The 20th International Parkinson’s Disease and Movement Disorders Society Meeting

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So, this excellent meeting was back during those halcyon days (Pre-Brexit) when plans for new UK-European science collaborations were still an exciting, cross disciplinary, potential reality and England football fans were contentedly in the “phase of optimism”, with every expectation of Euro2016 being their year...it all seems like such a long time ago. The MDS meeting, in contrast was an unarguable success.

Personalised Medicine

The most recurring theme throughout the week (plenary lectures by Susan Fox then Reikko Kruger) was the subject of Personalised Medicine in Parkinson’s disease (PD). So many trials of neuro-protection have failed – CoQ10, Creatine, Minocycline, Pioglitazone – perhaps at least in part because we simply lump all PD patients together when recruiting.

A wealth of examples of the variability of PD were presented to underline the point:
1. COMT genetic variation predicts response to Entacapone,
2. Rasagiline response varies according to dopamine D2 receptor variants,
3. GBA mutation carriers have higher risk for dementia,
4. Alpha synuclein polymorphisms have relationship with cognitive impairment,
5. Protective effects of caffeine may depend on GRN2A allelic status,
6. Positive outcomes from DBS relate to reduced alpha synuclein expression...
...and perhaps the most robust is the development of a cumulative genetic risk score – Using a panel of 19 Single nucleotide polymorphisms, it appears possible to accurately predict time to progression to Hoehn & Yahr stage 3 (Mike Nalls et al.)

All of this emphasises our need to focus on which aspect of PD pathophysiology is being targeted by any specific symptomatic, or disease modifying approach to have any hope of writing sensible inclusion criteria and defining appropriate outcome measures when designing trials.

The most clear demonstration of personalised/precision medicine is the use of gene silencing, now a real possibility. Small interfering RNAs, zinc finger protein repressors and anti-sense oligonucleotides (very nicely reviewed by Pedro Gonzalez – Alegre) can target genetic mutations leading to a toxic gain of function and such approaches are now a reality and are in clinical trials in Huntington’s disease (led by Sarah Tavbriz).

Encouraging outcomes can be expected to lead to this approach being adopted in other single gene disorders like DYT1 dystonia or the Spinocerebellar ataxias. If we can get the dose right, perhaps it might even be conceivable that targeted silencing of alpha synuclein expression might become a possibility for PD.

Other ways of tailoring approaches to PD genetic subtypes were also presented. Although there are concerns that the current raft of LRRK2 inhibitors may lead to excessive lung toxicity, there still remains hope that this precision medicine approach might ultimately reach the clinic as a potential solution to PD patients with the LRRK2 G2019S mutation. At the risk of Coenzyme Q10 fatigue, there was recurrent mention of the use of this agent and/or Vitamin K2 specifically for use in patients with mitochondrial forms of PD i.e. arising as a result of parkin/Pink1 types. Indeed, Patrik Verstreken/Melissa Vos have shown improvement in mitochondrial complex 1 function in fruit flies with Pink1 mutations which (Christine Klein tells me) has already led to plans of a formal randomised trial of CoQ10 in this subgroup of patients.

In other “parkin” news, Dr Koentjoro presented a fascinating story of a young PD patient with parkin mutations whose mother turned out to be homozygous for parkin mutations (and had no active parkin detectable in skin fibroblasts) but yet had almost zero signs of parkinsonism. It turned out that she had preserved mitophagy as a result of an “alternative mitophagy protein” which can be manipulated by viral vectors or even protein inducers....

While still with relevance to the mitochondrial PD subgroup, fibroblasts from DJ1 patients seemingly have loss of mitochondrial dynamics as a result of absence of the DJ1 protein due to mis-sPLICing of RNA. Very neat creation of a new U1 splicing small nuclear RNA restores the splicing machinery and can enable functional DJ1 protein to be translated.

Pathway convergence

In contrast however, it was also clear from one of The Controversy sessions that we’re not all (particularly Eduardo Tolosa) in agreement that Movement disorders treatment approaches are (as yet) in any way dependent on genetic results.

Indeed while we may need to look at PD subgroups for some approaches towards disease modification, other approaches may have a broader reach. These include direct targeting of alpha synuclein e.g. the vaccination trials being set up by Affiris, Prothera, Biogen which, if successful, should have relevance for a far larger pool of PD patients. In this field, Jeff Kordower is developing the use of “intrabodies” (antibody fragments engineered to target intracellular alpha synuclein) which apparently have been shown to have positive behavioural effects in rodents. Furthermore we may yet have additional “convergence” along the lines of Oliver Bandmann’s work on turnip fibroblasts playing a role for Ursodeoxycholic acid (UDCA) to combat mitochondrial dysfunction yet seemingly this same compound also helps neuronal dysfunction of LRRK2 origin, i.e. is precise and yet broad...

Analogous with this, Ole Bacson and others have previously shown that GCase levels (the enzyme associated with Gaucher’s disease and Glucocerebrosidase (GBA) related PD) fall in the Substantia nigra during aging even in sporadic (non-GBA) PD patients. Targeting single gene disorders may therefore lead to therapies for many other individuals aside from those with a specific gene mutation. Indeed, gene therapy delivery of GCase can seemingly rescue alpha synuclein pathology in a wide range of animal models.

In further contrast to the emphasis on patient “subgrouping”, James Surmeier explained that the pattern of PD neurodegeneration occurs according to the brain connectome albeit with some synaptic partners being resistant to spread, and other cells degenerating even in the absence of Lewy pathology. His work has shown that some aspects of neuronal vulnerability depend on calcium dependent pace-making activity. So why do we have this energy sapping system? This is supposed to have advantageous activity on mitochondrial energy...
production to help us continue to move in emergency circumstances (such as lion attacks – his example), however “This design comes at a cost” with mitochondrial and proteostatic dysfunction ultimately arising in the context of a large energy demanding axonal arbor. We will find out in a year or two whether this vulnerability can in fact be reversed by his trial of the calcium antagonist isradipine.

Another approach that was presented is to search for medications associated with slower disease progression in the data from previous cohort studies/trials. This has identified that amitriptyline (of all neurological cliches) was associated with prolongation of time from diagnosis before needing dopaminergic treatment. This unexpected finding gains some support by observations that amitriptyline has been shown to bind to alpha synuclein in culture, and retrograde transport of preformed fibrils of alpha synuclein is markedly diminished with the related drug, nortriptyline.

Alongside this, the problem that unites most PD patients is the core dopaminergic loss that characterises the disease. Stephen Pařík presented his data on Prosavin (a gene therapy construct containing all the genes necessary for the biosynthesis of dopamine), and described the current plans for further work using a more potent vector developed by Oxford Biomedica, due to start recruitment in France and UK this year.

Other PD stuff

In more immediate, clinically relevant news; Eduardo Tolosa also discussed prodromal PD, highlighting that 91% of REM sleep behavior disorder (RBD) patients convert to PD by 14 years, and that submandibular gland biopsies from RBD patients contain alpha synuclein pathology (in 8/9 patients compared to 0/26 controls). Murat Emre also highlighted the relevance of RBD to the later development of Dementia with Lewy Bodies (DLB). Among 174 RBD patients followed up for 10 years-90% developed a neurodegenerative synucleinopathy (DLB, PD or MSA). Murat also described how CSF measurement of A-beta42 may help distinguish DLB from AD and it seems quite reproducible that low levels of CSF A-beta42 predicts rate of cognitive decline not only in AD but also even in the Lewy body dementias.

There are also some new PD drugs available. Angelo Antonini reviewed the additional beneficial effects of the newly launched drugs Safinamid and Opicapone, both of which can improve motor OFF time by 30-60 minutes and launched in the UK in 2016. He described the additional potential for the future use of the Adenosine receptor antagonist Tozadenant, and the pros and cons of Rytary (the bead formulation of L-dopa allowing for extended release), which include the need to significantly increase the daily dose of L-dopa to achieve the same plasma levels. There is also new data on the Accordion pill (constructed from multiple layers of L-dopa) which gradually releases in the stomach for up to 12 hours. A poster presentation of the Neuroderm (subcutaneous L-dopa) data also suggests clinically relevant reduction in OFF time alongside reduction in L-dopa induced dyskinesias.

The prospects for cell repair in PD have had mixed news; strengthened by recent post mortem evidence from a patient who died 24 years after transplant confirming extensive reinervation but, in previous patients, with the existence of alpha synuclein pathology within the graft. And in the 18 year follow up data from patients transplanted in the Freed trial, now with a disease duration of 28-36 years, 5/40 are still alive, 4/5 have had DBS, 2/5 are on very low meds, 2 are living independently and DATScan imaging in 3 shows survival of tissue. However graft induced dyskinesias are present in 2/3, and these individuals still accrue non-motor symptoms consistent with the progression of disease. The evidence of trans-synaptic spread of alpha synuclein grows, with recent data from Patrik Brundin’s work showing that preformed fibrils of alpha synuclein injected into the olfactory bulb spreads across multiple synapses over 12 months even in wild type animals.

So what else?

In an excellent lecture by Katie Lunnon we were taught about EWAS – epigenome wide association studies. Epigenetics is all about tissue specific gene silencing – enabling necessary differential gene expression in brain, heart etc, requiring DNA methylation that occurs based on the intact presence of >450k methyla
don sites across the genome. In an EWAS using post mortem entorhinal cortex from Alzheimer brains, the top locus for association was ANK1, alongside a strong correlation between an increase in methylation and disease severity that is consistently reproducible. Our “Movement disorder” priority of course, is to reproduce this type of work using nigra/ striatum from brains of PD patients and while there were posters on EWAS in peripheral blood from PD patients, I was pleased to hear from colleagues that the post mortem region specific work is indeed underway in the UK.

The huge range of videos shown at this meeting are always an excellent clinical aid for those seeing a variety of movement disorder patients. We saw several videos of patients with: whispering dysphonia (so no excuses for forgetting that this is due to TUBB4 mutations); a lady with spasmodic dysphonia, torticollis, and jerky hand movements, the clue to the diagnosis was the presence of multiple lipomas frequently seen in MERFF; and if you see someone with ataxia, dystonia or parkinsonism with bulging eyes, might be worth testing for SCA3.

And if you like collecting genes, Rab39B is yet another cause of (X-linked) dominant, but otherwise typical dopa responsive PD. It is a regulator of vesicular trafficking and leads to alpha synuclein toxicity in yeast.

Grand Rounds

These were great – all the experts performed very well, and the diagnoses were all very get-able if you were on the ball.

1. Young onset jerky movements plus postural tremor, father was an alcoholic – all the information you need! Myoclonus Dystonia

2. Young onset dystonia parkinsonism in several members of same generation. Presenting with odd dystonic gait. Possible parental consanguinity. Homozygous Pink1 mutation.

3. Rapid onset speech disturbance, and inability to walk. Jaw dystonia (Sardonic smile), swallowing difficulty, Clear parkinsonism on examination. (Dan Healy diagnosed Rapid onset dystonia parkinsonism due to ATP1A3 mutation just by seeing his facial expression as he came on stage...)

4. Childhood onset ataxia and speech problem followed by dyskinetic type movements – lower facial movements, dystonic gait. We debated ADCY5 but this time I won – Ataxia telangiectasia. NB – If you suspect Ataxia Telangiectasia, do not do any X-rays! – This disease is characterised by DNA fragility therefore the patients are very sensitive to radiation!

5. Severe dystonic head tremor in young man, dystonic speech and some balance issues, little intention tremor and slow horizontal saccades – otherwise pretty normal examination. Family History of tremor, ataxia but also MND – Spinocerebellar ataxia type 2 (with 42 CAG repeats).

Video Olympics

James Gratwicke went to the Video sessions and scrupulously recorded the descriptions and diagnoses while I had to attend another meeting. General feedback was that these were good but perhaps too many videos crammed into one session. (Our own Huw Morris performed admirably as a panel expert).

1. A young woman with neck stiffness, loss of dexterity, slow finger taps and tongue movements, with hypomimia and poor R arm swing. She had some improvement in symptoms with Ldopa. MRI, DATscan, and PET imaging were all normal. Anti-GAD titre was > 50.000. In this lady there was no evidence of underlying malignancy and
she had some improvement with IVIG.

2. A 60 year old male with subacute short term memory impairment and agitation and a background of 20 yrs focal epilepsy controlled on carbamazepine. He had a recent increase in seizures, and unexplained collapses. Chronic smoker. He had exaggerated round the houses vertical eye movements, a cerebellar syndrome, slow downward saccades. His MRI showed cerebellar atrophy. Anti-Ma2 Antibodies were positive and were causing an encephalitis in association with Hodgkin lymphoma.

3. A 65 year old male, with 10 year history of gait dysfunction, bilateral hearing loss, dropping objects for most recent 7 years. He had a vertical supranuclear gaze palsy, and round the houses eye movements, autonomous movements. He was confirmed to have Niemann Pick type C.

4. A 19 year old male, with episodic involuntary movements for 1 yr, occurring 10-100x/day lasting 30s-5min. His EEG was normal, bloods and metabolic profile were normal but he had a low Parathyroid hormone.

5. A 14 year old female with 3/12 history of ataxia. A 3 year old member had the same condition. Her MRI revealed a swollen cerebellum, with dilatation of the ventricles. WCC 27,000. MRI revealed a swollen cerebellum. Temperature 39 degrees, 2 days later had onset of axial tremor of gait dysfunction, bilateral hearing loss, dropping objects for most recent 7 years. She had some improvement with IVIG.

6. A 72 year old male, with no past medical history. He had slowly progressive gait difficulties. After developing a Left C8 radiculopathy, he had C3-T1 laminctomies and cervical spinal fusion. 2/12 later he had neuropathic pain in the C4/S dermatomes in arms, severe when sitting or standing, mild on lying i.e. postural symptoms. Then he developed involuntary movements of head, neck, shoulders and arm movements persisting for one year after implantation of a Vagal nerve stimulator. When she turned her neck to the left, her left arm rose involuntarily. This was due to an aberrantly placed VNS lead.

7. A 62 year old female with a previous left middle cerebral artery stroke. Afterwards she developed brief episodes of painful abdominal repetitive contraction on the right side. Epilepsia partialis continua causing belly dancing on video.

8. A 78 year old with AF who was warfarinised. He developed sudden onset involuntary movements in all four limbs. The EMG showed grouped rhythmic ndischarged in C5-innervated muscles on standing only (not lying), and c-spine x-rays showed a misaligned anterior plate at C4/S.

9. A 32 year old female with abnormal neck and arm movements persisting for one year after implantation of a Vagal nerve stimulator. When she turned her neck to the left, her left arm rose involuntarily. This was due to an aberrantly placed VNS lead.

10. An 8 yr old with recent onset symmetrical choreiform movements. Hypotonic. Treated with tretabenzene, then one year later developed a generalised mobile dystonia. Treated successfully with trihexyphenidyl. Positive for a GNA1 de novo mutation. 2 paediatric cases have responded to DBS.

11. A 14 year old female with 3/12 history of Bipolar disorder found unconscious. A few days later had onset of axial tremor of neck. Her lithium levels were normal on admission. Temperature 39 degrees, WCC 27,000. MRI revealed a swollen cerebellum. CT showed no evidence of solid tumours. NMDA-Receptor antibodies were negative. Repeat Lithium levels were very high. She was plasma exchanged and improved except the axial head tremor. This was “SILENT” (syndrome of irreversible lithium induced toxicity).

12. An 8 year old with severe developmental delay who had stopped clonazepam and then developed sudden onset involuntary movements. The MRI showed a hypoplastic cerebellum, with dilatation of the ventricles. = pontocerebellar atrophy type 2.

13. This 61 year old male had slowly progressive gait difficulties. The EMG showed grouped rhythmic ndischarged in C5-innervated muscles on standing only (not lying), and c-spine x-rays showed a misaligned anterior plate at C4/S.

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