Wilson’s Disease: Aspects of Diagnosis and Treatment

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Sir,

The case report on Wilson’s disease by Singal P, et al, published in JAPI 2013, July Issue, pg.78-79 (Wilson’s Disease Unmasked by Antitubercular Therapy Induced Liver Injury) makes a very interesting reading. We would like to add a few observations regarding the same.

Tests for copper turnover and metabolism are often abnormal in chronic active liver disease (CALD). In such cases parameters reflecting metabolism of copper e.g., hepatic copper content, urinary copper excretion, are often abnormal and may overlap values found in Wilson’s disease.²,³

We like to share our experience regarding the above, wherein a patient, 17 yrs, female, with tuberculous lymphadenitis under antituberculous treatment (ATT) had her underlying Wilson’s disease unmasked following ATT. The patient was ultimately diagnosed by analysis of mutation of ATP7B, the candidate gene for Wilson’s disease.

Cases of Wilson’s disease which present on the background of chronic liver disease, in our opinion, are the appropriate candidates for molecular diagnosis by mutation analysis and detection of haplotypes. However, since hepatic decompensation following ATT is not a very uncommon situation, the cost involved should also be kept in mind, especially in view of the fact that the number of mutations reported till date are more than three hundred.

A further note about the simultaneous use of trientine and zinc. The combination of zinc and trientine can induce serious sideroblastic anaemia and the result is a dramatic worsening of neurological signs. Secondly, the logic of treating a patient with a metal (zinc) and a chelating agent is difficult to follow; one will combine with the other and neither becomes effective. If this strategy is to be followed, it must be made very clear to the patient that different drugs must be given many hours apart.³ Thirdly, chelating agents like trientine should always be given before meals, as observed with a test dose of radio-copper that it mobilizes more copper when given before meals than when given after meals.

References

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Sir,

The manifestations of Wilson’s disease are protean, and the recognition of its possibility in a given case is difficult, leading to an underdiagnosis of the disease. The delay in work-up increases the risk of permanent damage to liver and/or brain. Once the disease comes under consideration, a battery of investigations undertaken to establish the diagnosis, which includes urine copper, blood ceruloplasmin, slit-lamp examination for Kayser-Fleischer rings, and liver biopsy with quantitative copper assay.

First-degree relatives of any patient newly diagnosed with Wilson’s disease must be screened by history and physical examination (including subtle neurologic symptoms and signs), and appropriately worked-up with the above-mentioned tests.

The value of molecular genetic testing for mutations in ATP7B is limited due to the high number of possible gene mutations. These can occur anywhere along the entire 21 exons, which makes the identification of gene defects particularly challenging. Molecular diagnosis is reserved for family screening of first-degree relatives of patients with Wilson’s disease.

Excellent therapies exist for both the prophylaxis and treatment of Wilson’s disease. However, no two patients of Wilson’s disease are same, especially in their response to treatment. Management plans are, therefore, empirical, and differ with institutional experience. The mainstay of treatment for Wilson’s disease remains lifelong pharmacologic therapy; liver transplantation is reserved for severe or resistant cases. There are four drugs being used as anticopper agents. These are zinc, which blocks intestinal absorption of copper, penicillamine and trientine, both of which are chelators that increase urinary excretion of copper, and tetrathiomolybdate which forms a tripartite complex with copper and protein, and can block copper absorption from the intestine, or render blood copper non-toxic.

American Association for the Study of Liver Diseases (AASLD) recommends that initial treatment for symptomatic patients, or those with active disease, should include
a chelating agent (penicillamine or trientine).² Penicillamine is no longer the treatment of choice, as there is a growing experience with a safer and more effective alternative.⁴ Trientine may be the best choice for initial therapy. Typical dosages are 750 to 1500 mg/day in 2 or 3 divided doses. It should be administered 1 hour before or 2 hours after meals. Trientine also chelates with iron and their coadministration should be avoided. A reversible sideroblastic anemia may be a consequence of over-treatment.

Treatment of presymptomatic patients (individuals over 3 to 4 years old identified as patients by family screening) or maintenance therapy of successfully treated symptomatic patients can be accomplished with zinc.² ³ Dosage in adults is 150 mg elemental zinc per day, in at least 2 divided doses to be effective. Acetate salt has less gastrointestinal distress compared to gluconate and sulfate. Taking zinc with food interferes with absorption and effectiveness of treatment, but dose adjustments can be employed to compensate for this effect if taking zinc around meal-time ensures compliance.

Zinc is also recommended for the treatment of the pregnant patient, because of its complete efficacy and lack of toxicity.⁵

Alternately, some centers use zinc as the initial therapy in symptomatic patients; and some authors recommend chelating agents for maintenance therapy also.

Combination therapy in which zinc is utilized in conjunction with a chelating agent (given at widely spaced intervals) has a theoretical basis in both blocking copper uptake and eliminating excess copper.² The trientine/zinc combination is advocated as the next treatment of choice for all symptomatic patients with liver or neurologic disease because its efficacy is equal or slightly superior to that of penicillamine and because it has a much lower incidence of side effects.⁵

For the initial treatment of patients presenting with neurological disease tetrathiomolybdate, may be preferred. Penicillamine may lead permanent neurological worsening, and zinc is too slow-acting to be optimal.⁵

Additionally, antioxidants, mainly vitamin E, may have a role as adjunctive treatment.² Foods with very high concentration of copper should be avoided (nuts, chocolates, mushrooms, shellfish, organ meats).

Adequacy of treatment of Wilson’s disease is judged by clinical and biochemical improvement and by measuring 24-hour urinary excretion of copper. Once disease responds, usually 2 to 6 months following initial therapy, maintenance dosages of chelators or zinc therapy may be commenced.²

References