Muscular Dystrophy Ireland

Facioscapulohumeral Muscular Dystrophy Information Day

Saturday 1st October 2011

On Saturday 1st October, Ireland’s first information day on facioscapulohumeral muscular dystrophy (FSH MD) took place. The following is a report on this very successful day, which had informative presentations and opportunities to meet other people with this condition.

Jacqueline Turner, Genetic Counsellor, National Centre for Medical Genetics:

“Genetic Counselling for Facioscapulohumeral Muscular Dystrophy”

The National Centre for Medical Genetics (NCGM) is based in Our Lady’s Children’s Hospital in Crumlin, and is composed of 3 specialist departments:

1. Clinical Genetics Department
   a. 4 Consultant Clinical Geneticists
   b. 7 Genetic Counsellors (2 part-time)
   c. Secretarial support
2. Cytogenetics Department
3. Molecular Genetics Department

Clinical Genetics Department

The Department sees families and individuals with a genetic condition. They also see individuals who have various medical problems and/or developmental delay to see if there is a genetic basis to their problems.

- This service is free and funded by the Department of Health
- They do not take self-referrals, except when the family is known to the Department
- It is a national service based in Crumlin Hospital but with clinics in Galway, Cork and Limerick

Genetic Counselling

Genetic counselling is a communication process which deals with human problems associated with the occurrence of a genetic disorder in a family. This process involves an attempt by one or more appropriately trained persons to help the individual or family to:

- Comprehend the medical facts including diagnosis, probable course of the disorder, and available management.
- Appreciate the way hereditary factors contribute to the disorder and risk of recurrence in specified relatives.
- Understand the alternatives for dealing with the risk of recurrence.
- Choose a course of action which seems to them appropriate in view of their risk, their family goals, and their ethical and religious standards and act in accordance with that decision.
- To make the best possible adjustment to the disorder in an affected family member and/or to the risk of recurrence of that disorder.

(American Society of Human Genetics, 1975)
Facioscapulohumeral muscular dystrophy (FSH MD)

Other names: Landouzy-Dejerine muscular dystrophy, Facioscapuloperoneal muscular dystrophy

Historical: First described by Landouzy and Dejerine in 1885. It was not until 1991 that FSH MD was mapped to subtelomeric region 4q35 (Mathews et al. 1991).

Incidence: Approximately 1 in 20,000 (Lunt et al 1995).

Muscle involvement:

- Facial muscles
  - usually the lower facial muscles
  - difficulty whistling or pursing lips; blowing up balloons
  - sleeping with eyes partially open
  - unable to bury eyelashes

- Shoulder muscles
- Upper arm muscles
  - biceps affected; triceps spared

- Dorsiflexors of the foot
  - ankle weakness

Shoulder weakness: scapular winging is the most common initial finding. There is weakness of the scapular stabilizer and the shoulders tend to slope forward.

Other symptoms:

- Abdominal muscle weakness; appearance of large tummy with exaggerated lumbar lordosis
- Legs are variably involved, peroneal muscle weakness with or without weakness of the hip girdle muscles
- Vision usually unaffected
- Approximately 60% have abnormal audiogram with high-tone sensorineural hearing loss.

Disease Characteristics

- FSHD typically presents before the 20’s (>90%) with weakness of the facial muscles, some milder affected present later and some remain assymptomatic
- Variable condition; even within some families. Women tend to be less severely affected than men
- Infantile onset with severe progressive disease and large deletions; usually new mutations or had parents who were mosaic
- Infantile onset is rare- not a complication in existing families
- Assymmetry of limb and shoulder weakness is common

The condition is slowly progressive; some individuals describe a stuttering course with periods of inactivity followed by decline. Eventually 20% will require a wheelchair, however lifespan is not affected.
Chromosomes

- Our body is made up of millions and millions of cells
- Present in each cell of our body is a set of chromosomes
- We have 23 pairs of chromosomes (numbered 1-22) and a pair of sex chromosomes XX for female and XY for male

Genes

- A chromosome is made up of lots of different genes
- A gene is a stretch of DNA that codes for a protein
- We all have about 30,000-40,000 genes
- As we have two of each chromosome, one from each parent, we have two copies of each gene

Inheritance

- FSH MD is an Autosomal Dominant condition
- Molecular analysis detects gene changes in >95% of clinically affected individuals
- New mutations are common (10-30%); family history of the condition in 70-90%
- As we have two of each chromosome, one from each parent, we have two copies of chromosome 4 and therefore two genes for FSH MD
- Only one of those genes has the gene change that causes FSH MD, the other gene would work fine if the altered gene wasn’t present

Testing

- Genetic analysis
- Serum concentration of Creatine Kinase- can be raised; not specific
- EMG- shows mild changes
- Muscle Biopsy- Mononuclear inflammatory reaction (~40% individuals) Only used when FSHD suspected and not confirmed by genetic analysis

Gene for FSH MD

- The area consists of a repeated piece of DNA 3.3kb in length designated D4Z4
- Individuals without the condition have between 11 and 100 repeats
- Affected individuals have between 1 and 10 repeats (Molecular tested shows this change in 95% of affected individuals)

How does the gene change cause FSH MD?

- We do not know!
- Each D4Z4 locus encompasses a gene called DUX4. Is it to do with expression of DUX4?
- Postulated that repeats prevent transcription of genes on 4q35
- When contraction of repeats occur, transcription of genes goes ahead in muscle and cause the condition.
Complicated Genetic Testing

- Borderline alleles D4Z4 locus with 10 or 11 repeats; individuals in this range have full range of symptoms. FSH MD associated if clinical signs are present
- The shortened repeat must be coinherited with a specific fragment of DNA (4A161) in order for the person to be affected; when inherited with other haplotypes, the person is unaffected

New Mutations

- In these the condition has started for the first time in the individual concerned
- 50% are somatic mosaic; they have two cell lines; some with FSHD others normal; can have variable symptoms; males tend to be worse than females
- 50% change occurs in the germline
- Important to test parents of new cases; could be mosaics or have mild symptoms
- If parents are found to carry the gene change; the risk to siblings is 50%
- If parents do not carry the gene change and the risk of parent being germline mosaic is low; the risk to siblings is <1%

Penetrance

- Penetrance is the percentage of the people with the gene change that display symptoms of the condition
- Penetrance for this condition is 83%; it is greater for males (95%) than females (69%)

Pregnancy in Women with FSH MD

- 50:50 risk as to whether the child you are having is affected
- Tend to have higher rates for low birth weight babies and operative deliveries
- Worsening of weakness occurred in 24% of pregnancies (Ciafaloni, E. et al. 2006)

Can we predict the severity based on the molecular test?

- There is a suggestion that those with larger contractions have earlier onset of symptoms and more severe symptoms than those with smaller contractions
- New mutations tend to have larger contractions than familial ones and the disease tends to be more at the severe end of the spectrum

Management / Treatment

- Angle/foot orthoses can improve mobility and prevent falls
- Surgical fixation of the scapula can improve range of motion of the arms; can be short lived your condition is rapidly progressive
- Lubricants for dry eye

Prenatal Testing

- Condition needs to be confirmed molecularly in parent
- Prenatal testing is possible: CVS and amniocentesis
- Can predict presence of disease but not age of onset or severity of symptoms

Preimplantation Genetic Diagnosis

- Available in the UK and other EU countries, currently not in Ireland
- Essentially an IVF procedure, with testing of fertilized eggs
- Unaffected fertilized eggs are transplanted back into the uterus
Traceyanne Pilato: FSH-MD Support Group, UK

Support, Information, Encouragement

The FSH-MD Support Group was started by Lorraine Jonas in the 1980’s after she placed an advert in the Muscular Dystrophy Campaign “Target MD” newsletter to see if anyone was interested in starting up a support group. The first meeting of around ten people took place in London and this was the start of things to come.

The aims were:

- To enable people with FSH-MD and their families to meet and share experiences as everything at that time seemed to be focused around DMD
- To keep up to date with research
- To help people to come to terms with their diagnosis
- To be a focal point for support, information and encouragement.

The group underwent a makeover in 2009 to bring it up to date and widen its appeal. It now provides support in various ways:

- FSH-MD 25 Questions Answered leaflet: published with help from the Muscular Dystrophy Campaign. This leaflet is currently being updated.
- Newsletter: the group publishes two newsletters per year. To receive a copy, you must be on the FSH-MD Support Group’s mailing list and it can be sent via email.
- “Meet and Eat”: regional groups meet socially as a way of making new friends and sharing experiences of living with FSH-MD. There are two groups set up so far with around 15 members. They meet up for trips to the theatre, meals out, Christmas parties etc.
- Annual get-togethers: the venue and region varies to try to include as many members as possible. Some of the topics they have covered include research, image, care management, campaigning, neuromuscular centre, Care Advisers, independent living, scapular fixation, physiotherapy and nutrition.

For more information about the group, visit www.fsh-group.org

Traceyanne also spoke about her own experiences. She was diagnosed with FSH-MD when she was 13. Later she recalls being told in no uncertain terms by doctors not to get pregnant. She decided to do so however and now has two sons, neither of whom appears to have FSH-MD. However, she is aware of how lucky she has been in this regard. After various experiences, Traceyanne realised that she couldn’t go it alone and joined the support group where she now has an active social life. As part of the FSH-MD Support Group, Traceyanne advocates for improved supports for people with the condition. The NHS wastes £31 million per year on people with muscle disease who require inpatient emergency care. With the correct management, this could be avoided.
**Jason Baxter: FSH-MD Support Group**

**Experience of Scapular Fixation**

A common problem in FSH-MD is weakness of the muscles that stabilise the shoulder blade (scapula), resulting in scapular “winging”. This can result in a difficulty raising the arm above the shoulder, impacting on daily functions such as brushing or washing the hair, reaching, eating and drinking. Scapular fixation is a surgical procedure that stabilizes the scapula by attaching it to the rib cage to prevent it from “winging.” The procedure is extremely specialized, few are performed each year compared to most orthopedic procedures, and there are very few orthopedic surgeons with significant experience.

Jason spoke about his experience of having this surgery. In 2005 he had it done on his left shoulder. He had a fixed plaster cast for nine weeks and then a week of intensive physiotherapy and hydrotherapy. In 2006, the right shoulder was done. For Jason, the surgery worked out very well. It gave him a lot of confidence and he was also able to do simple things that he had not been able to do before such as showering and doing his own hair and changing a light bulb.

Having the surgery is not a decision to take lightly. It involves a general anaesthetic and a long recovery, and is not suitable for everyone with FSH-MD. People can have difficulty moving their hand behind their back after surgery. However, in Jason’s case, the benefits and vastly outweighed the negative effects.

**Dr. Mark Pickering, Postdoctoral Researcher, University College Dublin**

**FSH-MD: Current Research Directions**

Underlying this condition is damage to muscle tissue. There are two strategies to developing a potential treatment:

1. Prevent the damage in the first place: we need to know what causes the damage?
2. Repair the damage after it happens: we need to know can muscle be regrown?

A potential therapy might combine both of these approaches.

**What causes muscle damage in FSH-MD?**

The chromosome 4 repeats lead to decreased gene expression. However, in FSH-MD, the reduced number of repeats leads to increased gene expression. Two of the genes that are affected are:

- **DUX4**: the full length protein is toxic to muscle cells. However, some amount is essential as it is involved in muscle repair
- **FRG1**: too much seems to cause muscle cell death but if there is no FRG1, muscle cannot develop properly.

**Can we prevent the damage in the first place?**

- Currently, it is impossible to “replace” the missing repeats
- Decreased repeats lead to an excess of certain proteins. So can we selectively “switch off” or “tune down” the genes for these proteins?
  - Gene silencing: genes can be switched off with RNA interference

**Silencing the gene FRG1**

A proof of concept study was published in June 2011. Mice genetically modified to express excessive amounts of FRG1 have symptoms of myopathy. The mice were then treated using a virus (AAV) to deliver interfering RNA and
this resulted in improved muscle function. AAV gene silencing is currently in clinical trials for a number of other conditions, but is so far unproven as a treatment.

Plan B: if we can’t prevent the damage in the first place, can we repair it?

Basic principle: If FSH-MD results from muscle cell loss, FSH can be treated by replacing the lost muscle cells. But how do we do this? Could stem cell treatment be an option?

The diagram to the right shows different types of stem cells. In muscle, there is a type of stem cell called a satellite cell. When muscle is damaged, satellite cells divide. Some satellite cells develop into new, repaired muscle and some develop into more satellite cells.

However, satellite cells have a limited capacity to reproduce themselves. In dystrophic muscle, sustained satellite cell activation empties the reserve of these cells.

The challenge is understanding how to control the muscle stem cells. This requires a simplified system to examine satellite cell development: grow muscle cells in culture. An unlikely ally in this area is food science.

The diagram to the left shows the different genes switched on at different stages during the process by which a muscle stem cell matures into a muscle cell. We are starting to understand the underlying process that controls muscle cell development (when various genes switch on and off and so forth), which raises the possibility of being able to manipulate that process in the future to control stem cell development.

FSH research: what happens next?

- Why do DUX4 and FRG1 lead to damage only in specific cells?
- Are there molecules that can inhibit DUX4?
- Gene silencing: delivery?
- Can “druggable targets” be found?

There has been a huge increase in FSH-MD related publications in the last 2 years. This is set to continue. The AFM (Association Française contre les Myopathies) 2011/2012 funding call explicitly states FSH related proposals will be given priority and this is very good news for the future of FSH-MD research.

For more information contact Karen Pickering, MDI Information Officer on 01 6236414 or email karen@mdi.ie