BASL Wilson's disease SIG meeting - 25.11.22

Via Zoom

Apologies - Paul Worth

Present: Aftab Ala, Maggie Burrows, Mary Bythell, Oliver Bandmann, Jan Coeberg, Jane Collier, Chris Cussen, Harpreet Dhaliwal, James Dooley, Miranda Durkie, George Firth, Pierre Foskett, Godfrey Gillett, Bill Griffiths, Girish Gupta, Tammy Hedderly, Andrew Holt, George Kagugube, Chaya Kelgeri, Deidre Kelly, George Kostakis, Carys Lippiatt, James Maurice, Steven Masson, Rosa Miquel, Osob Mohamed, Joanna Moore, Helen Patrick, Rupert Purchase, Mike Samuel, David Sheridan, Sam Shribman, Karolina Stepien, Manolis Tsochatzis, Karen Tuschl, Tom Warner, Evangeline Wassmer, Val Wheater, James Liu-Yin

Minutes from 19.11.21 meeting approved as accurate.

Matters arising (BG):

Trientine: as Cufence no longer requires refrigeration whether opened or unopened (this is advice pharmacies are giving to patients) some vigilance is worthwhile. RP explained that the dihydrochloride form of trientine (Cufence) has a lone pair of electrons on each of the two secondary amino sites, which could influence the medium and long-term stability of this salt. The fully protonated tetrahydrochloride (Cuprior) has no lone pairs of electrons on the amino sites, and is intrinsically more stable than the dihydrochloride. The storage temperature of Cufence needs to be borne in mind. Please also read this cautionary tale: Rupert Purchase. Talk at o8 meeting.pub (wilsonsdisease.org.uk).
BG is pursuing a pilot of blood/urine testing for patients on Cufence via Alcura homecare.

Guidance: published in Lancet Gastro Hepatol Apr 2022 - disseminated in the UK via most of the relevant specialist societies. Feedback has been positive. Going forward - dissemination via additional societies (eg admin@bspghan.org.uk) and Royal Colleges - working group to action. AA - sustainability can be enhanced via publication of joint reviews.

Discussion about barriers to rapid genetic testing which if circumvented could bring genetics further forward in the diagnostic algorithm - MD explained backlog & shortage of trained scientists but that urgent requests can be prioritised and the clinical eligibility criteria via the national genetic testing directory are not too rigorous.

NHSD update - Osob Mohamed / Mary Bythell

OM presented Blueteq data now obtained for 2019-2022 ie since trientine commissioned via NHSE. 120 patients on trientine dihydrochloride (64F, 56 M). Prescriptions are mostly from Centres of Excellence. New prescription numbers: 72 in 2019, 25 2020, 15 in 2021, 8 in 2022. The fall in numbers may relate to uncaptured data on the tetraHCl form. Next steps - capture additional patients, geographical mapping.

MB described the NCARDRS timeline: Mar 2020 COVID support, Oct 2021 NDRS transition to NHSD, Nov 2021- merger (NHSE/NHSD/HEE/NHSX) announced for Mar 2023, Oct 22 Dept of Health announced accelerated merger for Jan 23. Issues with recruiting/redundancies.

Regarding database longevity and opportunity for research: rare disease framework published Jan 2021, NHSD working across devolved nations (which broadly now have legal permissions to work on adult rare disease) to standardise work, opportunity via large MRC/NIHR funding call for integrated rare disease

research nodes, ongoing work with genetic databases and tapping into the cancer registry experience and infrastructure. There is significant potential to study our established sizeable cohort in more detail if SIG members can provide personnel and funding.

New chelators - George Kostakis

GK explained that his work has involved developing unconventional ways to make new catalytic pathways. Work includes predictive properties of chelators eg trientine & BAL not predicted to cross BBB, TMDQ20 and Salpyran predicted to cross BBB. Trientine has high selectivity for copper over zinc compared with Salpyran. Properties vary according to solvent used. PhD funding is available to study copper-chelating small molecules as a treatment for neurodegeneration and WD. Discussion revolved around the fact it does not appear clear whether any of the currently used chelators are able to cross the BBB. RP suggested that Cu^{1+} would be a better target than Cu^{2+}. Collabators welcome, in vivo studies moving forward - please contact via g.kostakis@sussex.ac.uk.

Case presentations - Jan Coebergh

JC described 5 adult cases. The first three were patients with mildly abnormal copper indices but without definite copper-related disease seeking either WD treatment or copper replacement. The hallmarks of presentation were functional neurological symptoms and 'fabrication'. Clues in the psychosocial history were present. The remaining cases had WD but with functional overlay due to contributions from frontal lobe pathology and neuropsychiatric manifestations. One had a good neurological response to TTM therapy. The cases demonstrated the complexity of neuropsychiatric WD, the need for personalised care, importance of elucidating the dominant pathology and awareness of functional overlay to help interpret fluctuations and target treatment. TH mentioned that functional neurology is also important in children/adolescents and the role of social influences. G Gillett advised checking for variants in the Cp gene to potentially help provide an explanation for relevant patients, also that John Walshe had advised caution with TTM in children due to the potential for skeletal abnormalities. SS advised that damage to the anterior insular cortex in WD can specifically affect 'sense of self'.

RP comment: please note that the word 'copper' is used in the WD literature as shorthand for metallic copper (Cu(0)), cuprous copper (Cu(I)) and cupric copper (Cu(II)). The diet contains Cu(II), intracellular copper is mainly Cu(I), Kaiser-Fleischer rings are thought to contain Cu(0). Cu(II) is excreted. Copper metal or powder, if accidentally or deliberately ingested, is unlikely to be absorbed?

Less common manifestations in WD - Chris Cussen

These relate either to a direct effect of toxicity or due to treatment/complications. The salient purported manifestations outwith the liver and brain are: cardiac, renal, joint/bone related, haematological, endocrine and skin related. Some interesting data on fertility and recurrent miscarriages in women. AF appears to be twice as common in WD. Of note, trientine is being trialled in HOCM (TEMPEST study). *Slides will be sent round to all as requested* (BG).

AASLD update - James Liu-Yin / Aftab Ala

WD was well represented with two specific sessions at AASLD. JL presented a number of abstracts covering the new chelator ARBM-101 (byproduct of methanobactin - shows efficacy in rats), epigenetics, firstline treatment results for tetraHCl form of trientine (Weiss), observations from CHELATE and ALXN1840, NCC methods, WD neuropsychiatry. *Slides will be sent round to all as requested* (BG).

PET imaging in WD - George Firth

GF described dvances in 'total body FDG-PET' with the new 'explorer' scanner coming - 40th of normal dose, acquisition in seconds vs 20 mins, unrivalled kinetic and dynamic info with high resolution imaging. There is a useful review of PET metallomics in Chem Bio 2022 (Firth et al).
Radioactive isotopes of trace metals for trafficking study include Zn-63, Zn-62, Cu-64, Cu-62, Mn-52 - PET shows differential uptake in organs. Cu-64 GTSM is a metastable lipophilic chelator that penetrates BBB and delivers Cu into the brain. Alzheimer mice show greater Cu accumulation. TTM does not appear to pull Cu out of the brain. A Kings health partner grant has been awarded to convert the GTSM compound to GMP pharmaceutical grade and to produce it with a view to study in humans. Further work includes studies in ATP7B mice (collaboration with Tamir Rashid).

G Gillett mentioned that Cu-65 is a stable isotope which gives similar diagnostic discrimination as Cu-64 - currently not available from Glasgow, unfortunately (https://www.trace-elements.co.uk/65copperprotocol.asp). TW raised whether iron can be examined via this method and whether studying WD will be difficult because of the protracted time to develop copper overload. We look forward to further work in this area (BG).

ATP7B heterozygotes - James Liu-Yin / Aftab Ala

JL presented a retrospective study of genetic results at Kings since 2015. 90 simple heterozygotes (M54, F36, age 4-77 years), 40 via family screening, 50 symptomatic. 10/90 had diagnosed WD. 5 deaths, none due to WD. Mean Cp for non WD cases 0.18 (0.1-0.3) - a few had Leipzig score of 4 or 5. Variants - 25 VUS, 26 pathogenic, 15 likely pathogenic, 1 likely benign. Discussion around whether more actually had WD and whether some variants are still correctly classified or whether there is a missing second variant. BG thanked for sharing this work.

Genotype/phenotype project - Helen Patrick / Miranda Durkie

HP presented the general assumptions that severe LOF variants are associated with hepatic early onset disease and milder variants are associated with neurological later onset disease. Defining correlations could yield useful prognostic information. So far data on 148 patients from the Sheffield diagnostic genetic service - 23% variants in exon 8 and 13 with 19% His1069Gln. Comparing predicted severity of variants with type of onset of disease - no correlation thus far. Limitations - functional protein information, misdiagnosis, accurate definition of phenotype, accurate disease onset information. Future work will include expansion to 400 patients (collaboration with Kings), intronic variant analysis, link with NHSD phenotypic data, correlation with age of onset.

G Gillett mentioned analysis of sib pairs could be useful. G Gupta (Birmingham) has also offered to collaborate.

Cognitive deficits in WD - Sam Shribman

Based on the CROWD study neuroimaging pipeline. Previously shown that Voxel-based morphometry illustrated atrophic changes discriminating neurological vs hepatic presentations and atrophy of basal ganglia worsens with neurological disease severity. Cognitive deficits in WD are common, usually mild and worsen as neurological disease worsens. Subtle deficits are also seen in hepatic presentations illustrated particularly by the recognition memory test for faces (BG afterthought - interestingly the animal naming test is advocated for minimal hepatic encephalopathy diagnosis). In basal ganglia volumetric analysis the putamen volume correlates with executive function. Cognitive deficits associate with cortical volume loss

in WD. Subtle cognitive deficits in hepatic presentations represent a distinct neurological phenotype which is associated with diffuse cortical and white matter pathology - this may precede the classical neurological phenotype associated with basal ganglia damage. A binary phenotypic classification for WD may no longer therefore be appropriate.

SS emphasised the importance of distinguishing cognitive deficits from psychiatric manifestations though they may overlap clearly. SS suggests that all WD patients, especially adolescents, should have in depth testing for cognitive deficits. Chelation may improve cognitive deficits in the early stage of treatment (in response to DK). Though 'normal' MR brains have been described in neuroWD, newer MR techniques are likely to show abnormalities.

Clinical trial update and future studies - Aftab Ala

AA presented the recently completed, ongoing and upcoming clinical trials in the UK. ALXN1840 phase 3 (presented already) and 2 x phase 2 studies (copper/molybdenum balance, copper concentration/histological changes) have recently completed. Ongoing studies include the 'Yale' natural history/registry study which is hoping to fund additional sites in the UK, the iWilson international registry (Orphalan), paediatric study of ALXN1840, UNITED study (pharmacokinetics/ dynamics related to dosing of Cufence). Studies in set up - Ultragenyx UX701 study and Vivet VTX-801 gene therapy trials.

Planned trials:

1) PIPELINE - diagnostic potential for ATP7B peptide dried blood spot testing in neuropsychiatric WD - funded feasibility study for 1000 patients to be screened with 100 positive controls.

2) ASCOT - pilot study of hand held OCT for KF ring characterisation - with a view to multi-centre study across interested UK sites.

Slides to be sent round to all as per request (BG).

The WD SIG wishes to acknowledge the recent sad passing of Dr John Walshe.

Date/place/format of 2023 meeting: TBA