

World Muscle Society International Congress

A report from a McArdle perspective by Kathryn Wright

The 12th International Congress of the World Muscle Society was held at Giardini Naxos in Sicily, Italy from 17th to 20th October 2007. The conference provided an opportunity for me to meet, talk to and share ideas with clinicians, scientists and all those involved in the diagnosis and research into neuromuscular disease. A wide range of diseases were covered, including mitochondrial defects, Duchenne Muscular Dystrophy, Spinal Muscular Atrophy, and Glycogen and Lipid Storage Diseases.

The three main topics of the Congress this year were:

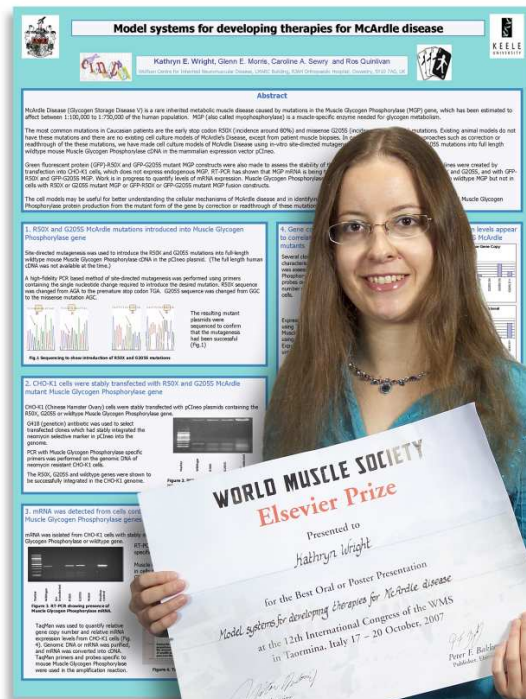
- 1) New developments in metabolic disorders of muscle (including disorders of glycogen, lipids and mitochondria),
- 2) Update on congenital muscular dystrophies and congenital myopathies and
- 3) What is new in the therapy of neuromuscular disorders?

Due to the emphasis on the Glycogen Storage Diseases, there were 24 posters on Pompe Disease (GSDII), and six posters on McArdle Disease (GSD V). There was also one poster on Glycogen debrancher enzyme deficiency (GSD III) and one poster on Phosphorylase b kinase deficiency (GSD IX).

The McArdle Clinic at the RJAH Orthopaedic Hospital was well represented by Dr Ros Quinlivan (Clinician), Kathryn Wright (PhD student) and Meredith James (Physiotherapist). Dr Quinlivan presented two posters, "Clinical Aspects of McArdle Disease in the UK", reviewing the genetics, disease, and descriptions of the clinical symptoms of the 45 confirmed cases of McArdle Disease which she has seen in her clinic. She also presented a poster "A pilot study of neuropsychological performance in McArdle disease" from work done in collaboration with the psychologist Dr Nicky Edelstyn from Keele University. I presented my poster "Model Systems for Developing Therapies for McArdle Disease". Dr Quinlivan and I both presented the same data at the AGSD Conference in Reading on 13th October 2007.

I was primarily interested in the other posters about McArdle Disease. This included a poster about muscle weakness in McArdle Disease, presented by T. Stojkovic from France. They had reviewed 80 patients with McArdle disease seen at the Institute of Myology in Paris. They found that 8 of these patients (10%) had muscle weakness, which occurred between the ages of 40-60 years. This muscle weakness increased very slowly over time. Research by clinicians such as Drs Quinlivan and Stojkovic on the progression and long term effects of McArdle disease based upon clinics which see larger numbers of McArdle patients will provide valuable information about whether there are changes in symptoms or muscle strength in McArdle patients with age.

A research group from Spain who are clinical scientists primarily involved in the diagnosis of McArdle Disease described two patients with newly discovered mutations. This was very interesting to me because it demonstrated how the precise amino acid sequence of Muscle Glycogen Phosphorylase would have to be corrected to treat McArdle disease, unlike some other diseases where many different amino acid sequences may still produce a functional protein.



Kathryn Wright received a prize and a certificate for her display about her work with model systems for developing therapies for McArdle Disease.

There was a poster presented by A. Martinuzzi from Italy about a trial of the ACE inhibitor drug Ramipril. It has been suggested that the form of the ACE enzyme which people have may affect glycogen uptake into muscle cells. This was first identified in top sports people, but has now been investigated in McArdle patients. Everybody has two genes for the ACE protein; which may result in having just the 'I' form, the 'D' form or both the 'I' and 'D' forms. Previous research suggests it may be useful to have less ACE activity, possibly using an ACE inhibitor drug. This trial was only conducted on a very small number of patients (eight). Patients felt that the drug improved their quality of life, however, it did not produce any change in the amount of exercise patients were able to do. There is other data which suggests a different result of ACE inhibitors may have been seen if this trial had been tried on more women (only one woman took part) as it may have a more noticeable effect on women than on men.

It is very interesting to see some of the research being carried out into McArdle disease, and of course there is other research which was not presented at this Congress. It is important to bear in mind that much of this research is still in preliminary stages, and that the data has not been peer reviewed to assess its reliability and reproducibility. With drugs trials it is important to consider the risk of the placebo effect, and in the long term, trials must be carried out on larger numbers of patients to ensure results are genuine and will apply to the wider population of patients. (This is particularly a problem with many published papers where food supplements were tested on McArdle patients but only one or a few patients were tested. Results must be shown to work reliably and reproducibly on larger numbers of patients before they can become a recommended treatment.)

I was also very interested to see potential therapies being used for other similar diseases. Many of the neuromuscular diseases share similar causes – usually a mutation in the gene which prevents production or correct functioning of one or more proteins. If a cure or treatment could be found for this mutation in one disease it could have applications for many other similar diseases. There is a wide range of treatments being considered and explored. The most stunning recent success has been that of the Genzyme enzyme replacement treatment for Pompe Disease. Unfortunately this therapy is not suitable for McArdle Disease. Other potential treatments being explored include exon skipping to produce a shortened form of protein which may be sufficient to improve some muscle diseases; gene replacement therapy by removing cells from the body, adding a correct copy of the gene and replacing cells into the body; or by injecting copies of the gene in a harmless virus directly into muscle cells (a prototype of a design of a machine to do this was presented at the Congress, although it may be a painful and impractical treatment!) Several posters were also presented on the use of the PTC124 drug in Duchenne Muscular Dystrophy. The drug is well tolerated (and appears safe) in humans, however, it has not been tested at doses high enough to increase muscle strength and provide the desired improvements. This drug may be a potential treatment for McArdle Disease in the future. Unfortunately a lot of these treatments are still a long way from being used in patients, as their reliability, safety and efficacy have yet to be determined.

Research is often carried out on cell culture models using cells which have had genes for the disease put into the cells, or in cells taken from patients and grown in the lab. For several diseases there are animal models. The genes of mice can be altered deliberately to create animals with the disease. But in other cases, for example Muscular Dystrophy, there are several breeds of dogs (Golden Retrievers and Labradors) which were found to have the disease naturally. These animals have been invaluable to the scientific community as they have provided an ideal opportunity to try novel forms of treatment which are not safe enough to be tested in humans. In McArdle disease the sheep with naturally occurring McArdle Disease have provided a good opportunity to test several possible treatments although no data was presented at this Congress.

There were also many cases of newly discovered uncharacterised diseases which had not been previously identified. This included a muscle form of Glycogen synthase deficiency (GSD 0) which results in an absence of glycogen production. (It was debated whether this could therefore be described as a "Glycogen Storage Disease" at all.) It had previously only been described as a liver form. It was described in a talk by Salvatore "Billi" Di Mauro who has been working in the field for over 30 years.

I was surprised and delighted to receive a prize worth €500 (£350) for my poster presentation. I won one of four Elsevier prizes for the best oral or poster presentation by a young researcher. There were a total of about 16 prizes, although I wasn't eligible for several. To put this into context, there were over 400 posters presented at the Congress by an international group of researchers and clinicians.

I would like to thank AGSD (UK) for providing me with £250 towards my expenses. I also received one of the 55 fellowships of €500 from the WMS Congress fund, which was the registration fee to attend the Congress, and The Roberts Fund at Keele University covered all my remaining expenses.

After note by Andrew Wakelin, Type 5 rep.

It is very encouraging to hear about McArdle studies going on around the world, and it is excellent to see the research work we have helped to fund being presented on a world stage. We are very grateful to Kathryn for all her hard work and congratulate her on her prize.

McArdle Disease has featured on the cover of the Annual Report of the Institute of Orthopaedics, based at Oswestry where Kathryn Wright of the Centre for Inherited Neuromuscular Disease at the RJAH Orthopaedic Hospital is undertaking McArdle Research.

The caption states: "McArdle Disease is caused by the lack of muscle glycogen phosphorylase enzyme in muscle cells due to a mutation in the gene.

A cell line model has been created by transfection of a plasmid containing muscle glycogen phosphorylase gene into CHO-K1 cells. Expression of the enzyme is detected using antibodies to give a red stain. The nuclei of the cells are stained blue. If a mutation is introduced into the gene, expression of the enzyme is not detected, providing a good model of McArdle cells.

