Wilson's Disease SIG meeting 19.11.21 via Zoom

Welcome - Bill Griffiths

Apologies - Jerry Tucker, Barbara Hoeroldt, Phil Blower, Steve Masson, Bill Simpson, Neil MacDougall

Present - Talal Valliani, Val Wheater, Rupert Purchase, Girish Gupte, Tom Marjot, Bill Griffiths, Joanna Moore, Tom Warner, Jan Coebergh, David Nicholl, Paul Worth, David Sheridan, Graeme Alexander, Maggie Burrows, Tammy Hedderly, Paul Selby, James Dooley, Osob Mohamed, Sam Shribman, Godfrey Gillett, Karin Tuschi, Mary Bythell, Miranda Durkie, Peter Beresford, Rachael Kimaru, Carys Lippiatt, Chayarani Kelgeri, Karen Doherty, Andy Holt, James Yiu Lin, Aftab Ala, Karolina Stepien, Mike Samuel, Sunitha Vimalesvaran, Deirdre Kelly, Frank Proudlock, Manolis Tsochatzis, Anil Dhawan, Abu Sharif, Lizi Wheater

Minutes of 20.11.20 approved as accurate, matters arising dealt with and/or discussed in this meeting

Meeting agenda

Trientine NHSE pathway (chair Bill Griffiths)

Paul Selby presented the findings of an online survey of specialist centres. Responses were received from 12 specialist centres (10 Adult/2 paediatric), headlines:

- 75% of centres have no formal guideline for shared care
- Urine/blood monitoring - 100% of specialist centres perform this in-house, about half have their non-specialist spoke centres undertaking this also
- Annual review is completed using variety of mediums with 75% F2F.
- 2/3 of respondents felt home monitoring to be somewhat or very valuable
- 80% of Trientine being prescribed is in the form of Cufence. Tillomed's trientine is not being used.

The feedback from the SIG was that homecare could work better - patient and clinician feedback appears less than satisfactory, particularly in terms of communication (Alcura was mentioned in this regard), clinicians would not be confident about blood/urine monitoring unless results come back directly. At least 2 centres are using Cuprior but experience is too early to judge how the transition from Cufence is working - as a rule clinicians are tending to be conservative with the base salt conversion ie not going straight to 60%. F2F is seen as important particularly from a neurological perspective. Rupert Purchase pointed out that, with respect to Cuprior, the idealised conditions in the Eur. J. Drug Metabolism Pharmacokinetics paper, which recommended the 0.6 factor, are unlikely to be reproduced in the 'real world 'of daily food intakes. The example shared care guideline from Cambridge is available via the BASL website (under About - SIGs - Rare Disease - resources) but may need to be tailored for an individual institution's requirements. Importantly, we are now getting access to Blueteq data directly via NHS Digital (below).

Action: Paul S to liaise with homecare companies regarding their established/intended blood and urine monitoring practices

Wilson's Disease Guidance document overview (chair Bill Griffiths)

Sam Shribman and Tom Marjot presented a summary of the intended aims - addresses delays in diagnosis and treatment, targeted at general physicians, practical guidance, multidisciplinary working, role for specialist centres; timeline - Nov 20 proposal - Jan 21 literature review - Mar 21 working party meetings x 6 - June 21 consultation - Sep 21 guidance finalised - Oct 21 manuscript submission; overview - indications for testing, interpretation of initial investigations (routine/wider screen), additional tests (eg genetic testing, neuroimaging), initial management, monitoring and follow up, family screening. The guidance is didactic eg what to do with a result, when to contact a specialist centre, and is 'packaged' into a 1 page summary figure which will be helpful for end users. Publication under consideration at Lancet GH. Acknowledged - working party, WDSG-UK, WD SIG, BASL/BSG/ABN. Dissemination needs some coordination - of note David

Nicholl has been asked to do a review for Practical Neurology. SIG members suggested the following additional societies to be included: BPNA, RCPCH, BSPGHAN.

Action: working party to establish a guidance dissemination process

Research (1) - (chair Tom Warner)

CROWD / associated work

Sam Shribman outlined that neuroimaging in WD behaves unpredictably in response to chelation therapy and copper indices do not correlate with neurological disease. Brain MRI abnormalities in WD are multi-faceted and to date 'scores' have concentrated on a single aspect/specific brain area and have been unable to show correlation with clinical or biochemical indices. The CROWD study comprised 40 WD patients (23 neuro/17 hepatic, 5 active/35 stable). Four separate MRI modalities, incorporating whole-brain methodology, were analysed with the following conclusions: subcortical atrophy is a promising prognostic/predictive biomarker, FLAIR abnormalities are less useful for monitoring than anticipated, diffusion abnormalities are promising monitor biomarkers, abnormal cortical iron deposition suggests an integral role of iron in pathogenesis. The findings were accepted for publication in *Brain* (July 2021). Future directions discussed.

NHS Digital WD project

Mary Bythell explained how NDRS (national disease registration service) has been moved into NHS digital. NDRS consists of NCARDRS (congenital anomaly team and rare disease team)
and NCRAS (national cancer registration and analysis service). Now under section 254 of health and social care act 2012 - new legal permissions do not need to be granted annually (as per previous section 251). NDRS has legal permission to collect patient data to use it to protect the health of the population. NDRS can collect, analyse and publish data for scientific research and statistical purposes. External research can in theory be conducted within the framework of NHS Digital, if research teams have their ethics in place - the message here being early liaison with NDRS during the ethics process to ensure alignment.

Osob Mohamed explained that DSAs had been set up with 49 Trusts, 28 of which have provided all their cases. Additional cases were sought via SAS labs and the CROWD study. Other data sources include molecular data from Sheffield 2011-2021, death certificates, primary care prescribing data via NHSBSA. There are >600 registered cases, 424 from clinicians and death certificate/CROWD sources. The rest are derived from linkage data - molecular, HES APC (admitted patient care) and primary prescribing. Demographic data showed a bias towards London/SE/East of England. HES data (1997-2020) has been broken down to look at specific ICD10 codes, eg psychiatric diagnoses, and admission data (no. of admissions, length of stay). It should be possible to evaluate the path to a diagnosis of WD. Ongoing work to link sources and confirm cases with centres. On the subject of trientine, the Blueteq data is now accessible - this will be interrogated shortly. Of note prescribing data suggests that GPs are still prescribing the drug in some pockets.

Action: Paul S to work with Osob re Blueteq data

Pharma trial update

Aftab Ala discussed bis-choline TTM mechanism of action and recent/ongoing trials: a phase 2 clinical trial has completed which showed efficacy and an acceptable safety profile. A copper balance study has enrolled 10 patients (5 in UK - Richmond pharmacology, London) some of whom are treatment naive, aiming to show excretion>uptake, effect of dose increment and clearance of the IP (ALXN1840). A phase 3 randomised multi centre study is ongoing - 48 wks of ALXN1840 vs SOC - commenced 2018, primary outcome - % change in NCC from baseline to week 48. Phase 2 histopathological study with primary outcome liver copper concentration from baseline to week 48. Further details of studies are on www.clinicaltrials.gov. A TTM early access programme has just

launched for previously exposed patients. Rupert Purchase mentioned that TTM might chelate copper *in vivo* from a wide range of copper-dependent enzymes. Aftab noted that TTM has a dose-related but transitory effect on liver transaminases.

Other studies ongoing/in setup:
UNITED - pharmacokinetics/dynamics of trientine 2HCl (Cufence), open label, from age 5 upwards.
CHELATE - randomised open label study of trientine 4HCl (Cuprior) - primary outcome non-inferiority to D-penicillamine, completing Jan 2022
UX701 - AAV mediated gene transfer - Ultragenyx - phase 1/2/3 - opening Q1/Q2 2022
VTX801 - GATEWAY study (Vivet) -phase 1/2 - open in US but not recruited yet, more complicated than UX701 - requires nuclear medicine collaboration, setting up at Guildford

Education

Graeme Alexander discussed a project to produce a BASL/WDSG educational video via Kevin Moore (Professor of Hepatology) at the Royal Free and £10K from Orphalan. This would be based on the guidance document - seeking 12-20 volunteers to cover the sections of the document which would form the individual chapters of a 45-60 minute programme. It could be edited with developments down the line. Timeline - framework in place by January - filming 1st half of 2022, ready for viewing at the July WDSG annual patient meeting.

Action: willing volunteers from SIG to contact Graeme via email: g.alexander@ucl.ac.uk

Research (2) - (chair Aftab Ala)

Aftab discussed his recent MRC application based around 'scale' which was not competitive enough but established a team for further collaboration/grant application. One work stream of the project proposal was copper imaging. Unfortunately Phil Blower (Professor of Imaging Chemistry, King's College London) was not available to present his work in this area but some of his work was shown. 64Cu PET imaging offers non-invasive, dynamic monitoring of copper distribution and trafficking between tissues to map quantitatively the movement and transport of radio copper for up to 48 hours (in future 10 days with total body PET). The novel tracer ^{64}Cu-GTSM can cross the blood-brain barrier allowing evaluation of copper chelation therapy in WD. Data on work in mice was shown including the effect of TTM. It is hoped that Phil Blower will be able to present his work in more detail at the next meeting. A note on the chemistry and application of ^{64}Cu-GTSM is available from Rupert Purchase.

James Liu Yin discussed a proposed psychiatry project which was well received. US data suggests psychiatric issues precede organic presentation by a mean of 2.36 yrs. The aim is to study new referrals at the Maudsley hospital, one of Europe's largest centres for research in psychiatry which includes adolescents. Questions will include frequency of testing of Cp/Cu, whether biochemical abnormalities were it acted on, diagnosis of WD, referral rate to psychiatry of known WD, time to diagnosis, local practice of testing. The overall aims are to see if there are 'missing' diagnoses amongst this cohort and whether diagnosis is significantly delayed. Sam Shribman suggested including brain imaging in the analysis. Tammy Hedderly suggested drilling down into the psychiatry diagnoses of WD patients and also mentioned that there are paediatric psychiatrists at Maudsley and WD patients are managed though KCH with psychology and psychiatry input when needed. Mary Bythell said that psychiatric-related drugs and admissions can be looked in depth at a population level through the registry.

Action: James to liaise with Mary Bythell re potentially enhancing the study with NHS Digital input

Ocular Coherence Tomography

Frank Proudlock, Associate Professor in Ophthalmology at Leicester, gave an introduction on OCT which is a key high resolution 3D imaging technique. Some devices have lenses for both anterior segment and retina.

Retinal changes can occur in Alzheimer's, MS and schizophrenia. A portable OCT device can diagnose KF rings when slit lamp findings are negative and has the potential to grade severity ie could be used for monitoring/adherence in WD. An OCT grading tool is being optimised and there is a study proposal to examine 40 patients with WD at Leicester over an 18 month period. Centres within a reasonable distance are encouraged to participate. David Nicholl mentioned that they have been using OCT in their clinic (Susie Mollan). Deirdre Kelly was interested in use in children. Maggie Burrows mentioned 'Spectrum 10K' - a DNA study in autism currently recruiting 10,000 children and adults (University of Cambridge).

Action: funding application going in (Aftab/Frank/WDSG/et al)

Clinical Case

Jan Coeburgh presented a neurological case with delayed diagnosis which improved on TTM but is developing worsening slurred speech and tremor on penicillamine currently. A discussion followed about functional neurological disorder (FND) where WD could be missed if not careful.

Paediatrics (chair Deirdre Kelly)

Tom Marjot introduced and presented the work of Collins et al (Seattle group) published in Gastroenterology this year ('Direct measurement of ATP7B peptides is highly effective in the diagnosis of Wilson disease', *Gastroenterology*, 2021, **160**, 2367–2382). 216 WD patients, 48 obligate carriers and 150 controls were compared. Dried blood spot immuno-SRM testing of ATP7B peptides showed excellent sensitivity and specificity for WD diagnosis. Of note the 17 false negatives had rarer atypical genetic profiles. The group propose a novel algorithm for diagnosis incorporating ATP7B peptide testing.
Miranda Durkie pointed out the difficulties of VUS, genetic prevalence of disease, hypermorphic partial function variants and an overall lack of functional data to determine significance.

Debate: 'this house believes that neonatal screening for WD should be implemented'
16 were in favour of neonatal screening prior to the debate. Abu Sharif argued 'for' - could save lives, prevent severe disability, be cost beneficial to society, improve understanding of the disease and help to optimise treatment. He gave an example of where gene therapy could work if diagnosis is made early (Crigler-Najar type 1). We are moving towards neonatal genome sequencing. Sunitha Vimalesvaran argued 'against' - the immuno-SRM technique has a false positive rate, genotype-phenotype correlation is not understood, WD patients can present decades later, large phenotypic variability, not clear when to commence treatment, burden on clinicians, unproven whether outcomes would be improved. After the debate 14 were in favour - accepting that some people may have left the meeting, the motion was defeated.

Action: the paediatric members to consider developing a workstream here

AOB - nil

Bill G thanked all who attended and the contributions from the speakers in particular.

Date of next meeting - TBA