Cerebellar ataxia research update

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Annual Conference
4 – 5 October 2019
Overview

- Ataxia UK update
- Developments in the diagnosis of the ataxias
- Developments in identifying new treatments
- Global ataxia research initiatives
- Current clinical trials
- Opportunities to take part in research
What does Ataxia UK do to promote research?

- Ataxia UK Research Strategy:
  ‘Ataxia UK aims to maximise the impact of research in improving diagnosis and developing treatments that are available to patients’

Fund a wide range of projects, and work as the link between researchers and ataxia community.

Organise conferences and workshops:

Collaborate with researchers, pharma companies and other charities.

2019

International Ataxia Research Conference

November 14-15-16
Developments in the diagnosis of the ataxias

Inherited ataxias
Inherited ataxias

• Advances in our knowledge of the genes that cause ataxia mean that more inherited ataxias can be identified
  o Ataxia gene panels test for many forms of genetic ataxia in one test
  o 195 genes on the panel in use at the Sheffield Ataxia Clinic

• Due to advances in sequencing technology, the whole genome of a patient can be rapidly sequenced
  o Increases the chance of finding a genetic diagnosis
  o NHS Genomic Medicine Service to be launched, to offer whole genome sequencing across England, and standardise genetic testing regardless of hospital funding.
  o Also a key aim of ARCA Global – more on this later in the presentation.
  o Building on 100,000 Genomes Project, which took place across UK.
100,000 Genomes Project

• Some people with ataxia took part in the 100,000 Genomes Project.
• Established to sequence 100,000 genomes from NHS patients affected by a rare disease, or cancer – completed in 2018.
• To date, actionable findings have been found for 20-25% of rare disease patients that took part.

If you took part and have yet to receive any results:
• When your data has been analysed, results will be sent to your clinical team.
• In many cases, no clear answer will be found at first.
• Your data will also go into a research database. As our knowledge grows, researchers will continue to analyse your data. They will let your clinical team know if they find anything in the future that could be important for your, or your family’s, health.
UK-based researchers identified the genetic cause of CANVAS

CANVAS
‘Cerebellar ataxia, neuropathy, vestibular areflexia syndrome’

May be common cause of late onset ataxias

April, 2019

Professor Mary Reilly, joint last author, explained: “The identification of the novel recessive repeat expansion underlying CANVAS and late-onset sensory ataxia is of major interest, not only because of its prevalence, which may be as frequent as Friedreich’s ataxia…; but also because this finding highlights that late onset disorders can be commonly caused by an autosomal recessive mutation.”
Developments in the diagnosis of the ataxias

*Non-inherited ataxias*
Non-inherited ataxias

Prof Marios Hadjivassiliou from the Ataxia UK-accredited Sheffield Ataxia Clinic is a leading expert in non-inherited ataxias.

• **Gluten ataxia**
  - Caused by sensitivity to gluten, which is found in wheat products
  - If diagnosed, can be treated by adhering to a *strict* gluten-free diet
  - Possibly under-diagnosed, so work taking place to increase diagnosis by making sensitive tests more widely available.

• **Primary Autoimmune Cerebellar Ataxia (PACA)**
  - The cerebellum can be the target of immune-mediated conditions - when a person’s immune system attacks an area of the body, after wrongly identifying it as a threat
  - Could be treated with immuno-suppressants
Developments in identifying new treatments
Antisense Oligonucleotides (ASOs)

DNA is unwound into a single strand

Single strand is read to produce protein

SCA mutation = Disease-causing protein

+ ASO

No disease-causing protein

Disease-causing protein

DNA unwound into a single strand

Single strand read to produce protein

SCA mutation

No disease-causing protein

ASO
Gene therapy in SCAs

- ASO drug development projects are ongoing for a number of ataxias, including SCA1, SCA2, SCA3 and SCA7.
- A number of pre-clinical studies have shown success in animal models of SCA.
- In May 2019 leading gene therapy company uniQure announced preclinical data on its gene-silencing candidate, AMT-150, for the treatment of SCA3.
- An ASO drug has been approved for treatment of spinal muscular atrophy (SMA), and clinical trials in ALS and Huntington’s disease are showing success.
DRPLA project

- Ataxia UK-funded collaboration between ICM in Paris, King’s College London and Ionis Pharmaceuticals.
- DRPLA is a rare form of ataxia.
- Ionis are a leading company in ASO research – developed the SMA treatment and experimental Huntington’s Disease treatment.
- Designing ASOs against the gene that causes DRPLA, to be tested in animal models.
Dr Lorenzo Cingolani from Genoa, Italy.

EA2 occurs when mistakes happen in the genetic code of a calcium channel, known as the P/Q-type channel.

Brain cells try to compensate by producing more of the other types of calcium channels found in the brain. However, this isn’t very effective because these other types aren’t as efficient as the P/Q-type channel.

Dr Cingolani and his team are studying a gene editing technique, to convert these calcium channels into more efficient versions.

| P/Q-type calcium channels = EA2 | Brain cells increase less efficient channels | Gene editing can switch them to efficient forms |
Global ataxia research initiatives
Global initiatives for common and rare ataxias

- **SCA Global** – Dominant ataxias
- **ARCA Global** – Recessive ataxias (not FA or AT)

Goals:
- To create a network of Ataxia Specialists worldwide who work together
- To agree on standardised data collection on ataxia patients to help with trials
- To facilitate access to people with ataxia who are willing to participate in clinical trials
- ARCA global – focus also on diagnosis
How will this be done?

**Participation**
- Ataxia clinical specialists
- Patient groups

**Database**
- Common registry
- Other local registries

**Harmonisation and standardisation**
- Clinical data
- Brain imaging protocols
- Biosampling
SCA Global and ARCA Global update

• **Conferences** to launch and encourage involvement
  • March 2019: First SCA Global in Las Vegas
  • April 2020: Second SCA Global in Bonn
  • March 2020: First ARCA global

• **Working Groups** formed and working on policies and protocols
• **Next steps:** Data collection and new projects
• **Future** SCA and ARCA Global meetings will be included as part of other ataxia research conferences.
• **New website** launched
Current clinical trials

Cerebellar ataxia
Current clinical trials

• Cerebellar transcranial Direct Current Stimulation (tDCS)
  • Ataxia UK is funding a tDCS trial taking place in Italy
  • Recent studies have reported that applying a low electrical current to the scalp may alleviate symptoms of ataxia.
  • Range of ataxias (FA, SCAs, MSA)

• Deep brain stimulation is being studied as a treatment in Brazil.
Cadent trial

- Benefits in animal models of EA2 and SCA2
- Phase 1 trial showing good safety
- CAD1883 operates by acting on potassium channels in CNS potentially restoring neuronal firing regularity and improving motor function.
Biohaven trials

• Phase 2/3 clinical trial evaluating Troriluzole vs placebo in SCA patients, 8 weeks
• Troriluzole is a symptom relief treatment and may be useful in a range of SCAs
• No difference between treatment and placebo in SARA (primary endpoint)
• Continued open label so had data for one year on drug vs natural history
• New trial: longer study 1 year, focus on SCA1 and SCA2, higher dose, 230 participants
Opportunities to take part in research
Natural history studies

• Aim to create patient registries and carry out natural history studies to assess how the conditions progresses over time

• ESMI
  • Multi-centre European **SCA3** project coordinated at the German Centre for neurodegenerative diseases in Bonn

• EUROSCA
  • Similar project focussed on **SCA1, SCA2, SCA6 and SCA7**

• London Ataxia Centre is recruiting: If you have been diagnosed with any of the SCAs listed above and are interested in taking part, please contact the researcher Hector Garcia at **Hector.Garcia@uclh.nhs.uk**
Research survey: Patient attitudes to clinical trials in ataxia

- Developed by the team at the London Ataxia Centre, in collaboration with Ataxia UK and FARA
- Aims to investigate the attitude of patients towards clinical trials in the UK
- Results will help researchers to design better trials for the future, with patients in mind
Research survey: *Physical Activity for people with Rare neurological Conditions (PARC)*

- Developed by researchers at UCL and Cardiff, with Ataxia UK as one of the patient representatives
- Aiming to understand the level of physical activity among people with rare neurological conditions – including the ataxias
- The next step is to develop a self-management program to support physical activity in people with rare neurological diseases
Both surveys can be found on our website.
Thank you!

www.ataxia.org.uk
Breakouts 14.15 – 15.15

14:15 Breakouts

- **Own Your Own Home** – Mariana Senior  
  Room 19
- **Managing Gluten Ataxia** – Dr Heidi Urwin and Ruth Passmore  
  Room 4
- **Yoga** – Kirty Solanky  
  Room 10
- **Nicotinamide trial** – Julie Greenfield and Paola Quinti  
  Essex 1/2
- **Benefits and Grants** – Carlos Hagi  
  Essex 3
- **Neuro Physio for people with ataxia** – Grace Sheppard  
  Room 7
- **Managing Mental Wellbeing** – Malena Hallahan  
  Room 11
- **Music Therapy** – Elaine McGregor  
  Room 12

15:15 Break

Next: CA Doctors’ Q&A in Essex 1/2