Copper rings, blue moons and sunflower cataracts

Anéis de cobre, luas azuis e cataratas de girassol

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When (Samuel Alexander) Kinnier Wilson described a new fatal disease that involved the liver and the lenticular nucleus of the brain in 1912[1] he was unable to recommend any treatment. In 1948 John Cumings demonstrated copper accumulation in the liver and brain and suggested that chelation with British antilewisite (dimercaprol) might be efficacious.[2] Wilson's disease is now known to be an autosomal recessive disorder caused by over 900 different mutations in the ATP7B gene which encodes a P-type ATPase that mediates ATP-dependent transport of copper. The ATP7B gene facilitates the incorporation of copper into the carrier protein caeruloplasmin in the liver and promotes the biliary excretion of copper by sequestering copper into vesicles that are excreted into the bile by exocytosis. There is considerable variation in mutation frequency across different geographic populations and a substantial proportion of patients have compound heterozygous mutations, harbouring different mutations on each gene copy. Genetic screening should be offered to first-degree relatives and targeted toward the mutation already detected in the proband.

Because of its relative rarity (prevalence varies by geographical location but ~1 in 30000 individuals) very few neurologists see more than a few cases of Wilson's disease during their career and despite the disease being recognized for more than a century the clinical picture, its course and response to treatment still remain slightly blurred. Throughout the second half of the twentieth century, expert opinion was dominated by a few clinical scientists with contrasting convictions leading to different schools of thought and resulting in uncertainty in the minds of many physicians with regard to optimum management. Many now believe that all major advances in therapeutics are made by multinational pharmaceutical corporations, but in the case of Wilson's disease the currently available life-saving 'orphan drugs' were introduced as a result of individual or small team research.[3]

In this issue of the Arquivos de Neuro-Psiquiatria, Deguti and colleagues[4] describe the clinical presentation, genetic and imaging findings, course and treatment of 262 cases of Wilson's disease that had been seen and then followed up at the Faculty of Medicine at the University of Sao Paulo over the past 75 years. The clinical findings were similar to those reported in other large series[5–9] with hepatological, neurological, and neuropsychiatric presentations being most common and most occurring in the first two decades of life. The oldest age at presentation was 53 years of age reminding physicians an unexplained movement disorder, especially if it is associated with bulbar symptoms, behavioral changes and a suggestive family history (including consanguinity) demands a careful inspection of the cornea with a hand lens for copper deposition and the measurement of serum caeruloplasmin. Late presentations of Wilson's disease tend to be more benign than those occurring in childhood. The higher frequency of neurological presentations in men (68.1%) was hypothesized to be due to the fact that they have higher concentrations of ferritin-bound iron in the brain making them more susceptible to neurological damage. Only 1% of the patients with a neurological presentation did not have a Kayser-Fleischer ring, whereas MRI of the head showed no abnormalities in either the basal ganglia, brain stem, or cerebellum in 10% (5/54). The mean duration of follow-up was 9 years but there was a very wide range (0–45 years), and in the course of the decades of follow-up, 82 patients died and a further 55 were lost to follow up. The first three patients seen at the hospital in the nineteen forties all died within 5 years of onset reminding readers that Wilson's disease was uniformly fatal before the onset of treatment. Direct genetic sequencing of 128 patients led to the detection of an ATP7B mutation in 90% of cases with a mutation in both alleles in 84%. The authors conclude genotyping may help with early diagnosis in asymptomatic individuals but that it is unable to predict clinical presentation, response to treatment, or disease severity.

D-penicillamine (750–1500mg a day) a copper chelator, in combination with pyridoxine (25–50mg) was the treatment of choice for 229 of the 245 patients. Zinc (55 patients) which blocks the absorption of copper in the gut and trientine (30 patients) another copper chelator were used as second-line

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therapies. 86 of the 111 patients with a neurological presentation improved, 9 remained stable and 16 worsened. D-penicillamine can lead to an unexplained deterioration after initiating treatment in some patients and 21% of patients were forced to discontinue the drug because of adverse events with one patient dying from nephrotoxicity. Poor adherence to treatment occurred in a third of patients leading to clinical deterioration. The persistence of a Kayser-Fleischer ring after effective de-coppering was linked to an overall poor response to treatment and its recurrence was seen in relapses.9 of the patients with hepatic failure were successfully treated with liver transplantation.

Deguti and colleagues' review reminds us that despite the fact that Wilson's disease is treatable and many patients who were diagnosed in childhood have now lived long and fulfilling lives there is a need for safer more effective chelating agents. Early accurate diagnosis is still a challenge and why some patients worsen upon starting chelation therapy remains a mystery. Poor compliance with treatment especially in patients with significant disease-related behavioral disturbances is another challenge that requires careful and sustained vigilance by the treating physician.

Conflict of Interest
There is no conflict of interest to declare.

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