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Wilson's Disease: An Uncommon Presentation

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Abstract:

Wilson's disease (WD), also known as hepatolenticular degeneration, is an inborn error of metabolism inherited as an autosomal recessive trait, characterized by toxic accumulation of copper in the body, particularly liver, brain and eyes. In children,WD presents more often with hepatic manifestations like acute hepatitis,cirrhosis of liver or liver failure.We present an unusual presentation of WD in a 15 years old male child who presented with neuropsychiatric manifestations without hepatic involvement.

Keyword: *Wilson's disease, hepatolenticular degeneration, neuropsychiatric manifestations, autosomal recessive.*

Introduction:

Wilson's disease(hepatolenticular degeneration)is an autosomal recessive disorder caused by mutations in the ATP7B gene,a membrane bound copper transporting ATPase.ATP7B protein deficiency impairs biliary copper excretion, resulting in a positive copper balance, hepatic copper accumulation and copper toxicity from oxidant damage.As the disease progresses, nonceruloplasmin serum copper level increases, resulting in copper build up in other parts of the body.[1]The organs most affected are liver,basal ganglia of the brain, eyes, kidneys and skeleton.[2]WD has a drastically varied clinical presentations that lead to diagnostic difficulties.[3]Symptoms usually arise from age 5 to 45 years.[2]The presenting feature in young patient,in 1st and 2nd decade of life, is mainly of hepatic origin, ranging from asymptomatic, with only biochemical abnormalities, to acute liver failure or cirrhosis of liver.[3]Neurological damage tend to present in later adolescent.[2]Here we report a case report of WD with neurological features in a 15 years old child, as apposed to the hepatic involvement as expected in a patient of his age group.

Case Report:

A 15 years boy, 1st offspring of nonconsanguineous marriage, was admitted into DMCH with the complaints of slurring of speech followed by inability to speak, difficulty in swallowing and drooling for two years and difficulty in walking followed by abnormal posture and inability to walk for 1 year and involuntary, abnormal movements for last 6 months. All these complaints were preceded by some behavioral disorders in the form of excessive anger, occasional irrelevant speech and poor concentration. There was no history of jaundice, abdominal swelling, haematemesis or malaena. His developmental milestones were normal. Family history revealed no abnormality. Birth history was uneventful and no history of drug intake.

On examination, the patient was cachectic. His vital signs were within normal limits. There was no pallor, jaundice or clubbing. Liver was nonpalpable. Neurological examination showed severe dystonia with extreme posturing of extremities and trunk and tremor of arms and legs. There was severe muscle wasting, deep tendon reflexes were absent with bilateral planter withdrawal, but ankle clonus was present. He had abnormal eye movements and dysphagia. Other systemic examinations revealed no abnormality.

On investigations, complete blood count revealed Hb% 9.7 gm/dl and otherwise normal findings. MRI of brain revealed, bilateral symmetrical T_2 flair hyperintense areas noted at lentiform nucleus (globus pallidus and putamen) and head of caudate nucleus. T_2 flair hyperintense areas are also seen in brainstem involving periequiductal region.

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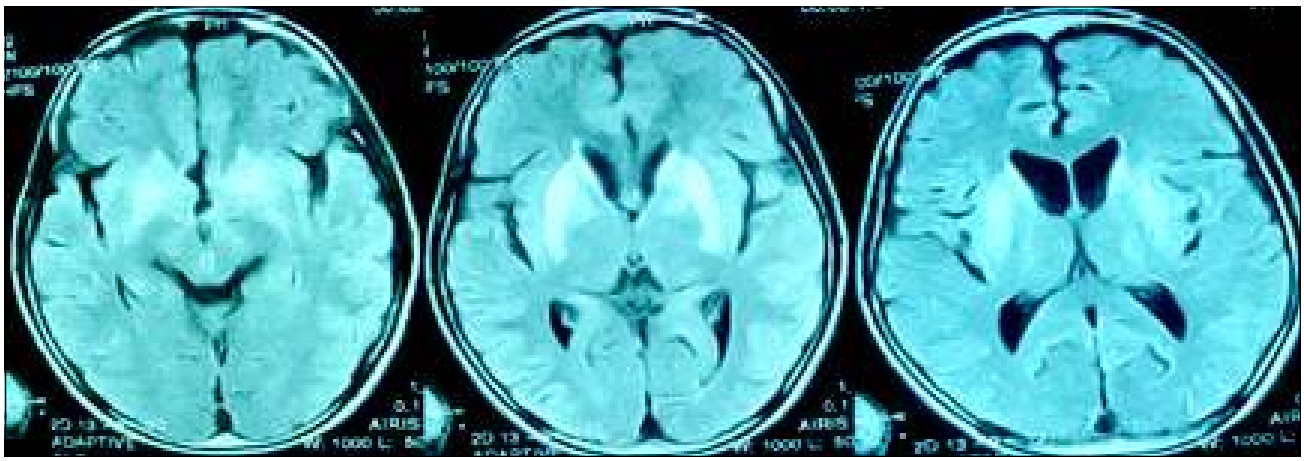

Figure: *T_2 flair showing hyperintense areas in various regions of brain.*

Presence of K-F ring was detected by slit lamp examination. Urinary Cu was 543 mic. gm/24 hr and S. ceruloplasmin level was low.liver function tests were normal and USG of W/A showed normal liver with uniform echotexture.

Initially treatment was started with penicillamine at a dose of 1g/day.Within 6 days some improvement was noted, like improvement of dysarthria and reduction of tremor. But after consultation with neurologists, penicillamine was switched to zinc 150mg/day,as penicillamine is documented to worsen neurological symptoms.[2]After omitting penicillamine, he started to deteriorate on zinc therapy alone. Next, combined treatment with both zinc and penicillamine was started with significant improvement.

Discussion:

Wilson's disease is an inherited autosomal recessive inborn error of Cu metabolism, characterized by toxic accumulation of Cu in liver, brain, cornea, and other tissues. The main etiology is credited to mutation in the ATP 7B gene, located on chromosome 13. What make this disease important is its diverse presentations and delayed diagnosis. Also it may be fatal to the life of the patient if it remains undiagnosed due to its progressive nature.[3]

Wilson's disease is present in most populations worldwide and particularly in those in which consanguineous marriage is common. The disease frequency is estimated to be between 1 in 5000 and 1 in 30000 and the carrier frequency is approximately 1 in 90.[4]

In 1st decade of life, Wilson's disease present more often with hepatic manifestation. The average age of onset for those who present with hepatic manifestations is 11.4 years. After the age of 20 years, 75% cases present with neurological manifestations and 25% with both hepatic and neuropsychiatric manifestations.[3] Our patient is 15 years old but presenting features were entirely neurological, which is usually not seen in a patient of his age group. No hepatic involvement was found.

Although copper accumulation begins at birth, symptoms of disordser appear later in life. The primary consequences in most individuals with Wilson's disease is liver disease, appearing in late childhood or early adolescence as acute hepatitis, liver failure or chronic liver disease.[5] Neurological manifestations at initial onset have been reported in approximately 18% to 68% . Most of these presentations are in late adulthood.

In case of neurological presentation, another important point is misdiagnosis and delay in diagnosis. The delay in diagnosis appears clinically significant as treatment outcomes have been reported to be better for those with a correct initial diagnosis. Walshe, who introduced penecillamine, trientine and tetrathio molybdate therapy, states that "no two patients are ever the same, even in a sibship and there is not such thing as a typical picture of Wilson's disease".

Because of the clinical heterogeneity,an understanding of the initial neurological signs and symptoms of Wilson's disease is diagnostically useful. Among initial manifestations, dysarthria is the most common, followed by dystonia, abnormalities of gait, tremor, parkinsonism and chorea. Tremor, dystonia and dysarthria can be sole disease manifestations. Moretypically, combinations of neurological features coexist, with a small number of features predominating. During the course of disease other neurological features include seizures, chorea, athetosis, myoclonus, ataxia, pyramidal signs, drooling and eye movement abnormalities.[6]

In absense of treatment, neurological symptoms are progressive and result in a severely dystonic akinetic mute state with relative preservation of cognition, as our patient presented to us. Psychiatric symptoms are ill defined and attributed to other causes, so diagnosis of WD is rarely made during the period in which psychiatric symptoms are sole manifestation. At diagnosis, the most common symptoms have been reported to be cognitive impairment, incongruous behaviour, irritability, depression and personality change.[7]

Till present date, no single test can exclude or confirm WD with 100 percent certainity. Diagnosis is based on clinical evaluation along with biochemical and neuroimaging confirmation. Biochemical studies reveal a low serum ceruloplasmin level(<20mg/dl) and increased urinary copper excretion(>100microgram copper per 24hours).Hepatic copper estimation of more than 250microgram/g of dry tissue,is the most definitive diagnosis. In WD patients, neuroimaging abnormalities occur in gray matter of lentiform,caudate and thalamic nuclei.[9]

MRI has been proven in our case an efficient method of documenting involvement of central nervous system in WD thus allowing better anatomical and clinical correlations.[3] In an individual with neurological or psychiatric dysfuction, the presence of Kayser Fleischer rings strongly supports the diagnosis of WD. In our patient only after the detection of KF rings on opthalmic slit lamp examination, a probable diagnosis of WD was made. However,the absence of KF rings in individuals with CNS dysfunction has been reported. In a study by Oracz et al,36 children(age 7 to 17 years)with WD KF rings were present in only two(5.6%).[3]

Prior to treatment era, the median survival following development of neurological symptoms was approximately 5 years. But with introduction of chelating agents, a specific feature of WD, now medical therapy is used to treat presymptomatic as well symptomatic individuals. But response to treatment is variable. Early onset of the disease may foretell a better prognosis than later onset. The disease requires lifelong treatment.[5]

Few studies have systematically investigated or reported the effect of treatment on individual neurological signs and symptoms. It has been suggested that tremor may be more treatment responsive than dystonia or dysarthria.[7] Penicillamine and trientine are copper chelator that increase urinary excretion of copper, however both drugs have some side effects. Zinc,which blocks absorption of copper in the stomach causes no serious side effects. Tetrathiomolybdate is an investigational copper chelating agent with lower toxicity profile.[5]Penicillamine is known to cause deterioration or onset of neurological disease in both presymptomatic and symptomatic patient.[9]But our patient was treated with penicillamine and zinc combination and showed improvement. Besides these low copper diet was recommended which means avoiding nuts, chocolate, dried fruit and liver. Symptomatic treatment of musle spasms, stiffness and tremor may include anticholenergics, tizanidine, baclofen, levodopa or clonazepum.[5]Growing knowledge of copper transporting gene,ATP7B,which in it's mutated form causes WD, should lead to design better therapies for this disorder.[5]

Conclusion:

If such neurological features are initial presentation of Wilson's disease in such a young boy without any positive family history or hepatic manifestations, diagnosis becomes somewhat difficult delayed. More and more reporting of such cases should be done to raise awareness and for easy diagnosis and betterment of the patient.

Conflict of Interest: None

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