Spinal Muscular Atrophy Information Day

Saturday 2nd October 2010

On Saturday 2nd October 2010 Muscular Dystrophy Ireland (MDI) held the first information day in Ireland for people with spinal muscular atrophy (SMA) and their families. This was the fourth in a series of condition specific information days that MDI has held since 2008, with Duchenne muscular dystrophy, Charcot-Marie-Tooth and myotonic dystrophy being covered previously. The following is a report on the SMA day.

Dr. Bryan Lynch, Paediatric Neurologist

Dr. Lynch is a Paediatric Neurologist in Children's University Hospital Temple Street and also runs the muscle clinics for children and teenagers in the Central Remedial Clinic (CRC). He gave an overview of SMA and current and future management strategies.

Dr. Bryan Lynch speaking at the SMA information day

SMA is a disorder of muscle weakness because of anterior horn cell loss. Muscles work when messages come from the brain down the spinal chord through the anterior horn cells. The anterior horn cells pass the messages down another nerve to the muscle. In SMA, there is a gradual loss of anterior horn cells which occurs at a different rate depending on the type of SMA.

History

The condition was described independently by Werdnig and Hoffman in 1891. It would be some years later in the 1960s, that the acute, chronic and late-onset variants were described. Then in the 1970s, there was electrical confirmation of motor neuron involvement. In 1990 a single gene was mapped to chromosome 5 and this was identified as the Survival Motor Gene. This discovery enabled diagnosis of SMA by genetic testing in 1995.

Classification
Several types of SMA have been identified:

- Type 0: severe, symptomatic before birth
- Type 1: evident at birth and in the first 2-6 months
- Type 2: onset at 16-18 months, sometimes earlier
- Type 3: onset after 18 months
- Type 4: rare, adult onset

Some general characteristics of types 1,2 and 3 would be:

- Type 1
  - Early infancy
  - Floppy / muscle weakness
  - Breathing muscles affected early
  - Abdominal breathing (using tummy muscles)
  - Face not affected, bright and alert
  - Eyes move normally
- Type 2
  - Onset at 6 months or earlier
  - Able to sit independently
  - Weakness greater in the legs
  - May have tremors, particularly of the hands
  - Normal intelligence
  - Overall above average intelligence in adolescence
- Type 3
  - Develop walking skills
  - At age 2-3 may fall frequently, have difficulty with stairs
  - Legs affected more than arms
  - Often remain stable, unchanged in weakness
  - May show slow progression of weakness in childhood or adulthood.

Cause
SMA is a genetic condition. The genes that are affected are:

- Survival Motor Neuron (SMN) gene is missing or impaired in types 1-4
- Neuronal Apoptosis Inhibitory Protein (NAIP) gene is deleted in 68% of type 1
- BTF2p44 gene deleted in 15% of people with SMA

There are two types of the SMN gene which are almost identical, SMN1 and SMN2. In SMA there is a defect of SMN1. Unfortunately SMN2 cannot fully compensate for the loss of SMN1, it only makes around 10-15% of useful protein. However, increased production of copies of SMN2 can help compensate and reduce severity or prevent the disorder, resulting in types 2, 3 or 4.

SMA is an autosomal recessive condition, meaning that in order for a child to have it, both parents must carry the defective gene. Every gene has two

copies, one copy received from each parent. Two parents who each have one defective SMN gene have a 1 in 4 chance of having a child with SMA.

Incidence and Diagnosis
The incidence of SMA is estimated at 4-10 per 100,000 live births, with carrier frequency 1 in 50 to 1 in 80. Carrier detection is difficult however. Antenatal diagnosis is possible but may not always be correct.
Diagnosis can sometimes be challenging as there are many disorders of the brain, spinal cord, muscle and nerves. Electrical studies of nerve and muscle can be used to differentiate between nerve and muscle disorders. If SMA is suspected, then genetic testing for the SMN gene can be performed. Muscle or nerve biopsies are not usually necessary for types 1 and 2.

Management
Quantifying the amount of SMN 1 and SMN2 may correlate with condition severity but it is not always reliable and so is not recommended. There are other disease modifying factors that are not yet known. Clinical typing is therefore most important at present.
Current management strategies include:

- Physiotherapy: management of contractures, posture
- Occupational therapy: seating, hand function, equipment, home adaptations
- Pulmonary: lung function
- Sleep disorders: related to breathing
- Nutrition
- Scoliosis
- Hip dislocation

Pulmonary management is very important. In type 1 oxygen and chest physiotherapy may be used. Mechanical ventilation has been rarely used but is not recommended. In type 2, either a CPAP (continuous positive airway pressure administered by a nasal mask) or BiPAP (intermittent positive pressure breathing device) may be used. A cough assist machine may also be beneficial as well as physiotherapy.

In SMA there can be problems with swallowing, opening the mouth and chewing. Type 1 babies require tube feeding from early on. Tube feeding is via the nose or gastronomy tube placed directly into the stomach by surgery. Type 2 children develop swallowing problems later and this occurs much later or not at all in type 3. The presence of reflux must be considered. This is when acid comes up from the stomach to the oesophagus. It can be treated with antacid medication and can occasionally require surgery – this should be considered before placing a gastronomy tube. Constipation can also be a problem with all disorders causing muscle weakness. A high roughage and fluid diet can be considered, and treatment may be prescribed.

Scoliosis affects almost all type 2 children and 50% of type 3. Management would be to delay surgical intervention in a growing child as long as possible. In the meantime, moulded orthotic devices may be used to help stay upright.

Surgery is ideally carried out when much growth has occurred and lung function is good.

Experimental Drug Treatments
Testing of various compounds is taking place to try to develop a therapy for SMA although at present there are no proven treatments available. The rationale at present is to promote more production of the SMN2 protein by upregulating the gene or converting SMN2 protein to SMN1. Some of the drugs tested so far are:

- Phenylbutyrate (old anti-inflammatory drug): early study showed promise but a definitive randomised study showed it was not effective
- Valproate (epilepsy drug): preliminary promise but subsequently unproven
- Albuterol and Salbutamol (beta agonist, asthma drugs): preliminary study suggested they may be effective but proper controlled studies have not yet been completed
- Riluzole (motor neurone disease drug): ultimately not effective.

Gene therapy and stem cell transfer are also being looked at but these will take some time. Particularly in regard to stem cell transfer, while there are some results in experimental mice, there is no evidence in humans yet.

Prof. Richard Costello, Consultant Respiratory Physician

Prof. Costello is a lung specialist based in Beaumont Hospital. Prof. Orla Hardiman refers adults from the muscle clinic to the respiratory clinic, which takes place on Friday mornings. This clinic has an open door policy for adults with neuromuscular conditions. The aim is to keep people well and out of hospital. Prof. Costello ran a question and answer session at the information day.

Prof. Richard Costello with MDI Chairperson Garry Toner

Q: What are your thoughts on BiPAP and cough assist as proactive / preventative treatment?
People with neuromuscular conditions can have problems breathing in (breathing is shallower when lying down at night). An oxygen test can be used to measure this, and this would be scheduled for every year or second year. People can also have problems breathing out, which may not be apparent until a person has a chest infection and finds that their cough is weak. Physiotherapy, BiPAP and cough assist can all be used, depending on the individual's needs. It would be beneficial to practice using these assistive devices before it is really necessary. It would also be beneficial to monitor breathing from an early stage to ensure that treatment can be introduced at the right time.

Q: What tests should be carried out in people with SMA to assess breathing?
A detailed overnight sleep study will give a lot of information but there are also tests which can be done as an outpatient. This would give maybe 10-15% less information but is also less disruptive as there is no overnight stay in hospital. A problem with sleep studies is that disruption in the room can lead to disturbed sleep and this is counter productive to getting accurate results. There are practical issues and cost implications about why it is not feasible to do a full sleep study at home. However, oximeters do give useful results and a small compromise in the amount of information gathered for the benefit to the person in not having to spend overnight in hospital is considered better. These oximeters have really only become available and useful in the last five years or so.

Q: What can be done to try to prevent chest infections developing?
A chest infection can strike very quickly. When a person has a weak cough, they cannot clear the secretions from their lungs effectively. It is recommended to always have a cough bottle at home and also to have an antibiotic at home ready. Timing is essential so antibiotics should be taken early along with aggressive use of the cough bottle. The cough bottle should be taken until the cough has died off. The usual advice not to take antibiotics too soon does not apply to people with neuromuscular conditions. Carers should be trained and ready to help with techniques such as chest physiotherapy and use of equipment.

Q: How do you tell the difference between a cold and a chest infection?
Do not assume that it is just a cold and will go away. Treat it as the worst case scenario.

Q: Is there a particular antiobiotic that would be recommended?
There is no particular recommendation. This is a discussion to have with your GP to get the antibiotic that suits you best.

Q: If you use the same antibiotic for 10-15 years will it lose effectiveness?
This is something that your GP would be monitoring so take their advice.

Q: Is there any benefit from breathing exercises?

Breathing exercises could be very helpful, along with practising techniques for chest drainage. Training in a more effective cough technique might also be useful. It would be beneficial to include carers in training, including chest physiotherapy techniques and use of equipment.

Karen Pickering, MDI Information Officer

Karen Pickering gave a short presentation on SMA standards of care, the SMA registry and support available from MDI for people and families affected by the condition.

SMA Standards of Care
A consensus statement drawn up by a panel of international experts for standards of care in SMA was published in the Journal of Child Neurology in 2007. TREAT-NMD worked with this group to create a user-friendly summary of the recommendations. The standards begin with diagnosis and how to differentiate between the different forms of SMA. Clinical classification is based on age of onset, highest function attained and typical features. However, when providing care it should be tailored to the individual's functional status rather than the original classification of type of SMA. Genetic testing procedures are also set out in the standards.
The management of SMA includes pulmonary care, gastrointestinal and nutritional care and orthopaedic care and rehabilitation. The person with SMA and their family are put at the centre of the guidelines and there is recognition of individual differences. These are recommendations not rules.

SMA Registry
The SMA registry collects information about people affected by the condition. It is run by TREAT-NMD and is open to people from the UK and Ireland. Registration is voluntary and your details can be entered online: www.treat-nmd.org.uk/registry
The benefits of the registry are:

- It can be used when recruiting participants in clinical trials
- Registered people are kept informed about research results
- Registries give specialists knowledge about prevalence and the natural history of SMA
- Registries can be used as a tool to raise funding for research as they provide information about the numbers of people affected.

In order to register your or your child's details you need your genetics results. You can access genetic testing through the National Centre for Medical Genetics in Our Lady's Hospital Crumlin (www.genetics.ie) and via your neurologist. The online registration also includes a questionnaire asking about diagnosis, physical condition and symptoms. There are measures built in to the registry to protect your personal data.

MDI Support
At the time of the conference MDI had 562 individuals registered with the organisation as having a neuromuscular condition. 43 of these have SMA which is the fourth highest diagnosis after Duchenne MD, Charcot-Marie-

Tooth and myotonic dystrophy. MDI provides a range of support to people with neuromuscular conditions and their families:

- Nationwide information service
- Information days and conferences
- Family support service: 8 Family Support Workers throughout the country
- Respite service: respite breaks, short term and emergency respite
- Youth service: 5 Youth/Respite Workers throughout the country
- Transport
- MDI newsletter published quarterly
- Website: www.mdi.ie
- Clinic support at muscle and respiratory clinics in Beaumont, the CRC and Temple St.
- Fundraising and PR support to members
- Funding research

EUROPLAN

EUROPLAN is a project funded by the European Union. Its main goal is to develop recommendations to establish a National Strategy for Rare Diseases in each member state including Ireland by 2013. This will be of interest to people with SMA and all neuromuscular conditions covered by MDI as they are all classified as rare conditions. The strategy will cover centres of excellence, orphan drugs and access to treatment, research and patient empowerment and support.

Dr. Chiara Valori, SMA Researcher

Dr. Valori traveled from Sheffield University to present their research on gene therapy as a promising tool to treat SMA. The group that she works with published a very interesting research paper "Systemic Delivery of scAAV9 Expressing SMN Prolongs Survival in a Model of Spinal Muscular Atrophy" in Science Translational Medicine on 10th June 2010.

A viral vector expressing survival motor neuron has been found to increase the life expectancy of transgenic mice with spinal muscular atrophy. Dr. Valori's group explored different strategies for gene therapy delivery to motor neurons to achieve a more clinically relevant effect.

They found that a single injection of self-complementary adeno-associated virus serotype 9 expressing green fluorescent protein or of a codon-optimized version of the survival motor neuron protein into the facial vein 1 day after birth in mice carrying a defective survival motor neuron gene led to widespread gene transfer. Furthermore, this gene therapy resulted in a substantial extension of life span in these animals.

These data demonstrate a significant increase in survival in a mouse model of spinal muscular atrophy and provide evidence for effective therapy.

Further pre-clinical work is necessary in order to investigate any potential side effects, look at dose scaling and to scale up production according to good manufacturing practice.

Prof. Costello, MDI CEO Joe Mooney and Dr. Lynch at the SMA information day