BASL Wilson's Disease Special Interest Group Meeting
Thursday 14th February 2019
Queen Square House, Institute of Neurology, UCL

Meeting report

Attendees (24):
Aftab Ala, Aidan Ryan, Andy Duncan, Bill Griffiths, Chris Harrington, Eileen Joyce, Godfrey Gillett, Graeme Alexander, Indra van Mourik, James Dooley, Jan Coebergh, Jeanette Aston, Jerry Tucker, Maggie Burrows, Mary Bythell, Mary Fortune, Michelle Camarata, Oliver Bandmann, Paul Cook, Rupert Purchase, Sam Shribman, Shahzrad Shahmehri, Tom Warner, Val Wheater

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 14 June 2018 meeting were agreed as accurate. Actions had either been dealt with or were in process and any matters arising were to be further discussed during this meeting.

National work - chaired by Prof Aftab Ala.

Bill Griffiths updated the SIG regarding the Specialist commissioning of trientine across England, now off tariff. A policy document published by NHSE 21.12.18 summarises criteria for the use of trientine dihydrochloride as a 2nd line agent in Wilson disease ie for those intolerant to penicillamine or where penicillamine is contraindicated. This will take into effect on 1.4.19. The SIG was grateful for the tireless work of James Dooley in getting this policy through. The document includes a patient pathway involving Specialist Centres with requisite expertise either in-house or via networked arrangements. These Centres would set up shared care arrangements with local hospitals for trientine prescribing. New patients will need to be seen at the Specialist Centre for trientine initiation and then annually for monitoring purposes. Existing trientine patients will be able to continue with local prescribing arrangements.

A list of centres with Specialty leads put together by BG was discussed by the SIG. There was some debate about whether a smaller number of centres would be more appropriate but it was recognised that geographical coverage is an overriding factor, namely for patient access and support of neighbouring DGHs, and smaller Specialist Centres would be able to develop their experience. To this end it was agreed that Plymouth have the requisite expertise and could serve the South West. Oliver Bandmann pointed out that Sheffield has an established paediatric Wilson's service which could continue to link with the Leeds service. James Dooley suggested that 2 named experts in each field would be advantageous for the purpose of cross-cover - expert leads should be able to nominate a deputy.

Appendix 1 - Wilson Centres with Specialty leads

Action: BG to submit the list of agreed centres to NHSE ahead of the publication of a circular going round to all trusts

Graeme Alexander on behalf of the HPB Clinical Reference Group updated the SIG regarding a submission for Specialist Centres for Wilson disease for all aspects of care. A further meeting is taking place on 21.3.19 followed by a Consultation exercise. This is part of a wider proposal to develop hub

and spoke care for liver disease with defined pathways to improve care and channel funds appropriately. It is likely that NHSE will accept the list of Centres for trientine as a start but other centres could join as they develop expertise. Each Centre would need to describe details of their service and networked arrangements, a point raised by Jerry Tucker. Sam Shribman pointed out that allied health professionals are vital for the management of neurological Wilson disease and should be included in the service specification.

Action: BG to continue to liaise with Graeme Alexander re HPB CRG submission

Mary Bythell on behalf of Public Health England updated the SIG regarding ongoing project work. The Case confirmation exercise is continuing but would benefit from returns from the larger Trusts yet to submit data. 18 responses from 49 Trusts have resulted in a total of 100 Wilson's cases. Of 110 suspected cases via HES, 50 were confirmed. 48 additional cases outwith HES were submitted and 2 cases have been picked up since. Prescribing data on 55 patients showed 34 using penicillamine, 17 trientine and 13 zinc with some on combination. The treating clinician (possibly biased) of 77 cases was hepatologist (69), neurologist (12), gastroenterologist (9), psychiatrist (2), biochemist (1). Prospective data collection is planned via the SAS trace element labs along with a plan to capture Molecular Genetic data. Michelle Camarata will have an honorary contract shortly to help push the project forward and link the various data sources - mortality, prescribing, HES, CROWD study (data sharing agreement being set up). The project should answer questions regarding the epidemiology and care of WD across England. There was discussion about primary care data sources - Aftab Ala described the RCGP route which he has used for PBC, Graeme Alexander mentioned Helen Jarvis who is the liver champion for primary care and would be a good person to link in with.

Action: Michelle Camarata to now help accelerate PHE work and report back in due course

Neurological and psychiatric aspects - Chair Prof Tom Warner

Oliver Bandmann introduced the topic with fascinating early cinematography by Samuel Kinnier Wilson of a patient with WD in the garden of Queen Square (1924). Simple revealing tests for neurological WD include abnormal tongue movements, dystonic hand posture and stiffness of gait. Weakness is not typical and ataxia and chorea are not features *per se*. A sensory deficit excludes the disorder. 5% have seizures and unusual presentations include muscle cramps. Severity of symptoms does not correlate with free copper measurement or genotype (Ferenci *et al* 2018). Neurological presentation may correlate with 'epigenomic' signatures according to recent data (Mordaunt *et al* 2019.

In terms of MR imaging, basal ganglia change is common but abnormality can be seen elsewhere as per Chinese study on 364 patients with neuro WD - 100% abnormal brain MR affecting putamen, pons, midbrain and thalamus (Yu *et al* 2019). The role of routine follow up MR is uncertain. The main treatment concern is neurological worsening on chelator treatment in at least 20% of patients. OB suggested a potential UK trial comparing chelator +/- a neuroprotective drug/mitochondrial rescue agent or autophagy enhancer.

Discussion included mention of guidelines published in India in January of this year, the role of deep brain stimulation (some publication bias) and the unclear benefit of liver transplantation.

The SIG was delighted to welcome Prof Eileen Joyce. Psychiatric diagnosis is typically 2nd to 4th decade with respect to WD (Gioia *et al* 2017). 20% may present with symptoms prior to physical manifestations (cf Parksinon disease up to 5 years prior). 33% of WD develop neuropsychiatric symptoms early and 66% at some stage, not always clear if reactive or due to the pathological process. There is a wide range of psychiatric manifestation in WD and a high prevalence of symptoms. Typical features are personality change, depression of which some can manifest as bipolar disorder. Schizophreniform features occur in 8% (cf 1% general population). Cognitive impairment can include a dementia type presentation which can reverse with chelation - frontal white matter change is typical. Behavioural symptoms are common (Biswas *et al* 2017). Suicidal ideation can be present in WD in part

secondary to depression. In terms of treatment, adjunctive therapy to chelation includes lithium, mood stabilisers, anti-depressants, and anti-psychotics.

As part of the bigger picture, there is a move to improve psychiatric input for patients with neurological disease in general. A proposal via NHSE to commission neuropsychiatric services within recognised neuroscience Centres is towards the end of a Consultation exercise. Also there is a push by charities (eg Parkinsons UK, Neurological Alliance) with a meeting in June re improving access to mental health services for patients with neurological disease. Paul Cook suggested that a simple blood panel could be devised to improve the pick up of WD in younger patients presenting with for example psychosis. GPs are mandated to check bloods in psychotic patients for drug monitoring purposes.

Action: SIG to work with Eileen Joyce going forward to improve psychiatric input into WD

Case presentations - chaired by Dr Godfrey Gillett

Sam Shribman presented a case of advanced neuro WD where off treatment 24 hour urinary copper measurement suggested might now be over-treated, the risk being super-imposed myelopathy due to copper deficiency. It was agreed that a dose reduction would be sensible and MR spine can help exclude myelopathy development.

BG presented a case where the diagnosis in the daughter of a patient with WD may or may not have WD, the genetics suggestive but not conclusive until parental genetics is known. As the MR brain is possibly abnormal a referral to neurology/psychiatry suggested and test for relative exchangeable copper. BG also presented a case of ribosome stalling explaining how a homozygous synonymous mutation due to a single base pair substitution (Phe764Phe) could result in WD - highlighting a potential pitfall in 'negative' ATP7B sequencing.

Aftab Ala presented a case of diagnostic doubt where the high tissue copper alone swung the diagnosis (according to Leipzig criteria) but may or may not have been accurate. The case illustrated the usefulness of sharing experience.

Godfrey Gillett presented a case of difficult EPS in a patient on longstanding penicillamine, with presumed skin changes related to copper deficiency, as well as 2 cases where abnormal haematological indices were under-recognised as related to WD.

Research - chaired by Prof Oliver Bandmann

Sam Shribman updated the SIG on the CROWD study which is now underway and seeking to recruit nationally. 35 completed questionnaires have been received, 1 visit completed and 5 booked in.

BG updated the SIG on 3 commercial studies - 1 in progress, 1 in set up and 1 future:

The FOCuS study is now run by Alexion (WTX101 now ALXN1840) and 3 sites open for recruitment (Birmingham, Cambridge, Royal Surrey). Only new patients within 28 days of starting treatment can be enrolled at present. As the drug is meant to reduce neurological worsening it may be of interest for centres to recruit new cases of neurological disease. The study will remain open for the rest of 2019.

Action: BG to enquire re information leaflets that could go round via the SIG and to enquire about drug stability data as per Rupert Purchase's request

CHELATE is in set up. GMP-Orphan are looking to trial trientine tetrahydrochloride in penicillamine-stable patients. There will be a 1:1 randomisation and 24 week study period, looking for 'non inferiority' and at safety. Some UK Centres are engaging with the company to become study sites. Potential study sites should have at least 6 potentially eligible penicillamine-stable patients. The study would give experience of using a supposed equivalent trientine drug which does not need refrigeration and if licensed could competitively bring down the price of trientine in the UK. It is

currently only commercially available in Germany. Of note no head to head RCTs to date penicillamine vs trientine.

Actions: BG to provide relevant information for the WDSG re this forthcoming study and for the current bis-choline TTM study, WDSG to update website accordingly

Vivet are looking at a first in man phase 1 trial late 2019 for a novel adenovirus associated vector (AAV) which incorporates a reduced form of the *ATP7B* gene and aims to correct the defect in the liver. Mouse data is encouraging. The company is looking for a couple of interested sites in the UK.

Aftab Ala updated the SIG regarding an oral presentation at AASLD 2018. This looked at trends in hospital admissions in the US over a decade. There was an increasing trend in those >50 years and at teaching hospitals compared with non-teaching hospitals, with an overall increased burden on health care. Mary Bythell suggested something similar could be looked at via PHE.

Michelle Camarata updated the SIG regarding the US registry study collecting very detailed data (along with biological samples) on patients with WD primarily at Yale but with other US sites and Royal Surrey due to come on board this year. Preliminary data shows a significant number with a depressive disorder. The study is being adopted by NIHR and the hope is to enrol additional sites in the UK.

Laboratory methods - chaired by Dr Chris Harrington

Andy Duncan discussed the difficulty in measurement of caeruloplasmin and copper both in tissue and plasma. He described a study where samples of liver copper were sent to 26 labs and there was significant imprecision and inaccuracy - only 51% met the imprecision standard (0-5%) for 'within batch' and only 31% for 'between batch'. 28% met the standard for accuracy (0-5%) and 21% were wholly inaccurate (>50%). Samples > 3mg had improved imprecision/accuracy. Measurement of 'calculated' non caeruloplasmin bound copper was very imprecise across labs and included 'negative' (impossible) results. Caeruloplasmin is more of an issue than copper itself. Measurement of caeruloplasmin is compromised if below the detection limit of that lab, which varies in itself. Glasgow's caeruloplasmin reference range needed adjustment after the company changed the reagent which dropped all the levels (now 0.16-0.47 g/l). Copper levels must be referenced according to age and gender with higher mean levels in females.

Dr Duncan also described the 'copper 65' test which shows good discrimination for WD and separates heterozygotes vs normals to some extent. This test could be useful in cases where there is diagnostic doubt. The patient swallows 3 ml of 65-Cu (non radioactive) and samples are taken up to 72 hours with analysis in Glasgow.

BG mentioned that the recent paper in JIMD by the Weiss group shows that 'off treatment' 24 hour urinary copper is probably the most useful of the various copper monitoring exercises in WD. In terms of having standards for monitoring of WD in the UK, the SIG could develop some simple parameters that Centres could espouse and embed within smaller hospitals seeing patients with WD.

Action: BG to draft a monitoring toolkit for ratification by the SIG

Date of next meeting: early Autumn, not a Thursday, Queen Square again if possible, WDSG are kindly offering to pay for refreshments if BASL unable (to avoid needing Pharma to sponsor).

Other relevant meeting:
May 9-12 Wilson Aarhus, abstract deadline 1.3.19 - email mf@clin.au.dk

Appendix 1 appended (Wilson Centres with Specialty Leads)