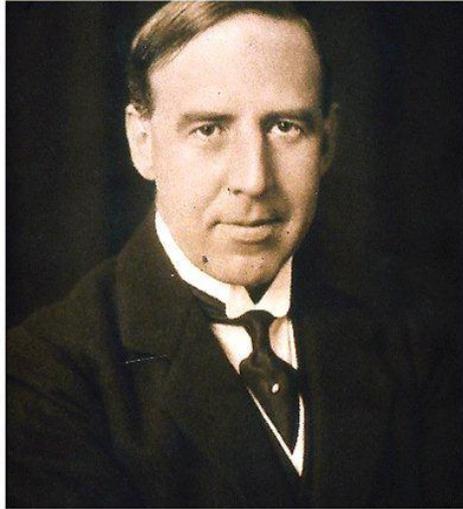


Wilson's disease: a centennial symposium

Held at the Royal College of Physicians, Regent's Park, London, on 5th- 6th October, 2012



Dr Samuel Alexander Kinnier Wilson (1878-1937)

Introduction

The **Wilson's Disease Centennial Symposium** commemorated the first description (in 1912) by Dr Samuel Alexander Kinnier Wilson of what is now known as Wilson's disease. The meeting was arranged by **Dr James Dooley** (UCL Institute for Liver & Digestive Health, London) and **Dr Rupert Purchase** (Wilson's Disease Support Group – UK), together with the British Association for the Study of the Liver (BASL). It was sponsored by the EuroWilson network, the British Society of Gastroenterology, Univar Ltd, Wilson's Disease Support Group – UK, and The Kohn Foundation.

Opening the meeting, **Dr Dooley** reminded delegates of highlights in the history of what, in 1912, Wilson had described as 'progressive lenticular degeneration'. These included in 1948 the relationship to copper; in 1952 the role of low serum caeruloplasmin; the development, between 1955 and 1986 of the therapies D-penicillamine, trientine, zinc, and ammonium tetrathiomolybdate; and, in 1993 the isolation of the causal gene, *ATP7B*.

Current aims in the study of Wilson's disease, explained Dr Dooley, include research into its cellular and molecular biology and into its early recognition and diagnosis. Treatment aims include research into predictors of poor response, and a better understanding of the modes of action of therapies.

Clinical features of Wilson's disease

Dr Michael L. Schilsky (Yale University Medical Centre) discussed the hepatic manifestations of Wilson's disease. Whilst the clinical presentation can be asymptomatic, or with hepatic, neurologic or psychiatric symptoms, Dr Schilsky pointed out that some degree of hepatic involvement is present in all patients and therefore that hepatologists are now usually the primary clinicians involved. Such hepatic manifestations typically occur earlier than other symptoms, but the time to onset and the severity of disease is variable. Medical treatment arrests or reverses hepatic inflammation and synthetic dysfunction of the liver. Liver transplantation when necessary is curative, even using livers from heterozygous carriers. Hepatocellular carcinoma may occur rarely, but the true incidence is not known and at present expert guidelines do not recommend screening and surveillance.

Professor Anna Czlonkowska (Institute of Psychiatry and Neurology, Warsaw) concentrated on the neurological manifestations of Wilson's disease. These include as tremor; dystonia; rigidity dysarthria; drooling; and Kayser-Fleischer rings. Neuropsychiatric symptoms occur more frequently and earlier in men and hepatic signs occur more frequently in women. Patients homozygous for the p.H1069Q mutation show a later

presentation of first symptoms which are usually neuropsychiatric. A neurological diagnosis is relatively easy when Wilson's disease is suspected and, typically, includes low serum caeruloplasmin and a high urinary copper excretion. Kayser-Fleischer rings and MRI changes are seen in 90% of cases. The majority of neurological patients have speech disorders and drooling, and behavioural/psychiatric problems. Behavioural problems occur in patients and can include personality changes, excessive talkativeness, irritability, aggression, and antisocial and criminal behaviour. Severe psychiatric problems, which occur in up to 25% of patients, include, major depression, mania, bipolar affective disorders and schizophrenia like psychosis.

Diagnosing Wilson's disease

Dr Peter Ferenci (Medical University of Vienna) listed (and demolished) some of the textbook misconceptions of the condition: namely, that it occurs only in children and young adults, that it is only a neurologic disease, that it can be excluded if ceruloplasmin is normal, and that it is very rare. He explained that, clinically, it could present as liver disease or as neurologic disease. One study has shown the phenotypic presentation to be hepatic in 49%, neurological in 37% with 14% asymptomatic siblings. Diagnosis, he explained, may be challenging. Two or more of the following would be typical findings: Kayser-Fleischer rings, low ceruloplasmin, compatible neurologic symptoms, and a raised urinary copper. When characteristic findings are absent or equivocal, a scoring system for these and other findings has been published to aid in diagnosis.

Professor Mohit Bhatt (Medical Research Institute, Mumbai) presented the Global Assessment Scale for Wilson's disease (GAS). He emphasised the importance and value of tracking patients using this scale. Using visual case histories, he illustrated that the two tier GAS was a method of grading the multi-systemic manifestations of the disease. Tier 1 scores the global disability in four domains: liver, cognition and behaviour, motor features, and osteomuscular. Tier 2 is multidimensional scale for a fine grained evaluation of the neurological dysfunction. Professor Bhatt suggested that GAS for Wilson's disease is a practical tool with potential applications in the management of patients.

Dr Jean-Marc Trocello (Hôpital Lariboisière, Paris) explained the rationale behind relative exchangeable copper (REC): a recently proposed biomarker for Wilson's disease diagnosis. He presented data on the reliability of exchangeable copper determination in patients with Wilson's disease.

Professor Joanna Seniów (Institute of Psychiatry and Neurology, Warsaw) explained that Wilson's disease patients are a heterogeneous group in terms of their cognitive-behavioural functioning and each one requires individual assessment. Behavioural impairment can interfere not only with patients' social functioning (including professional activity) but also their approach to medical treatment. Diagnostic assessments of emotional functioning should not only be based on the patient's self-reports; interviews with key relatives are also necessary. Therapeutic efforts should be made to improve patients' behavioural self-control. Psycho-education and psychological support should be provided to the patients' family members who should be made aware that some of the patients' reactions result from brain damage and are unintentional. Treatment requires co-operation between members of the therapeutic team including physicians, physiotherapists, psychologists, speech pathologists and occupational therapists.

Copper metabolism and genes involved in Wilson's disease

Professor Stuart Tanner (University of Sheffield) discussed the similarities and differences between Wilson's disease and other conditions in which copper metabolism is abnormal, such as intrahepatic cholestasis and infantile copper toxicosis. **Dr Eve A. Roberts** (University of Toronto) discussed her work on metalloproteomics, which identifies large sets of proteins associated with metals and analyses their regulation, modification, interaction, structural assembly, and function in disease states, and how in Wilson's disease, copper-metalloproteome is the main interest. She explained copper's role throughout the phyla and the development of a systems biology approach to studying copper in biological systems.

Dr Dominik Huster (University of Leipzig) discussed the function and dysfunction of the *ATP7B* gene which has been mapped to chromosome 13 and of which the functionally important protein domains are the N-terminal domain, ATP-binding domain and the actuator domain. Wilson's disease is caused by mutations of *ATP7B*. More than 500 different *ATP7B* mutations have been identified, with the number still growing. Differentiation between disease associated mutations and genetic polymorphisms is important. Dr Huster suggested that future studies may reveal targets for intervention and improved therapy strategies. **Dr Ferenci** discussed the lack of any clear evidence for a correlation between *ATP7B* genotype and clinical phenotype.

Treatment of Wilson's disease

Dr Karl Heinz Weiss (University of Heidelberg) presented an overview of medical treatment options in Wilson's disease. The sequential treatment concept involves a decoppering phase followed by maintenance therapy. The mode of action of the chelating agents (D-penicillamine, trientine and, tetrathiomolybdate) is the direct complexation of copper in serums and tissues, the renal elimination of copper, and the induction of endogenous chelators. Zinc interferes with intestinal copper uptake and induces endogenous chelators. Its overall decoppering potential is lower than that for chelating agents. The chelating agents are highly effective in hepatic patients. Zinc monotherapy can be equally effective in neurologic and presymptomatic patients, but might be insufficient to control liver disease. Chelating agents and zinc together combine different modes of action but are very complicated for the patient as both drugs should be taken at widely spaced intervals to avoid possible interference between zinc ions and chelator.

Dr Fred Askari (University of Michigan) presented evidence on the potential of tetrathiomolybdate. Given with food, it blocks copper absorption and re-absorption of endogenously secreted copper, resulting in an immediate negative copper balance. Given between meals, it is absorbed and complexes potentially toxic copper of the blood, rendering it unavailable for cellular uptake. Dr Askari emphasised that tetrathiomolybdate dosing must be monitored for side effects and, in this context, he suggested that lower, longer dosing regimens have fewer side effects.

Dr Elisabeth Mintz (Laboratoire de Chimie et Biologie des Métaux, CEA, Grenoble) discussed the new Cu(I) chelators targeted to the hepatocytes. Cu(I) enters the hepatocytes where it binds to the Wilson's disease ATPase that excretes the Cu(I) to the bile canaliculus. Dr Mintz and colleagues have designed a molecule specifically targeted to hepatocytes there to chelate Cu(I). This molecule not only enters cultured hepatocytes, but also decreases the concentration of Cu(I). The new compound is currently being tested *in vivo* on a mouse model.

Prof Anil Dhawan (King's College Hospital, London) discussed liver transplant in Wilson's disease. He pointed out that with a fulminant presentation, there is a mortality rate of nearly 100% without transplantation. However, with liver transplant, there is a good long-term patient and graft survival and it has been shown that there is improvement and stabilization of neurological manifestations and a good quality of life following the procedure. Living related donors are suitable.

Dr Hartmut H.-J. Schmidt (Universitätsklinikum Münster, Germany) explained how current research into microRNAs (MiRs) has the potential for the correction of the metabolic defect. MiRs are small non-coding RNAs that regulate mRNA expression and serum miR-122 serves as a marker for liver disease. Research with Long-Evans Cinnamon (LEC) rats shows that miR-122 increases significantly earlier in a model of Wilson's disease as compared to other hepatitis-associated serum markers and allows the monitoring of the restoration of disease after cell-based therapy.

Dr Jean-Marc Trocello (Hôpital Lariboisière, Paris) explained how the EuroWilson Network in France offers a multidisciplinary approach to Wilson's disease. Patient empowerment is a part of this project to focus effort on patient priorities and the network exists to improve knowledge and access to information. With centres around France and patient organisations in Paris and Lyon, the network runs a national registry which has gathered much important data and has exploded some of the misconceptions about the disease (e.g. that it is primarily a young person's condition). From the patients' point of view, the network offers a better access to experts in France with consultation, telemedicine, a source of information and guidelines. A website questionnaire survey allows data on patient priorities to be collected and actioned. From a specialist's point of view, the website allows access to clinical and research advances in Wilson's disease and Dr Trocello urged delegates to contribute interesting and relevant abstracts to the network's academic website, which, he added, receives hits from all around the world.

The centennial celebration

In keeping with the title of the Symposium, a special session paid tribute to Dr Samuel Alexander Kinnier Wilson and the history of Wilson's disease. **Dr Edward Reynolds** (King's College, London) described research by himself and Samuel's son into the fascinating first descriptions of movement disorders in ancient Babylon. He then presented an excerpt from a 1925 film in the possession of Samuel's grandson, in which examples of

movement disorders, including Wilson's disease, are illustrated by his grandfather. Dr Reynolds suggested that the high quality of the production might have involved the influence of Samuel's close friend, Charlie Chaplin.

Dr Kinnier Wilson's youngest son, **James Kinnier Wilson** (Wolfson College, Cambridge) entertained delegates with reminiscences illustrating his father's personal qualities. These included his exactness of definition, his love of words and languages (he spoke four fluently) and his wit and keen sense of humour. Mr Kinnier Wilson described the origins of his father's emerging interest in the disease which now bears his name when his attention was drawn to a group of families with typical symptoms and which eventually led to the publication of his famous paper in *Brain*.

This 1912 paper and Dr Kinnier Wilson's career were recounted by **Professor Niall Quinn** (National Hospital for Neurology and Neurosurgery, London). S. A. Kinnier Wilson was educated and first practised medicine in Edinburgh, before continuing in Leipzig and Paris. He was then a registrar in London where he first identified Wilson's disease, winning a gold medal for his research. At King's, as a consultant neurologist, he instigated new medical journals and contributed outstanding papers to the *Lancet*, defining extrapyramidal disease. He died prematurely at the age of 59. Dr Quinn has researched into some of the patients described in the *Brain* paper and read out some particularly pertinent excerpts, in particular, the remarkably prescient observations which adumbrated what we now know about the disease.

Finally, **Dr John Walshe** (Cambridge), whose first paper was published in 1950 and his most recent in 2012 at the age of 92, took delegates for a trip down the Wilson's disease 'memory lane' – from the first discovery of the role of copper to his own early experiences involving the first use of D-penicillamine (the subject of perhaps Dr Walshe's most significant paper).

Sponsors of the meeting (who had no influence on the content) were EuroWilson, Univar, the British Society of Gastroenterology, the British Association for the Study of the Liver, the Kohn Foundation and the Wilson's Disease Support Group, UK; the Symposium Organising Secretariat was GBPCR Ltd.

Charles Wroe, Medical Writer: November 2012

Reports of the proceedings of the Wilson's Disease Centennial Symposium were sponsored by WDSG-UK.