WILSON’S DISEASE

A case report and a historical review

Egberto Reis Barbosa¹, Alexandre Aluízio Costa Machado¹,
Eduardo Luiz Rachid Cançado², Marta Mitiko Deguti², Milberto Scaff¹

Abstract – The purpose of this report is to present a short review of the history of Wilson’s disease and to describe the first diagnosed case at the Neurologic Clinic of Hospital das Clínicas of São Paulo University Medical School. The topics of the historical review are the first contributions of authors along the second half of the XIX century, the seminal monograph of Samuel Alexander Kinnier Wilson (1912), the landmarks in the investigation of mechanisms of the disease and the introduction of the first effective treatment by John Walshe (1956). The first case studied in our Clinic, in 1946, was a 20-year-old male whose main neurological manifestations were postural tremor (“wing beat”) and dysarthria and could be characterized as Westphal-Strümpell form of the disease. Along the discussion of this case difficulties to establish the diagnosis and to treat the patient at that time are highlighted. We conclude with a brief history of the development of researches on Wilson’s disease in our Clinic, with an honor to the pioneer contributions of Horacio Martins Canelas.

Key Words: Wilson’s disease, historical review, copper metabolism.

Wilson’s disease (WD) is an autosomal recessive disorder of the copper metabolism leading to the accumulation of this metal in different organs and tissues. Hepatic and neurological symptoms are the main clinical features of the disease.

Some authors¹–³ attribute to FT Frerichs the first case report of WD, in 1861. The patient described by Frerichs was a 9-year-old boy who developed neurological symptoms characterized at the beginning by speech changes and difficulty to control the movements of the limbs. He later developed intention tremor, difficulty in swallowing and died at the age of 10. The autopsy revealed abnormalities compatible with cirrhosis of the liver.

Westphall⁴, in 1883, reported the study of two cases which had as the main neurological manifestation a tremor similar to that seen in patients with multiple sclerosis but their necropsy did not show the typical white matter lesions of this disease, well-known at that time. For this reason, Westphall used the term “pseudosclerosis” for this new disease.

Strümpell⁵,⁶ reported in 1898 and in 1899, three other cases of pseudosclerosis and the pathology of the third one revealed the presence of cirrhosis of the liver.

Gowers (apud Tyler⁷), in 1888, described the cases of a 10-year-old boy and his sister, in which there were a predominance on the clinical picture of a kind of move-
ment disorder that was named by the author as “tetanoid chorea.”

In 1906, Gowers (apud Wilson), in his new report named “On tetanoid chorea and its association with cirrhosis of the liver” described with more details the neurological abnormalities seen in one of the patients as: “both arms presented slow changing tonic spasm... at times the spasm changed so that the fingers were spasmodically extended; occasionally they were spread out and moved irregularly in a manner resembling athetosis”. This description shows clearly that Gowers referred to what today is called dystonic movements and postures. Illustrating this report there is a photo of the patient where we can see the dystonic postures of the four members. The pathological findings of both cases revealed the presence of cirrhosis of the liver while there were no defined lesions in the brain.

Ormerod, in 1890, reported a similar case in a 10 year-old child with rapid-onset of neurological manifestations along 3 to 4 months and he described them like this: “weakness of right hand and arm, with cramped position of the fingers, soon followed by difficulty of speech. Drawing of the face, then an unnatural gait. Speech gets worse; he seems silly; has some difficulty in swallowing. Gait much worse. Lastly some affection of left arm and hand’. The progression was fast and the death came 8 months after the beginning of the symptoms. In this seminal report, we can identify some neurological features that are hallmarks of the disease: the presence of a motor disorder affecting at the beginning, the right hand and arm suggesting dystonia; the early and severe involvement of speech; the facial expression compatible with rnisus sardonicus; and the quick progression to death in less than a year, as it can occur in the dystonic form of WD. The necropsy showed necrosis of the external segment of the lentiform nucleus (putamen) and the presence of cirrhosis of the liver. These pathological findings are in agreement with the diagnosis of Wilson’s disease. In this remarkable report, Ormerod emphasized the great similarity between his case and those reported by Gowers two years before with the patients described by Homén in the same year (1890). Homén’s report included 3 siblings (two males and a female) with ages at the onset of the disease ranging from 12 to 21 years old, and neurological manifestations similar to those described by Ormerod, although with a slower progression. Severe damage of nucleus lentiform and cirrhosis of the liver were also observed by Homén in his cases, despite he thought these were related to syphilis.

In 1902, Kayser reported the presence of a greenish-brown ring around the cornea of a 23-year-old man, thought to have multiple sclerosis. In the following year, Fleischer (1903) described the same pigmented ring in a case of “pseudosclerosis” and in another case of multiple sclerosis.

In 1911, Wilson presented his monograph describing the “progressive lenticular degeneration” that resulted in the publication of a historical paper in Brain journal, in 1912, with the title “Progressive lenticular degeneration: a familial nervous disease associated with cirrhosis of the liver. Briefly versions of the same study were published in 1912, in two other journals: the “Lancet” and the “Revue Neurologique” (Paris). In these seminal reports Wilson described four personal cases (three of them with neuropathological study), two referred (but not studied) by Gowers and Ormerod and six other cases from the literature (the cases described by Gowers; Ormerod and Homén). He emphasized the familial character of some cases and the presence of cirrhosis of the liver, mostly asymptomatic, but claimed that the liver did not contribute to the clinical progression of the disease. Bramwell, in 1916, was the first to realize the importance of liver pathology in WD, when he described a family in which 4 siblings died of “acute fatal cirrhosis” all between 9 and 16 years of age, and suggested that this cases might have been related to those reported by Wilson 4 years before.

Wilson did not see at his first papers a relationship between his cases and the pseudosclerosis of Westphal-Strümpell. However, two years later, while writing on “progressive lenticular degeneration”, Wilson mentioned similarities between the two entities.

In 1920, Spielmeyer, contesting the ideas of Von Hoeslin and Alzheimer concluded that, from the neuropathological point of view, pseudosclerosis and WD were the same disease.

The controversy between the followers of Wilson’s ideas about the unity of the two entities and Westphal, Strümpell and Alzheimer’s school, who considered them as independent, was definitely over in 1921 with the publication of Hall’s monograph. This author, based on the review of 64 cases of literature and studies of four personal cases, demonstrated in a conclusive way the identity between the two diseases. Furthermore Hall pointed out their inheritable character and assembled the two diseases under the name of “hepatolenticular degeneration”.

Once established the clinical characterization of the disease, the studies started to be orientated toward its etiopathogenesis.

Rumpel, in 1913, had already mentioned by the first time the increase of the amount of copper in the liver of a patient with pseudosclerosis.

According to Scheinberg and Sternlieb, Vogt, in 1929, Haurowitz, in 1930, and Glazebrook, in 1945, demonstrated the accumulation of copper in the liver and in the basal ganglia of patients with WD.

In 1948, some important discoveries brought a great advance to elucidation of metabolic disorders of WD. In this year Mandelbroe et al. studying the copper me-
tabolism in multiple sclerosis noticed that in the control group, that included patients with other neurological diseases, one patient with Wilson’s disease presented an increase of urinary excretion of copper. In a two-hour period the patient with WD excreted 41.7 µg of copper, whereas none of the other twelve patients studied excreted more than 18 µg. In the same year Cumings 18 definitely proved the accumulation of copper in the liver and in the brain of patients with WD.

Along the 1950s the investigation on WD concentrated on the study of the copper metabolism and on the treatment of the disease aiming to reduce copper accumulation. In 1952, Scheinberg and Gitlin 19 demonstrated the decreased level of ceruloplasmin in patients with WD and, in 1954, Cartwright et al. 20 reported the increase of serum free copper, not bound to ceruloplasmin, in patients with WD.

The attempts of treatment with copper chelating agents were unsuccessful until the introduction of the penicillamine by Walshe 21, in 1956, what made possible the long term treatment of the disease, so far always fatal. The efficacy of penicillamine in the treatment of WD was recognized only after several years. To illustrate this fact in the book published by Boudin and Pepin 22 on WD, in 1959, this drug was put in the same plane of others therapeutic options that later revealed completely ineffective such as isoniazide and sodium thiomalate.

From 1946 to 1961, six cases of the WD were evaluated in the Neurologic Clinic of the Hospital das Clínicas of São Paulo University Medical School (HC-FMUSP). The first of these cases, evaluated in 1946, is the objective of this report.

CASE

A 20-year-old white male, was admitted to the Neurologic Clinic in March 29th, 1946 under the care of Drs Ibrahim Mathias and Oswaldo Lange (Fig 1). He had an 18-month history of tremors. At the beginning, he noticed tremor in his right arm when holding a cup or a glass. After 2 months, the tremor became continuous and extended to the left arm, head and legs. He also noticed speech changes with the disease progression. The tremor kept occurring, now at rest, making it difficult for the patient to perform all motor activities, leaving him bedridden at last. At this time, he was admitted to the Neurologic Clinic.

The ophthalmologic evaluation showed the presence of the Kayser-Fleischer’s ring (Fig 2). On physical examination the main findings were: jaundice, enlargement of the liver, splenomegaly and the presence of abdominal collateral circulation.

The neurological examination disclosed an intense tremor involving the four limbs, specially the right side, and the head (on Fig 3, it is possible to notice the image of the tremor in the upper limbs). It was of wide amplitude, present at rest, and would get worse during voluntary movements. Hypotonia of the upper limbs was also present. The orthostatic position was only possible with a wide base, a feature maintained during gait. He also had dysarthria with scanned speech. The tremors interfered with the motor evaluation, specially in the tests for cerebellar function such as the index-nose and alternating movements of the hands to check for dysdiadochokinesia. Deep-tendon reflexes were normal and the plantar reflexes were flexor. The facial expression was described in this way: “the patient has a face of almost constant smile and his lips remain in the assumed posture in opposition to the rest of his facial mimic”. From this description, it is possible to deduce that the patient presented the risus sardonicus, as it can be seen in Fig 4.

The patient was submitted to a pneumoencephalograph that showed “ex-vacuo” enlargement of the third ventricle and lateral ventricles. The therapeutic measures adopted just to relief the symptoms were: low fat diet, scopoline and phenobarbital. Along the course of the disease, he presented aggressive behavior which became progressively more intense and required his transfer to a psychiatric hospital (Hospital do Juquery), where he died five years after the onset of the disease.

DISCUSSION

We present in this report, the first case of WD seen at the Neurologic Clinic of Hospital das Clínicas of São Paulo University Medical School (HC-FMUSP), in 1946.

The patient presented the Westphal-Strümpell’s form of the disease, with onset in third decade of life and neurological manifestations dominated by postural tremor. The authors describe the tremor as being of great amplitude, especially in posture and during movement, and the photo observation, where the image shows clearly the movement of the upper limbs, demonstrate that the hyperkinesia represents the typical postural tremor of WD, called “wing beat” tremor.

At that time, the diagnosis of WD was based only on the neurologic and hepatic features as well as the presence of the Kayser-Fleischer’s ring, since the copper metabolism disorders and the reduction of ceruloplasmin level were not known. It was twelve years later, in 1958, that Cumings 18 described the copper abnormalities in WD and posteriorly, in 1952, Scheinberg and Gitlin 19 showed that the ceruloplasmin levels were low in most of WD patients.

The pneumoencephalograph images were compatible with subcortical atrophy, as it was expected in patients with WD.

The treatment is this case was palliative as at that time there was no specific therapy available. The therapeutic strategies adopted included: low fat diet, recommended in face of the evident hepatic involvement, scopoline as an attempt to control the tremor and phenobarbital as a sedative. The disease, as expected, followed its natural course and the patient died 5 years after the onset of his first symptoms. It’s important to emphasize that in Westphal-Strümpell form of the disease, as presented by this patient, the duration of the disease until death is longer
than that seen in Wilson’s form in which prevail dystonic manifestations. In patients affected by Wilson’s form of the disease the evolution is faster and the natural course of the disease frequently lasts less than 3 years.

The first treatment attempts with the chelating agent dimercapro (British Anti-Lewisite-BAL) were done in 1951 by two independent groups: Cumings in England and Denny-Brown and Porter in the USA, with little improvement of disease symptoms. In 1956, as it was mentioned before, Walshe introduced penicillamine that revolutionized WD treatment.

In conclusion, this historical report demonstrates that WD diagnosis is mostly based on the clinical features of the disease and for its confirmation, even today, the neurological manifestations and the presence of the Kayser-Fleischer’s ring practically make the diagnosis. The crucial difference between that time and nowadays is the current availability of effective treatment options.

The Brazilian neurological literature registers one WD case report before this one, made by Austragélio Filho in 1944. The author described the patient main neurological manifestation as torsion spasms (possibly dystonic movements) suggesting a dystonic form of WD. In this report the author did not mention the presence of Kayser-Fleischer’s ring but the age of disease onset (18 years of age), the progression to death after 4 years and the hepatic cirrhosis and brain abnormalities found at the necropsy indicated that the patient indeed had WD.

As mentioned earlier, after this first case of WD recorded in our Clinic, other 5 were evaluated later along the 1950’s. In all of them, the progression was always fatal despite any treatment attempts with the copper chelating BAL, already available in several countries since its introduction as a rational treatment for WD, in 1951.

In the beginning of the 1960’s, penicillamine had already been used in several countries in Europe and in the USA and its efficacy was definitively proved. Thus WD had left a long list of untreatable inherited metabolic neurological diseases and had begun to attract the interest of a growing number of researchers all around the world, worried about the precise diagnosis and the correct treatment. At that time, in our country, Horacio Martins Canelas developed a project to investigate WD which would become in the following decades one of the most profitable lines of research at the Neurologic Clinic (HC-FMUSP). To develop this research project, Canelas had the collaboration of Francisco Bastos De Jorge that would cooperate with the laboratorial support, essential for the study of the disease.

In this way, in 1962, Canelas published, with De Jorge and Costa-Silva’s collaboration a paper focusing copper determination methodology in biological materials. In the following year, Canelas published with De Jorge and Spina-França’s participation, a study concerning normal values of copper in blood, cerebrospinal fluid and urine. In 1964, again with De Jorge’s collaboration, a study of ceruloplasmin levels in normal individuals was published by Canelas. In the same year, Canelas and his collaborators achieved an international publication in Clinica Chimica Acta (Amsterdam, Holland) concerning copper concentration in saliva, salivary glands and pancreas. With these studies, pioneers in our country, Canelas and his team achieved the know-how of laboratorial tools to evaluate copper metabolism.

Besides the investigations in the laboratorial domain Canelas and his team reported important clinical studies. Thus, in 1963, Canelas and his collaborators published a detailed study of 3 cases of WD, two of them with neuropathological examination. In 1967, Canelas and his collaborators published in the Journal of Neurology, Neurosurgery and Psychiatry an interesting comparative study of copper metabolism in patients with WD undergoing a vegetarian and mixed diet. With these publications, Canelas put the Neurologic Clinic (HC/FMUSP) as a national reference Center for WD research.

This line of investigation is up to nowadays one of the most traditional of the Neurologic Clinic (HC-FMUSP) and for the last 20 years, has counted with an effective participation of researchers from the Gastroenterology Department.

REFERENCES

8. Ormerod JA. Cirrhosis of the liver in a boy, with obscure and fatal nervous symptoms. St Bartholomew’s Hosp Rep 1890;26:56-68.