Editorial

Problems in Diagnosis and Management of Wilson's Disease in India

"Why can't you Doctors diagnose Wilson's Disease early? We have seen so many Pediatricians with conflicting opinions, and done so many tests with varying results. By the time our son was finally diagnosed, it was too late"-A frustrated father expressing his anguish in a recently held National Seminar on Wilson's Disease in Mumbai.*

What is Wilson's Disease?

Wilson's Disease (WD) is an autosomal recessive inborn error of metabolism characterized by toxic accumulation of copper (Cu) in liver, brain, cornea and other tissues. The disease was first described by S.A.K. Wilson in 1912 as an "invariably fatal disorder of the nervous system caused by a toxin generated in connection with hepatic cirrhosis that is always found after death"(l). In 1948, Cumings identified this toxin as Cu(2), leading to the important development of Cu chelation therapy which has proven to be life saving provided it is started early and given regularly(3,4). Unfortunately, diagnosis of WD is often delayed, causing significant hepatic and neurological damage with resultant death or handicap.

With the declining incidence of Indian Childhood Cirrhosis (ICC), WD has become one of the leading causes of chronic liver disease in India(5). In our center in Pune, 78 children of which 53 are on regular follow up. A large series of 212 patients of WD (adults included) was presented at the Mumbai Conference from NIMHANS, Bangalore. Large numbers are also being followed up in Mumbai and Delhi (personal communication), and it has been suggested that the incidence of WD in India may be higher than the reported western figures of 1 in 30,000 to 1 in 100,000(6,7).

Why is it Difficult to Diagnose Wilson's Disease?

Variable Clinical Features(8-10)

The age of presentation can vary from 4 to 40 years though more than half present before the age of 15 years. The manifestations are more likely to be hepatic in early childhood and neurological in adolescents; other forms of presentation are also seen. Early symptoms are often vague and non specific such as lethargy, anorexia, abdominal pain and epistaxis. The spectrum of hepatic manifestations includes all forms of chronic or acute liver disease. Commonly the presentation is that of chronic hepatitis (CAH), portal hypertension with variceal bleed, and active or inactive (compensated) cirrhosis. Often WD presents like a typical acute "viral hepatitis" and sometimes like a fulminant hepatic failure (FHF). Presence of edema and ascites in a child with presumed viral hepatitis should suggest WD, especially with a history of a sibling dying of a similar disease.

* National Seminar on Wilson's Disease held at K.E.M. Hospital, Mumbai (23rd June, 1996); Convenors: Dr. B.A. Bharucha and Dr. D.P. Pane

Neurological abnormalities can be equally varied and include clumsiness, speech difficulties, scholastic deterioration, behavior problems and occasionally convulsions as also the well known choreoathetoid and dystonic movements. Most of these patients have past or concurrent history or biochemical evidence of liver disease.

The other type of presentation common in India is "osseomuscular" with bony deformities (knock knees) suggestive of resistant rickets (ll). Other manifestations include rashes, acute or recurrent hemolysis, hematuria and generalized edema.

With such diverse presenting features, the key to diagnosis is a high index of suspicion which can increase only on greater awareness of the disorder in the medical fraternity. Once suspected, it is theoretically easy to confirm or exclude WD by appropriate tests of Cu metabolism.

Unreliable Diagnostic Tests

Diagnostic tests of WD include: *(i)* high hepatic Cu (> 250 µg/g dry liver), *(ii)* low ceruloplasmin (Cp) (< 18 mg/dl), *(iii)* increased non-Cp Cu (free Cu), *(iv)* increased urinary Cu (> 100 µg in 24 hours increasing to > 250 µg in 24 hours) after test dose of penicillamine, and *(v)* KF rings as seen by slit lamp microscopy. Hepatic Cu and 'free Cu' are available only in a couple of centers in India. Twenty four hour urinary collections are not easy in children and early KF rings are often equivocal even by experienced ophthalmologists! Cp which is the most widely used test may be normal in up to 20% of WD patients, may be low in normal carriers; may be raised by CAH and reduced by hepatocellular necrosis. Further different laboratories use different techniques for estimation of Cp making comparisons difficult.

Histological features suggestive of WD (hyaline, nuclear glycogen, Kupffer cell hyperplasia) are likely to be over shadowed by changes of liver disease (CAH, cirrhosis or fulminant hepatitis). Cu stains (orcein, rhodanine) which are so characteristic in ICC are unremarkable in WD(6). Isotopic scanning of liver may show reduced uptake and CT or MR imaging of brain may show lucencies in basal ganglia and cerebral atrophy(12). Radioactive Cu studies are expensive, difficult to interpret and not yet available in India(13).

Therefore, positive tests can clinch the diagnosis. But, if tests are equivocal, one has to rely on circumstantial evidence such as high SGPT, evidence of hemolysis or low Cp in parents or sibs.

Why Such Varied Features?

Although manifestations of WD are multiorgan, the defective Cu homeostatis is confined to the liver or biliary tract. The faulty mechanisms appear to be decreased biliary Cu excretion and impaired incorporation of Cu in newly synthesized Cp (Ceruloplasmin itself does not appear to be faulty) (14). Cu accumlates initially in the hepatic cytosol. As the cytosol saturates, Cu is redistributed to lysosomes while some free Cu is released into the circulation. Sudden shift of intracellular Cu causes acute symptoms of FHF and hemolysis, while gradual shift leads to cirrhosis(15). Cytosolic Cu does not stain easily with orcein. Free Cu released in the circulation accumulates in the brain and other tissues giving rise to related symptoms. It is interesting that although Cu is deposited all over the brain, it is the basal ganglia that are chiefly affected(16). The exact mode of Cu toxicity at the cellular level is not yet known but is likely to be an oxidant injury (14).

Problems in The Management of Wilson's Disease

Once diagnosed, WD is theoretically a 'treatable' disease, implying a good outcome on adequate therapy. In practice this dose not always happens. WD cannot be prevented or controlled by a low Cu diet alone. Avoidance of chocolates, nuts, organ meats and Cu vessels for water is, however advisable.

The drug of choice especially for initial use is D Penicillamine 20 to 40 mg/kg/day up to a maximum of 1.5 g/day in 2 or 3 divided doses. The medication should be given atleast half an hour before or two hours after food. Patients must also receive Pyridoxine (50 mg/day)

because of the antipyridoxine effect of Penicillamine. The mode of action of Penicillamine appears to be two fold: *(i)* “decoppering" of tissues, and more importantly *(ii)* "detoxyfying" of Cu by induction of metallothionein (MT) and binding of free Cu(17). Adverse effects though rare in childhood (rashes, fever, proteinuria, marrow suppression) may require temporary discontinuation or complete withdrawal. Alternative drugs, trientene and ammonium thiomolybdate, also effective in initial decoppering are not easily available in India (18,19). Of special interest is the easily available and relatively safer zinc (Zn), which is also a powerful inducer of MT. The recommended dose of zinc as acetate or sulfate is 150 mg three times a day also on an empty stomach and not *with* Penicillamine. However, Zn alone may not be effective for initial decoppering though it may be suitable for maintenance therapy(20).

Maintenance therapy with any of the above drugs is necessarily life long giving rise to problems of monitoring and compliance. Frequent clinical and laboratory tests are essential to monitor the adequacy of medications and to control side effects. Blood counts, urinary protein, SGPT and 24 hour urinary Cu have to be inbuilt in the follow up systems. The greatest problem in 'life long' maintenance therapy however, is not medical but economical as penicillamine, therapy costs atleast Rs 1,000/- per month per child.

Despite initiation and maintenance of adequate Cu chelation therapy, the outcome is unpredicatable with upto 48% mortality in hospital series(10). The types of outcome seen are(6,21): *(i)* Rapid and complete clinical improvement especially of hepatic symptoms with reversal of parenchymal lesions including early cirrhosis; *(ii)* Initial deterioration particularly of neurological symptoms with eventual improvement but with residual handicap (speech, hand writing); and *(iii)* Relentless deterioration and death inspite of therapy as in FHF and hemolysis. Patients with advanced cirrhosis and its complications may also succumb after a prolonged survival. The only hope in such cases presently is an urgent liver transplant.

Asymptomatic Sibs: Recent Advances in Molecular Biology

Once WD is diagnosed, all the siblings must be screened and offered treatment if proven to have WD, even if they are symptom free. It is these children who have the best chance of normal health and longevity provided they take regular therapy(22). However, early biochemical diagnosis is not easy because Cu metabolism of normal neonates and infants resembles WD physiologically. Healthy carriers of WD also demonstrate abnormalities of Cu metabolism particularly low Cp. Early differentiation is however crucial, to avoid unnecessary commitment of normal and carrier sibs to life long, potentially toxic therapy. Exciting advances in molecular biology have helped clarify such situations even at birth.

The gene responsible for WD has been recently identified on chromosome 13, and the predicted gene product is Cu binding Ptype ATPase protein(23, 24). The genes for Cp and metallothionin (MT) are on chromosome 3 and chromosome 16, respectively suggesting that WD is not an abnormality of Cp or MT. Linkage disequilibrium studies using microsatellite markers have led to the identification of specific WD haplotypes(25). In an ongoing study from our center we found haplotype analysis particularly useful in determining disease status of 45 asymptomatic sibs (normal = 19, affected = 5 and carriers = 21; unpublished observations). These studies however, are not yet useful in the diagnosis of new cases of WD without any family history.

The investigation of great promise for new cases is mutational analysis. To date 25 mutations have been reported in the ATP7B gene responsible for WD(26). Identification of these and other mutations in our children is now under way.

Parent Support Group

One of the chief objectives of the Mumbai Conference was the formation of a National Parent Support Group. One such local group (registered body) exists in Pune since 1993 and is called ROWIKEM (RO for Rotary help, WI for Wilson’s disease and KEM for the hospital base). Notable achievements of ROWIKEM have

been: *(i)* Bulk buying of penicillamine directly from distributor thereby ensuring a regular supply, guarding against spurious drugs and slashing costs considerably; *(ii)* Sharing of experiences and emotional support of members especially in difficult times such as 'initial deterioration' and *(iii)* Educational and vocational rehabilitation of handicapped children. Agenda for the national body should include: *(a)* Widespread awareness of the disease and its treatment particularly amongst doctors; *(b)* Support research *(e.g.,* for molecular studies); (c) Manufacture of penicillamine cheaply in India; and *(d)* Help in setting up regional referral centers where standardized and reproducible Cu studies are available. The most significant contribution of the support group will be to provide a forum where parents can channelize their frustration and anguish into hope and attainment.

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NOTES AND NEWS

IAP RAIPUR BRANCH V ANNUAL SYMPOSIUM AND WORKSHOP

The Indian Academy of Pediatrics, Raipur Branch is organizing its 5th Annual Symposium and Workshop on Pediatric Gastroenterology on 23rd and 24th November, 1996. For further details please contact: Dr. D.K. Sur (Convener), Near L.I.B. Office, Byron Bazar, Raipur (M.P.) 492 001.