19th International Congress of Parkinson’s Disease and Movement Disorders


This meeting was my first visit to San Diego – if I’d have known better I would have brought my wetsuit and surfboard (I’ve learnt for next time), but this time I easily contented myself with the usual high standard of movement disorders presentations.

Plenary sessions
The first session presented by Werner Poewe, included a description of Rytary (IPX066), which is a prolonged release formulation of L-dopa now available in the USA, which alongside novel COMT (epicapone) or MAO-Bi (safinamide) agents represent further progress in the attempts to prolong the half-life of L-dopa and reduce motor fluctuations. These of course parallel the previously demonstrated benefits of continuous infusions of intrajejunal L-dopa (marketed as Duodopa or Duopa). Alexander Storch followed on with recommendations on the symptomatic treatment pathway in PD, and then (pleasingly for me) called for further investigation of GLP-1 agonists such as exenatide as potential disease modifying treatments in PD (a phase 2 double blind randomised trial is ongoing at Queen Square).

A session on rehabilitation therapies in the treatment of PD featured an excellent talk by Lynn Rochester. This included both “Exercise” in its broadest definition and “Compensatory strategies”, such as cueing techniques, both proven to have clinical efficacy in reducing freezing and falls. Lynn described how this evidence can be usefully “individualized” in the clinic i.e. starting group therapy in early PD then progressing to individualised risk avoidance, strengthening, endurance training and cueing (in isolation or combination).

Ted Dawson opened the main basic science part of the programme and described the consequences of different LRRK2 mutations on ribosome function, via phosphorylation of (S15) proteins of the ribosomal subunits; this appears to cause a global increase in protein translation in human dopamine neurons, and raises the question regarding which of these proteins are involved in the subsequent pathway of dopaminergic neurodegeneration, he presented unpublished work related to the potential disease modifying treatments in PD (a phase 2 double blind randomised trial is ongoing at Queen Square).

The second unofficial meeting of the clinic i.e. starting group therapy in early PD then progressing to individualised risk avoidance, strengthening, endurance training and cueing (in isolation or combination).

The second unofficial meeting of the conference and the second annual meeting of the Irish Movement Disorder Society (MDS) was held in Dublin on 27th and 28th November 2015. The meeting was attended by around 200 delegates from all over Europe and provided a platform for discussion and debate on a range of topics of current interest in the field of Parkinson’s disease (PD) research.

The conference included a wide range of topics, from basic science to clinical practice, and featured presentations by leading experts in the field. The main themes of the conference were the role of genetics in the development of PD, the use of new imaging techniques to study the disease, and the potential of new treatments for PD.

The conference was held in conjunction with the Parkinson’s Disease Society of Ireland (PDSI) and the Irish Parkinson’s Disease Association (IPDA), and was supported by a number of pharmaceutical companies.

The conference was a great success and provided an excellent opportunity for researchers, clinicians, and patients to share their knowledge and experiences. The meeting was well-received and attendees left with a wealth of new knowledge and ideas to further their work in the field of PD research.
While it is clear that there has been great progress in our understanding of PD pathogenesis, to date there has not been a single (proven), disease modifying treatment. Creatine and pioglitazone have recently failed, but with a degree of optimism, Tanya Simuni summarised the ongoing potential surrounding trials of isradipine, inosine, exemestane, nicotine, (alongside the safety data of both the Probetaena and Affris alpha synuclein vaccination programmes described earlier). Unfortunately it seems there’s currently precious little happening regarding trials in MSA, but of course the vaccination programmes will potentially also be relevant and there is additional interest in approaches like intranasal insulin (insulin signaling is in fact of growing interest related to a range of neurodegenerative processes).

James Surmeier gave a further critique of recent basic science breakthroughs, including the very recent publication from Peelaerts et al, on different alpha synuclein strains; ribbons (easily remembered as linguine) – these undergo thioflavin phosphorylation and cause glial cytoplasmic inclusions similar to MSA, but don’t cause dopamine cell loss unless in the presence of over expression of alpha synuclein, whereas fibrils (or spaghetti) cause greater neuronal loss in the striatum. He speculated whether perhaps these differing strains relate to different levels of calcium ions in different neuronal and glial cell populations. He also described work showing that alpha synuclein overexpression actually has a functional change on substantia nigra compacta dopamine neuronal firing pattern through potassium channel down regulation. (Unsurprisingly, given his original work with isradipine), he again speculated whether calcium may be involved in a subsequent spiral of neurodegeneration.

Other movement disorders were also covered including a great session on Dystonia phenomenology (probably the archetypal subject of appeal to clinicians who have evolved to become movement disorders specialists). Victor Fung reviewed both the recent classification, showing some great dystonia videos and emphasised that a movement disorders examination must include assessment of patients performing those specific tasks that provoke their symptoms! Despite the seemingly endless number of genes to remember relating to movement disorders eg Beta propeller associated neurodegeneration, BPAN – (consider when patients have childhood, deficits then remain stable through teenage years then have progressive degenerative change in adulthood), what has been reinforced at this meeting is the real importance of adenylyte cyclase 5 (ADCY5) – which seems to be a not uncommon cause of childhood chorea or dystonia +/- facial myokymia (autosomal dominant or de novo and usually survive to adulthood)…many videos with this genetic diagnosis were submitted to this year’s MDS Video Olympics.

Gunther Deuschl described the lessons that can be learnt by studying tremor in elderly people, measured simply using spiral drawing scores and the simple relationship between these scores, activities of daily living, cognition and mortality. Even after adjusting for potential confounders, “tremor” as a crude measure appears to be an independent risk factor for mortality, in contrast to the subgroup with a confirmed diagnosis of “Essential tremor” in whom mortality is not elevated. Furthermore using functional imaging apparently helps to reveal different neural networks involved in “age related tremor” versus essential tremor, further justifying why these ought not to be “lumped together”. (There was no comment where patients with dystonic tremor fitted into all this).

In a session on the overlap between movement disorders and epilepsy, Marina de Koning Tijssen described the myoclonus epilepsy syndromes, while Sarosh Irani discussed the autoantibodies associated with paroxysmal movement disorders including: LGII (faciobrachial dystonic seizures best treated with immunotherapy), NMDA receptor (variably presenting as a paraneoplastic ovarian teratoma associated encephalitis ranging to focal unusual chorea/dystonic syndromes), IgGn5 (this is a recently described autoimmune parasomnia causing involuntary movements in REM and non-REM sleep with additional axial signs) and Aquaporin4 (painful tonic spasms can occur as the major feature, not just classic neumyelitis optica).

Jens Volkmann reviewed the direction of travel of Deep Brain Stimulation highlighting the interest in “adaptive” or closed-loop stimulation – ie only stimulate when the local signals are abnormal, it seems that this approach is better than conventional DBS albeit in small numbers of patients in brief assessments. He also described the use of the PC+S device which may one day enable chronic delivery of closed loop DBS, although stumbling blocks include inter individual variation, and consistent beta (abnormal neuronal activity) was only seen in 7/14 electrodes that his group has tested. The device manufacturers are in stiff competition right now with the possibility of using multiple source current steering (as used in the VANTAGE trial) which allows clinicians to shape the stimulation field (but only along z axis), right alongside the possibility of directional stimulation (in either x or y axes) made possible with segmented electrodes. (Do these “advances” just compensate for poor surgery/imperfectly placed electrodes? A more forgiving view might be that the perfect targeting within the STN is still not clear, thus these approaches allow post operative flexibility.)

Young investigator awards

Drs Maurer & Balint received the young investigator awards for their work on resting state fMRI of functional movement disorders, and another rare antibody association (DPPX antibodies- seen again in the Video Olympics) as a cause of stiff person syndrome, respectively.

The Grand rounds

Our most eminent colleagues (who shall remain respectfully nameless), were then called on to display their history and examination skills on 5 patients drafted in for our education.

1. A 28 year old with recent onset of rest tremor of right hand, mild right hand bradykinesia and dystonic dystonia (+/- myokymia). MRI showed a cystic lesion in the left upper brainstem associated with a nigrothalamic deficit on DaTSCAN imaging. He responded well to L-dopa. The eventual diagnosis was that of Virchow Robin spaces ??! (not sure how convinced I was of this presumed diagnosis based on the extremely unusual cystic lesion in the midbrain we were shown on his MRI).

2. An 18 year old with onset of intermittent involuntary movements since childhood progressively getting worse, but with normal cognition. Bouts of severe jerks interfered with sleep, she had dysarthric speech, a profoundly weak neck, jaw opening dystonia, facial myokymia, and clonus. She had normal imaging, CSF, muscle biopsy and the diagnosis was (wait for it) yet another patient with an ADCYS mutation.

3. A 66 year old male with 20 years of hemiparkinsonism (+/- dystonia) who was responsive to L-dopa, had fluctuations and dyskinesia, freezing, loss of ollaction, bradykinesia with decrement and had a family history of Lewy body dementia (father)/ Dopa Responsive Dystonia (daughter). No surprises here – he was found to have a OCH1 mutation.

4. A 43 yr old woman with “cerebral palsy” (immediately think DRD), who had the diagnosis re-explored because of variable abnormal movements and abnormal sleep (the extra clue). She also had delayed milestones, and learning difficulties. The examination revealed slurred monotonous speech, and perhaps some subtle limb posturing. She had no dopa response. After a bit of discussion implicating both dopamine and serotonin biosynthesis problems, she was (of course) found to have sepiapterin reductase deficiency.

5. Finally a 73 year old retired surgeon with a 12 year history of gait and balance difficulty and recent postural and action tremor. Also mild
cognitive impairment – (that the patient repeatedly contested). Examination showed gait ataxia and finger nose ataxic tremor, (surely this was enough of a clue), also a grand-daughter with tremor. The MRI showed abnormal signal in the middle cerebellar peduncle, so (of course) the genetic diagnosis was FXTAS – an FMR pre-mutation (99 repeats).

The Parallel sessions
Of course you can’t go to all of these, but the highlights from those I attended (my own interests) included; the role of Deep Brain Stimulation beyond Parkinson’s disease as discussed by Michele Tagliati and my colleague Patricia Limousin, with excellent video footage of the utility of DBS in tremor subtypes, primary generalised and focal dystonias, tardive dystonia, and the growing evidence of its potential utility in Tourette syndrome.

Relating to potential disease modifying treatments, Anthony Schapira presented “Prospects for therapy in GBA related PD”. While the precise mechanism(s) through which GBA (the commonest genetic risk for PD) causes neurodegeneration is yet unclear, these may include substrate buildup (potentially restored by Miglustat), loss of GCase function (thus may be able to use gene therapy eg GBA-AAV), loss of lysosomal function (potentially increased via Ambroxol mediated increase in TFEB activity), or a toxic buildup of protein within the endoplasmic reticulum (again may be helped by Ambroxol or other small molecule chaperones, or HDAC inhibitors). Importantly these approaches may also have relevance to PD without GBA mutations.

The Video Olympics
This is always an unmissable session – the panel were uniformly quaking in their boots as they walked on stage, but Tim Lynch showed why he’s so highly regarded clinically on this international MDS stage.

1. A patient with Narcolepsy type 1 causing cataplexy.
2. A young man with DPPX Ab (a new cause of stiff neck syndrome) causing stimulus sensitive jerks with dysautonomia (Raynauds syndrome).
3. Gluten enteropathy (Coeliac disease) related to bilateral leg myoclonus, which persisted during sleep.
4. Myoclonus dystonia caused by a 6q deletion.
5. A lady with childhood seizures and developmental delay who remained stable then the deteriorated and had classic iron deposition in the nigra – this was the BPAN form of NBIA (WDR45 gene mutation).
6. An IGLON5 Antibody syndrome causing cognitive/tongue movements, behavioural problems and a post synaptic dopaminergic deficit.
7. Neurophylisins causing a subacute ataxic myoclonus syndrome.
8. Monoballismus in a deafferented limb due to a midbrain lesion, and then a further contusion and speculation about how this informs on basal ganglia output.
9. Dystonia Parkinsonism and facial numbness with classical imaging changes due to CLIPPERS.
10. Progressive cerebellar and dystonia and long tract signs with positive OCBs due to anti-GAD Ab.
11. Neurocytecterosis causing epilepsy partialis continua.

Blue Ribbon highlights
This is a great way of catching up with the important bits among the posters that you might otherwise have missed. Davis Standaert and Christine Klein had reviewed >1400 submitted abstracts and presented the following as the most worthy of mention;

a) Work by the Diesseroth group showing the use of optogenetics to switch ON and OFF dopaminergic cell grafts in rodents.
b) Blepharospasm being more common (relative to cervical dystonia) in more southern placed regions with greater sunshine.
c) A family with an A53T alpha synuclein mutation with variable penetrance (although admittedly, perhaps the asymptomatic mutation carriers had not yet passed through the age of risk).
d) A parkinsonian kindred with Xlinked dominant inheritance due to a RAB9B mutation.
e) GCase activity in PD patients with and without GBA mutations. (Even those without GBA mutations have lower GCase activity than controls).
f) Non manifesting LRRK2 G2019S mutations have an increase in risktaking behaviour (perhaps a PD endophenotype).
g) The exosomal microRNA profile (using array based technology) in the CSF of 5 patients with PD, which found a reduction of miR-1587, (which controls PLK2 which plays a role in phosphorylation of alpha synuclein perhaps relevant to how alpha synuclein is normally targeted to chaperone mediated autophagy.
h) Increased clearance of alpha synuclein by enhancing lysosomal function via overexpression of the transcription factor TFEB in rodents.
i) The FRET (Fluorescent resonance energy transfer) based system of alpha synuclein detection as a means of measuring “prionlike” forms of alpha synuclein.
j) Deleting mutant huntingtin from microglia in HD mice influences the behaviour of these cells BUT not the behaviour or histology of the animals.
k) The Predict PD study nicely defining the risk factors for incident PD.
l) Monitoring PD progression using smartphone technology.
m) Men with de novo PD have greater presynaptic deficits measured on DATSCAN imaging than females with de novo PD.

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17 September, 2015; Birmingham, UK
4. The Practical Cognition Course
1-2 October, Newcastle, UK
Contact: Ann Fitchett
E. 01182 897788
T. 0991 208 8320
www.practicalcognition.com

37th Clinical Neurology Course
5-6 October, 2015; Edinburgh UK
www.ed.ac.uk/schools-departments/clinical-brain-sciences/postgrad- uate-training/
edinburgh-clinical-neurology-course
E. judi.clarke@ed.ac.uk

November
Consultant PD Masterclass – Sheffield
Module 1 – 2, 3rd & 4th June 2015
Module 2 – 26th November 2015
Both modules must be attended
www.parkinsonsacademy.co.uk for further details.

23rd Annual Meeting of the European Charcot Foundation
26-28 November, 2015, Milan, Italy
www.charcot-no.org/en/
registration-information
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To list your event in this diary, email brief details to Rachael Hansford at Rachael@acnr.co.uk by 6th August, 2015