A CASE REPORT ON WILSON DISEASE

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ABSTRACT: A case of Wilson's disease, a rare autosomal recessive disorder of copper metabolism is reported here. The patient was presented with the difficulty in speech for 2 years .pain in the right elbow joint. He also noticed difficulty to perform any work by hands for 3 months. His speech was low volume slurred and monotonous, muscle tone was mildly increased, and gait was limping. Although it is not uncommon in India, variation in epidemiology, clinical presentation and course are reported. However, community-based incidence and prevalence rates are not available in India and incidences are limited to hospital based reports. Most often, the diagnosis is delayed.

Keywords: Wilson's disease, autosomal recessive disease, Chelating agents, Penicillamine, Zinc, Copper, Orphan disease, Liver transplantation

INTRODUCTION

SInitially described by Kinnear Wilson in 1912, Wilson's disease (WD, or Wilson disease), is the clinical condition resulting from mutations in the chromosome 13q14 in the region coding for the protein product ATP7B, and occurs in a sporadic fashion as well as inherited as an autosomal recessive disease (1). Homozygous, or, more commonly, compound heterozygous mutations lead to defective incorporation of copper into apo-ceruloplasmin and the subsequent formation of holoceruloplasmin, hampering the normal excretion of copper into bile. Wilson's disease (WD) is an autosomal recessive disease involving brain and liver secondary to altered copper metabolism. About 47% and 55% of cases reported have positive family history and consanguinity, respectively (2). The symptoms are nonspecific and the disease may present as hepatic disease or progressive neurological disorder (hepatic dysfunction being less apparent or occasionally absent) or as psychiatric illness with liver disease. The liver disease may be asymptomatic, with only biochemical abnormalities of cirrhosis (3). A patient (5-40 years old) presenting with liver disease, with a decrease in serum ceruloplasmin and detectable Kayser – Fleisher (KF) rings are generally regarded as having classic WD (4). Delay in diagnosis of WD is observed across all the health care levels (5).

Case report:

An 18year old patient was admitted with history of intermittent fever, difficulty in talking, slurring of speech, and pain in the right elbow joint. He noticed that he had difficulty in going up and coming down a staircase and in getting up from the squatting position. At the same time, he noticed difficulty in raising his arms up and in holding objects above the head. There had been no distal muscle weakness in the upper or the lower limbs. He could walk with support for the first 6 months of his illness but later, had required crutches. He was bedridden for 6 months prior to admission. All movements had been painful from the outset and more. His gait was noticed to be shuffling with a tendency to fall forward when trying to walk. At the same time, his face retained a wry smile and his speech became slurred and dysarthric. He frequently complained of generalized body pain and derived some relief when his clenched fist was helped open. He was also noticed to be emotionally labile.

Physical examination:

Pulse rate - 70b/m

Temp -96.5 F

B P -90/50mm of hg

Lab data:

Hb – 11.9g/Dl Rbc – 4.8 Pcv – 36% Mcv – 75fl Mchc – 32 Rdw – 16.1% Wbc – 5800

ESR – 20mm/Hr Neutrophills – 38 Lymphocytes – 50 Platelet Count – 1, 21,000

Discussion:

The cause of early age of onset in the present series and Eastern India remains largely unexplained; however, presumably, unrecognized environmental factors or habit of cooking food in copper utensils (in 40% of our cases) may be implicated as the triggering events for this illness. Male preponderance (67%) was observed in the present study, which has earlier been documented in the Indian literature (6,7). The mean delay in diagnosis was 25.2 months in the present series whereas this delay was noted to be 12.8 months in a study from western world. The long delay may be due to the illiteracy and ignorance of the patients along with absence of positive family history and the history of jaundice, which was recorded only in 2 (9%) and 3 (14.2%) patients in the abovementioned cases, respectively. The symptoms with which these patients approached (8).

The osseomuscular manifestations are encountered in this patient were those of renal rickets namely osteomalacia, osteoporosis and spontaneous fractures. These initially responded to vitamin D and calcium supplements (9, 10). The renal abnormalities that were present in our patient were aminoaciduria, renal tubular acidosis (type 2) and a reduced creatinine clearance. The latter two could well contribute to the genesis of the osseomuscular syndrome. Treatment with penicillamine was unsuccessful but patients of Wilson's disease with renal manifestations are known not to respond well to Penicillamine (11). Wilson's disease and extent of neuroimaging findings is controversial, the extensive lesions may correlate well with clinical severity. Most of the studies suggest a good clinicoradiologic correlation. We found basal ganglia hyperintensities in patients with dystonic, choreic symptoms and dilatation of frontal horns in patients with cognitive deficits. Patients with the late onset of disease had cerebellar atrophy. Five symptomatic patients had normal imaging. Overall, a fair correlation between the radiological findings and the clinical symptoms was observed.

Treatment:

The objectives of treatment, therefore, are to prevent appearance of symptoms in asymptomatic subjects, prevent clinical deterioration in affected subjects, and can also be life-saving in cases o acute-on-chronic hepatitis. Treatment principles in WD include the establishment of a certain diagnosis, since the

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treatment is life long, as well as the monitoring of compliance, early detection of complications, and integral management including early neuropsychiatric screening/evaluation and physiotherapy, as required.

Zinc: Initially its chloride salt, followed by its sulfate salt, zinc was first used in the early 1960s to treat WD but was kept unrecognized until 1978 (12). Zinc acetate is regarded to have a better gastric tolerance. However, in terms of efficacy, there is no difference between zinc salts (13). Its mechanism of action is different from the above mentioned agents, in that it induces enterocyte metallothionein, an endogenous chelator of metals, thus favoring copper entrapment into enterocytes and its elimination in the feces with the normal shedding of intestinal cells. Furthermore, zinc may also act beneficially by inducing intra-hepatic metallothionein, potentially providing further hepato-protection. Another possible mechanism of action of zinc is the inhibition of lipid peroxidation and the increase of available glutathione within hepatocytes, reducing oxidative damage. This drug has demonstrated to be efficacious in slowly creating a negative copper balance, and although initially it was favored only as maintenance therapy or in asymptomatic subjects, it is increasingly and successfully being used as first-line therapy as well.

D-Penicillamine: D-penicillamine, introduced in 1956 as the first oral agent for treating WD (14), chelates not only copper, but other metals as well. In fact, the initial racemic mixture that was available required the co-administration with pyridoxine (15), to avoid deficit of this vitamin, although supplementation with pyridoxine (25-50 mg daily) is still recommended. This drug favors urinary excretion of copper, but it also induces the endogenous intracellular chelatormetallothionein, favoring reduced absorption by elimination in feces. As D-penicillamine have some immunosuppressant properties.

Monitoring of treatment with all agents includes liver function tests, which should tend to normalize within a variable period of several months. With either D-penicillamine or trientine, plasmatic non-ceruloplasmin bound copper values should exceed 25 μg/dL at the start of therapy and should lie between 15-25 μg/dL during maintenance therapy. At the start of therapy, 24 h urinary copper excretion should be between 500 and 1000 μg/24 h (or from 300 to 1000 with trientine), and should lie between 200-500 μg/24 h during maintenance therapy (16, 17). Conversely, monitoring of patients on zinc therapy must ensure a reduction in urinary copper excretion (initially below 100 μg/24, and from 30-80 μg/24 h on maintenance therapy), with a normalization off non-ceruloplasmin-bound copper (initially above 25 μg/dL, but 15-25 μg/dL on maintenance therapy). Additionally, urinary zinc excretion (which should be above 1.5-2 g/d) indicates adequate compliance to therapy. Furthermore, these two rare entities don't seem to share common pathways and their association appears incidental. It is interesting though that elevated serum copper levels can be found in various cancers, immune system diseases and lymphoproliferative disorders. Donghi et al. in 1995 reported an increase of serum copper concentration in Löfgren syndrome (a type of acute sarcoidosis with bilateral hilar lymphadenopathy and erythema nodosum). The authors concluded that, although the finding of an increase of serum copper in patients with mediastinal adenopathies is usually indicative of Hodgkin's disease, it can be related also to other conditions such as sarcoidosis.. On the other hand, environmental and occupational exposure to aerosolized copper and other metals (aluminum, barium, beryllium, cobalt, copper, gold, lanthanides, titanium, and zirconium) has been strongly correlated with granulomatous lung diseases that mimic sarcoidosis. [Newman LS. 1998, Metals that cause sarcoidosis]. Moreover, several cases of systemic sarcoidosis have been related with cutaneous foreign-body reactions to numerous elements, including copper, calcium, phosphorus, silicon, and aluminium (18).

Conclusion:

In the case discussed here, the coexistence of Wilson's disease with a seemingly idiopathic disorder such as sarcoidosis raises the question whether there is a potential link between these two diseases. One possible assumption is that the excessive copper due to Wilson's disease could have acted as an intrinsic factor that triggered an immunologic response in an immunologically predisposed patient and led to the manifestation of sarcoidosis. In any case, the coexistence of both diseases raises special considerations regarding the follow-up and future monitoring of the patient since they could share common hepatic or neurological manifestations.

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