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A Plethora of Movement Disorders in Wilson's Disease – A Case Report

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Abstract

Introduction: Wilson's disease (WD) is a rare autosomal recessive inherited disorder of copper metabolism with deposition of copper in the liver, brain and extra hepatic tissue. It is caused by mutation of the ATP7B gene located at chromosome 13. In the nervous system basal ganglia and midbrain are most frequently affected. Untreated Wilson's disease has progressive course and may be fatal. Here we report a case of Wilson's disease with neurological symptoms in early adult life.

Case History

A 23 year old lady presented with complaints of stammering speech, involuntary moments of limbs, lack of Co-ordination and unstable gait which are progressive over 3 years. On neurological examination, Tone was increased in all 4 limbs (rigidity). Cerebellar examination demonstrated gaze evolved nystagmus, wing beating tremors and abnormal finger-nose and finger-finger-nose test and rebound phenomenon. Ophthalmological examination revealed greenish brown ring in both eyes-KF ring, confirmed by slit lamp examination. Laboratory investigation- CBC, urine microscopy, Renal and liver function test were normal. Targeted evaluation for WD exhibited Serum ceruloplasmin <9.00 mg/dl, Serum Copper-310 mcg/L and 24hour Urine Copper-219.79 mg/l. MRI brain with contrast shows symmetric T2/FLAIR hyperintense signals involving bilateral basal ganglia, thalamus, mid brain and pons with sub cortical atrophy. Ultrasonography of abdomen- showed, increased diffuse heterogeneous parenchyma with hyper

echogenicity and perihepatic fat of liver with features of Portal hypertension. Patient was started on Zinc acetate 150 mg daily in 3 divided doses, Propranolol 10 mg thrice day and 2 months later patient was started on D-Penicillamine 1gm twice daily.

Conclusion: WD is plethora of multiple dyskinesias. WD should be considered a prime differential in patients with multiple dyskinesias, unexplained neurological symptoms and multiple localising lesions.

Keywords: Wilson's disease, Movement disorder, Tremors, Kayser- Fleischer ring, Panda sign, Copper chelating agents.

Introduction

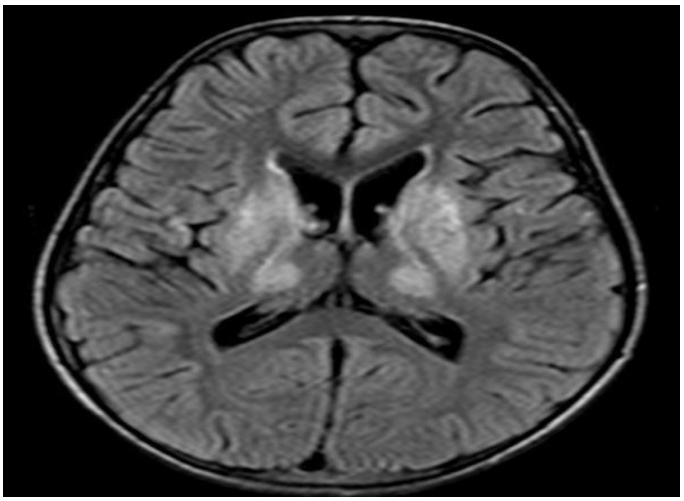
Wilson's disease (WD) is a rare autosomal recessive inherited disorder described first by Samuel Alexander Kennier Wilson in 1912. The incidence of WD is estimated to be one in 30000 births[1] and 1 in 90 carriers of disease[2]. It is caused by mutation of the ATP7B gene located at chromosome 13 that encodes hepatic copper transporting P-type ATPase which is located in the Trans -Golgi network and cytoplasmic vesicles. Defective ATPase in WD hinders Ceruloplasmin synthesis and biliary excretion of copper. Excess Serum non-Ceruloplasmin bound copper leads to tissue toxicity via oxidative stress and cellular apoptosis resulting in broad ranging clinical manifestations dominated by signs of liver and brain injury[3]. The chief neurological manifestation is abnormal movements such as tremor, chorea, dystonia and bradykinesia, difficulty in swallowing, poor articulation and excessive salivation.[4]. WD has varied presentations, classified into three movement disorder syndromes: Dystonia, Ataxia and Parkinsonian [5]. Although mixed presentation is noticed, rarely reported in the literature. Most often the disease tends to be underdiagnosed; timely diagnosis remains a challenge. Early diagnosis is the key to preserve irreversible brain impairment and quality of life. Here we report a case of WD with mixed syndromic neurological symptoms in early adult life.

Materials and Methods

A 23 year old lady presented with complaints of stammering speech, involuntary moments of limbs, lack of Co-ordination and unstable gait which are progressive over 3 years. No history of weakness and associated sensory, autonomic or cranial nerve involvement. She had history of secondary amenorrhea for 2 years. No similar illness in the family. General physical examination was within normal limits. On neurological examination, higher mental function was normal (mini mental status-24/30). Motor examination revealed normal bulk, power and reflexes. Tone was increased in all 4 limbs (rigidity). Cerebellar examination demonstrated gaze evolved nystagamus, wing beating tremors and abnormal finger-nose and finger-finger-nose test and rebound phenomenon. Tandem walking could not be pursued. She also had other movement abnormalities like head titubation, resting tremors of both hands and oro-mandibular dystonia leading to drooling of saliva. Examination of sensory, autonomic and cranial nerves did not reveal any abnormality. Ophthalmological examination revealed greenish brown ring in both eyes suggestive of Kayser–Fleischer (KF) ring (Fig: 1), which was confirmed by slit lamp examination.

Fig. 1: Picture demonstrating greenish brown KF ring at sclera-corneal junction in both eyes.

Fig. 2: Picture of MRI Brain demonstrating, T1 hyper-intensities in basal ganglia bilaterally.



Laboratory investigation such as CBC, urine microscopy, Renal and liver function test were within normal limits. Targeted evaluation for WD exhibited Serum ceruloplasmin <9.00 mg/dl (20-35 mg/dl), Serum Copper-310 mcg/L (700-1520 mcg/L) and 24hour Urine Copper-219.79 mg/l (20-50 mcg). MRI brain with contrast shows symmetric T2/FLAIR hyperintense signals involving bilateral basal ganglia, thalamus, mid brain and pons with sub cortical atrophy (Fig:2). Ultrasonography of abdomen to rule out liver involvement showed increased diffuse heterogeneous parenchyma with hyper echogenicity and perihepatic fat of liver with features of Portal hypertension. Diagnosis is established according to the Leipzig clinical scoring system (2001)[6].

The following treatment was initiated:

1) Restriction of copper rich foods.

2) Zinc acetate 150 mg daily in 3 divided doses.

3) Propranolol 10 mg three times a day.

2 months later patient was started on D-Penicillamine 1gm twice daily with monitoring of CBC, urine microscopy. Doses were adjusted based on 24hrs urinary copper estimation. Screening of family members for Wilson's disease was recommended. The patient provided written informed consent for the details to be published.

Discussion

WD is a disorder of copper metabolism. More than 500 mutations have been identified in ATP7B gene thus far. Most common mutation worldwide is H1069Q[6]; In India C27X1, G1101R, C813A are commonly encountered[7]. Upon chronic exposure to abnormal copper concentrations, astrocytes and neurons undergo morphological changes. Hydropic swelling of myelin sheaths and demyelination is the earliest consequence of cerebral copper overload[8]. Most severe abnormalities are present in putamen in the form of putaminal necrosis and cavitation in thalamus, dentate nucleus or white matter[9].

Wilson's disease presents in childhood with a clinically silent period, followed by sub clinical hepatitis, liver cirrhosis and appearance of Neuro psychiatric manifestation[1]; however, similar to our case, Neuro psychiatric manifestation may precede hepatic manifestation if the presentation occurs late in 2nd to 4th decade[10.] The youngest Wilson's disease patient with neurological symptoms was aged 6 and the oldest 72 years[11]. In a study done by Das SK, Ray K, et al. neurological symptoms are the initial manifestation in 40-50% of Wilson's disease patients. Neuro-psychiatric presentation is predominantly seen among males (60%), while our patient falls among the less commonly affected population, i.e, female (39%) [12].

Among the 3 primary neurological syndromes described, Dystonic form is seen in 69% of WD patients. It manifests as focal, segmental, multifocal or generalised symptoms[13]. Focal dystonia of vocal cords and articulation muscle may produce dysphonia, dysarthria and dysphagia. Other focal involvement may produce Torticollis, blepharospasm and risus sardonicus- a fixed smile because of dystonia of risorius muscle[14].

Involvement of nigrostriatal dopaminergic pathways leads to Parkinsonian form, described in 19-62% of WD patients, that presents as symmetric bradykinesia, imbalance and cogwheel rigidity[14]. Ataxic form, seen in 30% of Neuro WD patients, arises due to compromise of the dentate nucleus and demyelination of the cerebellar tracts[15]. It presents as abnormalities in posture, gait, dysdiadokinesia, dysmetria, hypotonia, occulomotor abnormalities, intentional tremors and speech disturbances[16]. Our patient had movement abnormalities falling in all 3 neurological syndromes. This may be due to involvement of multiple areas within the brain.

Tremors are the first neurological symptom in 55% of the individuals, although noticed in 90% of patients with WD[4]. Tremors may be of dystonic, rubral, parkinsonian, essential or mixed type[17]. Rubral tremor (Wing beating tremor) is characteristic of WD; a proximal tremor of high amplitude better seen with out-stretched arms, due to the involvement of dentatorubro thalamic tracts[18]. Prashanth K, et al. study on neuro Wilson's disease patients, found that 14.5% had seizures, 68.7% of them had partial seizures while the rest had generalised seizures (31.3%) [19]. Milder form of cognitive impairment, concentration inability and progressive deterioration in school and work performance is seen in 4.5% of WD. To note, our patient is also a drop out from graduation course. Other atypical neurological presentations are ocular motor abnormalities (nystagmus, conjugate ocular palsy and saccades), dementia, hypokalemic periodic palsy, occulogyric crises, muscle cramps, distal dysesthesias, myoclonus, tics, headache, taste and olfactory dysfunction, restless leg syndrome and sleep disturbances[16]. Psychiatric symptoms commonly seen are depression, emotional lability, irritability and disinhibition[19]. As the disease progresses the classic syndrome evolves causing dysarthria, dysphagia, drooling of saliva, fixity of facial muscles with mouth constantly agape- vacuous smile, extreme rigidity, flexed limb postures, immobile and mute.

Conclusion

WD is plethora of multiple dyskinesias. WD should be considered a prime differential in patients with multiple dyskinesias, unexplained neurological symptoms and multiple localising lesions.

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