



McArdle Disease
Research update

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Our research in context

How rare is rare?

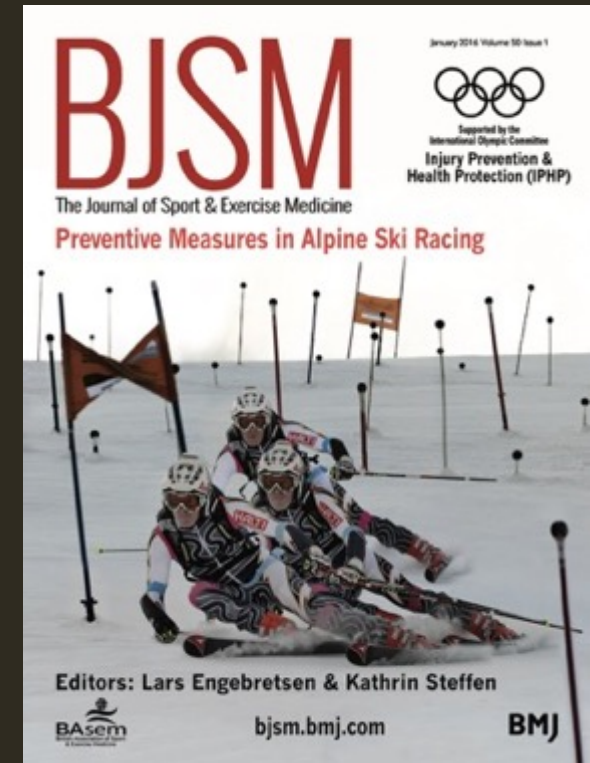
- **McArdle's** incidence about 1 in 100,000
- **Heart disease** – incidence about 1 in 3
- **McArdle's** – c4,000 diagnosed cases worldwide
- **Diabetes** – c300 million diagnosed cases worldwide
- Rare is defined as: EU <1 in 2000, US <1 in 1500
- McArdle's may be 50 or 100 times more rare than rare



How much research do we get?

- McArdle's – the first metabolic myopathy.
- The most numerous muscle GSD.
- Of interest to exercise and sports scientists.

We therefore attract far more research than our numbers and severity would suggest.



The need for multi centre trials

- Few patients in each country.
- USA may have 1,500, but a big country and not co-ordinated.
- Europe may have 1,500.
- To get reliable data large cohorts needed
- Multi-centre trials are the solution.
- Euromac Registry is helping to facilitate these.
- CoRDS Registry coming 2020.

Patient registries

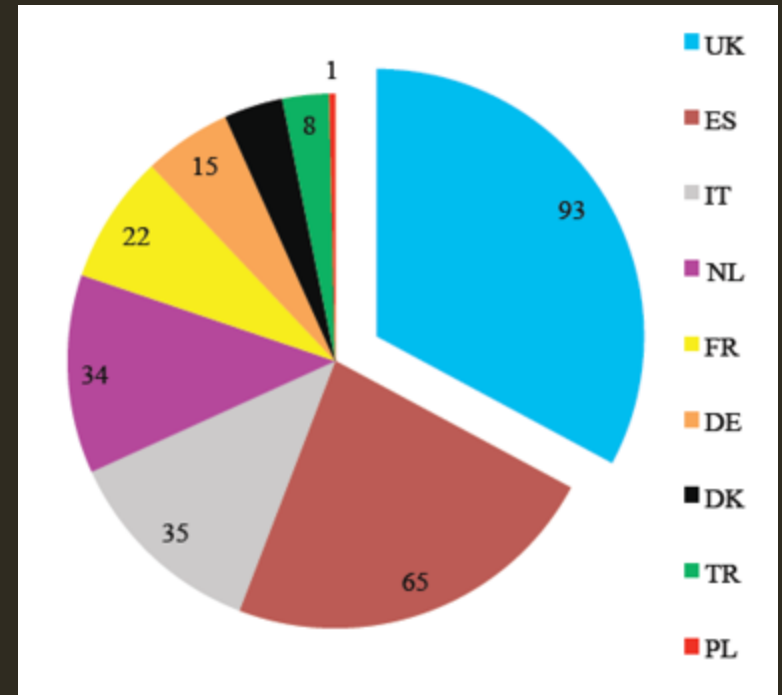
EUROMAC

- Established registry.
- Global, but focused on Europe.
- 14 research bodies are members.

CoRDS

- New registry with Sanford Research.
- International, but focused on North America.
- Research to be attracted.

Euromac collated data



Current situation

- Highest ever number of concurrent trials – about 8
- Ranging from minor useful info to full treatments
- Centres active in: US, UK, Denmark, Spain, France, Germany, Italy
- Several are multi-centre trials

- lamGSD maintaining contact, help with:
 - patient centered outcome measures
 - consulting on trial protocols
 - recruiting trial participants

Sodium Valproate – background

- Existing low cost drug used in other conditions
- Reappearance of the brain isoform, as happens in regenerating muscle
- Sheep, and mouse model
- London (UK) and Copenhagen (Denmark)
- 15 patients in total



Sodium Valproate – outcomes

After 6-months treatment with sodium valproate

- **12-minute walk test:**
 - No significant improvement in walking distance**
- **Cycle test:**
 - Pre second wind present in all visits – valproate did not reduce the barrier to second wind**
- **Forearm test:**
 - No lactate increase**
- **Biopsy:**
 - No enzyme activity**


Sodium Valproate – Report

- 20mg/kg/day sodium valproate was ineffective in stimulating the expression of the brain glycogen phosphorylase enzyme in skeletal muscle.
- Further research into sodium valproate as a treatment option is discouraged.

Triheptanoin – background

- An oil used as a dietary supplement, reduce other fats and carbohydrates.
- The study looked at whether Triheptanoin treatment could boost the breakdown of fat and increase the energy available for working muscles in McArdle's.
- Copenhagen (Denmark) and Paris (France)

The effect of Triheptanoin in adults with McArdle Disease



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Triheptanoïn – technical

- McArdle patients cannot increase fat oxidation to *fully compensate* for the energy deficiency due to a slow turnover in the tricarboxylic acid cycle (TCA).
- Metabolism of the 7-carbon fatty acid, triheptanoïn, generates acetyl-CoA and propionyl-CoA, which enter the TCA and can therefore potentially boost fat oxidation in McArdle patients.
- Double blind placebo-controlled crossover study.

Triheptanoïn – results so far

- Biochemical analyses of plasma TCA intermediates and fatty acids are ongoing.
- These preliminary data show no effect of triheptanoïn treatment on exercise capacity and tolerance or muscle energy metabolism in McArdle patients.
- Full paper just published!

Strength training

- Major work in Spain.
- You have heard all about it from Dr Alfredo Santalla.
- Re-confirmed by small case series at the London clinic.
- Will help all, but ...
- Highly beneficial to those with weakness or reduced muscle mass.



“Third Wind”

- Investigation of patient-reported “third wind” effect.
- Brunel University & McArdle Clinic London (UK).
- 10 participants.
- Investigating further metabolic changes after “second wind”.
- Pilot study appears successful.
- Further study planned.
- May lead to improved management advice.

Ketogenic diet

- Pilot study in Bochum, Germany.
 - 10 people – study of ketogenic diet and exercise.
 - Completed successfully.
 - Publication awaited.
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- Trials on-going or planned in Denmark, UK, Italy, Germany, USA.
 - Individual patients receiving dietary support around the world.

Metabolic study

- Dallas (USA)
- Dr Ron Haller will be giving details at AGSD US conference

“To identify the cause and possible effective treatment for the oxidative defect that accompanies blocked glycogen breakdown in McArdle disease”



Gene therapy – 1

- Paper accepted September 2019.
- Virus based delivery of a functional copy of the *PYGM* gene ameliorated disease in a mouse model of McArdle disease.
- Australian team.
- Plan to trial in McArdle sheep.
- May then lead to human trial.

Gene therapy – 2

- Toronto (Canada)
- Commercial development?
- Early stages
- Treatment that may work for many conditions

Ultimately...

We could have a range of options:

- Therapeutic aerobic exercise
- Strength training / muscle building exercise.
- Dietary advice alleviating many symptoms
- Drug therapy alleviating almost all symptoms
- Gene therapy – a one-off cure?

What we can do to help

- **Make sure we are DNA confirmed.**
- **Join the patient registries – Euromac or CoRDS.**
- **Volunteer for trials and studies.**
- **Join in patient-led initiatives.**
- **Raise funds to support research.**