BASL Wilson's Disease Special Interest Group Meeting Thursday 14th June 2018

Dale Room, Wellcome Collection, 183 Euston Road, London NW1 2BE

Attendee list: Appendix A

Apologies received: Appendix B

Meeting report

This was the second BASL Wilson's SIG meeting. 34 attendees from the following centres participated (in no particular order) – Sheffield, Kings, Birmingham, RF/UCL/Queens Square, Southampton, Newcastle, Cambridge, Royal Surrey, Grampian, Manchester, Royal London with expertise within metabolic medicine, clinical chemistry/biochemistry, Hepatology and Neurology including adult and paediatric representation. Dr Mike Schilsky from Yale, US was also in attendance. In addition Public Health England (PHE) and the Wilson's Disease Support Group (WDSG) contributed to the meeting. From BASL perspective the purpose of the SIG is to be democratic, inclusive and demonstrate proof of function.

Following introductions the previous minutes were discussed. A point of inaccuracy was that for the bis-choline TTM trial. One quarter of patients, not one third, will be treatment naïve. The minutes were, other than this point, accepted. Actions from the previous meeting were either to be taken forward during this meeting or had been dealt with, except the circulation of the WTX-101 phase 3 protocol. This will be circulated following the meeting along with appendix D from the previous minutes (proposed specialist Wilson's Disease centres in England).

Discussion of the agenda items and further action points were as follows:

Specialist Centres and National Data collection – chair Prof Aftab Ala, Royal Surrey

- **NHS Trientine Policy Update** - Dr James Dooley from the Royal Free presented an update on the NHSE trientine policy. The clinical panel wanted a revised policy document which is being submitted and will then go out to consultation. Further work was requested on the role of zinc as an option and the treatment for 'asymptomatic' patients., The place of trientine in patients with pre-existing conditions where penicillamine might be avoided *de novo* had also been raised Although not relevant to the policy, Mike Schilsky pointed out that he understood that additional formulations of trientine are in development. The SIG formally thanked James Dooley for his time and effort in the coordination of the Group's feedback to this important NHSE Policy document.

Action: JD to continue leading the working party and to report back to the SIG again in due course

- **PHE update** - Jeanette Aston from PHE presented provisional data from a proof of concept study on case-finding for Wilson's disease (WD). This is a collaboration between PHE NCARDRS, the

SIG, BASL and BSG. A project overview was given and data from the following: primary care prescriptions, HES, ONS, NHSBT. Martin Ward Platt clinical lead for NCARDRS was present to lend support and answer questions.

Prescription data: these were not specific to WD and were not therefore able to identify individual patients from the source data. The plan is to cross reference these data to confirmed WD cases. Prescribing patterns may then emerge.

Hospital episode statistics (HES) data: 863 patients with E83.0 ICD code were identified between 2011 and 2016. These data are limited by this code including non-Wilson copper disorders, patients coded as WD even if this was not the correct diagnosis, and the fact that this strategy relied upon inpatient rather than outpatient episodes. The 2011-16 window also introduced limitations. The data collected have been fed back to several centres since the last SIG meeting. Initial feedback was that many cases listed did not have WD, and many known WD patients in those units were missing from the data collected. The dataset has been simplified for core data capture with a view to national roll out – see the action below. The SIG indicated its support for this study notwithstanding some of the work involved had limitations.

Office for National Statistics (ONS): The ONS records modified death certificate data and has been interrogated for WD being present from data collected between 2001 and 2015. The data may be biased towards death related to WD rather than WD patients who died of another primary cause (and WD is not mentioned). Approximately 70 WD patient deaths were retrieved, fairly equal distributed across the age ranges 0-29 yrs, 30-49 yrs and >50 yrs. Men aged 30-49 yrs was the largest group (22 patients). The SIG was interested in further work to identify the cause of death in patients with WD.

NHS Blood and Transplant (NHSBT): 56 patients who had had a liver transplant for WD were identified between January 2007 and December 2017. Some patients had received a second transplant.

Action: PHE to collect cases of WD from every Trust in England based on HES data as part of a national audit with BASL/BSG support. Following there will be a prescription matching exercise, cross referencing with ONS and NHSBT data, and prospective data collection. There is also a plan to approach the SAS trace element laboratories to explored analysis of their data.

- **US registry data** - Michelle Camarata from the Royal Surrey described the aims and provisional data for this study. Comprehensive data has been collected thus far from 25 patients at Yale. The mean age at enrolment was 44 years of age, and the mean age at diagnosis, 22 years of age. A significant number of patients had psychiatric symptoms at presentation. The SIG commented that psychiatric involvement and interest in WD in the UK appears extremely limited and is an important area for development within the proposed multidisciplinary team structure.

  Treatment in the Yale cohort was mainly zinc followed by trientine, with 65% converted from penicillamine This interested the SIG in terms of the reasons for the switching of treatment. However, this finding may not be representative of US practice in general. By December 2018 five additional US sites and the Royal Surrey should be participating. Discussion followed centred on the Eurowilson database which was active between 2004 and 2007. This ceased when funding

for the project came to an end. Data collection for this project was also very intense and there were inevitable gaps. The SIG agreed that appropriate funding greatly facilitates data input, as well as its storage. Graeme Alexander mentioned that 'NHS digital' will play an increasing role in capturing large data sets in the future and this tool is worth exploring for WD.

Action: Michelle Camerata to report back to the SIG in due course. Other sites in UK/Europe could participate in the US registry, and UK registry approaches are not mutually exclusive. Sites interested in participating should contact Michelle Camerata/Prof Ala.

- **Specialist centres** – Jerry Tucker from WDSG emphasised the theme, in the establishing of Specialist centres, of the NHS recognising that it must 'listen to the patient'. Several documents exist with this focus including the UK strategy for Rare Diseases and the NHS paper 'putting patients first'. An important concept within these is 'life long care'. There is a recognised lack of services to support the mental health needs of patients with WD with such problems.

  There are several principles for service development including a holistic/MDT approach, consistent diagnostic and treatment pathways, training aspects, capturing outcome data to demonstrate improvement, and the interfacing with R&D. There is likely to be an important role trained clinical nurse specialists to provide a responsive and personal approach and to establish patients on 'care plans'.

  A national service needs to be developed consisting of multidisciplinary Centres of Excellence with clinical leadership providing long term monitoring of patients with WD. This will lead to improved patient outcomes and should prove cost-effective.

Action: Jerry Tucker to work with the SIG in developing the document required for NHSE that will align with the (HPB) CRG proposal already submitted. The document will define the requirements for specialist centres for WD, incorporate necessary standards, present named potential centres and arrange external validation of those centres, to strengthen this initiative. A draft document will be written as a basis for this initiative between now and October 2018.

Research – chair Prof Oliver Bandmann, Sheffield

- Cohort research on Wilson's disease (CROWD study) – Sam Shribman from Queens Square/UCL presented an update. He reminded the group that there are two arms to the study: 1) genetic determinants of clinical phenotypes via GWAS based on DNA from saliva samples from any patient with WD 2) neurological biomarkers in a specific cohort of 40 patients with neurological disease recruited over the next 3 years. WDSG stated that they will be happy to promote this study to members. Prof Ala recommended study adoption by both liver and neurology NIHR Clinical Research Networks.

Action: Study invitation letters to be circulated via the SIG and WDSG.

- Clinical trials – this section was omitted due to lack of time. Bill Griffiths planned to discuss that the phase 3 WTX-101 trial has now recruited 28 patients worldwide, with a target of 100 patients in total (with 25% having received less than 28 days of treatment). Three sites are being established in the UK – Birmingham, Royal Surrey and Cambridge. The recruitment window is open until the end of 2018.

Action: BG to circulate the Phase 3 study protocol as the SIG members had not received this after the last meeting.

- EASL 2018 update - Prof Aftab Ala at Royal Surrey presented three abstracts from the EASL meeting in Paris. 1) The 72 week extension phase data from the phase 2 WTX-101 trial which showed non-caeruloplasmin bound copper (NCC) levels maintained on the drug 2) The global prevalence of WD by J Mann et al. This group used established genetic databases to demonstrate 787 unique variants, 569 disease causing variants and estimated a 14/100,000 prevalence based on allele frequencies with highest prevalence in East Asia (37/100,000). The results raised questions about variation according to ethnicity. 3) A gene therapy 'proof of principle' study by a Spanish group. Using an AAV-ATP7B vector they demonstrated improvement in ALT, caeruloplamsin levels and copper excretion in an ATP7B knockout mouse.
- US perspective – Dr Michael Schilsky from Yale described the provision of care for WD including multidisciplinary working, clinical and scientific training and involvement in various strands of basic and clinical research including outcomes based research. He emphasised that there is room for several types of approach when it comes to databases – some benefitting from a 'deep dive' and others, such as prescription data, being useful on a more superficial level. Decentralisation of biochemical laboratories in the US is unhelpful in supporting standardisation of monitoring patients with WD. Dr Schilsky described a number of unmet needs in WD including: the improved definitions of endpoints and 'treatment failure', reliable biomarkers or a suitable matrix for clinical evaluation, the lack of comparable treatment trials, the lack of prognostic indicators, neonatal screening, transition from paediatric to adult care, care of older patients, gene therapy as a cure, and raising the awareness of WD more generally. Regarding neonatal screening he described a proteonomic method in development. He suggested that there is probably a cost-effective argument to support neonatal screening for WD.
- Potential for DNA/RNA therapies – Dr Julien Baruteau from UCL described a number of gene therapy approaches, the pros and cons of each, their local expertise and what might be applicable to WD. The liver is ideal for genetic manipulation given it is a tolerogenic, highly vascularised organ with fenestrated endothelium. Whilst gene therapy could be potentially prevent disease onset it may be more challenging in the already diseased liver. He described gene addition and gene editing approaches. Gene addition involves non-viral or viral vectors, the latter including integrating and non-integrating (eg adeno-associated virus AAV). AAVs had their first 'success' in haemophilia B. A constraint for AAVs in humans is 'pre-immunisation' as well as acquired immunity to the vector. An issue for the paediatric liver is a dilution effect as the liver grows. Gene editing involves transgene insertion, in situ gene correction, integrating lentiviral vectors, mRNA therapy via liposomes and an exosome approach which avoids the immunity issue (exo AAV). In relation to WD, from ATP7B KO mouse work, approximately 40% of hepatocytes need to be transduced to reverse the hepatic phenotype. The pharma company Vivet are planning a gene therapy trial in WD in 2019 using an engineered AAV – units in the UK could participate.

Action: BG to d/w Julien Baruteau re Vivet contact and sound out further interest from SIG.

Laboratory diagnostics and disease monitoring – chair Godfrey Gillett, Sheffield

- Genetic testing – Richard Kirk from the Sheffield Genetics Laboratory described the various types of genetic analysis that are in place ranging from simple genotyping to whole genome sequencing. Genetic testing for WD is currently performed in several centres across the UK. For the past decade there has been a WD scheme running across Europe to ensure quality of reporting. 'Procurement' is on the horizon with 7 genomic lab hubs across England of which two to four will provide ATP7B gene sequencing. There will be a national genomic test directory and rare disease gene testing will be split into core and specialist (ie ATP7B) centres. The plan is that the clinical information entry will become standardised to improve overall quality of data collection.
- Biochemical monitoring – Paul Cook from the Southampton SAS trace element laboratory discussed the issues with caeruloplasmin (Cp) and Cu monitoring. By way of introduction, apoCp rapidly degrades. 95% of Cu is bound to Cp but the importance of this is for Cp's ferroxidase activity rather than its transport in serum (though it is clearly important for this). Total Cu correlates with Cp level. Monitoring is important to detect over or under treatment, and treatment compliance. There are published ranges for urinary copper output and free copper levels 'on' and 'off' chelator treatment. There are also targets for urinary zinc output in patients treated with this agent. When considering Cp bound Cu (NCC) ie 'free Cu' concentrations there is a huge range across labs; 20% are 'negative' (ie impossible) values which relates to the use of immunological rather than enzymatic measurement of Caeruloplasmin (the later measuring biological active Cp). Exchangeable Cu, a method introduced by a French group, is that bound to albumin/amino acids. Results obtained for this method at Southampton are in line with values reported in the literature. This approach could provide a more robust method of monitoring for compliance/treatment effect although it is currently manual method. Paul Cook concluded that there was no evidence to support any particular monitoring method; the cut-offs are variable and calculating free Cu is unreliable. Dr Gillett mentioned data from Vienna that is in press in the Journal of Inherited Metabolic Diseases reporting 'on' and 'off' treatment urinary copper. Dr Gillett also mentioned that the Sheffield range for normal 24 hour urine copper has been revised downwards to <0.6 umol/L.
- Measurement techniques – Chris Harrington from the SAS trace element lab at Guildford described further details and some of the pitfalls regarding the measurement of Cu and Cp. Cu can be measured using ICP-mass spectrometry, 'AAS' or spectrophotometry and is EQA covered across the country. Cp is difficult to measure by whatever method. An issue with exchangeable Cu is that the method can strip some Cu off Cp. HPLC-ICP-MS is an accurate method for direct Cu measurement. There are currently approx. 8 SAS trace element labs in the UK and further centralisation is likely to occur along with other pathology services.
- Hepatic/paediatric perspective – Deirdre Kelly from BCH described the presentation of WD in children. Most acute hepatic presentations of WD underwent transplantation although some patients with chronic liver disease also may require transplantation. Of those transplanted, the median survival was 15.5 years and half of this group have transitioned to adult care. The Eurowilson database was discussed from a paediatric perspective with 219 children analysed (out of 4000 total cases). 55% were on penicillamine. There are data on age and mode of presentation but from the clinical descriptions some subtle neurological abnormalities and psychiatric manifestations in children may be not have been recognised.

Indra Van Mourik also from BCH described the challenge of early diagnosis in children where some parameters can be normal such as Cp and 24 hour urine Cu. For family screening it is recommended to include parents, offspring if consanguineous and siblings from the age of 2 years – the screen includes examination, Cp level, LFT and genetics. Monitoring in presymptomatic individuals is challenging. The recent ESPGHAN guidelines (2018) are not clear with regard to monitoring, but they do describe a stepwise diagnostic pathway from clinical/biochemistry (step 1) to genetics (step 2) and then liver copper estimation (step 3).

Some general discussion followed: there is a clear need for more robust methods and consistency of approach for monitoring. Dr Schilsky emphasised ALT as an early indicator of under-treatment. Dr Gillett mentioned that spot urine Cu in children is useful for excluding non-compliance. In fulminant Wilson's there may be a role for MARS/plasma exchange in rescuing patients who would otherwise need emergency transplantation, but the data are not robust for this at present.

- Prof Oliver Bandmann, Sheffield: Neurological perspective – due to lack of time it was agreed that this section be delayed until the next meeting ()

Action: The SIG should develop best practice guidance for the diagnosis and monitoring of WD in children and adults based on the laboratory expertise available. Laboratory leads to consider drafting a document for the next meeting.

Date of next meeting: TBA. Suggestions were considered for late 2018 or January 2019. BASL funding for a further SIG meeting to be confirmed with the secretariat.

Appendix A - Wilson's Disease SIG attendees: 14th June 2018

NAME	AREA	INSTITUTION
Adrian Bomford	Hep	Kings
Aftab Ala	Hep	Royal Surrey
Aidan Ryan	Clin chem	Southampton
Andrew Fraser	Hep	Grampian
Anil Dhawan	Paed Hep	Kings
Barbara Hoeroldt	Hep	Sheffield
Bill Griffiths	Hep	Addenbrookes
Bill Simpson	Biochemist	Grampian
Carla Lloyd	Res manager	Birmingham
Chris Harrington	Lab science	Royal Surrey
Deirdre Kelly	Paed hep	Birmingham
Emmanouil Tsochatzis	Hep	Royal Free
Godfrey Gillett	Metabolic	Sheffield
Graeme Alexander	Hep	Royal Free
Indra van Mourik	Paed hep	Birmingham
James Dooley	Hep	Royal Free
Jeanette Aston	NCARDRS	PHE
Jerry Tucker	Patient group	WDSG
Julien Baruteau	Genetics	UCL
Maggie Burrows	Neuro	UCL
Martin Ward Platt	Neonatal & paediatric	NCARDRS / Newcastle Hospitals
Michael Schilsky	US physician	Yale
Michelle Camarata	US clinical research fellow	Yale & Univ of Surrey/Royal Surrey
Oliver Bandmann	Neuro	Sheffield
Paul Cook	Metabolic	Southampton
Pierre Foskett	Mol geneticist	Kings
Richard Kirk	Mol geneticist	Sheffield
Sam Shribman	Neuro	UCL
Sanju Mathew	Hep	Royal Surrey
Shaun Greer	Hep	Manchester
Steve Masson	Hep	Newcastle
Sushma Saksena	Hep	Royal London
Tom Warner	Neuro	UCL
Valerie Wheater	Patient group	WDSG

Appendix B - Wilson's Disease SIG apologies: 14th June 2018

NAME	AREA	INSTITUTION
David Nicholl	Neuro	University Hospitals Birmingham
John Ealing	Neuro	Salford Royal Hospital
Rute Vieira	PHE stats	University of Newcastle
Sangeeta Scotton	Neuro	University Hospitals Birmingham