European Spinocerebellar Ataxia Type 3/Machado-Joseph Disease Initiative (ESMI) – lay summary of the results of this 4-year Consortium study

Background

SCA3 (also known as Machado joseph disease) is the most common dominantly inherited ataxia worldwide, and although the gene causing the condition has been long known, unfortunately there are no treatments available to slow or stop the progression of the condition. However, there is hope. Recent advances in our understanding of the disease mechanisms suggest promising avenues for developing effective therapies. These include medications for symptom relief as well as exciting approaches for reducing or silencing the gene causing the condition (ie: gene therapy approaches).

In order to design and run successful trials it is important to first understand SCA3 and how it progresses over time and to develop the best way to measure the potential effect of a medication in a trial. To address this, a few years ago six European Centres with expertise in ataxia created a European Consortium to study SCA3. The Consortium was successful in obtaining funding from the 'EU Joint Programme for Neurodegenerative Disease Research' (JPND) for a three year project called ESMI. The ESMI project started in May 2016 and was completed in March 2020. This research has been coordinated at the German Centre for Neurodegenerative Diseases in Bonn, Germany. The other Consortium partners are in London (UK), Azores (Portugal), Coimbra (Portugal), Tübingen (Germany) and Nijmegen (Netherlands). Sites in Aachen, Essen, Heidelberg (Germany), Groningen (Netherlands) and Santander (Spain) also contributed. Euro-ataxia has been a collaborator and a representative has been on the Steering Committee.

Project aims

The main aim of this project was to get ready for high quality clinical trials in SCA3. This included:

- Creating a large database of SCA3 patients in the participating Centres and merging the data found in two pre-existing databases.
- Seeing patients annually and doing standardised assessments of the ataxia (eg: ataxia rating scales) to understand how the ataxia changes with time and use this information when designing trials
- Collecting blood samples and samples of cerebrospinal fluid (the fluid that surrounds the brain and spinal cord) to test for potential 'markers' for SCA3 that can be used to test the effect of a treatment in a trial
- Performing brain scanning (MRI) on people with SCA3 over time to see if we can detect changes that again can be used in trials.

In addition to people with a diagnosis of SCA3 taking part it was important to also include people who were at risk of developing SCA3 (ie: relatives of patients) and 'healthy' controls. This is important so that you have a comparison of what is different in SCA3 compared with the general population and also it may be useful in identifying a sensitive marker of the condition that may become apparent before symptoms start.

Results of this project and impact

The ESMI consortium has successfully established the **largest cohort** of systematically characterised patients with SCA3 worldwide. The cohort consists of around 270 SCA3 mutation carriers (with the majority being people with SCA3 and a small proportion of pre-symptomatic individuals) and nearly 100 age matched healthy control subjects. This is an extremely useful resource for running trials in Europe.

The researchers defined standardised quality-controlled protocols for clinical assessments, brain imaging and collection of body fluids (blood and cerebrospinal fluid) that now form the basis for a worldwide consensus in the framework of the SCA Global initiative.

Another essential requirement for clinical trials is the availability of biomarkers for SCA3 that can be used to assess the effect of treatments. Finding more sensitive markers to the ones currently available is very useful as it means that you may be able to do trials with fewer participants and get results more easily. The ESMI Consortium discovered and successfully established a new protocol for measuring volumes of particular regions of the brain using MRI. It was already known that there is a reduction in volume of particular areas of the brain in SCA3, but this project led to the discovery that a particular brain region starts decreasing in size up to 20 years before ataxia onset. It means it is a very sensitive measure of the condition that can be useful in clinical practice as well as in trials.
The researchers also found a ‘protein marker’ of nerve cell damage within blood samples that is highly sensitive to measuring disease progression, which could be useful in trials. For future gene therapy trials, which will attempt to silence the disease gene and reduce the amount of mutated ataxin 3 protein (that is toxic to cells), it is essential to develop a way of measuring the reduction in the ataxin 3 protein. This Consortium succeeded in developing such an ultra-sensitive assay in biofluids providing a significant step forward for future gene therapy trials in SCA3. Lastly, ESMI completed the first assessment of the impact of lifestyle on SCA3 worldwide as well as working on a number of other biomarkers that will be published in due course.

With the resources built up and the newly acquired knowledge of biomarkers for SCA3, the ESMI Consortium has laid important foundations for future clinical trials. This is reflected by huge interest of academic institutions and industry companies in long-term cooperation with ESMI.

Future plans

Although the funding from JPND has ended the ESMI partners are working with interested pharmaceutical companies to set up collaborations to ensure the continuation of this important project.