Wilson’s disease: the 60th anniversary of Walshe’s article on treatment with penicillamine

Doença de Wilson: o 60º aniversário do artigo de Walshe no tratamento com penicilamina

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Wilson’s disease (WD) is a rare autosomal recessive metabolic disease resulting from mutations in the \textit{ATP7B} gene, which has been mapped to chromosome 13q141,2. The \textit{ATP7B} gene encodes a copper-transporting adenosine triphosphatase (ATPase) protein, which is expressed most abundantly in the liver and is responsible for biliary copper excretion. Because of defects in this gene, copper accumulates in several organs, especially the liver, brain (basal ganglia) and corneas1,2. Clinically, patients present with predominantly hepatic, psychiatric and neurological symptoms, particularly dystonia, tremor and parkinsonism. The Kayser-Fleischer ring is an important physical sign, and the most important laboratory tests are serum ceruloplasmin and urine copper levels1,2. The worldwide prevalence of WD is 1:30,000 and more than 400 distinct disease-causing mutations in the \textit{ATP7B} gene associated with WD have been identified1,2. Treatment options for WD patients include copper chelating agents such as penicillamine, trientine, ammonium tetrathiomolybdate and zinc salts1,3. First used in patients with WD 60 years ago, penicillamine is considered the most effective treatment for the condition1,3. Treatment options for WD patients include copper chelating agents such as penicillamine, trientine, ammonium tetrathiomolybdate and zinc salts1,3. First used in patients with WD 60 years ago, penicillamine is considered the most effective treatment for the condition1,3. This review describes historical aspects of WD and emphasizes the important contribution made by Professor Walshe to the treatment of this disease with his pioneering use of penicillamine.

WILSON’S DISEASE – HISTORICAL MILESTONES

Samuel Alexander Kinnier Wilson (1878-1937) published his masterpiece “Progressive lenticular degeneration: a familial nervous disease associated with cirrhosis of the liver” in 19121,3. He described twelve patients: four cases he had seen himself, two additional cases from the records of the National Hospital, Queen Square, London, UK, and six cases previously published in the literature1. From 1913 to 1952, several researchers published important contributions to the understanding of WD, including Rumpel (described excess copper in the liver), Gerlach and Rohrscheiner (reported excess copper in corneal rings), Kayser, Fleischer (Kayser-Fleischer corneal ring), Hall (introduced the term hepatolenticular degeneration), Cumings (suggested treatment with British antilewisite), Bearn and Kunkel, and Schieberg and Gitlin (reported deficiency of ceruloplasmin in the serum)1,3. Three years later, Walshe proposed the use of penicillamine for WD treatment, and his seminal paper was published in 19561,4,5. Five years after that, Schouwink described the use of zinc salts in the treatment of WD1,3, and in 1969 and 1984, Walshe reported the use of trientine and tetrathiomolybdate, respectively, for this condition1,3. In 1982, Starzl et al. published the first report of liver transplantation for WD1,3, and in 1993, three different groups identified the gene responsible for WD on chromosome 13q141,3.
JOHN M. WALSHE AND PENICILLAMINE

Walshe (Figure 1) worked with penicillamine (dimethylcysteine), a product of the hydrolysis of penicillin, in the early 1950s in Prof. Charles Dent's laboratory at University College Hospital, London, UK. He subsequently moved to the liver unit in the Thormdieke Memorial Laboratory at Boston City Hospital, Boston, USA, where he worked under the supervision of Prof. Charles Davidson. In the same hospital, Prof. Denny-Brown was working on WD and treating patients with British antilewisite, a drug with important side effects. Based on his previous studies, Walshe suggested to Prof. Davidson that penicillamine could be used as a copper-chelating drug. Following this suggestion, penicillamine was used in one patient with WD, and an increase in his urinary copper excretion was observed. However, because of various problems, additional tests proved inconclusive. Walshe then returned to the UK and restarted his studies with penicillamine in WD patients. The first WD patient to use penicillamine regularly was Ms S.F., who started treatment in 1955, and after one year of follow-up, clinical examination showed that penicillamine had been effective. In 1956, Walshe published a paper in the American Journal of Medicine under the title "Penicillamine, a new oral therapy for Wilson's disease" (Figure 2). Penicillamine was the first effective treatment for patients with WD. However, initial reactions from other researchers studying WD were less than enthusiastic, and both Denny-Brown in the USA and Cumings in London were very critical of Walshe's discovery. In 1960, Walshe published another paper on the treatment of WD with penicillamine in The Lancet. Ten years after penicillamine was first used to treat WD, its toxicity became evident and several side effects were observed. These were related to immunologically-mediated reactions, including skin lesions (elastosis perforans serpiginosa, epidermolysis bullosa), systemic lupus erythematosus, nephrotic syndrome, Goodpasture syndrome, Ehlers-Danlos syndrome, myasthenia gravis, polymyositis, thrombocytopenia and agranulocytosis. In some patients using penicillamine, a worsening of the neurological clinical picture (dystonia, parkinsonism) was observed. Walshe and Yealland found these unexplained side effects in 11 of 137 patients with predominantly neurological signs. Various hypotheses have been put forward to explain this paradoxical worsening of neurological symptoms, including a sudden release of ionic copper, the redox potential of copper, a low level of urate in the plasma following treatment with penicillamine and genetic mechanisms (unfavorable mutations in the ATP7B gene). The neurotoxicity and reversible side effects of penicillamine motivated various researchers, including Prof. Walshe, to look for new drugs to treat WD, and their efforts led to trientine, thiomolybdate and zinc therapy being used to treat this condition. Although penicillamine still remains the drug of choice for the treatment of WD, in recent years it has become the subject of some controversy because of its well-known side effects, particularly worsening of the neurological symptoms. In 1999, the journal Movement Disorders published three very interesting papers about this controversial issue by Walshe and his colleagues. Clinical Studies

Penicillamine, a New Oral Therapy for Wilson’s Disease

J. M. WALSH

Penicillamine is an increased concentration of copper in both the liver and brain of patients dying of Wilson's disease (hepatocerebral degeneration). Elevated copper levels are also found in the serum and urine of patients with Wilson's disease, and these levels can be reduced by the administration of penicillamine. The drug is well tolerated by most patients, and side effects are generally mild. However, some patients may experience an exacerbation of neurological symptoms, particularly those with pre-existing neurological conditions. The mechanism of this paradoxical worsening of neurological symptoms is not fully understood, but it may involve a sudden release of ionic copper, the redox potential of copper, or genetic factors. Penicillamine is still widely used for the treatment of Wilson's disease, but its use is monitored closely, and alternative therapies, such as trientine and thiomolybdate, are also available. In some cases, surgery may be necessary to remove copper from the liver and brain. Penicillamine is a safe and effective treatment for Wilson's disease, but it is important to be aware of the potential side effects and to monitor patients closely during treatment.
Prof. Walshe ("Penicillamine: the treatment of first choice for patients with WD"), Prof. Brewer ("Penicillamine should not be used as initial therapy in WD") and Prof. LeWitt ("Penicillamine as a controversial treatment for WD"), but no consensus about its use was reached, and penicillamine continues to be a treatment option for WD patients.

CONCLUSION

Professor John Walshe pioneered the treatment of WD and discovered various drugs that can be used to treat the condition, including penicillamine, trientine and thiomolybdate. His seminal paper published 60 years ago described the first study in which penicillamine was used as oral therapy for WD. Penicillamine remains an effective drug for treating patients with WD. However, neurologists should be aware of the advantages and disadvantages associated with its use.

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References