Report on International Ataxia Research Conference

March 2015

This international conference was organised by 4 patient organisations, Ataxia UK, Ataxia Ireland, FARA-USA and goFAR. Other ataxia organisations, FARA- Australia's, FARA Ireland, Federacion de Ataxias de Espana- Spain and the National Ataxia Foundation- USA were associated with the event. It was hailed as a great success for the advancement of Ataxia research with new collaborations formed and ground breaking research being presented. Delegates arrived from all over the world to discuss the latest research in the Ataxias, and around 340 people attended in total. The conference included presentation all ataxias. As most neurologists are seeing all types of ataxia, two of the four patient organisations (P.0.) funding this conference cover all types of ataxia and the fact that there is some crossover between ataxias., it was a good use of time and expertise to cover all ataxias at the conference. This report is aimed to inform those with Friedreich's Ataxia (FA) on the latest developments in the field.

New genes & developments in diagnosis of ataxias

This is an area that FAer's might take for granted and feel it is unrelated to them. However, we all know of people who have been mis-diagnosised, sometimes, with disastrous consequences. Confusion between FA and Vitamin E and CO-Q10 deficiency comes to mind. However, FA is not always easy to diagnosis and a poster (UCL London Brown S 2014) on this topic showed even if you have atypical symptoms there is chance it could be FA. Out of 2000 people with SCA symptoms, 4 have confirmed FA with 11 are carriers, and 25 are still under investigation. While this number is very small, it would be important for the person concerned from a genetic viewpoint of their family. Presentations from several recessive ataxias and dominant ataxias and the posters showed prevalence of different ataxias from all over the world with FA is seldom seen in Finland, South Africa.

Genetic and molecular mechanism of the ataxias

This session focused on how the diseased and expanded gene in FA affected other areas on the gene with **presentations** from USA, UK, Australia with presentation on SCA from Germany and Portugal. Such germination of ideas. Dr Arnie Koeppen, (pictured below) spoke of the cardiac remodelling which happens in FA. Even though, he is the expert on post mortem specimens, he suspects that abnormalities in the heart start even before a person develops symptoms of FA and that inflammation in involved in the pathology of the FA heart.

He pointed out that the iron accumulation in FA is very different from iron accumulation in the heart due to the iron storage disease, haemochromatosis. He is still keen to have PM specimens and clinical details including recent MRI scans from FA community and other ataxias too. He considers that many of those with sporadic ataxia, could have multiple system atrophy (MSA).

Cellular and animals models in Friedreich Ataxia

Cellular and animal models of FA were discussed for a whole afternoon with a separate session for FA & SCA. It has been difficult to reproduce mice with exact FA pathology, FARA have in combination with Jackson university have supported the availability of 9 different mouse models. It has been possible to develop a FA mouse with sensory abnormalities and scoliosis now Other cellular models include induced pluripotent stem cell derived neurons (iPSC), large sensory neurons, yeasts and flies. .

Cellular and systematic pathways

Cellular and systemic pathways focused on SCA3. in FA was a morning session on FA and other SCA. Dr Javier Diaz-Nido outlined his work in neuron like cell models from olfactory mucousa stem cells from FA people and it showed DNA repair related proteins and well as an increase in inflammatory markers and both would be involved in the pathophysiology of FA. The effects that frataxin deficiency had on the heart, dorsal root ganglion was discussed

Drug discovery and emerging therapeutic strategies

The initial part of this session was dominated by presentations from the pharmaceutical companies. Repligen started the session on histone deacetylase inhibitors (HDACi). Two new drugs have been identified and further tests need to be done to see if they will produce toxic side effects. Bioblast Pharma told us about their drug BB-FA (TAT-MTS 9cs)- Frataxin) exhibits promising potential as a replacement for FA.. RaNA Therapeutics spoke of developing a strategy to upregulating genes by targeting mRNA end regions.

Dr Kevin Kemp, University of Bristol, UK told us of his experiments using bone marrow stem cells mobilisations and stem cell factor displaying strong neuro-protective properties and activate cell survival pathways in mature neurons and cells derived from people with FA..

Dr Roberto Testi lab in Rome is trying to increase frataxin levels, by preventing degradation using new compound, frataxin 3 ligase, and increase frataxin in cells. A further presentation from his lab told us that Src inhibitor increase frataxin expression in frataxin deficient cells from FA patients

Dr Tremblay, Canada outlined his work, very clearly, with gene therapy AAV9 vector injection via the abdomen at 5-9 days old and 21 days later but symptoms reappeared 15-20 days later. The vector improved the heart as measured by stroke volume. The hFXN was detected in muscle, liver heart, kidney and very small amount in brain. In essence he proved the data which Dr H Puccio, Strasbourg, produced on her gene therapy on mice and their hearts.

Biomarkers and functional measures

FARA -USA had produced ideas in this area from a collaborative meeting, which included academics, clinicians, and companies interested in developing drugs for FA. The potential biomarkers include:

- Frataxin protein and mRNA (specifically in affected tissues, protein is generally considered more informative).

- Metabolic compounds (indirectly measuring frataxin activity).
- Cardiac MRI studies or other investigations looking at cardiac aspects of FA.
- Structural MRI studies to look at neurological changes.
- Gait measurements to look at functional changes.
- Auditory, OCT and speech studies

One opinion we got in this area was from, Dr David Lynch who felt one should use the biomarker most appropriate to your population. An Australian at Dr Martin Delatycki's clinic found speech was the only thing that changed after 1 year despite doing extensive neurological examination. Dr Ian Harding. Psychologist, Melbourne, Australia did some extensive testing on the integrity of brain activity and connectivity with the cerebello-thalamo- cerebral systems. Not surprising, he did find evidence of cerebellar and cerebral pathology when complex conceptualization was tested.

Neuro-imaging was studied by Dr Pierre-Gilles, Minnesota, US and Dr Vavla, Padua. Italy and their results were broadly similar. Both showed that a comprehensive MRI protocol consistently discriminates FA patients from controls with significant differences when MRI scan were repeated annually .

In this section, Dr Mark Payne, Indiana, USA gave a lovely heart felt talk when he told the audience about the phone calls he gets from distressed relatives about FAers during surgery. From his best judgement, he feels that problems arise during surgery as

- NPO (nothing by mouth)
- No glucose in IV during surgery
- BP is lowered during surgery and due to poor perfusion in FA makes it all worse

His talk was entitled fatty oxidation in FA heart. The heart usually uses fat preferentially but will use glucose if necessary. His work has showed him that FA patients have impaired ability to utilise fatty acids for energy in the heart. Early biomarker analysis suggests that inflammatory and fatty acid biomarkers are raised which suggests that FA hearts respond poorly to physiological stress (surgery or a chest infection) and therefore require additional metabolic support. i.e. ensure glucose supply
Ensure adequate cardiac perfusion (BP)
Monitor for cardiac compromise (e.g. troponin)

Dr Schulz told us what the European community have learnt from the €6,000,000 EU money spend via the EFACTS study. London and Milan have the largest centres. There are almost 600 patients enrolled. The EU community have classified onset by
a) early < 14 year, b) intermediate 15-25 years and c)late onset as <25 years.
(The Australians have classified their age of onset at lower ages). Age of onset and disease progression is related to a larger number of repeats but GAA repeats account for only 36% of the variability of age of onset.

The SARA ataxia rating scale was used and it collated well the patient reported information on quality of life. In passing, Dr Schulz said that 27% of the patients were on idebenone (he did not give dosage) and they did not show any improvement over and above people who were not taking antioxidant.

The final presentation in this section was from Dr Martin Delatycki on the pre-symptomatic testing of minors. This is something, I suspect, that everyone on FAPG has an opinion on. He

plans a questionnaire which he hopes to send to siblings of FAers. Interestingly, this issue was also addressed in the poster session by Dr Muthuswarmy, New Delhi, India.

Clinical trials and trail design

Dr Festenstein, London opened this section, by giving us the science behind the recent 8 week trial that used the HDCAi, nicotinamide was safe to use in FA. It did cause nausea but not sever enough to need people to stop taking it. . They used the biomarker for frataxin mRNA and it did show an improvement. Plans are well advanced for a follow-up clinical trial in nicotinamide.

Prof Pandolfo continued the session and discussed general ideas about quality of clinical trials in particular the need for good ground work, clear indication before starting a clinical trial. He emphasized that randomized controlled trials (RCT) are the gold standard and he paid tribute to Dr Mariotti, Milan, (pictured below in fore ground at one of the poster session) as a leader before her time in running a randomised controlled trial even before it was popular using idebenone in 2002.

Poster session in Ataxia conference

Prof Pandolfo then introduced Dr Pavel Balabanov, Neurologist who currently works for EMEA and an interview with him ensued. In his opening remarks, Dr Pavel complimented Dr Festentein on his work and said it was exactly the kind of background needed before applying for EMEA approval. He said while there is expense in applying for a licence, it was considerably reduced for orphan drugs and further reduced if you were from and small business or a university department. He advised anyone interested in drug development to apply early or even seek advice from EMEA. Given the international flavour of the audience, he went on to say that it would be advisable for this gathering to apply to FDA and EMEA concurrently. There is also considerable liaison between EMEA and EURORDIS, the European organisation for rare diseases.

Retrotope pharmaceutical company then told us of their upcoming study in using stabilized polyunsaturated fatty acid in FA. They plan a 6 month phase 1b/2a trail in 33 people with FA which Retrotope expect to start soon. Unfortunately I had to leave as Reata Pharmaceuticals talked of their study a RTC which will study 16 people over a 12 week period. I understand there has been considerable changes to FARA pipeline chart which show one most if not all this detail.

General Observations

The scale of this conference cannot be underestimated when one considers that the first international conference was in Philadelphia in 2003 with only 50 delegates. I understand there was a lot of advertising done in advance to let them know it was on. This time 300 people enrolled and they had to pay for that privilege. As the conference got under way, there were several more requests for doctors and scientists to attend.

Our pharmaceutical colleagues were there in significant numbers. Some were from the pharmaceutical companies already involved in drug treatment in FA. As one representative put it, FA is a longterm disease. If there is a treatment which requires people to take life long medication there is a benefit in it for them. There are also advantages for companies to look at research in this area and see if it can be applied elsewhere to their benefit. The debate over the need for double blind randomised clinical trials (RCT) ensued with some of the pharmaceuticals companies favouring not RCT.

Kyle Bryant’s standing ovation after his inspirational talk