BASL Wilson's Disease Special Interest Group Meeting
Friday 29th November 2019
Queen Square House, Institute of Neurology, UCL

Meeting report

Attendees (36):
Aftab Ala (adult hepatology, Kings/Royal Surrey), Andy Holt (adult hepatology, Birmingham), Barbara Hoeroldt (adult hepatology, Sheffield), Bill Griffiths (adult hepatology, Cambridge), Carys Lippiatt (clinical biochemistry, Leeds), Chris Harrington (clinical biochemistry, Royal Surrey), Eirini Kyrana (paediatric hepatology, Leeds), Emmanouil Tsochatzis (adult hepatology, Royal Free), Evangeline Wassmer (paediatric neurology, Birmingham), Godfrey Gillett (metabolic medicine, Sheffield), Graeme Alexander (adult hepatology, Royal Free), Ian Low (neurosurgery, Queens), Indra van Mourik (paediatric hepatology, Birmingham), James Dooley (adult hepatology, Royal Free), Jan Coebergh (adult neurology, Royal Surrey), Jane Collier (adult hepatology, Oxford), Jeanette Aston (PHE), Jeremy Cosgrove (adult neurology, Leeds), Joanna Moore (adult hepatology, Leeds), Maggie Burrows (adult neurology, UCL), Mary Bythell (PHE), Mary Fortune (WDSG), Michelle Camarata (PHE), Mike Samuel (adult neurology, Kings), Oliver Bandmann (adult neurology, Sheffield), Osob Mohamed (PHE), Pierre Foskett (clinical genetics, Kings), Pramudi Wijayasiri (adult hepatology, Nottingham), Robert Przemioslo (adult hepatology, Bristol), Rupert Purchase (chemistry, Brighton), Sam Shribman (adult neurology, UCL), Suresh Venkatachalapathy (adult hepatology, Nottingham), Talal Valliani (adult hepatology, Bristol), Tammy Hedderly (paediatric neurology, Guys/St Thomas), Tom Warner (adult neurology UCL), Val Wheater (WDSG)
Apologies: Eileen Joyce (Neuropsychiatry, UCL)

Welcome/minutes/matters arising/actions

Bill Griffiths welcomed everyone, including new SIG members, and thanked Tom Warner and Sam Shribman for hosting the meeting at Queen Square. The minutes from the 14th February 2019 meeting were agreed as accurate. Actions had either been completed or were to be incorporated into the current meeting, matters arising similarly.

National work - chair Aftab Ala.

Commissioning/Specialist Centres update - Bill Griffiths

BG updated the SIG regarding the Specialist commissioning of trientine across England. A policy document published by NHSE 21.12.18 summarises criteria for the use of trientine formulations (both dihydrochloride and tetrachloride acceptable as far as NHSE is concerned) as a 2nd line agent in Wilson disease ie for those intolerant to penicillamine or where penicillamine is contraindicated. This took into effect on 1.4.19. The document includes a patient pathway involving Specialist Centres with requisite expertise, core being hepatology, movement disorder neurology and clinical biochemistry. These Centres should be setting up shared care arrangements with local hospitals for trientine prescribing and paediatric centres should have transition arrangements for adulthood. Trientine has recently been recognised by Blueteq for this purpose and all patients require completion of a form. Existing trientine patients will be able to continue with local prescribing arrangements but require 'annual review' via the Specialist Centre. It was suggested that 'annual review' could serve a greater purpose eg opportunity to discuss research (Aftab Ala). NHSE is due to audit this all in due course.

A list of Specialist Centres was provided. There are 3 additions all represented at today's meeting and ratified by the SIG for inclusion by NHSE, namely Nottingham, Oxford and North Bristol. A spreadsheet of Specialist centre expertise was shown which will be sent round for SIG members to modify. Currently this is not an advertised list but could be put up on the BASL and WDSG websites with permission.

Action: BG to send new list of Centres to NHSE and to send the expertise spreadsheet round to SIG members for modification as required

The Clinical Standards document for WD Centres of Excellence (C of E), circulated following the previous meeting, had received welcome feedback particularly from the Movement Disorders Group of the Association of British Neurologists. The modified document was presented for discussion. It was suggested by the Paediatric representatives that Clinical Psychology should be added as an important discipline. Differentiation of core from non-core was thought to be helpful (Aftab Ala). The document has been further modified in light of comment at the meeting and will be re-circulated. This document will be presented to the HPB CRG (clinical reference group) in due course. Questions about funding for services arose (Andy Holt) which will be addressed if NHSE agree to take on board and commission accordingly (via the HPB CRG). The HPB CRG had paused the proposal earlier in the year but it is still on their agenda. C of E should aspire to upskill the smaller centres diagnosing and seeing patients with WD.

Action: BG to send version 1.2 round for further comment and to liaise with the HPB CRG

PHE project - Mary Bythell, Osob Mohamed

Michelle Camarata (present) had provided significant input into the project prior to parental leave. MB described several strands which feed into NCARDRS - Clinical information, Genetic data (which is original), data from the CROWD study, data from the SAS labs. NB it was pointed out (Godfrey Gillett) that there are labs outwith SAS which analyse copper/caeruloplasmin and could provide additional data, including immunology. In addition the data from ONS (office of national statistics) has a bi-directional relationship with NCARDRS. Prescription data in both primary and secondary care is now also being interrogated. A list of cases ascertained by each Centre was displayed. Of note some Centres have not submitted their data. Sheffield (Oliver Bandmann) pointed out that they have many more WD cases than seemingly captured and will along with other Centres be invited to submit their 'missing' data. Of note the original form had two parts - the second for patients that NCARDRS had not been able to identify.

Mortality data was presented (OM) and which will form part of an EASL abstract /subsequent paper submission. Of note HCC was listed on the death certificate in a not insignificant proportion of patients and a larger analysis may be able to gauge incidence, as well as linking in with cancer registration data. Preliminary prescribing data was displayed and genetic data is to be linked in due course. Genetic data from Sheffield since 2011 was shown and of note a significant proportion of cases labelled as WD did not have at least 2 mutations - this may be due to inaccurate phenotyping or incomplete sequencing/recognition of pathogenic variants at the time. Genetic data from Kings and pre-2011 Sheffield data is pending. It was suggested that the association of clinical biochemists could be worth approaching with regards lab data. Blueteq forms will provide data on trientine treated patients in due course. Transplant data has already been obtained from NHSBT and it should be possible to answer the question (from WDSG) 'what percentage of patients have received a liver transplant?'.

MB proposed a 3-5 year plan for the project including the following components: peer review papers, audits, long term outcomes, genotype/phenotype correlation, diagnostic odyssey, Bioresource. There is a plan to extend to Wales and Scotland in the near future.

Action: PHE to develop ideas discussed during the meeting, Centres which have not as yet returned data to be encouraged to do so, PHE will re-contact Centres in order to obtain the 'missing' cases

Clinical - chair Dr Bill Griffiths

Primary care awareness - BG

The WDSG are concerned that GPs are not picking up cases of WD in a timely manner. BG explained that Hepatology centres are mostly now providing clear guidance to GPs regarding caeruloplasmin measurement in the context of a raised ALT/AST in younger people. The neurologists felt that secondary care is challenging enough for WD diagnosis let alone primary care and given the rarity. Perhaps a combination of tremor and raised ALT should trigger WD testing (Sam Shribman). It was suggested by Oliver Bandmann that a review in the BMJ might target GPs effectively.

Action: Sam Shribman/Oliver Bandmann/BG along with interested SIG members to work on a BMJ review in 2020

HCC surveillance in Wilson's cirrhosis Y/N? - Emmanouil Tsochatzis

An initial show of hands showed that most hepatologists present are systematically monitoring WD cirrhotics for HCC. Evidence was presented which suggests that WD cirrhosis does not meet the accepted 1.5% annual incidence threshold for screening (EASL and AASLD HCC guidance). It is important to recognise the 'harm' of surveillance in addition to the benefit (Taylor et al, Hepatology 2017). 3 papers were discussed - Walshe, QJ Med 2003, van Meer et al JGH 2015, Pfeiffenberger et al Liver Int 2015. All 3 suggest low incidence. The larger Pfeiffenberger study included all WD patients. Of note the incidence of cholangiocarnioma was similar to HCC. One limitation is that reported incidence will be lower if people are not screening routinely (Graeme Alexander).

Action: to incorporate into consensus monitoring document (BG)

Deep Brain Stimulation (DBS) in neurologic refractory WD - Ian Low / Mike Samuel

MS introduced the topic with an anatomy lesson showing basal ganglia connections and the circuits/brakes which drive the final common pathway for movement from the cerebral cortex. Subthalamic nucleus (STN) electrical stimulation was approved by NICE in 2003 for Parkinson's disease (PD) and there have been several positive RCTs. In 2006 DBS was approved for tremor and dystonia. In 2013 a Commissioning policy was approved. There are now recognised centres for DBS across England / Scotland (currently a network of 17 centres). In general, DBS is less effective if there is structural brain damage and ADLs are an important parameter.

Re DBS suitability in WD important to identify: the specific symptom to treat, timing, and the likely response rate, any clotting disorder in those with significant hepatic disease, MRI signal changes and whether they are likely to be irreversible, psychiatric and psychological state, infection risk (generally low, but ongoing), not a substitute for continuing medication.

IL presented a case of WD with some dystonia and prominent tremor, the latter clearly had a significant impact on QOL and ADLs. This patient received bilateral posterior subthalamic area- subthalamic nucleus deep brain stimulation (PSA/STN-DBS) with 92% reduction in tremor and an unexpected improvement in the movement and disability components on the BFM dystonia scale of 65% and 74% respectively. The marked improvement in tremor and dystonia was still apparent three years after surgery. Literature reviewed but this is very limited worldwide.

TW commented that DBS is likely to only be relevant to a minority of patients due to the fact that the dystonia is often fixed, and speech and swallowing problems are relative contra-indications for the procedure.

Action: ABN movement disorder group (OB) to continue to refine the place of DBS in WD and ensure nationwide access to DBS MDTs

Research - chair Oliver Bandmann

Nottingham prevalence study - Pramudi Wijayasiri

PW introduced known data on prevalence and highlighted the approximate 1:4 ratio of clinical vs genetic diagnosis of WD in the UK. Penetrance and case ascertainment will be contributing to this difference. The Nottingham population based study involved identifying potential cases of WD from various sources including NCARDRS, low caeruloplasmin levels, elevated urinary coppers, histology reports and prescribing data across the CCG. From an initial 4 WD patients recognised, the subsequent analysis found an additional 9 patients and 23 potential cases (low caer/raised urinary copper). Of note 30% of patients were under psychiatry follow up. The study suggests that not all patients with WD are being identified. It was pointed out that prevalence needs to be calculated with caution as the catchment for laboratory sampling may not correlate exactly with the CCG population.

Action: Nottingham to link with PHE for mutual benefit in optimising case finding

CROWD - Sam Shribman

SS updated the SIG on the study which is going well. An amendment has been pushed through to make it easier/faster to invite potential participants. Re the genetic determinants arm, 96 online questionnaires and 98 saliva samples have been received to date. DNA extraction with next generation sequencing to be performed on the saliva samples and additional participant identification sites in progress. Re the biomarkers arm, 38/40 recruited. Baseline data, neuroimaging, follow up visits and fluid biomarker assays as next steps. The WDSG patient register was a helpful aid to the study.

Best of AASLD re WD - Aftab Ala

1) Pan-US study (Haq K et al) demonstrating doubling of the cost of care for WD patients between 2001 and 2012. Over the same period a tripling of hospitilisations, 2/3 of which were into teaching hospitals. The study strengthened the association of WD and co-morbidities.
2) Use of 64CuCl2 PET to evaluate copper metabolism in WD (Sandahl TD et al). The Aarhus group presented data showing increased hepatic Cu accummulation in WD cf heterozygotes and wild-type. Ratio of mean hepatic SUV (standardised uptake value) at 90 mins and 20 hours accurately diagnosed WD in 100% of cases. The technique may be useful in diagnosis and monitoring of WD and the data was interesting to see. GG pointed out that John Walshe had done similar studies in the past and that a stable isotope method is already available through Glasgow and Guildford (presented by Andy Duncan at the previous meeting).
3) Potential role of heavy metals in immune liver diseases (J Dyson, Newcastle) could be extended to WD - PHE could do this and link in with 'exposure' data/experts.
4) Trientine dihydrochloride pharmacokinetic data (Dogterom et al, including Univar). 2 types of capsule with different dissolution rates were found to be comparable. Of note food within 30 minutes prior to administration delays absorption and reduces exposure to trientine by 44%.

Pharma trials - BG

1) FOCuS - ALXN1840/WTX101-301 (Alexion): bis-choline TTM 36 wks vs SOC, 62 active sites including 3 in UK (Cambridge, Birmingham, Royal Surrey). Cohort 1 (stable) 89 patients enrolled, target 135. Cohort 2 (new) 33 patients enrolled, target 45. Hoping to complete 180 target by 31.12.19 (122 currently so looks like will extend).
2) CHELATE (GMP-Orphan) - trientine tetrahydrochloride (Cuprior) in pencillamine stable patients to evaluate efficacy and safety, non inferiority study. 18-20 sites including 2 in UK which have recruited 3 patients. Close to recruitment target.
3) The Vivet study (VTX-801 miniATP7B-AAV) not yet started, phase 1/2 open label, site visits underway.

Laboratory - chair Godfrey Gillett

Trientine tetrahydrochloride - Rupert Purchase

RP described triethylenetetramine tetrahydrochloride - first reported in 1920, melting point 266-270 C, prepared by the addition of hydrochloric acid to a solution of the free base - Cu coordination noted in 1936. The marketed dihydrochloride product (Cufence in Europe) contains 200 mg free base per capsule and costs 15p/mg free base at the NHS list price. The tetra formulation (Cuprior) comes as a 150 mg free base tablet at a price of 25/mg free base at the NHS list price. Cuprior is stable at room temperature and, according to the manufacture, has higher bioavailability than Cufence such that 60% dose adjustment is proposed cf the mg equivalent of Cufence. It was thought that proton pump inhibition ought not to affect the absorption of Cuprior. The free base is available as technical grade (60-70% triethylenetetramine) from a Japanese company at the cost of 0.0006 p/mg. It was noted that Cuprior has taken over as the leading trientine formulation in Germany and is now available in the UK - Scotland have approved and NHSE support it within their commissioning policy.

Laboratory assessment of non-caeruloplasmin bound copper - Chris Harrington

Serum copper (Cu) is low in WD but can be normal or raised in acute liver injury. 24 hr urinary Cu can be <1.6 (the WD cut off in EASL 2012 guidelines) in 16-23% of WD eg children and asymptomatic individuals. Caeruloplasmin (Cp) is typically measured using nephelometry which can over-estimate and this leads to errors in calculating non-Cp bound Cu (NCC) - as such this method is not recommended if using nephelometric caer measurement. The enzymatic method for Cp is more accurate as excludes Cp not bound to Cu however this is expensive and unlikely to become universal across labs. Exchangeable Cu (ExCu) not validated and can over-estimate if not well controlled. Relative ExCu shows promise but not validated. These methods rely on the assumption that EDTA does not remove Cu from Cp and that Cp-Cu is not pulled through. Hepatic Cu content - errors if sample mass is low. An accurate NCC method has been published (Solovyev et al Analytica Chimica Acta) using strong anion separation coupled to inductively coupled plasma mass spectrometry. This identifies all Cu containing complexes and can subtract Cp-Cu from the total Cu as well as identify the non-Cp bound components.

In terms of monitoring the goal of treatment is to remove circulating 'free Cu' but perhaps to maintain the Cp-Cu level ie not overtreat. Currently urine Cu excretion (UCE) is used to adjust treatment with EASL guidelines suggesting

<1.6 umol/24 hr 48 hr after cessation of chelator as satisfactory. UCE might not tell you about Cp-Cu maintenance (if important). A questionnaire was sent round to centres prior to the meeting. The limited replies suggested variation in which tests were being used in terms of diagnosis and monitoring eg UCE on or off treatment, calculated NCC at diagnosis or for monitoring. Some feedback related to the difficulty of obtaining UCE results in patients for logistical reasons. It was agreed that a revised form might be sent out after the meeting to specifically include thresholds which clinicians are using in practice. The form will be simplified to the extent that it will focus on Cu/Cp measurement only.

Action: CH and BG to revise the 'consensus monitoring' questionnaire and send out again

Date of next meeting: TBA