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Another case of organ blindness in the history of combined eye-kidney disorders
Wilson's disease

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Wilson's disease, or hepatolenticular degeneration, is a rare genetic disorder of copper metabolism. The disease leads to the accumulation of copper in the brain, liver, eyes and kidney. The dominant triad of the syndrome is nodular liver cirrhosis, Kayser-Fleischer ring in the corneas, lesions of the cortex and basal ganglia. In addition, a defect in proximal tubule reabsorption has been noted. The syndrome has been named after Samuel Alexander Kinnier Wilson (1878–1937). It was initially considered a purely brain disease, described by Frerichs in 1861. In 1883, Carl Westphal in Germany described two cases of what he termed "pseudosclerosis". These and other reports led Wilson to propose the existence of the new clinical entity with degeneration of the brain lenticular nucleus and of the liver in 1912. "Pseudosclerosis" and "Wilson's disease" were later found to be the same disease. In 1913, Rumpel introduced the study of copper in the liver in a case of pseudosclerosis. The renal dysfunction included the discovery of aminoaciduria, glycosuria, increased urate excretion, reduced renal plasma flow (RPF) and glomerular filtration rate (GFR), and specific histological lesions. A complete physiological study of the kidney was then presented in 1957 by Bearn and Gutman, who confirmed the reduced RPF and reduced GFR, and reduced secretory and reabsorptive tubular function. The ocular findings in Wilson's disease were identified in 1902 by Bernhard Kayser and Bruno Fleischer in Germany, who first described the typical ring in the cornea that still brings their names. In conclusion, the history of renal and eye involvement in Wilson's disease appears as another case of organ blindness; that is, attention to the predominant symptom leads to neglecting the involvement of other organs in multisystemic diseases. The sequence of discoveries and hypotheses reflects the technical advancement of each specific historical period.

Μια ακόμη περίπτωση τύφλωσης οργάνων στο ιστορικό των συνδυασμών νεφρικών και οφθαλμικών διαταραχών: νόσος του Wilson

Περίληψη στο τέλος του άρθρου

Key words

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Organ blindness
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1. INTRODUCTION

Wilson's disease, or hepatolenticular degeneration, is a rare genetic disorder of copper metabolism. The disease leads to the accumulation of copper in the brain, liver, eyes and kidney. The dominant triad of the syndrome is nodular liver cirrhosis, Kayser-Fleischer ring in the corneas, lesions of the cortex and basal ganglia. Besides, a defect in proximal tubule reabsorption has been noted.[1] The syndrome involving the basal ganglia degeneration and liver damage has been named after Samuel Alexander Kinnier Wilson (1878–1937).

The modern description of combined liver-brain disease probably starts with Frerichs in the 1850s, who focused on the liver damage, and Karl Westphal in 1883, who focused on the nervous disease. The kidney problem emerged many years afterward. Certainly, other cases of hepatolenticular degeneration were observed before; however, the neurological and neuro-pathological doctrines were not sufficiently mature to make them distinguishable from other cases, and the attention to liver cirrhosis was also immature. Regarding the kidney, we shall see that even though Bright's disease and the Fanconi Syndrome were formulated, they did not attract the physicians' attention enough, a phenomenon we call "organ blindness".

Concerning the neurological and neuropathological doctrine, the mid-1800s was a gold period, with a convergence of neurological anatomy and pathology, and

several important neurologists including: (a) Moritz Heinrich Romberg (1795–1873), who wrote the "Lehrbuch der Nervenkrankheiten des Menschen" in 1846, the first neurology textbook; (b) Theodor Meynert (1833–1892) who taught Sigmund Freud, Karl Wernicke, Sergei Korsakoff, Auguste-Henri Forel, Paul Flechsig, (c) Carl Westphal (1833–1890). Regarding liver disease, it is useful to remember that the term "cirrhosis" was introduced by Renè Laennec (the inventor of the stethoscope) in his treatise "De l'auscultation médiate" in 1819.[2] The term was then made common by William Osler (1849–1919) in his widely used textbook "Principles and Practice of Medicine" in 1892. However, "liver induration" had already received attention at the time; see e.g. John Browne (1642–1700)[3] and Matthew Baillie (1761–1823).[4] Baillie was also one of the fathers of pathology based on the study of organs of the body, which, as shown below, was part of the methodology used by Wilson. This suffices to explain Frerichs' interest.

1.1. From Frerichs to Wilson

Friedrich Theodor von Frerichs (1819–1885), head physician at the Charité in Berlin was an eminent physician of the time. He had very famous students such as Paul Ehrlich, a Nobel prize winner for his contribution to immunology and chemotherapy and Paul Langerhans, who discovered the cells producing insulin. He wrote the first German book on nephrology and made a microscopic study of Bright's disease (today called Chronic Kidney Disease). He first described aminoacids in urine and the theory of uremic intoxication or "Frerichs' theory".[5] He also gave a first description of the hepato-renal syndrome. Frerichs was greatly interested in liver diseases, which he studied using autopsy, and in 1854 wrote the classic "Treatise on Diseases of the Liver".

In the second volume of the treatise, he reported a case of combined brain and liver disease (Observation no VIII). The patient, named Carl Zeppner, was 10 years old and suffered from progressive, rapid neurological deterioration (dysphagia, anarthria, tremor); the boy died after a few days. At autopsy, Frerichs observed a small liver "its surface was covered with nodules, varying in size from a pea to a bean". This case later came to Wilson's attention, who acknowledged the famous physician for this early observation. However, Frerichs described this case as part of a series of liver diseases in the chapter "Varieties of granular induration of the Liver, and Illustrative cases". He was not interested in the neurological symptoms, and the autopsy of the boy was indeed focused on the liver and did not cover the brain.

At the extreme opposite, a contemporary famous neurologist, Carl Friedrich Otto Westphal (1833–1930), in Germany, focused entirely on the neurological symptoms and failed to focus on the liver. Westphal was an influential psychiatrist who worked in Berlin at Charitè. The nucleus of the third pair of cranial nerves is named after him (Edinger-Westphal nucleus). He had Arnold Pick and Karl Wernicke as students. In 1883, he described two cases of what was almost certainly Wilson's disease: neurological aspects similar to "multiple sclerosis", but without white matter degeneration at autopsy.[6] Westphal named the disease "pseudosclerosis", without noticing the liver involvement. Wilson knew this work.

Afterward, five other physicians reported cases of combined liver-brain diseases:

- Adolph Strümpell in Germany in 1898 described other cases of Westphal's pseudosclerosis, and in one case also the presence of liver cirrhosis.[7,8] These were also noted by Wilson. After Westphal and Strümpell, the term "Pseudosklerose" gained ground and was also used by Spiller in 1898[9] and Jakob in 1921.[10] No neurologist or liver physician at the time could recognise that Pseudosklerose and hepato-lenticular degeneration were the same entity, and two separate streams of studies started.
- Sir William Gowers reported a case (later cited by Wilson), published in 1906, of a fatal case of a girl of 15 with "Tetanoid chorea and its association with cirrhosis of the liver". "Tetanoid chorea" and Westphal's "pseudosclerosis" were likely the same disease. This work too was then reported by Wilson.[11]
- Gabriel Anton of Halle also published a separate case under the title "Dementia choreo-asthenica with juvenile nodular cirrhosis of the liver",[12] which Wilson later devised as a case of congenital syphilis.
- One case of combined brain and liver disease was also furnished by J.A. Ormerod in 1890.[11]
- Three other cases by Homén, of Helsingfors in 1890.[11]

These reports finally led Wilson in the UK to propose the existence of a new clinical entity with degeneration of the brain lenticular nucleus and of the liver, in 1911.[13]

Wilson was a British neurologist at the National Hospital, Queen Square, London. He presented a thesis entitled "Progressive lenticular degeneration: a familial nervous disease associated with cirrhosis of the liver", and the year after a famous paper in the journal *"Brain"*.[11] In his seminal work, Wilson recognised both Sir William Gowers and Dr JA Ormerod "for permission to utilise their notes".

It is not surprising that the same disease was renamed and re-discovered several times (granular induration of the liver, pseudosclerosis, tetanoid chorea, hepatolenticular degeneration with cirrhosis) over about 60 years. The methods were similar: neurological examination and autopsy. However, each author prioritised a specific symptom (neurological or liver disease) assigning secondary relevance to other symptoms. We already see here the origin of what we call "organ blindness". Such "blindness" or inattention meant it took 60 years to establish a clinical entity that was in essence already known.

Wilson was possibly aided by his knowledge of the latest advances in neuroanatomy and by his attention to liver disease during dissection. The personal story of Kynnier Wilson is instructive in this regard.

He was born in 1878, the second son of Agnes MacIntosh, the daughter of Hately, a composer and precentor of the Free Church in Edinburgh and of the Reverend James Kinnier Wilson (their daughter Anne was born in 1878). James, a Presbyterian minister from Ireland, studied at Princeton and was a renowned Assyriologist.

However, Samuel Alexander never knew his father because James died in 1879 from malaria. The family hence returned in Edinburgh, were his mother married Henry McIntosh and in 1882 had a son, Henry Walter McIntosh. The family's good financial status allowed Samuel to study medicine at Edinburgh and to make a stage in Neurology in Paris, with the famous Pierre-Marie and Babinski.[14]

Due to these studies, he was aware, and used, the Nissl staining to visualise neuronal bodies, invented by the Nobel-prize laureate Franz Nissl in Germany in 1885. He also used the staining of nerve fibres/myelin, invented by Karl Weigert in 1882. He knew (and cited) the famous neurologist sir William Gowers and Hughlings Jackson.

Moreover, at the time of his dissertation for the MD title in Edinburgh, when his seminal paper "Progressive lenticular degeneration: a familial nervous disease associated with cirrhosis of the liver" was published,[11] there was great attention to the "extrapyramidal system" and hence to the lenticular nucleus.

Finally, possibly the period was mature for greater attention to both the brain and liver because of the work on Kernicterus, cited by Wilson, by Schmorl (1861–1932): brain disease in neonatal jaundice.[15] In a series of 120 brains from jaundiced individuals, Schmorl observed intense yellow colouring in the basal ganglia (which include the lenticular nucleus). The pattern was previously also described in a case reported by Johannes Orth in 1875. Therefore, the time was ready for greater attention to the liver in case of damage to the basal ganglia.

Before leaving Wilson, we should remark on his hypotheses on the origin of the disease, which are reasoned by him as follows:

- "It seems certain that the disease is not due to a congenital or abiotrophic defect
- The presumption therefore is strong that the disease is acquired
- There is evidence to show that the disease is toxic in origin, but none to suggest that this toxin is syphilitic
- It is possible that this toxin may be elaborated in the liver
- The toxin has a specific action on the lenticular nucleus
- The nature of the toxin is unknown: it is almost certainly not microbial. Possibly it is chemical and of the nature of a lipoid."

It is remarkable that almost all hypotheses have since been confirmed. Wilson was wrong only when thinking about a lipoid toxin and that it was acquired, whereas it is inherited.

After Wilson, two major steps occurred: the fusion of the "Pseudosklerose" and "hepatolenticular degeneration" streams of study, and the recognition of corneal deposits.

1.2. "Pseudosclerosis" and "Wilson's disease" were found to be the same disease

After 1911, a debate started as to whether pseudosclerosis and hepato-lenticular disease were the same clinical entity. For instance, Fleischer noted the corneal pigmentation that carries his name in a case of pseudosclerosis in 1912. The work by Alzheimer and von Hosslin in 1912 demonstrated diffuse gliosis in the case of pseudosclerosis. Spielmeyer was the first, to our knowledge, to analyse the similarity (from a histological point of view) of pseudosclerosis and hepatolenticular disease, in 1920. In his work, Spielmeyer says "This seemed to support the opinion of leading neurologists that the clinical pictures mentioned are expressions of one and the same process - that Wilson's disease and pseudosclerosis mean the same suffering". According to Spielmeyer's report, Bielschowsky also did a histopathological comparison of pseudosclerosis and hepatolenticular disease, but concluded that there is a difference between the two.

In 1921, Hans Christian Hall also proposed that the two were identical.[16] Derek Denny-Brown reviewed the subject

in 1946 (in: Diseases of the Basal Ganglia and Subthalamic Nuclei), pointing out that "the work of Hall […] had obscured the remarkable differences between the two syndromes" (citation from Homburger).

Therefore, Homburger and Kozol revised additional cases in 1946. They favoured the Hall hypothesis and concluded that some cases of hepatolenticular degeneration may have been misdiagnosed in the past as parkinsonism, psychoneurosis or multiple sclerosis.[17]

Thereafter, the term pseudosclerosis was not used anymore and scientists focused on the causes of the disease.

1.3. Ocular findings

The field of ocular diseases was made mature by the invention of the ophthalmoscope by Hermann Ludwig Ferdinand von Helmholtz (1821–1894). This revealed a large number of ocular findings in many known diseases.

The ocular findings in Wilson's disease were identified in 1902 by Bernhard Kayser (1896–1954) and in 1912 Bruno Fleischer (1874–1965) in Germany who first described the typical ring in the cornea that still brings their names.

Kayser made his observation in 1902, describing annular "congenital [sic] greenish discoloration of the cornea" in a patient with nervous symptoms, incorrectly attributed to multiple sclerosis.[18]

Wilson did not appreciate the work by Bernard Kayser in 1902, who described the greenish corneal pigment in a case of pseudosclerosis.

Conversely, Bruno Fleischer was not studying hepatolenticular degeneration, but, rather, pseudosclerosis. In 1912, he reported the ring in a case of cirrhosis and neuropsychiatric abnormalities. He knew the observation by Kayser, which was similar to what he was describing: "I have recently had the opportunity to see two more such cases and to repeatedly examine them in detail. The result is in both cases completely consistent with the Kayser case". Fleischer recognised that the ring heralded a neurological disorder associated with cirrhosis, shown at autopsy.

1.4. Renal involvement

In 1913, Rumpel introduced the study of copper in the liver in a case of pseudosclerosis,[19] which was confirmed by Malory in 1925; Cumings, and in parallel Denny-Brown and Porter, in 1951, definitely supported the role of copper and the use of copper ligands as therapy.

The same Denny-Brown, with Uzman, was the first to report a case of aminoaciduria in hepato-lenticular degeneration, in 1948.[20] In 1950, Cooper et al confirmed the presence of aminoaciduria.[21] Copper accumulation in the kidney was described by Wintrobe in 1954.

Stein et al and Bickel et al characterised aminoaciduria and found a loss of glycine, histidine, threonine, cysteine, serine, alanine, glutamine, tyrosine, lysine, glutamic acid, leucine, phenylalanine. Their findings definitely excluded that Wildon's syndrome was an innate metabolism disorder. A complete physiological study of the kidney was then presented in 1957 by Bearn and Gutman, who confirmed the reduced RPF and reduced GFR, and reduced secretory and reabsorptive tubular function.

1.5. Organ blindness

A simple analysis of "discovery retardation" can be obtained using technical milestones as time points that should then enable scientists to make a new discovery.

The neurological examination was very mature in the mid-1800s. Specifically, Charcot introduced brain pathology in 1868. Therefore, it took only about 12 years for Westphal to identify the "pseudosclerosis" in the 1880s.

As for liver disease, considering the work by Laennec in 1819, it took about 40 years to have the first liver degeneration case described by Frerich. Surprisingly, with a delay of 50 years, Wilson merged the liver and cerebral diseases in 1912. No technical reasons could explain such a delay. It took only 10 years to merge the pseudosclerosis and hepatolenticular degeneration by Hall in 1921, even if the debate continued for more than 20 years, up to 1946! The third characteristic, the corneal ring, was discovered with a delay of 50 years from von Helmoltz's invention of the ophthalmoscope in 1851. Even then, 10 years passed before the ring was connected to pseudosclerosis in 1912 by Fleischer, and a further 10 years before it was linked to hepatolenticular degeneration.

As for renal defects, the technique to detect aminoaciduria was available since 1861, thanks to the work of Von Frerichs, and of G. Fanconi in 1831. Therefore, the late discovery of aminoaciduria in Wilson's disease by Uzman in 1948 cannot be ascribed to a problem in the techniques or lack of paradigms. We are here with a delay of almost 100 years! This is not the only case of such a phenomenon.[22]

2. CONCLUSIONS

The history of renal and eye involvement in Wilson's disease appears as another case of organ blindness; that is, the attention to predominant symptoms leads to ne-

glecting the involvement of other organs in multisystemic diseases. The sequence of discoveries and hypotheses reflects the technical advancement of each specific historical period.

ΠΕΡΙΛΗΨΗ

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Η νόσος του Wilson ή ηπατοφακοειδής εκφύλιση είναι μια σπάνια γενετική διαταραχή του μεταβολισμού του χαλκού. Η ασθένεια οδηγεί στη συσσώρευση χαλκού στον εγκέφαλο, στο ήπαρ, στα μάτια και στους νεφρούς. Η κυρίαρχη τριάδα του συνδρόμου είναι η κνίδωση με κίρρωση, ο δακτύλιος Kayser-Fleischer στους κερατοειδείς χιτώδες, οι βλάβες του φλοιού και των βασικών γαγγλίων. Επιπλέον, έχει παρατηρηθεί ένα ελάττωμα στην επαναρροή της εγγύς σωληναρίου. Το σύνδρομο πήρε το όνομά του από τον Samuel Alexander Kinnier Wilson (1878–1937). Αρχικά θεωρήθηκε μια καθαρά εγκεφαλική νόσος, που περιγράφεται από τον Frerichs το 1861. Το 1883, ο Carl Westphal στη Γερμανία περιγράφει δύο περιπτώσεις αυτού που ονομάζεται «ψευδοσκλήρυνση». Αυτές και άλλες αναφορές οδήγησαν τον Wilson να προτείνει την ύπαρξη της νέας κλινικής οντότητας με εκφυλισμό του εγκεφαλικού φακού και του ήπατος το 1912. Η «ψευδοσκλήρυνση» και η «ασθένεια του Wilson» βρέθηκαν αργότερα ως η ίδια ασθένεια. Το 1913, ο Rumpel εισήγαγε τη μελέτη του χαλκού στο ήπαρ σε περίπτωση ψευδοσκληρώσεως. Η νεφρική δυσλειτουργία περιελάμβανε την ανακάλυψη της αμινοξονουρίας, τη γλυκοζουρία, την αυξημένη απέκκριση ουρικών ενώσεων, τη μειωμένη ροή του νεφρικού πλάσματος (RPF) και την ταχύτητα σπειραματικής διήθησης (GFR) και συγκεκριμένες ιστολογικές αλλοιώσεις. Μια πλήρης φυσιολογική μελέτη του νεφρού στη συνέχεια παρουσιάστηκε το 1957 από τους Bearn και Gutman, οι οποίοι επιβεβαίωσαν το μειωμένο RPF και την μειωμένη GFR και τη μειωμένη εκκριτική και επαναπορροφητική λειτουργία των σωληναρίων. Τα οφθαλμικά ευρήματα της νόσου του Wilson εντοπίστηκαν το 1902 από τους Bernhard Kayser και Bruno Fleischer στη Γερμανία, που περιέγραψαν για πρώτη φορά τον τυπικό δακτύλιο στον κερατοειδή που φέρνει ακόμα τα ονόματά τους. Συμπερασματικά, το ιστορικό νεφρικής και οφθαλμικής εμπλοκής στη νόσο του Wilson εμφανίζεται ως μια άλλη περίπτωση τύφλωσης για τον ρόλο άλλων οργάνων. Δηλαδή, η προσοχή στο κυρίαρχο σύμπτωμα οδηγεί στην παραμέληση της εμπλοκής άλλων οργάνων σε πολυσυστηματικές ασθένειες. Η ακολουθία των ανακαλύψεων και των υποθέσεων αντανακλά την τεχνολογική πρόοδο κάθε συγκεκριμένης ιστορικής περιόδου.

Λέξεις ευρετηρίου: Νόσος του Wilson, Τύφλωση για τον ρόλο άλλων οργάνων, Ψευδοσκλήρυνση Carl Westphal

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