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A century for progress in the diagnosis of Wilson disease

Michael L. Schilsky*

Yale University School of Medicine, 333 Cedar Street, LMP 1080, New Haven, CT 06520, United States

A B S T R A C T

The diagnosis of Wilson disease has evolved from the original description of a neurological syndrome by Wilson and other contemporaries at the turn of the 20th century to where we recognize that there is a spectrum of clinical liver and neuropsychiatric disease diagnosed by a combination of clinical and biochemical tests and more recently by molecular genetic analysis. The history of the evolution of the findings that help us establish a diagnosis of Wilson disease are presented in the following brief summary of a century of progress toward this end.

Introduction

Even prior to the historic publication in brain of the monograph of the work of Samuel Alexander Kinnier-Wilson in 1912 [1], others had knowledge of movement disorders in relatively young patients characterized as “pseudosclerosis” or “tetanoid chorea” (cited in Wilson’s monograph: Westphal and Strumpell, Gowers, Omerod and Homen). Indeed there was recognition of abnormalities of the liver in some of these individuals. However none of these descriptions were as detailed as the careful case studies of 6 patients that led to the naming of the syndrome after the gifted author who so dutifully examined every detail of these patient’s lives and recorded them for posterity. The historical importance of this publication cannot be underestimated as it showed the brilliance of the author in postulating a connecting injurious toxin that led to the progressive lenticular degeneration and cirrhosis of the liver found in each of his cases. Later this toxin was shown to be copper, and the path from syndrome to our current molecular diagnosis of the disease was set in motion.

Manuscript

It is hard to believe in the current era, but even as late as the early 1960s the treatment of Wilson disease was reactive to the presence of symptoms. It was only during the late 1950s and 1960s that the transition of thinking of treatment to prevent symptom and disease onset took hold [2]. To accomplish pre-emptive treatment required disease diagnosis, and the insights and discoveries enabling this took nearly a century from the original descriptions of this disease and a syndrome.

In the turn of the 20th century, as described by Wilson and independently by Westphal and Strumpell, the disease that adopted the moniker “Wilson disease” was identified by the neurological features of progressive neurodegeneration of the lenticular nucleus giving rise to the classical features of tremor, involuntary movement, dystonia and spasticity (parkinsonian features were recognized only later on), dysphagia, dysarthria and anarthria. Another interesting observation probably represents the first identification of the psychiatric manifestations of this disease that range from labile mood to frank psychosis including bipolar disorder and schizophrenia when Wilson focused a segment of his manuscript on “emotionalism”. Though brilliant in his descriptions and insights, Wilson was however incorrect on a few fronts. He failed to recognize the true hereditary nature of the disease and felt it occurred sporadically and “familial”, and he thought the liver disease to be of interest only as a finding at death and that it did not manifest clinically during the patient’s lifetime. These important features were yet to be discovered.

The presence of corneal rings in patients who were later characterized as having Wilson disease was recognized independently by Berhnard Kayser in 1902 [3] and Bruno Fleischer in 1903 [4]. Initially these Kayser–Fleischer (KF) rings as they came to be known were thought to be due to silver deposition, but later they were recognized as copper containing deposits in Descemet’s membrane of the cornea. We now know that nearly all patients with neurological features of the disease like those Wilson described have KF rings, however only ~50% of patients with hepatic presentations have these rings when they are diagnosed.

The inherited nature of Wilson disease was first recognized nearly a decade after Wilson’s monograph was published by Hall in 1921 [5]. He was also astute in noting that the cases described as “pseudosclerosis” by Westphal and Strumpell were indeed patients with Wilson disease, something that Wilson initially denied but later came to accept.

* Tel.: +1 203 737 1592; fax: +1 203 785 6645.
E-mail address: Michael.Schilsky@yale.edu

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That copper was indeed the morbid toxin that Wilson postulated connecting the brain and liver disease in his patients was recognized as early as 1913 by Rumpell in cases of pseudosclerosis described previously by Westphal and Strumpell [6], however this finding was almost lost to history as initially Wilson was not willing to recognize the cases of pseudosclerosis as being the same disorder as progressive lenticular degeneration. Later descriptions appear again in 1930 of copper in the liver by Haurowitz [7] and then later in 1948 by Mandelbrote et al. [8] and by Cumings [9]. Therefore copper quantitation in the liver could be a useful diagnostic tool, however at this time this was mostly done post mortem as liver biopsy was yet to be developed and adopted (see below). Mandelbrote did however recognize that there was also increased urinary copper excretion in patients with Wilson disease. It was only later that the diagnostic utility of urine copper was explored when pediatric patients were subject to a penicillamine challenge to see if this copper chelator mobilized copper from excess stores [10]. This was later revisited in the more modern era by Dhawan et al. [11]; however, the utility of an elevated basal urine copper excretion in diagnosing this disorder may be equally useful when appropriate cutoffs are used [12].

A transition in thinking about Wilson disease appeared when the first screening tool for the diagnosis of this disorder, serum ceruloplasmin, was discovered. Though the protein was discovered by Holmberg and Laurell in 1948 [13], they were given serum of a patient with multiple sclerosis that was mistaken for Wilson disease. Therefore they did not make the discovery that is now credited to Scheinberg and Gitlin [14] and Bearn and Kunkel [15] that this copper protein, ceruloplasmin, is decreased in the circulation of patients with Wilson disease. We now know that assaying for concentrations of this protein either by its oxidase activity or by immunological methods is useful for helping the diagnosis of Wilson disease, but the sensitivity, specificity and positive and negative predictive value in differentiating patients from heterozygous carriers and unaffected individuals varies with the cutoff values utilized [16]. The theory that the failure to make this protein in patients with Wilson disease led to copper accumulation persisted for many years after this discovery however is well refuted by the finding that there is normal copper balance in patients with defects in the ceruloplasmin gene with aceruloplasminemia [17].

The other important transition in thinking about Wilson disease came with the advent of the percutaneous liver biopsy by Professor Menghini in 1958. With the ability to obtain hepatic tissue from patients with liver disease, it was possible to identify individuals with liver disease that had not yet developed the neurological features of Wilson disease. The next logical leap came with the recognition that these patients, once identified, needed treatment to prevent disease progression [2]. This subsequently led to the better elucidation of the natural history of Wilson disease as beginning with hepatic steatosis, inflammation and advancing fibrosis and cirrhosis. Ultrastructural abnormalities of the mitochondria due to copper toxicity were identified in Wilson disease patients and was used as an adjunct to diagnosis [18]. Copper quantitation was found to be useful and though a cutoff was established as greater than 250 mcg/g dry weight liver as diagnostic for Wilson disease, later work revealed that a lower threshold was more sensitive but less specific for disease diagnosis [19]. Histochemical copper was found to be useful and present mainly as copper in lysosomes; however, cytoplasmic copper, not identified by many histochemical stains, could be found by special sulfide detecting methods [20].

In the 1950s there were the first reports of acute liver failure with associated non-immune hemolytic anemia that were found to be due to Wilson disease. This presentation, affecting only about 5% of patients with Wilson disease, occurred more commonly in women [21] and could be identified even without biopsy of the liver by lower levels of alkaline phosphatase [22] and increased ratio of AST to ALT above 2 [23] and hemolysis with lower HgB [24].

The recognition that the defect in Wilson disease led to reduced biliary copper excretion led to the possibility of testing for lower copper in bile [25], however the practicality of this test was limited by the ability to obtain specimens non-invasively. Other methods for diagnosis included incorporation of ingested radiocopper into ceruloplasmin, a test that was most useful for helping to distinguish between patients and unaffected individuals with normal ceruloplasmin [26,27].

The typical evaluation for Wilson disease made use of the above testing, including ophthalmological evaluation for KF rings, serum testing for ceruloplasmin, urine copper excretion, liver biopsy and copper quantitation. While no single test was uniquely specific enough to diagnose Wilson disease, the combination of testing allowed for diagnosis in most patients. The next leap in diagnostics came with the identification of the location of the Wilson disease gene on chromosome 13, allowing for haplotype analysis of polymorphisms around the gene site [28]. This was followed in 1993 by the discovery of the gene for Wilson disease [29–31], and ultimately by the performance of genetic testing for mutations of this gene, ATP7B, initially by research and then by commercial laboratories. Over 500 disease specific mutations are now identified, and most patients are compound heterozygotes with one mutation on each *ATP7B* allele.

To help stratify whether to pursue a diagnosis of Wilson disease and establish or refute the diagnosis, a combination of clinical and biochemical and molecular testing was used to create a scoring system [32]. This scoring system was adopted into the diagnostic algorithm for Wilson disease by the EASL and recently published as guidelines [33]. Though seemingly simple, this algorithm incorporates knowledge and experience that has been gained over the past century for which this disorder has been recognized.

The next century may bring even better diagnostic testing, including neonatal screening and fist-line molecular diagnostics. Many of our historic testing modalities may still be useful for phenotypic characterization of patients for prognostication and for elucidation of relationships between genotype and phenotype and other environmental and extra-genic factors that influence the clinical expression of Wilson disease.

Conflict of interest

There are no conflicts of interest.

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