personality changes depression, anxiety, cognitive changes and psychosis can be seen rarely in these patients [2,3,4,5,9,14]. According to the medical literatures more than twenty percent of the patients are diagnosed with mental illness prior to the diagnosis of this disease [4, 9, 12, 18]. Also because of the diagnosis of psychiatric disorders, which do not have an additional examination and diagnosis is determined on the basis of psychiatric examination and criteria therefore, most of the time most of the medical causes of mental disorders are far removed (left behind) and causative diagnosis is made later. It is therefore necessary that all patients with mental disorder who did not respond to the treatment it should also be though about the rare medical cause of the disease (Wilson's disease) and it should be considered or rejected in the differential diagnosis of these disorders[3,4,7,9].

In this case the patient has come to the hospital with four months history of tremor, dystonia of limbs, sialorrhoea, dysarthria, lack of movement and sometimes lack of mobility of the body due to muscles stiffness and dystonia and mental disorders that, due to muscles stiffness and decrease of muscular strength he had disability in his daily activities and therefore condemned to bed which shows affection of basilar nucleus (Extrapyramidal features in the form of Parkinson and dystonia). Also a study or research by Panagariya and his colleagues in the northwest of India on twenty one cases of Wilson disease has been done and percentage of the symptoms like tremor (85.7%), abnormal speech (76.2%), dystonia (57.1%), brain higher tasks abnormality (57.5%) and epilepsy (38%) have shown that these features shows basilar nucleuses affection [10, 17]. Meanwhile, various

researches or studies have shown that 40 % of the patients with neurological symptoms, 40% of the patients with hepatic symptoms and 15-20% of the patient exhibit with mental symptoms [1, 3, 4, 7, 8, 9, 10, 12, 15, 18].

Although the clinical manifestations of the nervous system in the area where the copper is sediment differs with it the neurological findings of Wilson disease reflects disproportionate afflictions of nucleus caudate, putamen, brain cortex and cerebellum. When the diseases started before age of 20 years feature of dystonia or Parkinson with hyper-reflexes and extension response of the sole of the foot can be seen [4, 7, 8, 9, 12, 14, 16, 18].

Diagnosis of this case in according to the medical literature based on neuropsychiatric features, existence of kyser Fleischer rings at the eyes and assessment of laboratory examinations [10, 13, 17]. There are no particular or specific symptoms or tests for the diagnosis of Wilson diseases, but due to the sediment of copper in the various organs of the body affected organ symptoms can be pretend [3, 4, 13, 17]. In this case, the result of blood tests showed a decrease in cooper and Ceruloplasmin level of the serum and 24 hour urine test showed high level of cooper in the urine which confirms copper metabolism abnormality and it is helpful to put the diagnosis of Wilson diseases. Briefly all of these laboratory findings match further with medical literature. Because for the diagnosis of Wilson disease, the 24hour copper content in urine should be greater than 100mic/l, but new studies have found less than this amount to be enough for diagnose in this patients (16-23% cases) because, in asymptomatic cases when copper is accumulated in the liver urine copper level may remain in normal range. Serum Ceruloplasmin level in 5-15 % cases of Wilson disease may be normal or slightly decreased and in 10-20% cases with heterozygotes also showed decreased level less than 20mg/dl especially it is diagnosable or recognizable when it is with kyser fliescher rings and in 90-100% patients its level is below normal [3,4,8,9,10,16].

Clinical manifestation of liver contamination shows difference from asymptomatic state to hepatic failure manifestations [3,9,17]. In this study, neuropsychiatric symptoms are present without liver impairment that, neuropsychiatric symptoms may be presented without liver contamination [17].

Determination of copper concentration in biopsy of liver tissues is completely reliable test, but it is not pathognomonic because it may also be high in other liver diseases and copper level of liver tissue dry weight >3.1mmol/gr or 250mcg/gr is helpful for making diagnosis of Wilson diseases [3,4,7] but unfortunately due to offensive procedure, the inability to estimate copper in the liver dried tissue with hand held appliances in the country and dissatisfaction by family members of the patient did not perform.

According to the medical literature in this case ophthalmic examination is also positive for Kyser Fliescher rings. Copper sediments in descemet's membrane at corneal corners and limbus usually bilaterally (sometimes unilaterally) which was helpful for diagnosis of the Wilson disease, but it is not pathognomonic because in 5% cases of nervous system impairment of this disease nothing can be seen [3,7,17,18].

Imagine examination of nervous system, especially MRI in Wilson patients with impairment of nervous system is more sensitive that further shows impairment of basilar nucleuses, thalamus and

brain stem. In this case even though brain CT-scan and MRI of the patient were normal, but observed clinical manifestation like extrapyramidal symptoms (Parkinson and dystonia) shows impairment of basilar nucleus[3,4,6,7,8,16].

Treatment of Wilson disease patients is divided into four sections including nutrition (By reducing the consumption of copper containing foods), reducing the absorption of copper through the intestine, (by zinc and Tetrathiomolybdate), treatment for chelation increase and elimination (by Pinicillamine and Trientene) and liver transplantation. Treatment should not be stopped in the entire live even treatment should be continued after liver transplantation [4,5,12,18].

Because this illness dose not has any specific treatment and the treatment is palliative. So according to the medical literature a copper absorbent medication to precipitate excretion of sediment copper from body tissues, Beta blockers to reduce tremor, anti-Parkinson agents to treat symptoms of Parkinson, Anticholinergic to reduce dystonia and Zinc acetate is used for competitive absorption copper from intestine. Also for mood disorder tricyclic anti-depressants is used with patients. In the main time, in this case the patient was recommended to avoid fat and copper containing foods and also strictly avoid using copper dishes [8] .

The consequences of the illness in the course of six months of treatment are revealed and prognosis is very good with medical treatment, in case of no treatment the disease progresses and eventually leads to death. It is very dangerous situations that patients die undiagnosed. The prognosis is not good in cases of acute impairment of nervous system [4,8] .

As a result of this report, it is clear that after few months treatment follow up the patient returned to relatively normal condition and continues his normal activity as before and patient's family members were recommended to undergo all of their family members for neuropsychiatric and liver examination, evaluation of laboratory examination and ophthalmic examination for early detection of Wilson diseases.

All family members of affected patient should be evaluated for Wilson which includes history of hepatic and neuropsychiatric diseases, ophthalmic examination, determination of copper level in serum and urine, evaluation of serum Ceruloplasmin level and liver function tests, live biopsy and genetic examinations [3,4] .

Final result

In all patients between 3-45years old who presents with neurological manifestations (like abnormal movements), psychiatric disorders (especially like mood disorder and behavior disorder) and hepatic diseases (like cirrhosis and hepatic failure) always should be try to confirm and reject Wilson diseases, the goal is to treat these patients causatively. To prevent further delaying the diagnosis of this disease causes disability and death.

Of course, in our country there are no facilities for checking copper level, serum Ceruloplasmin level and genetic examinations. By providing it, it can help plentiful in the diagnosis and treatment of the patients. Also, after the diagnosis of Wilson disease treatment of the patients should be continued life time without pause or gap and patient should not get or use copper containing foods. Because this disease is a hereditary disease, if a member of a family has diagnosed Wilson disease, in order to confirm and for early diagnosis all other members of the patient's family should be

evaluated for Wilson disease examinations. It is also worth noting that efforts are being made to educate people about the risks of the transmission of hereditary diseases through marriages with closest relatives.

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