Wilson Disease (WD) usually presents in the first decades of life, although rare patients were diagnosed with this disorder in their fifth and sixth decades after late onset of disease presentation.\textsuperscript{1,2} Its clinical expression varies, and disease penetrance and modifying factors are not known. We report on the presenting features, diagnostic evaluation, and outcome with treatment in two septuagenarian siblings who were initially diagnosed in their eighth decade of life.

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ATP7B exons 1 through 21 were amplified with polymerase chain reaction (PCR), purified with QIAquick PCR purification kit (Qiagen, Valencia, CA), and sequenced directly using BigDye Terminator sequencing kit with an ABI Prism 377 DNA sequencer (both from PE Applied Biosystems, Foster City, CA). The primers used for ATP7B amplification were based on Petrukhin et al. To verify that the mutations were located on two separate chromosomes, the exons containing two different alleles were subcloned using the TA cloning kit (Clontech, Palo Alto, CA) after the PCR amplification. Plasmid DNA from individual subclones was sequenced as above. Results indicated compound heterozygosity for disease specific ATP7B mutations E1064A and H1069Q in both patients.

Patients were treated with trientine and zinc for the first 8 weeks, and then with zinc thereafter for maintenance therapy as part of a clinical research protocol. This protocol randomized initial therapy with trientine and zinc or tetrathiomolybdate and zinc, followed by zinc maintenance therapy. Both patients’ conditions stabilized and improved these last 5 years. Patient 1 died earlier this year of complications of bronchopneumonia. Patient 2 is alive and well, now 6 years after first presentation.

The confirmation of WD in these two siblings makes them the oldest patients at the time of diagnosis to date. The advanced age and different clinical presentations of these two subjects with identical ATP7B mutations raise the bar as to the age for which WD must still be considered. Furthermore, it begs the question of the degree of penetrance for these other ATP7B mutations. This is a critical issue when molecular genetic testing is used for disease diagnosis rather than biochemical and clinical evaluations that rely on phenotypical expression of the disease.

The clinical variability in the phenotypical presentation of many WD patients has led to the quest for understanding whether specific genotypes are responsible for a specific phenotypical presentation. An important confounding factor is the limited number of individuals with homozygous ATP7B mutations. In one of the few larger populations with homozygosity (H1069Q) in Europe, there is a predominance of neurological presentation of the disease and a slight increase in the average age of presentation compared with other patients. The presence of apolipoprotein E genotype 3/3 amongst these homozygous patients with H1069Q mutations may be one of the extragenic factors that ameliorates the disease and delays the onset of disease presentation.

Although the clinical phenotypes of WD and age of onset are often similar among sibling patients with the same genotype, rarely do younger patients show neurological symptoms earlier than their older siblings, and there are reports of markedly different clinical phenotypes appearing in siblings. Some phenotypical variability in patients with WD is likely attributable to other extragenic and environmental factors, as demonstrated by differences in mode of presentation, hepatic copper content, ceruloplasmin levels, and disease course in patients with the same ATP7B mutations, even in identical twins and siblings such as those described in this report. Multiple variables such as dietary copper and zinc intake, upregulation of intestinal metallothioneins, and capacity for countering copper-induced oxidative stress at the cellular level via glutathione, superoxide dismutase, catalase, and heat shock protein pathways may all be important in modulating the phenotypic expression of disease. Other genetic variations that modulate the expression or function of factors necessary for the intracellular sensing and trafficking functions of the ATP7B protein, including the HAH1 chaperone protein essential for delivery of cytosolic copper to the ATP7B protein, also may contribute to the phenotypical variation in disease expression of WD.

The normal ceruloplasmin present in our index patient may have contributed to the delay in the initial diagnosis of WD. The level of serum ceruloplasmin is reduced in...
most patients with WD to a level below 20 mg/dL, although at least 5% of patients have levels above this value. Interestingly, when patient 1 was treated for her WD, the level of serum ceruloplasmin became less than 20 mg/dL, indicating that the initial normal level was a response to acute inflammation that subsequently resolved with treatment.

In summary, this report on 2 individuals with WD identified in their eighth decade of life highlights the larger range of phenotypical expression for WD than previously recognized. We suggest the clinical need for excluding WD in patients of all ages with evidence of liver disease, neurological disease, or psychiatric symptoms.

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