Glisten

Glycogen Storage News

AGSD UK

Association for Glycogen Storage Disease

SPRING 2019

AGSD UK

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MESSAGE FROM THE CHARITY DIRECTOR

WRITTEN BY ALLAN MUIR

Welcome to our bumper edition of the Glisten Magazine, packed mostly with information from our conference and other meetings. The amount of drug development and research is phenomenal, considering the rarity of GSDs, and there is great hope that the new therapies for a number of GSDs will become available in the not too distant future.

The rapid move towards gene and cell therapies for several GSDs is encouraging, but we must ensure that, when they are authorised by the European Medicines Agency (EMA), they are accessible through our NHS. That will require approval by NICE who are currently resistant to approving high-cost drugs for rare diseases. We will continue to monitor the situation and campaign for fair access to drugs, aided by our close collaborations with other rare disease charities.

I would urge you to join our conference this year, it is always wonderful to see how people enjoy the developments in care and treatments, and sharing experiences with others in the same situation.

Looking for young Trustees

Our Board of Trustees has committed, in its new business plan, to actively recruit young Trustees. If you are interested, or have any suggestions, please contact Nick Jones (Acting Chair) or the Droxford office. We can talk you through the process and will provide you with a nomination form. “Young” in this case means between 16-25yrs. Since the average age of Trustee boards in the U.K. Is about 57.

It’s clear that more representation from young people is needed within the AGSD-UK leadership. We are committed to expanding our younger voice and empowering them to be heard. Our Trustees have committed to offering more induction, one-to-one help and will provide appropriate training.

MESSAGE FROM THE CHAIR OF TRUSTEES

WRITTEN BY NICK JONES – ACTING CHAIR, BOARD OF TRUSTEES

A brief update on the activities of your Board since you last heard from us:

Mike Porter stood down from the Board of Trustees at our recent board meeting and I have agreed to accept the position of Acting Chair until a new Chair is elected. Mike has done a splendid job as Chair over the last six years and we wish him all the best with his new found time. Under Mike's leadership there has been significant progress in improving the governance of the charity. His first priority was to stabilise and improve our financial situation which has been achieved, together with the introduction of a number of important policies and procedures to ensure good governance and compliance with legalities. Mike also worked very hard on the updating of our website which was launched very recently to great acclaim. We also now have an Annual Report and a 3Yr Business Plan in place, all essential at raising our profile.

Andrew Wakelin (our Chair before Mike and our McArdle Disease Coordinator) has just turned 70. Andrew does an enormous amount of work for our charity and recently has been working tirelessly to import all the data onto the new website. I know you will all want to join me in wishing him a very Happy 70th Birthday.

We are currently reviewing our membership criteria and will be introducing a new category for corporate membership, so if your employer might be interested in supporting or sponsoring AGSD-UK please do get in touch with Allan.

We have felt it very important to consult with our many volunteers to ascertain their needs and whether there is anything more we can do to support them. This work has been led by Jane Lewthwaite and Ailsa Arthur.

Although we will have to find significant funding to do so, we are researching the setting up of a registry which is one of our priorities in our Business Plan.

Finally, we have now started the process of recruiting our first CEO. More details can be found on the new website.

MEMBERSHIP

AGSD-UK values its members as outstandingly important supporters who can influence the direction of our association and provide fresh ideas and an assured supply of volunteers for the future. So, from 1st May 2019, if you choose to join or renew your AGSD-UK Full Membership, you will receive a small thank-you that includes the following:

- Welcome/renewal letter
- Personal membership card and unique membership number
- AGSD-UK cotton bag containing:
  - AGSD-UK Annual Report
  - Glisten Magazine
  - Membership Lanyard
  - AGSD-UK pen

In addition, you will enjoy the current benefits of full membership:

- Contribute to major policy decisions through the right to vote at General Meetings.
- Elect the Board of Trustees of the Charity.
- Stand for election onto the Board of Trustees.

Visit the AGSD-UK website for all membership details.

Membership is for individuals only, so if other family members wish to join, they must do so independently; there is currently no family membership category.

CORPORATE MEMBERSHIP

AGSD-UK has created a new class of membership to raise awareness and support from the many businesses that we all interact with. For instance, your employer, your own business, or organisations that you work with, or use their products.

We currently offer a single tier of corporate membership for an annual fee of £250. Membership benefits include:

- A joining announcement in our Glisten magazine, on our AGSD-UK website through social media
- Company logo and link to their website posted on our website
- Company logo and acknowledgement of support in the AGSD-UK annual report
- Personalised membership certificate to display in the company's workplace
- Printed copy of the AGSD-UK annual report
- Printed copy of the Glisten magazines throughout the year of membership
- AGSD-UK Corporate member logo for use on the company website

How to promote membership

Please suggest corporate membership to your employer and other businesses who you think would support our values.

You can either direct a senior staff member to the membership form on our website, or you can provide details to our Droxford office; staff will then approach the company on your behalf.

It would be helpful if you could provide contact information, including:

- Company Name and website
- Contact person's name, email address and phone number

If you would like more information about the scheme, please email admin@agsd.org.uk or phone the Droxford office on 0300 123 2790.

The online form may be accessed directly at: https://eu.jotform.com/AGSDUK/corporate-membership

KEEP AGSD-UK UPDATED

Please keep AGSD-UK Updated with your contact details. Make sure that you receive all of our important announcements, news and mail deliveries.

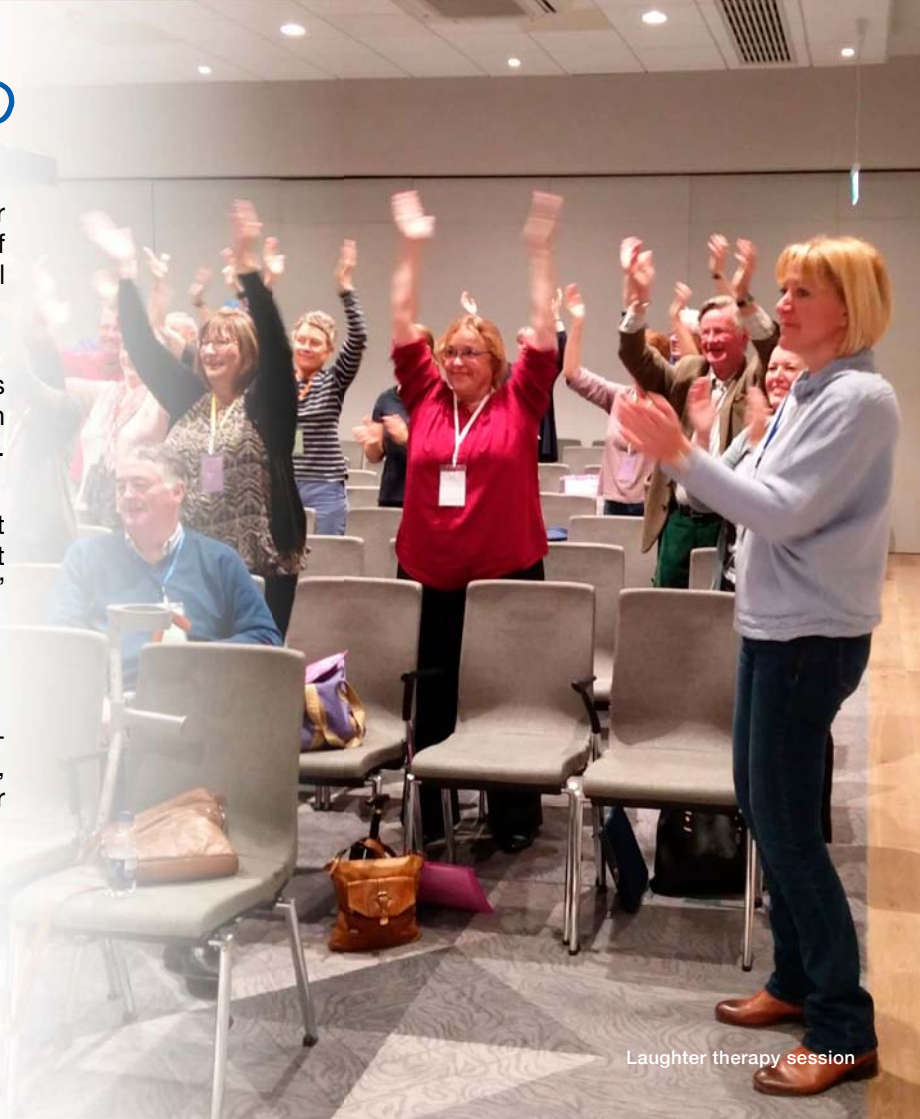
As we all move towards an online society, it's easy to forget to update organisations with changes in mailing address and phone numbers.

If any of your details have changed over the last few years, you can update our GPRS-compliant records by completing the "Register or Join" button at the foot of every page on our website:

www.agsd.org.uk

Keeping all of our records updated should minimise the number of items that get lost in the post, and improve the support we can offer to all our members.

Thank you!



Laughter therapy session

AGSD-UK CONFERENCE 2019

Weekend of
5 and 6 October 2019

Daresbury Park Hotel

AGSD-UK CONFERENCE 2019

Keynote Speaker Baroness Walmsley

Liberal Democrat Deputy Leader in the House of Lords.

Vice Chair of the All Party Parliamentary Group for Children.

We are extremely fortunate to have Lady Walmsley open our conference this year as our keynote speaker.

Conference registration fees reduced

Daresbury Park hotel is a much more affordable conference venue and we are happy to pass the cost savings on to delegates. The residential package will cost just £70 for an individual and £110 for a couple. The price includes overnight accommodation on Saturday 5th October, together with lunches and all refreshments on Saturday and Sunday. Please see the booking forms for our conference fees:

For families and individuals:
https://eu.jotform.com/AGSDUK/Individual-Family-Reg-2019

For healthcare organisations:
https://eu.jotform.com/AGSDUK/HCP-conference-reg-2019

Conference Programme

Because Daresbury is the birthplace of Lewis Carroll (Charles Dodgson), we hope to lift the proceedings a little by creating a wonderland of GSD workshops; we also expect to organise a Hatter's Tea-Party and fun hat-making activities for the children; so please dress your little ones accordingly!

The programme will follow our usual format:

Saturday 5th October

11am	Welcome receptions for Pompe, McArdle and Hepatic GSDs
12 noon	Buffet Lunch
1pm	Keynote Speaker: Baroness Walmsley
	Welcome and charity update
	GSD Workshops:

- Von Gierke (GSD 1)
- Ketotic GSDs (GSD 0, 3, 6, 9)
- McArdle and other Muscle GSDs
- Pompe

Hatter's Tea Party and Conference Dinner

Sunday 6th October

9am	AGSD-UK Annual General Meeting
	GSD Workshops continue.
1pm	Conference Close

A crèche will be available throughout both days of the conference.

Bedrooms can accommodate two adults and one child, so we may need to make special arrangements when more than one child is attending.

Further information about making reservations, workshop programmes and travel directions will be updated on our website as the arrangements develop. Go to www.agsd.org.uk and follow links to the conference page.

If you don't have access to the internet, please contact the Droxford Office for further information and booking forms.

Weekend of
5 and 6 October 2019

Daresbury Park Hotel

CONFERENCE 2018 REPORTS
HEPATIC WORKSHOP REPORT

INTRODUCTION BY JASON MCMILLAN

Again, we had a very successful conference with a full schedule covering many aspects of interest for all the Hepatic GSD's. Topics included:

- Glyde: Glycosade Study Update by Dr Helen Mundy,
- Gene therapy trials update by Dr David Weinstein,
- Liver transplantation, is there a role? By Dr Roshni Vara
- Healthy Pregnancy in GSD by Dr Elaine Murphy
- Preventing bone and lipid problems - Dr Charlotte Dawson
- Genetic causes of GSDs without a known defect Discussion - Ilan Small
- Rare disease and mental health, a patient perspective by Lauren Thompson
- Muscle involvement in hepatic GSDs - Ulrike Steuerwald and Jonathan Mosedale
- Extra protein in ketotic GSDs - Ulrike Steuerwald
- Clinical Updates in Glycogen Storage Disease Type III – Stephanie Austin

The highlight for me was the Gene Therapy update from David Weinstein and exciting news about opportunities for research and other GSDs.

I do appreciate that it can be difficult to come along to these conferences, but as you'll see from the wide range of presentations, there was an amazing amount to be learnt by attending.

Networking with professionals and meeting others who are experiencing the same things as you is invaluable. Having your child meet other children who are facing the same challenges and questions and knowing that there are not alone, these things are priceless.

There is so much that can be gained from just talking to other people over a coffee at the refreshment break, at the dinner or breakfast table, or listening to other professionals discussing their professional experiences. These are the times when I find we all get some of the most valuable information that helps to answer some of your unanswered questions.

The connections and people you meet at a GSD Conference will last a lifetime, and can make a gigantic difference to the GSD community.

To the right are descriptions of a few of the talks presented during the hepatic workshop.

Stephanie Austin

Clinical Updates in Glycogen Storage Disease Type 3

Stephanie Austin, Genetic Counsellor, Duke University

Stephanie discussed how progressive hepatic fibrosis is commonly seen in patients with GSD III, and liver failure, hepatic adenomas and hepatocellular carcinoma have been reported in some cases. Duke have created a canine model and generated a novel AGL knockout (KO) mouse model. Both the animal models developed similar liver pathologic features shown in human patients, such as elevated liver enzymes, increased hepatic glycogen content, and progressive hepatic fibrosis leading to cirrhosis. Hepatocellular adenoma was also described in an 18-month AGL KO mouse. These features correspond to findings of similar elevations in ALT and AST, as well as hepatic fibrosis in GSD III patients, in addition to a previously undescribed cohort of child and adult GSD III patients (n=11) with hepatic fibrosis.

Robust animal models, such as these, can prove invaluable in the development of novel therapeutic agents to prevent hepatic fibrosis and other complications of GSD III.

Stephanie concluded her summary of GSD 3 with these points:

- As life expectancy of affected individuals with GSD III improves, the risk for long-term hepatic complications increases and needs to be followed carefully
- Dietary treatment alleviates symptoms however our histology results show that irreversible liver damage is still ongoing.
- Irreversible fibrotic changes are noted as early as 9 months of age
- Noninvasive biomarkers and imaging tools are needed to diagnose and monitor ongoing liver disease
- Glc4 is a valuable noninvasive biomarker to monitor liver disease progression.

After highlighting the animal models and the benefits of Continuous Glucose Monitoring (CGM), Stephanie described a proposed study to test their hypothesis that the Enzyme Replacement Therapy for Pompe disease (Myozyme) will clear some of the stored glycogen in people with GSD 3. Results from a short-term study suggest that Myozyme may be effective, but only at very high doses. There are plans to commence a clinical trial in the future.

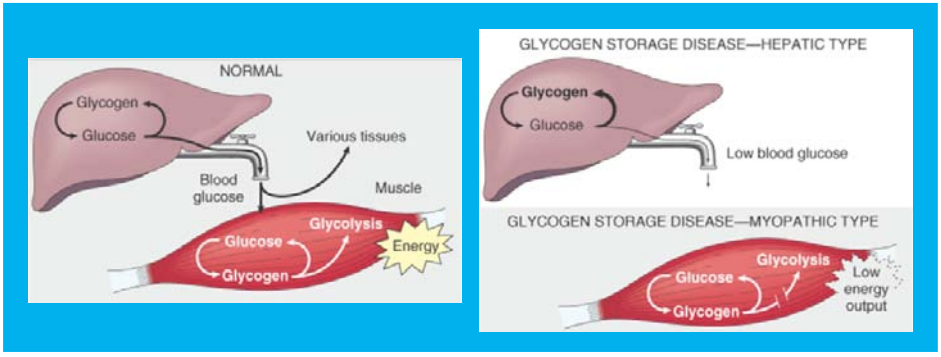
Duke are also investigating a novel gene therapy approach to correct GSD 3 both in muscle and liver using dual AAV vector. Future studies are needed to define the levels of GDE protein expression for effective phenotype treatment.

Glyde - Glycosade Update

Dr Helen Mundy, Evelina London Children's Hospital

Dr Mundy gave a comprehensive history of the need for an improved starch to give controlled release of glucose in GSD 1. Comparing the performance of Potato, Rice, Arrowroot, Tapioca and corn-starch; the latter gave by far the best performance.

The efficacy of uncooked corn-starch in the UK was reported on by Dr Phil Lee in 1996 and studies to find a slowly digestible, palatable starch have been performed since then. Experience in the USA, UK led to the development of Glycosade, a modified corn-starch that extended the fasting tolerance of GSD 1 and 1b patients.



Glyde is a collaborative study between specialists in the USA, UK, Netherlands and France. Its overall rationale was to develop a trial to compare uncooked cornstarch with Glycosade. It aimed to:

- Obtain data on efficacy within all hepatic GSD
- Understand differences in efficacy
- Obtain more long term clinical data in existing patient groups:
  - To ascertain the impact of Glycosade on growth
  - To determine if any changes in dietary quality
  - To identify if Glycosade improves quality of life

The first patient was enrolled in February 2016 and the study will complete in the second quarter of 2020.

Liver transplantation – is there a role?

Dr Roshni Vara, Evelina London Children's hospital

Dr Vara began her talk by discussing the work of surgeon and researcher Thomas E Starzl who worked in

Colorado and then Pittsburgh in 1982. He has over 2000 publications and died in 2017, aged 91. He performed early experiments in dogs to perfect organ preservation, transplant pathophysiology and surgical technique as well as investigating immunosuppression.

Despite its potential, liver transplantation was, at the time, deemed feasible but impractical. However, in the 90s surgical techniques improved with the ability to spilt livers and increase the donor pool. Intensive care, perioperative care and immunosuppression continued to improve, optimising liver transplant in children.

Thomas Starzl

The indications for a liver transplant are that:

- Transplant will improve the patient's survival
- Following transplant the patient should have a 50% chance of surviving 5 years
- The patient's quality of life may be currently unacceptable due to the underling condition and that this would be improved by a transplant.

Discussing Organ Donation in the UK, the majority of residents are asked to register if they wish to donate their organs on a national registry. Since 2015, Wales has operated an opt-out system similar to Spain, Austria, Belgium and 20 other European countries. Significant evidence to show that opt out systems lead to an increase in donation rates and shorten transplant waiting times.

Considering what is trying to be achieved with Liver Transplant in IMD, it can be thought of as a crude form of enzyme replacement or even gene therapy, where we are attempting to correct the underlying defect with liver replacement. We certainly achieve a cure in some disorders and create a milder phenotype in others. We see reduction in metabolic decompensations and aim to prevent end organ damage especially in the central nervous system. For most cases, we aim to see an improved quality of life without dietary restrictions, and without the constant risk of metabolic decompensation and hospitalisation.

	Benefits	Risks
Liver Transplantation	Excellent patient and graft survival Improved metabolic control Improved quality of life	Mortality Limited donor pool Lifelong immunosuppression
Medical Therapy	Proven medical treatment Achieves good growth Complications rare in childhood	Risk of hypoglycaemia Risks of NGT feeding Poor quality of life Availability of expertise

Experience of liver transplantation is limited in GSDs, some published data was presented and to finish Dr Vara highlighted the pros and cons of transplantation versus medical therapy.

In summary, Dr. Vara said she had given a brief outline of outcomes in some metabolic conditions, the importance of understanding the natural history of the disease, and the need for optimising outcomes with this understanding. We are however trading places and we need to be very clear about the indication, before suggesting a liver transplant.

Planning a pregnancy with GSD

Dr. Elaine Murphy, Charles Dent Metabolic Unit, National Hospital for Neurology & Neurosurgery.

Dr Murphy opened her presentation with the statement that "Women with GSD are having successful pregnancies with healthy babies". There are, however, a number of things to consider:

- Glucose control & energy requirements
- Heart involvement
- Muscle involvement
- liver cirrhosis or adenoma.

Nutrition should be designed to ensure an adequate supply of nutrients and energy to the foetus. Maternal liver glucose production increases to meet demands of foetus and mother. During pregnancy, glucose crosses the placenta and is used by the baby to grow and women with hepatic GSD are at risk of lower glucose levels than normal. Increased energy requirements can give rise to 'morning sickness' and will manifests as maternal hypos (low glucose) and possible slowed growth of the foetus.

- Ensure you have a working glucometer (+/- ketone meter) at home
- Expect to be asked to do more monitoring at home – early in the morning, before meals

Preparing for a pregnancy with GSD

- Let your medical team know (or any other relevant teams eg. hepatology, cardiology)
- Optimisation of weight and general health (smoking, alcohol) and metabolic control
- Vaccinations – rubella before pregnancy
- Get a prepayment certificate if taking regular medications
- Check if your current medications can be continued - (statins (lipid lowering), ACE inhibitors (blood pressure), bisphosphonates (low bone mineral density).

Will my baby have GSD?

Most GSDs are autosomal recessively inherited (I, III, VI) so the risk of your baby having GSD is extremely low. However there are exceptions:

- Cousin / relative marriages
- Small, isolated communities e.g. Faroes
- Just by chance

GSD IX (9) – can be autosomal recessive or x-linked inheritance, so it may be passed onto children

Preparing for pregnancy - in the metabolic kitchen

Bring your partner, mum or a friend to try uncooked corn-starch in various forms and learn about menu planning and organisation. You should also be able to test your blood glucose and ketone levels.

Dietary supplements may also be required; the following are recommended:

- Folic acid, 400 µg daily before pregnancy until 12 weeks (higher dose if you suffer from diabetes, epilepsy or have previous children with neural tube defects)
- Vitamin D, 10 µg daily during pregnancy and breastfeeding
- If you are currently advised a multivitamin – then switch to one that is recommended in pregnancy (lower vitamin A)

Vouchers for milk and vegetables:
https://www.healthystart.nhs.uk/healthy-start-vouchers/do-i-qualify/

NHS Prescription Prepayment Certificate:
https://apps.nhsbsa.nhs.uk/ppcwebsales/patient.do

A prescription currently costs £8.80 per item, but prepayment costs:

- £29.10 for 3 months - card payment
- £104 for 12 months - card or Direct Debit (10-monthly instalments of £10.40)

Once you are pregnant then apply for a maternity exemption certificate
https://www.nhsbsa.nhs.uk/exemption-certificates/maternity-exemption-certificates

Doing a pregnancy test

Wait at least until the first day of your missed period before testing (a few days later if you can!) or 21 days after unprotected sex. Tests that you buy in a reliable pharmacy have the same accuracy as that done by your GP. You can self-refer to antenatal services – but with GSD it is probably best to ask your GP to refer you.

During pregnancy

Obstetricians / midwives can get quite excited when you also have a rare condition. It can be frustrating but it is your opportunity to educate them. More foetal scans are likely to be requested, particularly if you have had frequent low blood glucose levels.

If your GSD Team have concerns then they will ask for a detailed foetal anomaly scan at 20 weeks, regular growth scans after that and ongoing review by a paediatric development team after the baby is born.

Standard medications

Pain-killers: Paracetamol

Anti-sickness medication: Yes

(avoid dehydration, eat small frequent meals including carbohydrate)

Exercise in pregnancy

If you exercise regularly then you can continue; swimming, yoga in pregnancy, and walking are all good. It's probably best to avoid contact sports, underwater diving and sports with a high risk of falling, e.g. downhill skiing.

During and after delivery

Labour is energy intensive (particularly if prolonged), so you should try to eat regularly, making use of uncooked corn-starch and possibly an intravenous dextrose infusion. The infant will need to be watched for rebound hypoglycaemia. Some women choose (or are advised) to have a planned c-section

Follow-up

Breast or bottle-feeding is approved, although breast feeding requires more maternal energy than pregnancy!

Normal paediatric follow up should be arranged for weight, vaccinations, development etc. If you have specific concerns you can contact your GP or health visitor, your paediatric development team or your team at the metabolic unit.

Risk of cardiomyopathy (heart involvement) in GSD 3

In a normal pregnancy, the heart works harder. It is recognised that increased foetal and maternal morbidity and mortality can occur in women with underlying cardiac disease of any cause. It is recommended therefore, that a pre-pregnancy plan should include an up to date cardiac assessment in GSD 3.

Pregnancy in GSD III - cirrhosis

Cirrhosis may have some impact on fertility, result in smaller babies, and increase the risk of prematurity. Mothers with advanced disease, may suffer from excessive bleeding, particularly if coagulopathy and/or they suffer from portal hypertension. Nutritional intake very important as is having regular reviews with hepatology.

Hepatic adenoma in GSD 1

Hormonal changes in pregnancy can lead to growth of adenoma and risk the possibility of bleeding or rupture. If you have an hepatic adenoma then this will need monitoring by ultrasound. Alternatively consider its removal prior to pregnancy.

Pregnancy after liver transplant

Many uncomplicated pregnancies now described in medical literature. You should wait at least 1 year after transplant; you should have a stable liver function and be stable on immunosuppressive medication.

Cholesterol and bone problems in GSD I and how to prevent them

Dr. Charlotte Dawson. Consultant in Adult Metabolic Medicine, Queen Elizabeth Hospital Birmingham

GSDs affect the conversion of glycogen to glucose; when liver cells sense that blood sugar (glucose) levels are low, glycogen should be converted to glucose. However this is not possible in some GSDs because of lack of an enzyme required for the conversion and the consequence is hypoglycaemia.

In GSD 1, Glucose 6-phosphate accumulates and is converted to, Uric acid, Lactate, Cholesterol and Triglycerides (fats). A recent study in GSD I suggests that there may also be an increased risk of heart disease. Each of these has consequences that need to be addressed, for example:

- High uric acid can lead to uric acid crystals building up; causing painful joints (gout).
- High lactate makes the blood acidic which, over time this causes loss of minerals from the bone. That weakens them causing a condition called osteopenia which increases the risk of fractures. The risk is increased if calcium or vitamin D intake is low.
- High cholesterol builds up in blood vessels around the heart over many years; they may become so narrowed that the blood cannot flow well. This restricts the oxygen supply to the heart causing angina (chest pain). If they become completely blocked it causes a heart attack

The goal of the current treatment is to provide a continuous supply of glucose to maintain plasma glucose concentrations above the threshold for mobilisation of glycogen stores from the liver. These levels are specified as:

- Plasma glucose > 4.2 mmol/L
- Blood lactate < 2.2 mmol/L

To achieve this there must be an adequate energy supply from a balanced diet, supplemented with cornstarch, and fructose should be limited – one portion of fruit is OK, but people should be beware of processed foods sweetened with 'high fructose' corn syrup.

There are other measures that should be taken to prevent long-term complications.

Preventing osteopenia

Bones can be strengthened by regular weight-bearing exercise, such as walking or jogging. Dietary calcium and vitamin D should be optimised and alcohol intake should be limited to safe weekly limits. Patients should avoid smoking

Preventing gout

A healthy diet should be maintained with limited alcohol intake and plenty of fluids. Allopurinol may be prescribed to lower blood urate level.

Preventing heart disease

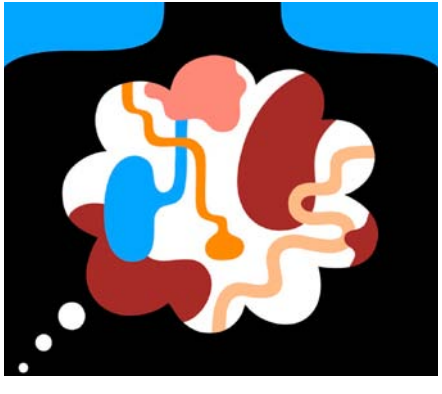
Patients should avoid smoking and take part in cardiovascular exercise, such as brisk walking or jogging; this should be combined with a healthy diet. Statins may also be prescribed.

CONFERENCE 2018 REPORTS
MCARDLE'S WORKSHOP REPORT

For the McArdle's group the workshops at the conference this year were possibly the best ever. That is in terms of the attendance, probably the largest we have had, and in terms of the presentations and very lively discussions. It is somewhat ironic, as unfortunately all our plans this year for presentations by professionals fell by the wayside one after another and we ended up with no professionals able to join us. We certainly made up for it with some excellent presentations from McArdle-ites.

After the introductions when we all gave a short account of our background and experience, I gave a presentation on "Diagnosis by media?". We do of course help to put a lot of people on course for diagnosis via our website and our social media groups. But here we were talking about the mainstream media. There have been several instances in recent years of media coverage leading to somebody getting a diagnosis. The main story which I covered was the case of a young woman written up in the New York Times with fairly typical McArdle's history. The newspaper series is linked to a TV programme on Netflix called "Diagnosis".

Several of us including myself contacted the company making the programme and explained why we thought this could be McArdle's. They were very excited by our input and I ended up recording a one hour Skype call with one of their researchers, followed by a similar call with the young woman herself. The programme is due to be released any time now, so it will be very interesting to see if our efforts have resulted in a diagnosis of McArdle's. Both AGSD-UK and IamGSD will be endeavouring to maximise such opportunities through the web, social media and mainstream media to help people get diagnosed as early as possible.



Andy playing his favourite sport better than ever before

Andy Williams, recently resident back in the UK from Singapore, gave a presentation on his personal experience of using the ketogenic diet. This story dates back to July 2014 when he was undertaking a fast for health reasons and discovered that his McArdle symptoms seemed to have evaporated. I suggested to him that this was due to the fast putting him into ketosis. He continued to develop the approach and wrote about it in a blog. Although a few others had mentioned the ketogenic diet, this was the first time that it started to be considered, investigated and discussed - resulting in the establishment of the "Ketosis in McArdle's" Facebook group. Andy reported how he was fitter now than he had ever been in his life. He continues to follow a low carb healthy fat diet, and tactically uses fasting before activity such as his cricket matches. He was keen to emphasise that using this approach enabled so much more aerobic activity and exercise, which of course we all know is hugely beneficial for us.

We had a short presentation from Vitaflow regarding dietary supplements to support a ketogenic diet. This is a very promising area. If ketogenic diets are scientifically proven to be as effective as they are reportted to be by patient experience, then having the supplements may be one way of reducing the challenge of maintaining the diet.

We watched a video "Ketosis in McArdle Kids" presented by Lucia Aronica, telling the amazing story of Letizia Minati who had degenerated severely when put on a high carbohydrate diet and had been reduced to using a wheelchair. Whereas now on a ketogenic diet she is living a very normal life and doing very well. She lives in Sweden where her

mother Barbara has been able to access excellent medical support for her use of the diet.

David Thompson gave an account of his experience with joining the Triheptanoin trial at the Neuromuscular Centre in Denmark. Triheptanoin is a manufactured oil which is used in some other medical conditions. He had travelled to Copenhagen for four weekends. David's wife travelled with him for one weekend, but the others were quite rushed with an evening flight from Heathrow, staying in the patient "hotel", having a standardised breakfast, doing the assessments and getting a lunchtime flight back to Heathrow. The aim of the trial was to see if Triheptanoin could enhance the breakdown of fat and increase the energy available for working muscles in McArdle patients. It involved Triheptanoin oil and placebo oil, with two weeks on each and a two week washout inbetween. Participants were tested on a static cycle for oxygen consumption and heart rate to compare the two treatments. Unfortunately the preliminary data shows no effect of the treatment on exercise capacity and tolerance or on muscle energy metabolism. David felt the experience was certainly worthwhile.

The exercise lab at the Copenhagen Neuromuscular Centre, Denmark.

Next up, I gave a short presentation on developments in gene therapy. This has been around for quite a few years in McArdle's, with no great progress. However, there are now several research establishments contacting IamGSD for information and assistance with looking into possible trials. The big change has been the development of techniques for delivering gene therapy to the targeted gene. As these developments mature in more common genetic conditions there may well be a cascading effect down to more rare conditions such as ours. There is already a pilot gene therapy trial in a single person with GSD1 in the USA. We may well see rapid development over the next 5 to 10 years. Of all the areas of interest in research for McArdle's, gene therapy is the one that offers the prospect of a real cure.

Sonia Worthy is a member of the Patient Liaison Panel (PLP) at the McArdle's clinic in London. She updated everyone with developments at the clinic. Patient numbers are now well over 200 and there is great pressure on the slots for follow up appointments. The recruitment of an understudy consultant for Dr Quinlivan should ease the pressure. Dr Renata Scalco has moved on to running neuromuscular trials for a pharmaceutical company in Switzerland. Sherryl Chatfield, neuromuscular physiotherapist, has returned from maternity leave so Aleks Pietrusz who provided maternity cover has moved on within the hospital. Suzanne Booth, specialist nurse, has moved to a new job at the hospital as has Helena Coskeran, secretary to Dr Quinlivan and service

manager. Sonia explained the role of the PLP is to help and advise the clinic and its staff from the patient perspective and they attend the annual review with the NHS commissioners. Andrew has stood down from attending every clinic as patient advocate and after a lot of discussion with the clinic it is finally agreed that AGSD-UK will recruit a team of about six volunteers to cover three or four clinics per year each.

As Dr Richard Godfrey had to cancel, Andrew presented a roundup of recent, current and planned research. He gave some information on progress with the Euromac Registry, the UK has the largest number of entrants so far at 93, followed by Spain with 65. An analysis of the first 300 patients in the registry is to be published soon. Dr Renata Scalco sent a brief report from the sodium valproate trial which has completed but is not yet published. Unfortunately the results were not positive, it had not stimulated a expression of the brain form of glycogen phosphorylase in skeletal muscle. It appears that this avenue of research is now closed, but other existing drugs which might be repurposed may yet to be investigated. Dr Scalco sent her best wishes and thanks for all support and inspiration that McArdle's patients had given her during her time at the clinic in London.

Nick on the treadmill at Brunel University.

Nick Jones had joined the exploratory "Third Wind" study at Brunel University and reported on that experience. It had involved getting into second wind on a treadmill, establishing a comfortable pace, and then walking for 2 1/2 hours non-stop. During this time exhaled air was analysed at intervals and other samples taken. This must be the longest ever exercise assessment of people with McArdle's. It will be fascinating to see results in due course.

I reported on the plans for an IamGSD-sponsored International workshop on the future of nutrition for McArdle disease. This to be held in November at CNMD, Queen Square, London, and chaired by Dr Ros Quinlivan. Clinicians and researchers in McArdle's are booked to come from Denmark, Germany, the Netherlands, Italy and USA as well as UK. The objective is "To overview the current evidence on nutrition for GSD5 and to discuss outcome measures and research considerations related to the use of nutritional ketosis in the management of GSD5 and related muscle GSDs."

All told, a busy and stimulating sets of workshops. Many thanks to all who contributed, not just the presenters but everyone attending.

CONFERENCE 2018 REPORTS
POMPE WORKSHOP REPORT

A REVIEW FROM JOHN FOXWELL, PST.

Lozenges for users of non-invasive ventilation machines

We were fortunate to have samples at this year's conference for people to try.

As a user of a BiPAP machine I always suffer with a dry mouth. I have tried a range of different solutions from gel to drinking lots of water, the gels were good for a short amount of time but didn't last long, whilst water was effective there were the normal repercussions associated with drinking large amounts at night. I was fortunate to be doing a talk to clinicians at a local hospital and mentioned this problem, as I always do, when one of the gastroenterologist consultants suggested I tried a lozenge called XyliMelts. She told me that she recommended them to her patients who do not produce their own saliva (Sicca Syndrome).

Having never heard of them I Googled them and found them on a number of sites, the main importer is The Mouth Ulcer Shop in Bournemouth, they are not available on the NHS yet and cost about £8 a packet of 40, so I ordered them and they worked.

They are a small round lozenge that has two sides, one is grey and sticks to the gum or tooth and remains in place for about 3 hours. The other side presses gently against the inside of the cheek and slowly dissolves moistening the mouth. I can put one in at night when I go to bed and it stops my mouth from drying out, you can apply as many during the night as you need and they last hours. They can also be used during the day and stay in place when eating or drinking. If you want to remove it, and you don't need to as it dissolves, but if you do, then just apply a gentle pressure and it comes away. It doesn't damage the teeth and can be swallowed easily, it also comes in two flavours, plain or mild mint.

Pompe Camaraderie at the Conference

Having attended this year's conference, it is only the second I have been to since my diagnosis, I found that the opportunity to talk with others who have Pompe is one of the most helpful aspects of the days.

Living with a disease that is hard to quantify when it comes to everyday quality of life is difficult, especially to those that don't understand the enormity of limitations it places on simple tasks such as getting out of a chair or picking something up off the floor. Trying to explain that if it is below waist height then it might as well be on the moon or as I always think, 'if it's on the floor it's staying there'. But talking with others who face the same issues is always a major reassurance and extremely helpful in finding solutions.

As most of us live miles away from each other, meeting up is often

impossible so sharing can be a real issue. Our virtual Pompe family on Facebook is always a good place to discuss issues but sitting down with a hot drink and a biscuit (don't tell the dietitians) is so much more rewarding and fulfilling.

Every time I speak with others with Pompe I learn so much and realise that I am not the only one living with these problems. So, if you are thinking, 'Why come to next year's conference?' the one reason might be to sit and talk with others that understand what you face every day.

I look forward to seeing you next year and sharing what's new, what's different and what we have in common.

Pompe Support Team

Pompe Support Team Presentation

Members for the PST gave an update on their activities on behalf of the Pompe community:

Gemma Seyfang

Believes that it is important to take every opportunity to speak out about Pompe to improve diagnosis and treatment. Gemma produced a Christmas singing video to raise awareness. She has gathered together photos in a calendar competition that was available for purchase.

John Foxwell

Went to his own medical review, spoke to the consultant about Pompe and asked whether there are speaking opportunities. John was then invited to the Wales Thoracic Society to present to a large gathering of respiratory consultants.He asked at his own medical centre and was again invited to speak at the Cardiff Hospital. John worked hard on the recipe book with Ben Parker and Jane Lewthwaite. It is finished and now available for purchase.

Theo Biggs

Attended a medical review with his mother, met two people in the clinic and spoke to them about AGSD-UK, getting in touch with us, publications and conference. Please try to promote the message to others you meet in clinics. It is easy to reach out to them as another patient, try to talk to them.

Ben Parker

Ben is acting as social media influencer during the conference, taking photos of Hope and delegates together. Hope Travels is the Pompe mascot. Every child in the UK with Pompe was sent one as a gift. See Hope Travels Pompe Awareness on Facebook, it is an international project.

Jane Lewthwaite

Jane wanted to speak about work with children and young people. They have different needs, especially teenagers. There are only 13 Pompe teenagers in the country and they are very spread out geographically. They experience difficulties moving to secondary school and coping with puberty as well. There were great entries to the Teens Competition and some will be made in to a leaflet.

Angela Biggs

Reminded everyone about the publications available, which are many. Including the risk alert card, Pompedoo, Medical Overview leaflet and Top Tips.

Gemma Seyfang: Patient Experience of Being part of a Clinical Trial

My name is Gemma, I am 34 years old and was diagnosed with Pompe Disease just over 2 years ago. I have probably been suffering since I was around 13 years old, but never understood why I found certain things difficult so I just put it down to being unfit.

My sister started to experience the same difficulties and went for testing so it prompted me to do the same. I had my tests completed at Royal London Hospital but then transferred to Addenbrookes in Cambridge because they have a specialist unit and team.

My sister had heard about clinical trials and told me that they may want to speak to me about doing one. As soon as my sister told me I started to worry. A trial sounds really scary, and my perception of what a trial is and what it entails at that moment in time was so fabricated; all I could imagine was the worst.

In my first meeting at Addenbrookes I was nervous but the staff are so knowledgeable that it put my mind at rest. My doctor and nurse explained the trial briefly in my first visit, but they didn't overwhelm me with information. I was asked to return for baseline tests, either way, if I started on the trial or not, they needed my baseline results. I was then given a more detailed explanation of the trial and what I was to expect. My doctor explained it to me like this: "Imagine that the current treatment, Myozyme, is a key that enters the body looking for the correct padlock. Well, the investigational drug enters the body with 12 keys." So, they are aiming to prove that this drug is more effective in getting to the correct place to do the job it is required to do.

The trial I am on had specific requirements, for example:

- I must be treatment naïve (never had Myozyme)
- My lung function and muscle strength tests need to fall below specified levels.

Once we knew I was eligible for the trial, I took a few weeks to decide what I was going to do. No matter what I decided, I would start a treatment, so either way I will be having ERT, but if I decide to do the trial I could be receiving a better drug than the current standard of care (Myozyme).

The first year of the trial is "blinded" - I would not know which drug I receive -but the remaining 2 years are "Open Label", so I will definitely be receiving the trial drug. So, in one case I'll have 2 years of the

investigational drug, or alternatively I'll have 3 years of the investigational drug.

I will be in hospital for every treatment, so if anything did go wrong I am in safe hands, surrounded by professionals. The hospital is just over an hour away from our home, but my travel expenses are covered by the trial, as are any food or drink I wish to have whilst at hospital. At Addenbrookes there is a new Clinical Research ward which is just like being in a private hospital and all rooms are side rooms, so you have your own privacy.

Every 3 months I am required to come into hospital for Lung Function tests and strength test and on 2 occasions I must stay at the hospital overnight to give a blood sample 10 hours after my infusion finishes.

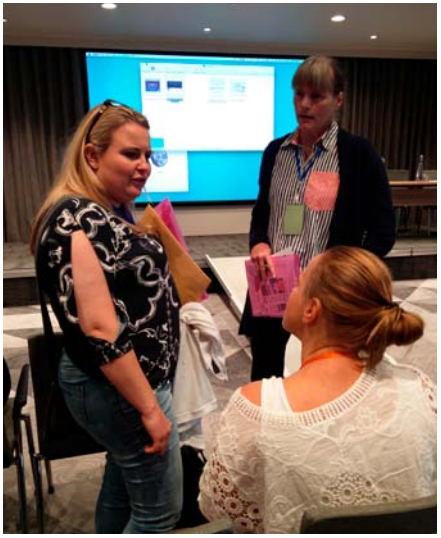
By taking part in a trial, if this drug is eventually approved by the regulatory authorities, then I could be helping my sister and my Pompe friends around the world, as well as myself.

Once I had all the information, I realized that this is a Phase 3 trial, so the risks are at their lowest. I asked my partner and family what they thought, but ultimately they said I am the one that needed to decide, and when talking to others I was advised that after knowing all the facts I then need to go with my gut.

I was also made aware that I could pull out of the trial at any point, but that influences the study and its results, especially one that is for a rare disease as the number of participants is small, so I wanted to be extra sure before starting. Once I had made my decision I had to wait for about 3 months while the hospital gained approval as a trial centre.

Once again my doctor and nurse ensured I understood fully and answered all my questions before I signed the consent forms.

I now have just 1 year remaining on my 3-year trial. 2 years has flown by, my 2-weekly visit has simply become a part of my life. The research team are so kind, professional and compassionate, they are only a small team of about 10 and so they have taken their time to learn about this rare disease and have watched me improve and are genuinely excited to be a part of my journey. My specialist nurse is so supportive, no matter what questions I have she always makes time to listen and answer.



Gemma Seyfang

There are a few things that take time in the trial such as letting my nurse know when I am feeling ill, if I take any paracetamol or injure myself. For the first 18 months, I was travelling to hospital every 3 months for lung function and physio tests, but now I only need to go every 6 months. My nurse organized it so

that I could complete both in the same day to save me having to make 2 trips. I have a very small amount of paperwork to fill in every 3 months such as questionnaires and I also have an ECG and a checkup with the Consultant. The medical team has also spoken to me about what happens once I have competed the 3-year trial. Because I was one of the first on this trial, I will be finished before they have collected enough data for this study. They hope for me to continue with the trial drug as part of a study for further investigations.

I am very hopeful about the future because scientists are doing so much research and therefore require us to participate where possible to enable these studies. I would not hesitate to take part in another study; my experience has been such a positive one, mostly due to my response to the drug and the smooth running of the trial thanks to all those involved.

Malcolm Knightley: Patient Experience, Independent Infusions

Timeline

- Pompe diagnosed May 2009
- Started Myozyme infusions August 2009 (Salford Royal)
- Started home care (Medco) January 2010
- Independent infusions from April 2010 to present

Main points

On first home infusion visit the home care nurse asked whether we would like to consider self-cannulating and becoming independent 'infusers'. Our response was that we would give it a try!

The home care nurse reassured us that we would well supported and that we could move forward with it at our own pace. We became fully independent after 4 months.

The main benefit to us has been that we have the freedom to select a convenient time of the day and occasionally the day itself. We sometimes adjust the day to suit holidays and trips we make.

From our experience we have found becoming independent has been well worthwhile and would encourage others, in the right circumstances, to consider it as an option.

Malcolm Knightley

Dr Mark Roberts

Neurologist, Salford Royal NHS Foundation Trust Hospital

Manchester Metabolic Centre for Clinical Neuroscience.

Introduction:

- Since 2006 when ERT was first introduced, Pompe has become treatable.
- The Late Onset Study 2010 (LOTS) - Symptomatic patients showed improvements in breathing and walking after six months using ERT.

- IOPD - Infant data after ERT showed improved cardiac measures. Unmet needs remained and there are variations in response to treatment and duration of effect. Some improve as little as 4%.
- IOPD - We now have children aged 16-18yrs surviving for the first time. Some evidence that there might be cognitive impairment in children.

Summary of Current Research

1 - Second Generation ERT - trials

- Sanofi-Genzyme. NEO1 – trialled for LOPD, 24 patients globally over 3.5 yrs. Initially showed promising improvements in walking and in the GSGC test ('gate, stairs, gower, chair' which means things like getting off the floor and similar physical checks). This is now in Phase 3 trials. Called COMET for children (age 3+) and adults. There is now also MINI-COMET trial for those children not doing well on current treatments.
- Amicus. Current trials for ATB200 with AT2221 = a replacement enzyme with a chaperone. The chaperone stabilises the artificial enzyme as it travels through the blood and helps it to get to the lysosome as well. It might be less immunogenic and so cause fewer reactions. After 18 months on trial, showing improved walking times and improved motor function across all patients (both treatment naive and those switching from current ERT and those who are ambulant and non-ambulant). Improvements also reported on a self-report FSS (fatigue severity scale). CK and HEX4 also improved. The treatment naive group (who had never had Myozyme) improved the most. 24 month results are awaited soon.
- Valerion. VAL1221. Subjects switch from Myozyme. This aims to target both the lysosome and the cytoplasm, having two modes of uptake in two different receptors in the cell. It can work in different parts of the body, including the brain where it might clear glycogen build-up. The Charles Dent Unit at The National Hospital London is the only site offering this trial. Reports awaited.

2 - Gene therapy

Why look for a gene therapy?

- Single administration not every two weeks
- Get steady enzyme levels = less monogenic
- Potentially a greater effect on the course of a disease or even a cure.

Types of Gene Therapy:

- Vector (carrier) which is a virus that has been adapted to be neutral but can still transport the new gene to the right place. This might be injected in to muscle, blood or the brain (the latter via a lumbar puncture).
- Stem Cell Therapy – no current trials for GSD2.
- Gene editing – splicing out the bad bit and introducing a new good bit.

Gene Therapy Research Trials

Audentes

They have introduced trials for gene therapy for other conditions than GSD2. They expect human trials late 2019 or 2020.

Spark Therapeutics

Developing SPK-3006 on knockout in mice. Possibly humans in 2019.

Amicus-Penn

Aiming to get a gene therapy in to the brain.

Lacerta (Sarepta)

Aiming to develop a gene therapy with an immunotolerisation regime to avoid reactions to the vector.

Risks of Gene therapy?

- Might be one chance only, redosing problems?
- Unwanted immune reactions
- Targetting the wrong cells by accident
- An infection caused by the vector (virus)
- Possible tumour or other unexpected outcome

So, there will be close monitoring a long time, possibly five, ten or fifteen years. If gene therapy does not work it might be possible for patients to go back to ERT.

Discussion about possible treatment options available today.

- If a patient is deteriorating on ERT then consider a trial.
- If a patient is stable they might stay on Myozyme or consider switching to a trial for a new ERT.
- If a patient is newly diagnosed, treatment naïve and symptomatic, they might start Myozyme or go on to a trial of second generation ERT.
- If a patient is newly diagnosed and pauci-symptomatic they might consider Standard of Care (Myozyme) or a trial of a next generation ERT (if they meet the entry criteria).
- Gene therapy trials for humans might start in the next two years but wider use is a long way off, as a treatment five to ten years.

Physiotherapists' Question and Answer session

Nicola Condon – University Hospital, Birmingham

Andrew Oldham – Salford Royal Hospital

Nicola and Andrew answered questions that had been submitted and they also demonstrated some pieces of physiotherapy equipment.

Question 1

When I was diagnosed, I was advised not to over-exercise as that encouraged the "bad" muscle fibres at the expense of the good. I was then asked to do the "6-minute walk" test, but no account was taken of the 3-4 weeks it took to recover from the test. What is the current thinking on exercise?

Answer

The test was intended to test a patient's ability to walk in everyday life, but, whilst still a standard test for many promoters of possible therapies, there are now better ways of doing so, namely:

- The electronic "mat" which tests not only how far one can

walk on a given day, but also one's gait, imbalance and other elements of walking; and

- Activity monitors, such as Fitbit, which measure activity during everyday life.

Certainly, a test where the aftermath is not checked is flawed, but one should not forget that one can stop during the test, either to rest or if one has reached the end of one's tether.

Question 2

In exercising, is the mantra "Low weight, High repetitions, don't push to limit" the correct one?

Answer

primarily, it is the quality of movement that is important, as some prefer to follow the mantra (and that is probably the safer option), whilst it may suit some to use high weights with few repetitions. The key is to start low and pace yourself: don't push it, take, say, a week at each level or until one can do the level comfortably. Ho9wever, if one prefers. For a useful array of exercises, visit the Muscular Dystrophy Association website.

Question 3

How important is stretching?

Answer

Primarily it is the moving that is important, but stretching will help in getting the muscles ready for movement, particularly where the muscles are tighter or weaker than others. So include exercising the chest and hips and use gentle twisting as well as stretching movements.

Question 4

It has been suggested one does not exceed the "70% Rule", namely that one should not go to more than 70% of one's maximum. Any comments?

Answer

Occasionally, life requires more than 70% of one's maximum, it is important then to take rest days. The so-called 70% rule derives from the Borg Scale, which measures the subjective feeling of exertion, hence its sub-title "Rating Perceived Exertion"!

Question 5

Are there any exercises which can help with incontinence, (other than Pelvic floor exercises)?

Answer

Whilst there are other exercises, incontinence problems may have little to do with Pompe's. It would be better to investigate the specific problem with an expert in that field, as the solution may be medication, diet changes or the like.

Question 6

Are there any exercises which can help with shoulder and neck pain?

Answer

Primarily stretching by dropping one's head towards each shoulder in turn. Attend to one's posture, (e.g. when sitting push oneself back in the chair, try using an exercise ball- one that allows hips and knees to be at right angles, so one's thighs are parallel with the floor- or a wobbly cushion. However, the key point with their use is BE SAFE!).

Question 7

Are there exercises to help pelvic weakness?

Answer

Again, correct use of an exercise ball or a wobbly cushion can help, (see the answer to Question 6)

Nutrition Workshop

Abibat Gbadamosi, Dietitian Specialising in Inherited Metabolic Conditions, Royal Free Hospital, London

Louise Robertson, Dietitian specialising in Inherited Metabolic Conditions, QE Birmingham

Background

- Prior to 2006 and the start of ERT diet and nutrition were the main treatments available.
- A small group of UK dietitians from Specialist Centres working with GSD2 got together with Sanofi and Jane Lewthwaite AGSD-UK SCA to scope an LSD Nutritional Information leaflet.
- Jane later organized a meeting inviting all the dietitians for LOPD and IOPD together. At that meeting it was agreed there was wide variation in access and referral process for patients. There was variation in guidance being issued. There was also a need to review what firm evidence is available and what new research might help.
- ASGD-UK might be able to fund a small piece of research if we know what is needed.
- Abi issued a survey to all dietitians about clinics offered, resources available and referral processes, she is collating these results. For example, some dietitians see 47% of patients with GSD2, some see none at all.
- Abi also asked delegates with GSD2 to complete a survey and return it to her, about their own diet and access to nutritional advice.
- Abi was part-funded by AGSD-UK to conduct a literature review and produced 34 reports from the last 50 years. Abi is appraising these using a standardized formal system and will report on the content and quality of research. We are hoping to get some standardized dietetic practice.
- About half suggest high protein but the amount recommended varies. Some suggest 1.5 gms per kg of body weight. Others suggest 25-30% protein of all calorie intake.
- Differing assessments are made too, some use a grip strength measure.

Audience Vox pop – What have you heard about diet and Pompe?

- Diet as no effect
- Have high protein and low carbs
- 5:2 fasting diet is frowned upon
- Weight control is important
- I do the Ketogenic* diet
- Try changing the timing of foods to improve energy
- Certain foods cause lethargy and sluggishness
- Certain foods increase energy
- Avoid simple sugars

*This is when you have high protein with high fat and the body breaks down fat and produces ketones in the urine.

F.O.D.M.A.P

A few people have tried a FODMAP programme which excludes certain food groups for a period and then slowly introduces them one by one to see the reaction. This is useful for people with GI symptoms or IBS symptoms. There might be certain food groups that cause particular problems in different people; apples, fruit, lactose, pulses and so on. It has a good success rate in helping with IBS symptoms.

What happens in Pompe disease?

People with Pompe have increased protein breakdown so do they need to increase protein intake? Some research shows high protein is good and other research shows that high protein can lead to higher calorie intake, therefore weight gain and that in turn might cause impaired breathing.

Diet and Exercise

Some case studies cover both diet and nutrition. It might be the case that guidance for support should include both diet and physiotherapy together. These might both work well with ERT.

Q I cannot do enough exercise to lose weight so I have to modify my diet.

Try to work out what exercise you can do and include it within your routine, even if it is only a few minutes every day. This might include stretches whilst watching TV. Try to consider your respiratory rate to find out which exercise is best for you.

Q Should you have extra protein after or before exercise?

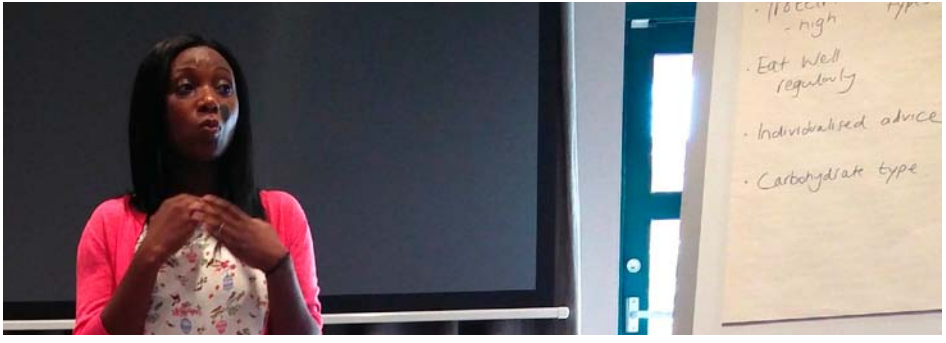
It is better to look at protein as a percentage of your whole diet.

Q What types of protein are best to eat?

Keeping calories down is important. Having a varied selection of proteins is good too. Try to keep sugar levels at a steady rate and avoid spiking. Use slow release carbohydrates such as oats and check on cooking methods. Include fibre and whole meal bran or cereal. Beans on toast is a good meal because is includes amino acids.

Q Should I just consider protein and avoid carbohydrate?

It is important to monitor sugar, fat and calories in order to avoid common conditions such as diabetes or high blood pressure.



Abibat Gbadamosi

Pompe Disease: An Overview and Strides made since Approval of Alglucocidase Alfa in 2006.

Stephanie Austin, Genetic Counsellor, Duke University, North Carolina

Abstract

Many advances in diagnosis and treatment had been made since alglucosidase alfa was first approved in the US in 2006. Newborn screening is being added across the US – currently used in more than 10 states for Pompe disease. As a result, we are diagnosing children with infantile and late onset Pompe disease earlier and have learned valuable lessons. Duke continues to study the natural history of Pompe disease including cardiac manifestations in late onset Pompe, the use of whole body MRI, increased dosing and rate escalation, and immune response.

Natural Course of Pompe disease

One mutation is commonly linked with LOPD in the USA called IVS1 (c.-32-13T>G). With all mutations, there is a progression from healthy muscle to irreversible muscle damage caused by the GAA enzyme deficiency. The aim should always be to intervene early with ERT to slow the disease progression.

Stage 1: Mild myopathy + normal mitochondria + lysosomal glycogen

Stage 3: Severe myopathy + abnormal mitochondria + dense lysosomal glycogen

Stage 5: Cytoplasm is filled with glycogen, complete loss of fibrils, cells bloated with oedema.

Discussion of the range of symptoms and new insights about LOPD from the New Born Screening programme in the USA.

In March 2015, Pompe disease was added to the Recommended Uniform Screening Panel (RUSP) in the USA. Since then US States have been adding Pompe to their screening programmes.

Prior to NBS it was assumed that prevalence was around 1:40,000 and that only IOPD (Infantile Onset) presented at birth and LOPD (Late Onset) presented later. Post NBS we now know that US prevalence is in the range 1:9000 to 1:24000.

LOPD presents at birth too or the first few months of life and we find that treatment started at birth shows much better outcomes and less muscle damage.

Case Study

- Baby had NBS, detected LOPD mutation. C.-32-13T7G. Was presumed asymptomatic. CK level elevated but ECHO and ECG normal.
- At 5 months the evaluation showed some gross motor delay, lower 10% of normal range. Started physical therapy.
- At 6 months showed weak muscles, regression in gross motor skills and ankle tightness, hip muscle weakness and the A.I.M.S. (physical assessment) score in 3rd percentile, CK continued to rise.
- Started ERT at 9 months and physical therapy increased to 3xpw. A.I.M.S. score improved to 43rd percentile and catching up on motor milestones such as head lifting.

Through NBS we learned that LOPD is not only an adult disorder and to start treatment as early as possible.

However, some other babies with LOPD are not showing so many symptoms and are still not having ERT, just physical therapy. Duke is trying to evaluate: What is the best start time for ERT for a baby diagnosed with LOPD through New Born Screening.

Some Lessons from Duke and other studies on LOPD Symptoms

- Recognising more phenotypes and differences in noticeable symptoms
- Cardiac issues are mainly rhythm disturbances
- Vascular manifestations – e.g. aneurysm and dilation of thoracic aorta
- Lingual weakness
- Speech dysarthria
- Ptosis (droopy eyelid)
- Bladder and bowel incontinence
- GI manifestations, dysphagia and GE reflux
- Scoliosis and rigid spine

Extent of cardiac manifestation in LOPD

Commonly:

- Left ventricular enlargement
- Non-specific valvular abnormalities
- Rhythm disturbances
- Left aorta enlargement

Study of cardiac symptoms

Of 184 Patients studied, 90 had LOPD and 83 had the IVS1 variant. 26 of those (1 in 3) had cardiac involvement, including tricuspid valve dysfunction, arrhythmia and left ventricular hypertrophia. However, some had other conditions such as Diabetes. Duke now recommends an ECHO every 2-3 years and ECG more often.

What have we learned about IVS1?

- No severe cardiac involvement
- Risk of arrhythmias
- There may be a potential protective effect with IVS1 variant against hypertrophic cardiomyopathy dues to residual enzyme activity.

Significance of Angiotensin-Converting Enzyme (ACE)

The net effect of ACE is to make blood vessels smaller. It is possible to test individuals for their ACE genotype and may be significant in their response to ERT. It is believed that ACE affects both blood circulation and the dominance of different muscle types (slow and fast-twitch for endurance and strength, respectively).

In Italy a study found that one ACE genotype was linked to increased muscle pain, earlier onset of disease, higher CK levels at diagnosis and faster disease progression. This might explain the difference between two siblings when one does well and the other does less well.

Stephanie Austin

Fat Infiltration into the muscle

Whole body MRI can be used to survey muscles and monitor fatty infiltration however it is not suitable for everyone because it requires lying flat for a long period.

Using MRI might be a good way to select subjects for a clinical trial. With ERT, MRI showed a slowing of the fatty infiltration in muscles with normal and high muscle-water mobility.

GAIT Analysis

Duke evaluated 22 people and found decreased speed of walking:

"Characterization of gait in late onset Pompe disease.". McIntosh PT, Case LE, Chan JM, Austin SL, Kishnani P. Molecular Genetics and Metabolism.

2116 (2015) pp 152-156.

Small Fibre Neuropathy

In LOPD some peripheral nerves have glycogen deposition. The Small Fibre Neuropathy Screen gives a figure for this. If you have under a certain score, then you have this neuropathy and a biopsy might be appropriate. SFN might be linked to mild pain symptoms such as pins and needles.

Continence

Duke have studied Lower Urinary tract symptoms and incontinence in 35 people with LOPD, average age 51. 27 had been on ERT for 54 months. They reported:

- 53% Males reported dribbling and weak stream.
- 78% Female reported dribbling and incontinence.
- 45% had bowel incontinence.

The study emphasizes the spectrum of LOPD is beyond isolated gross motor and pulmonary involvement and has a significant effect on the lower urinary tract.

Reference

"Expanding Our Understanding of Lower Urinary Tract Symptoms and Incontinence in Adults with Pompe Disease" Erin R. McNamara, Stephanie Austin, Laura Case, John S. Wiener, Andrew C. Peterson, and Priya S. Kishnani

Published online: www.ncbi.nlm.nih.gov/pubmed/25614307

Therapeutic Advancements from then to now

ERT

There are many therapeutic options with new developments in the pipeline. Current treatment standard is Myozyme. Next generation ERT are being studied.

Albuterol

This is prescribed on a case by case basis and might improve uptake of ERT.

Respiratory Muscle Training

Published results have shown regular respiratory muscle strength training can improve inspiratory and expiratory muscle strength.

Co-enzyme Q10 supplement

No published research but good reports.

Gene Therapy

ERT fails to reverse symptoms. Gene therapy aims to correct the GAA deficiency at the source. Gene therapy is unlikely to reverse symptoms due to

muscle damage. Limitations to gene therapy might include;

- Limited effectiveness
- The body can attack the vector (virus) that carries the gene.
- Toxic reactions
- Not suitable if you already have anti-bodies to the vector (virus).

Questions

Q. I take ACE Inhibitors but given what you say about ERT, do you recommend this or not?

A. At Duke we try to avoid patients taking beta-blockers along with ERT because they might reduce the efficacy of the enzyme. Propranolol decreases the efficacy of the ERT.

Q. What is the dosing criteria in the USA? All IOPD are on 40mg per kg.

A. A few adults are on 30mgs per kg or 20mgs per kg every 10 days to avoid decline in the last four days between infusions. Babies diagnosed through newborn screening are started on 20mg per kg or 40mg per kg subject to CK levels and other measures.

Q. Can I be helped to get back on to ERT, I have had reactions in the past?

A. At Duke the only reason patients are not on ERT is through anxiety. Duke team has always been able to slowly dose and increase the dose rates. If you would like to try again ask your medical team to get in touch with Duke who will help. See paper below.

"An individually, modified approach to desensitize infants and young children with Pompe disease, and significant reactions to alglucosidase alfa infusions".

El-Gharbawy AH, Mackey J, DeArmey S, Westby G, Grinnell SG, Malovrh P, Conway R, Kishnani PS.

Abstract online: www.ncbi.nlm.nih.gov/pubmed/21802969

Independent Infusions

Homecare Panel Presentation and Questions

Dawn Genders, Healthcare at Home

Dawn explained that all three companies were working to the same agenda and collaboratively. They wished to encourage independence and promote self-infusion – but only for those who wanted it. A letter introducing this important topic from the NHS was enclosed in the delegate packs (available from AGSD-UK office). There were now over 1,000 people using home treatment for LSD's. There was a cost for the drug and a cost for the Homecare service but there was a need to save some money for the group of people who needed infusions which included e.g. those with muscular dystrophy. When new drugs are introduced there is a huge cost so the NHS must be very careful who has them and there is an increasing need too. One way of saving money is to encourage self-infusion. ERT is not flexible enough. The budget goes much further if there is universal independence.

For those who could be interested in self infusion Homecare advisers would start with simple things

first such as removing the cannula. Homecare would be very flexible with their patients. Many more discussions need to be had with individuals who are interested in becoming more independent and at a pace to suit them. Infusion could be by a partner or family member or by self. The other important issue is about safety so Homecare staff would want to ensure that anyone administering an infusion was competent and safe to do so.

The benefits this provided were freedom, taking back control, knowing what is best for the individual, administering at the best time to suit and providing continuity and consistency, especially if a nurse is unable to reach you, e.g. in adverse weather.

Rene Sonders, Lloyds Pharmacy

Rene explained about the training provided by Homecare. This would be in conjunction with the hospital and all Homecare providers were using the same competency framework. There was no set time frame and full training and support was always available, there was help around ensuring infection control and training was only signed off when all parties feel confident. There are two routes:

1. Semi-independence, e.g. changing infusion bags, removing needles, etc.
2. Full independence, e.g. doing the full infusion or a family member doing it.

The training was 'step by step' with little steps to build confidence, usually starting backwards by removing the cannula, flush up, mixing drug and then inserting the cannula. There would be follow up support at any time. Homecare would be on call out of hours as well and there would be an annual review.

Alison Davies, Pharmaxo

There is no intention to force anyone to do self-infusion; just encouragement where appropriate. There is consistency across all three Homecare providers. Patients are individuals with different needs. Services will be fit and appropriate.

Questions & Answers

Q 1. What would be the consequences if no-one gave consent?

This is about making the money go further. If we are unable to release any money then we will have to reduce the support to an affordable level. This is about empowerment and choice for the individual. If there is a need, but it is not safe, then we will continue to provide a service as we do now.

Q 2. What is the protocol for mixing the drugs when I believe it should be a trained chemist?

We do not believe this to be the case. The mixing of drugs has to be done by someone competent to do so. That is the framework. Our staff are trained and we pass that training onto any individual who may be administering infusions.

Q 3. My drugs are delivered at home and made up at the home. Will this be abandoned in future?

No.

Q 4. Is it likely in future that with 3 commercial companies bidding for a contract that the one who can minimise nurse involvement is more likely to win the contract?

No, because there is a framework agreement. Contract awarding is

down to individual hospitals and it is usually spread over more than one provider.

Q 5. What if I am doing a self-infusion and I get a reaction right at the start which obviously is unexpected?

Training teaches you how to deal with any emergencies and phone support is always available.

Q 6. For those of us who receive DLA we get additional points for a nurse coming out. Will we lose this and therefore some/all entitlement if we do self-infusion?

There is a question on the PIP form, but Jane Lewthwaite said they did not give points for medical treatment but for receiving drugs and assistance which would continue to be the case. She does not see any change with the DWP.

Q 7. For someone doing self-infusion and they do some serious damage what are the consequences?

The training given includes understanding the different veins and is very detailed. Very small needles are used. It could be possible to miss/blow a vein but part of the training would be about how to deal with such an eventuality. They can't do any harm to themselves. All risks are identified during training.

You could find there is some scar damage but in such a case you are taught to go further up the vein and help is always available.

It would be a good idea as a back-up to inform your GP that you are self-cannulating so that another layer of help is available.

Q 8. When moving home, hospitals may not always change the address for another provider?

It is wise to double check that the hospital has transferred all care.

Q 9. I travelled to Germany and their medical staff were astounded that homecare was available in the UK. My experience was that drugs could not be delivered to another country.

This may be the case but if they can be then this adds to the benefit of flexibility. There is variability around care provided in the world. Canada and the USA are leaders in home care.

Homecare is not part of the label in all countries and is interpreted differently. The UK takes a pragmatic approach. The NHS is still administering homecare in the UK.

The role of the GP is changing. Many people no longer have a named GP and Super Practices are on trial where the same policy is adopted by all. This means that it is common for GP's within a practice to have no knowledge of Pompe. If you are still under a consultant, they will not give prescriptions which can make life very difficult.

WORLD ORPHAN DRUG CONGRESS EUROPE 2018

REPORT BY JANE LEWTHWAITE, ALLAN MUIR, AILSA ARTHUR AND JASON MCMILLAN

Barcelona was host to a recent conference discussing world orphan drugs. The conference brought together pharmaceutical, biotech, researchers, national health organisations and patient advocate groups. AGSD-UK took advantage of free VIP places that were offered by the organisers to Patient Advocacy Groups in Europe.

The event was designed as a series of presentations and discussion workshops, with up to 18 parallel sessions and over 40 workshops covering; clinical development, approval and access (ensuring drugs are approved and paid for by each countries government or a similar body), cell and gene therapy, science and strategy and pharmacological partnerships.

One of the main discussion points of the conference was gene therapy and how this is changing the whole industry and potentially healthcare for the future. This was a good opportunity to see and hear from other patient advocates groups, pharmaceutical and biotech companies about other rare disorders that are life-threatening and life-debilitating, the same as GSD. The likes of OTC, haemophilia, Adenosine deaminase (ADA) deficiency and Severe Combined Immune Deficiency (SCID) explained how they are progressing with gene therapy, showing amazing (sometimes miracle) results.

Another talking point was the importance of patient advocate groups. The requirement and need for patient involvement in, for example, the design and development of treatments, care programmes & clinical trials was evident. Edmund Jessop, a Medical Advisor for NHS England, mentioned that patients are always included in access negotiations for drugs, and Nick Sireau, CEO and Chair of the AKU (Alkaptonuria) Society, was encouraging patient groups to drive the research and fill the gaps. Another model of patient involvement was demonstrated by Hercules; a group of inspirational women from Duchenne UK have formed a collaboration between DUK and the pharmaceutical companies who are developing medicines to treat Duchenne muscular dystrophy. Consequently, they are in a position to provide a core base of quality evidence to speed up access and approval of these drugs through government bodies such as NICE.

Another example of patient empowerment presented demonstrated how a patient organisation for Porphyria is working hard to enable a new treatment in the UK via NICE. Patient Reported Outcomes (PRO) from trails etc are critical. Sometimes errors are made and evidence wrongly

interpreted, patient advocates can speak up and ensure their opinion about a new treatment is heard. Patients need to be unbiased and evidenced based because Approvers, e.g. NICE might think patients will push any treatment forward regardless of its value.

P.A.R.A.D.I.G.M - Patients Active in Research & Dialogues for an Improved Generation of Medicines. Until treatments were developed for AIDS, patients were never really included in discussions at all but during the 1980s they started to demand to be heard in every corner; science, industry, payers, approvers. The project will run for 2.5 years with the aim to create a framework and process for meaningful, ethical and systematic patient engagement with industry, drug developers and approvers. At the moment engagement is rather vague, ad hoc and unregulated and variable. There is a lack of trust between all parties due to lack of certainty about their roles and fears of impartiality and bias. It is hard for patient organisations to engage a lot due to lack of resources and they are busy providing daily support. The FDA might be ready to make patient engagement in clinical trial design compulsory. So PARADIGM work is needed urgently. Will patients be trained further and possibly paid to engage more? “Advocacy groups don’t know how much they are wanted, some will engage and some will not”.

Overall, the three-day congress provided considerable food for thought and provides AGSD-UK representatives with considerable understanding of the issues surrounding the development and access to new therapies. This is all good preparation for the day when the drugs, currently under development for GSDs, complete their Phase 3 trials and begin the application process for EU regulatory approval and then national reimbursement through our devolved NHS in England, Scotland, Wales and Northern Ireland. Here are some notes from some of the sessions:

Cell and Gene Therapy Presentations

The four main themes were: Clinical Development, Approval and Access, Cell and Gene Therapy, Science and Strategy. Stem cell and gene therapies appeared to dominate these discussions. Various companies gave examples of current programmes and future challenges. They are working with “development platforms” that will allow them to study other diseases, once they have successful outcomes for their current pipeline drugs.

- Vertex Pharmaceuticals discussed their CRISPR platform for gene editing. They announced that their molecular scissors have been shown to successfully correct a gene involved in a rare disease and their data allows the start of a clinical programme. “CRISPR is ready!” they announced.
- HealX have identified 250 rare diseases involving 100 million patients. They are using artificial intelligence to identify drugs and drug combinations to treat rare diseases. They encourage patient organisations to work with them.
- AvroBio have a Lentiviral Gene Therapy for Pompe Disease in the early stage of development. Their solution uses the same GILT (Glycosylation-independent lysosomal targeting) tag that BioMArin’s, now abandoned, Enzyme Replacement Therapy was using. The process involves harvesting stem cells from the

patient's own bone marrow, modifying it externally, and then replacing the gene-corrected cells after "conditioning" the bone marrow to accept them. Finding the optimal process is important because the conditioning drugs can be toxic at high doses.

Pricing, Reimbursement and Market Access Challenges of Orphan Drugs and Cell and Gene Therapies

The main take-away points from this session were:

- Autologous therapies differ from allogenic therapies in that they are personalised medicines that use a process that takes cells from the patient to develop the therapy.
- Some Autologous therapies may have a very short shelf-life, which can mean that patients must travel to a specialised treatment centre, close to the manufacturing facility. There may be only one centre in Europe.
- Autologous therapies carry a high financial risk if the patient cannot be available for treatment.
- EU Law allows patients to travel to other countries to receive a therapy, where the therapy is not available in their own country.
- Expensive therapies have been withdrawn after market authorisation for several reasons: e.g. cheaper alternatives are available, or lack of good evidence for funding bodies.
- When one or two health providers perform detailed assessments of Highly Specialised Technologies (HST), there should be little point redoing those assessments in other countries. NHE-England was cited as an example of having a high degree of competence in making HST assessments through NICE. The speaker was concerned that the EU would lose the ability to share such assessments after Brexit.
- It was suggested that the European Medicines Agency (EMA) should evolve their approval process to assist with the reimbursement decisions faced by health providers.
- Pricing policies were discussed, such as the International Reference Pricing (IRP) models used in some countries, compared with the Incremental Cost-Effectiveness Ratio (ICER) used by others. It was suggested that ethical correction factors are required to compare the net benefit for an infant against that for an adult.
- A final point drove home the fact that robust natural history data should be available at the commercial launch of a new therapy. This can best be provided by an established patient registry.

Innovative Approaches to Patient Finding in Rare Diseases

The main points from this session were:

- Currently rare genetic diseases are diagnosed through; new born screening, pedigree analysis (a family member has it), symptomatology.
- Aim to reduce time to diagnosis by; improving suspicion of rare disease and support for testing for rare disease.
- US Patient Insurance claims data is being used to analyse symptoms to predict where a rare disease might be found.
- Quantify the natural history of a disease and agree on the

top 40 clinical features then calculate the top 10.

- Identify the top three physician specialities and target those to help locate symptomatic patients.

European Reference Networks for rare disease, what are they expected to deliver?

Medical knowledge of rare disease can be sparse e.g. How can someone in Poland with a rare disease have access to specialist advice only available in Italy? 24 Rare disease ERNs each have a budget of E200,000 p.a. and bring together people or organisations with expertise to improve guidelines for disease management. Each ERN has a lead specialised hub in one country with secondary centres around Europe. There are 313 participating hospitals and 945 separate health units in the 24 ERNs. Only 22 of 66 countries are involved. ERN aim for better registries, shared research, partnering with the Orphan Drug industry, well treated patients. Sharing IT is a big barrier at the moment as well as data protection. Some countries are much more involved than others, east Europe has very few participants. For Metabolic conditions see MetabERN.

Realities of Orphan Drug Access

Aris Angelis + Panos Kanavos from London School of Economics will publish a paper on How do drugs get approved for use? in 2019.

Conclusions: A number of Social Value Judgements (SVJ) are included in approval decisions; measuring beyond simple cost and effectiveness. SVJ's might vary around Europe and this is also where PRO's become important in clinical trials. NICE uses an SVJ £ cost per QALY (quality adjusted life year) which means how many years of quality life can a treatment buy an individual? For Orphan Drugs a drug must provide £100,000 value per QALY + £30k per QALY. In Europe most orphan drugs get approved in the end but there is a delay due to price negotiation. The EMA (European Medicines Agency) works only on qualitative review of drugs, not the cost. Social Value Judgements are becoming more common in the decision process

Market Access for Gene Therapies

There are eight approved gene therapies, six are orphan drugs. Four formerly approved have now been withdrawn. There is a mismatch between information Payers need and what the Industry is providing. Payers need evidence of efficacy, sustainable budgets and price justifications. Industry is providing sales forecasts and has premium price expectations. If Industry does not adjust, gene therapy approval will suffer. Countries approach approval differently; UK decisions are based on 'value', German decisions are based on 'data', French decisions are based on 'budget'. Should the price of gene therapies be benchmarked against annual costs for orphan drugs for rare conditions? (e.g. If a GSD2 gene therapy is produced compare cost against the costs of Myozyme).

RESEARCH: AUDENTES POMPE GENE THERAPY SURVEY

LETTER FROM AUDENTES THERAPEUTICS

Thank you for your input!

In June of 2018, Audentes Therapeutics fielded a survey to the rare disease community to get to know what questions people have about gene therapy. Ninety participants from the Pompe community around the world submitted questions. We would like to thank everyone who participated; we truly value your contribution.

Each participant shared several questions – in total, the survey yielded hundreds of questions. Below is a summary of the main topics raised as well as some of the questions asked by the community

The Patient Advocacy & Engagement team at Audentes will leverage the questions from this survey to integrate the perspective of patients and their families in to the educational materials that they develop.

Audentes also shared insights from this survey with other organizations (both medical societies and umbrella patient organizations) whom are developing materials in order to guide their content.

Sincerely,

Patient Advocacy & Engagement at Audentes Therapeutics

How gene therapy works	What are the different types?
Administration	Is it injected? Where is it injected? How often?
Duration and re-dosing	How long will it last? How often do you get it?
Potential effects	Will it rebuild muscle? Is it a cure?
Potential side effects and/or risks	What are the risks? Is there a chance of rejection?
Timing	How long until clinical trials? When will it be commercially available?
Patient population	Limited to a certain age group? Is it for IOPD and LOPD?
Enzyme Replacement Therapy	Is this in combination with ERT?
Miscellaneous	What is the potential cost? Will the gene be passed on? How is the therapy developed? How does a gene therapy clinical trial work?

RESEARCH: WORLD 2019 VISIT REPORT

WRITTEN BY ALLAN MUIR

In February this year, I was accompanied by our Trustee, Rob Seaborne, at the WORLD Symposium in Orlando. The event is a showcase of ongoing research into medical treatments for Lysosomal Storage disorders (LSDs). Pompe disease (GSD 2) is one such disorder. It is also a fantastic opportunity to network with the researchers, medical teams and industry representatives working in LSD research.

Many medics and scientists within the LSD community have interests in other metabolic conditions; so GSDs are also discussed. As far as I can tell, LSDs and GSDs cover all genetic Storage Disorders, so I would like such events to cover both. However the acronym WORSD (We're Organising Research for Storage Disorders) may not be popular with the organisers!

COPA: Council of Patient Advocates

Monday morning was devoted to presentations relating to work by patient organisations and patient advocates. This year it was presented in the WorldFair format as a series of fourteen 15 minute talks. The highlight of the morning was the talk given by 15-year-old Grey Chapin who has created a support network and website for siblings after losing her sister Blair to Sanfilippo Syndrome.

www.theblairconnection.org.

Meetings and discussions

Following COPA, and throughout the week, we held short meetings with companies and researchers investigating therapies for Pompe disease and other GSDs. In each case, we were provided with an update from the organisation's representative, and we gave an update on AGSD-UK projects, including our annual conference, as well as discussing improvements to our governance and website.

I also introduced and discussed projects led by the International Pompe Association. For example, IPA are forming a Community Advisory Board under guidance by EURORDIS. It is hoped that this board will remove the need for individual companies to have their own Pompe advisory boards. There are three AGSD-UK members who sit on the CAB and I expect to be closely involved with them. Below are a few key points from our meetings.

Sanofi Genzyme – ***Gisela Linthorst, Director of Global Patient Advocacy, Rare Diseases***

Gisela is our primary Genzyme contact through the International Pompe Association (IPA). Genzyme are planning their own awareness campaign for International Pompe Day:

"We are > Pompe"

Whereas IPA are encouraging the Pompe community to send messages to a blog on the subject of:

"Moving on with Pompe"

Both encourage people living with Pompe to show how they are getting on with their lives, in spite of the condition; the IPA blog will hopefully encourage academics and companies highlight their research for future therapies and life-improving products.

Amicus Therapeutics

USA office: Jayne Gershkowitz, Chief Patient Advocate

Nita Patel, Senior Director, Patient & Professional Advocacy

UK Office – International HQ: Jennifer Wilson, Patient Advocacy & Communications Consultant, Lisa Bashorum, Senior Patient Advocacy Manager

We met twice with Amicus; one private meeting and one organised for patient representatives. In private we discussed preparations for the pivotal trial planned for their therapy ATB200; an enzyme replacement therapy taken intravenously together with an oral chaperone to stabilise the protein. UK study centres are now opening at the Royal Free, Salford Royal and National (London) hospitals. The company are working with logistics companies to prepare welcome kits for study subjects and they plan to give detailed training to the company so that they fully understand the needs of Pompe patients.

Audentes Therapeutics

Salvador Rico, Vice President, Clinical Development, Kimberly Trant, Director, Head of Patient Advocacy & Engagement, Chelsea Karbocus, Senior Manager, Patient Advocacy & Engagement

Audentes are preparing for a phase I/II clinical trial of their gene therapy for Pompe disease. They recently changed the vector being used due to safety signals of their earlier design; they expect to start clinical trials Q4 2019.

We joined a small round-table discussion with Audentes representatives and patient groups from USA, Canada and New Zealand. Audentes are very keen to engage with patients to establish which Patient Reported Outcomes (PROMs) are most suitable to build into their Pompe studies.

Ultragenyx

Kristin N. Voorhees, Senior Manager, Patient Advocacy, spent some time with me, discussing their GSD 1 and 3 pipelines:

GSD1a

Their gene therapy for GSD 1 has now dosed a cohort of 3 patients in a phase I/II clinical trial to test for safety. The results are very promising with all three showing benefit. The next cohort of 3 patients is now underway – they are all living in the US and will be dosed with three times the dose used for cohort 1. Results are expected in the summer.

GSD 3

A different approach is in pre-clinical assessment for GSD 3; mRNA being used to provide a template which liver cells will use to create a functional enzyme. This method will require frequent dosing as it provides DNA Blueprint for body to produce own enzyme, but degrades quite rapidly.

AvroBio

Fernanda Copeland, Director, Patient Advocacy (registered dietitian), Gabriel Cohn, VP, Clinical Development Lead

This was my first meeting with Fernanda and Gabriel who were very enthusiastic about leading us through their progress with lentiviral gene therapy for Fabry and Pompe diseases. Their Fabry study is showing promise and work with their Gene Therapy for Pompe has demonstrated safety and efficacy in mice. We expect that clinical studies for Pompe will be initiated in 2019.

Spark Therapeutics

Amy Fisher, Patient Advocacy Lead

Spark are planning to file their IND (Investigational New Drug) in late spring this year which will pave way for a Phase I/II clinical trial for their liver-directed gene therapy for Pompe disease. As with other companies Spark are interested in gathering information from patients about their Quality of Life (QoL) and in ideas for PROMs. They are also aware of the need for gene therapy education to alley any fears people may have about joining their clinical trials.

Amy suggested that Spark are interested in the IPA Community Advisory Board; they anticipate making use of the CAB twice per year.

It has recently been reported that Roche Holdings have bought Spark Therapeutics and so we might expect some delays in the information provided at WORLD.

Regeneron

Katherine (Kate) Cygnar, Senior Staff Scientist

Kate informed us that Regeneron are proceeding with their Gene Therapy platform but that Pompe disease may be 2 years before entering the clinic. They see their programme as providing a second-generation Gene Therapy.

They have a paper being presented at the European Society of Gene and Cell Therapy in Barcelona in October 2019; abstracts may be available much sooner.

Genethon

Giuseppe Ronzitti, Researcher, INSERM U951 and Genethon

Giuseppe spoke at our conference in 2017 and gave a presentation on secreted GAA For Pompe at WORLD. His argument was that using gene therapy directed at the liver should secrete a constant low-level of GAA in the blood, compared to the high peaks and troughs of ERT. They believe that their low dose (10^{11}vg/kg) will provide a therapy equivalent to ERT, but they are planning to dose higher (10^{12}vg/kg) to give a much-improved response. They are applying for an IND for their product SP-3006, so clinical studies could start soon.

We met with Giuseppe before his talk and it was encouraging that he is still very enthusiastic about his work with GSD 3. He acknowledged that Gene Therapy for GSD 3a was complicated as it affects both liver and muscle and that the gene fragment is very large. They are now looking at ways to reduce the active portion of the gene to allow it to be delivered by a single vector.

Valerion – ***Deborah Ramsdell, CEO***

Dr Ramsdell met with us to provide a brief update on their programme for Pompe and other GSDs. The last patient will complete their VAL-1221 study in April and they are hoping to move into their pivotal trial late this year or early 2020.

Valerion's therapy uses an antibody receptor to target muscle cells and clears glycogen in the cytoplasm as well as the lysosome. For that reason, they believe that it should be suitable for several other GSDs especially the Polyglucosan Body Diseases (GSD 4, 7, 15, Lafora) that are influenced by the RBCK1 gene.

UK Medical Teams

Visiting Orlando was also a great opportunity to meet up with many UK medical teams! I had many very interesting conversations about events planned for the GSD community in 2019.

Presentations and Posters

There were a huge number of presentations, arranged over three days; around 10 were specifically concerned Pompe disease covering:

1. Basic Science
a. Disease mechanisms, pathology and biomarkers
b. Developing therapeutic approaches in the laboratory
2. Translational Research
a. Gene therapy
b. Implementation and impact of newborn screening
c. Clinical trial readiness: Pre-clinical trial methods and studies
3. Clinical Trials
a. Clinical trials for registration
b. Clinical outcomes

Each day of presentations was accompanied with a fresh set of posters. There were about forty directly relevant to Pompe disease, showing the phenomenal interest that has grown in Pompe disease since ERT was commercialised.

CATS: CORI ACTION TEAM SUPPORT

CATS is a group of patients and carers who met back in the spring and with much encouragement and advice from Jane Lewthwaite, decided to launch a support group for with those with GSD 3 (Cori Disease). Our members are: Ailsa Arthur, Nikki Christie, Sylvia Wilson, Gary, Andrea and Lauren Thompson. Ailsa is also a trustee of AGSD-UK and Sylvia is the GSD 3 Coordinator.

We are spread throughout the UK and have various experience of GSD. As well as offering support to individuals and families we aim to recognise and promote the needs of the Cori community with medical staff.

We made our public debut at the conference in October with Lauren bravely speaking to the hepatic workshop about issues that have affected her. We do have another CAT in our group. 'Cori the Cat' has been adopted as our mascot and we hope to put him to some good work very soon. Watch this space!

CATS can be contacted through AGSD-UK. We need to confirm how many people have GSD 3 in the UK, what centres they attend and encourage them to register with AGSD-UK. CATS aims to describe the needs of our community. We are concerned about how many isolated people are struggling. So, please update your details by registering through our website, and make sure you are in touch with AGSD UK. If you are not, we cannot contact you and represent you.

Registration link: https://agsd.org.uk/help-us-help/register-or-join/

Membership costs just £15 per year, that's just 4p per day!

WALKING EVENTS SUMMER 2019 IN PEMBROKESHIRE

Gabi (Germany) and Stacey (Canada) above Bosherton Lakes next to our base.

Dan (USA) and Charlie (UK) take a break on a walk along the South Pembrokeshire Coast.

We are all set for this summer's Walking Course and the Children & Parents event. They will both be held in the Pembrokeshire Coast National Park, in the south west Wales. The walks will be well away from the usual high mountains of Snowdonia, and will include coastal walks, cliffs, beaches, estuaries and rivers. Probably with at least one hill thrown in.

We shall be staying at the National Trust Stackpole Centre, at Bosherton Lakes, where we have stayed twice before. It's a beautiful spot close to the lakes and with easy walking from the door around the lakes and to beaches, cliffs and a small harbour. This time the walking course will be in a larger unit so we could take up to 20 people. The dates are 19 to 26 July for the Walking Course and 24 to 28 July for the Children & Parents event.

This will be our ninth year of running the Walking Course and people have attended from all over the world, about 20 countries in all.

You don't need to be a super athlete to attend, you just need to be able to get into "second wind". There is always a wide range of people of differing backgrounds, experiences and fitness levels. It is a friendly, understanding, informative and supportive atmosphere and everyone is helped to improve their fitness and extend their boundaries.

Full details and a booking form are on the website. If you have any questions, please contact Andrew Wakelin on type5@agsd.org.uk.

CHANGES OF STAFF AT THE MCARDLE CLINIC

We are very pleased to welcome two new staff at the McArdle Clinic in London, Clinical Nurse Specialist Maria Patasin and service manager Yasmin Begum. They both started in January replacing Suzanne and Helena respectively, after they moved on last year.

The clinic is also recruiting a clinical fellow. This is a really important development to secure and expand the service. Since it moved to Queen Square, London, in 2011, having originally been in Oswestry, it has expanded from around 40 patients to over 220. The clinic also sees people with the other even more rare muscle GSDs, though not GSD2 (Pompe) which has its own services. In recent years, it has been difficult to schedule follow-up appointments as frequently as patients would like, and hopefully this can be addressed once the clinical fellow is in post.

The clinic is part of the Medical Research Council's Centre for Neuromuscular Disease, and is involved in research projects for McArdle's and other muscle GSDs.

Some members of the team at the McArdle clinic, led by Dr Ros Quinlivan

OTHER NEWS FROM THE MCARDLE'S WORLD

International workshop on nutrition

IamGSD hosted an international workshop on the future of nutrition in McArdle disease, which was held in November at CNMD, Queen Square, London, and chaired by Dr Ros Quinlivan.

The workshop was attended by three board members from IamGSD – the President, Stacey Reason (Canada), Jeremy Michelson (USA) and Andrew Wakelin (UK). Researchers and clinicians involved with McArdle's came from Denmark, Germany, Italy, the Netherlands, UK and USA, plus a US doctor and a dietician working with low carb diets, and one of the dieticians from the London Clinic.

It is anticipated that a paper reporting on the workshop will be published in Neuromuscular Disorders, the journal of the World Muscle Society.

US conference and walking course, Houston

Do you fancy a trip to Houston, Texas? IamGSD board members are planning to present at the AGSD US annual conference over 5/6 September 2019. It is hoped there will be a good attendance of people with McArdle's.

The plan is to add a few days to the end of the conference to run a short walking course based at the same hotel. This will be a great opportunity to meet others and to share experiences of walking with McArdle's.

Map of UK McArdle patients is back!

Following the redevelopment of the AGSD-UK website and the change in software, our map of UK McArdle patients went off-line. But now it is back and better than ever. You will find a link to it in the McArdle's "Information & Support" section of the web site.

To preserve privacy patient's locator pins are by default anonymous and are plotted only by the postcode district rather than the full postcode – ensuring that they are only in the approximate area and not accurately located to a street.

If you would like your name and your email address, telephone, mobile or Facebook ID shown on your pin, please confirm those details to Andrew on type5@agsd.org.uk. You may also choose to have your pin located to your full postcode if you prefer.

NICK PEARSON'S MOBILITY SCOOTER

WRITTEN BY ALLAN MUIR

Whilst talking with Nick Pearson during a film shoot for Amicus Therapeutics, he told me about his pride and joy; a pimped-up scooter that was colourfully painted by his mates in Ripon. "When I got a scooter I didn't want it to be boring; I wanted to make a point that having a scooter can be fun". He later added that "if it wasn't for the scooter, I would have not been able to get out of the house!".

In case you're wondering, the Amicus film we both appear in is to provide people with information about taking part in clinical trials. It will first be shown in the USA, but may be shown elsewhere in the future. I can confirm that it will not be called "Extraordinary Measures II", and we're not expecting any Oscar nominations.

WENDY HOUSE NURSERY SIGNS UP TO JEANS FOR GENES

CATS member Nikki Christie asked friends and family to fundraise for AGSD-UK via the national Jeans for Genes event that takes place every September.

ASGD-UK is registered as a partner, which means that when a business, company, school or nursery registers with the scheme, they can ensure that half of all donations come to us. That is the important part of course.

It is so simple, just register, promote the whole week or select one day then get as many people as possible to wear jeans to work or school and pay a 'forfeit' or make a donation. Make the day more fun and maximise the income by adding in a bric-a-brac sale or a raffle.

Jill Chiles, owner of the Wendy House Nursery in Erdington said, " It was easy to register with Jeans for Genes and we will make sure we have fun in September to raise money for AGSD-UK'.

Could you do the same as Nikki? You could ask friends, employers, schools or any group to wear denim for AGSD-UK

Posters and fundraising packs are available from Jeans 4 Genes website:

https://www.jeansforgenesday.org/sign-up

NHS LONG TERM PLAN

WWW.LONGTERMPLAN.NHS.UK

On 7th January, NHS England published its long-awaited long term NHS plan, setting out the strategic objectives for the NHS over the next 10 years.

As medicine advances, health needs change and society develops, the NHS has to continually move forward so that in 10 years' time we have a service fit for the future.

The NHS Long Term Plan is drawn up by frontline staff, patient groups, and national experts to be ambitious but realistic.

The plan states that the NHS can now be future-proofed for the decade ahead because of the new "secure and improved funding path", consensus on the changes needed, and work launched since the NHS Five Year Forward View is "beginning to bear fruit".

The plan is split into seven key sections:

1. A new service model for the 21st century
2. NHS action on prevention and health inequalities
3. Quality and outcomes
4. Workforce
5. Digitally-enabled care

6. Efficiency
7. Next steps (including legislative change)

One particular paragraph that holds some hope for improved diagnosis of GSDs states:

We will focus targeted investment in areas of innovation that we believe will be transformative, particularly genomics. The NHS will be the first national health care system to offer whole genome sequencing as part of routine care. As part of the NHS' contribution to the UK government's broader aims to reach five million genomic tests and analyses over the same timeframe, the new NHS Genomic Medicine Service will sequence 500,000 whole genomes by 2023/24. This builds on the legacy of the ground-breaking 100,000 genomes programme, that was made possible because of the unique partnership between Genomics England and the NHS. This project is already delivering results for patients, with early indications that at least one in four people suffering from a rare disease will have a diagnosis they would not previously have received. As part of this ambition, during 2019, seriously ill children who are likely to have a rare genetic disorder, children with cancer, and adults suffering from certain rare conditions or specific cancers, will begin to be offered whole genome sequencing.

SPORTS AND REMEDIAL MASSAGE TECHNIQUES

Effectiveness of Sports and Remedial Massage Techniques for Pompe Patients.

Sports Massage is commonly known as a therapy for athletes but it can also help to treat people with chronic diseases. Many doctors, consultants and other medical professionals recognise Sports Massage as a well-established, respected and beneficial therapy. The Benefits of Sports massage:

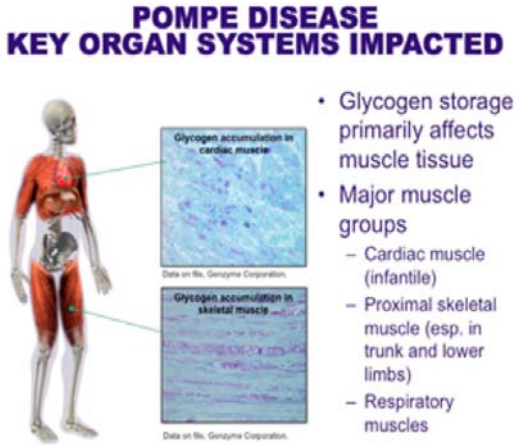
- Improves circulation;
- Lowers blood pressure;
- Enhances immune system;
- Improves muscle and joint flexibility;
- Relieves muscle aches and stiffness;
- Promotes deeper and easier breathing;
- Improves digestion and elimination;
- Helps relieve tension headaches;
- Improves muscle tone;
- Reduces swelling (oedema).

As a Sports Massage Therapist I treat a variety of people. These include professional athletes, musicians, office workers and also people with different medical conditions such as MS, Chrohn's Disease, Fibromyalgia and cancer and stroke patients. Each condition is different and affects people in different ways.

Sports massage for a patient with Pompe Disease case study.

One of my patients is a 43 year old gentleman with a history of Pompe Disease (Glycogen storage disease type II or Acid Maltase Deficiency). Pompe Disease is an autosomal recessive metabolic disorder which damages muscle cells throughout the body. The build-up of glycogen in the muscle cells causes progressive muscle weakness (myopathy) throughout the body and can affect various body tissues, particularly in the heart, skeletal muscles, liver and nervous system. The patient receives an enzyme replacement therapy (ERT) fortnightly as an IV and has associated significant myopathy, diaphragmatic weakness and relies on NIV (non-invasive ventilation) to breathe for approximately 20 out of each 24 hours. The patient is a full time wheelchair user and is unable to stand unaided.

During my assessment it was evident that the patient does find it difficult to complete long sentences and had adopted noticeable compensatory head movements to help assist his breathing when not using the ventilator. He presents with significant fatigue and find his activities very effortful. The patient feels that at present the weakness in his chest is the most debilitating and the effect this has upon his breathing is significant. He has tightness through the intercostal muscles and this affects his back, neck and shoulder health. Due to the lack of oxygen and overuse of muscles in general, the patient experiences cramps in his lower limbs. The muscles felt very weak, tight and tender when I performed palpation test. Visually muscular imbalance is obvious with muscles weakened towards the centre of the body, a pattern consistent with Pompe.



In Pompe the major muscle groups are all affected but this patient has particular difficulties with breathing and mobility. As this is a particularly complex case affecting the body as a whole I decided to prioritise. The patient complains of fatigue, muscle tightness and aching and is dependent on a non-invasive ventilator to breathe most of the time, so I started work on the main respiratory muscles (diaphragm, external intercostal and scalene muscles), and accessory breathing muscles of the neck and chest which the patient over uses. I combined this with working on the shoulders and upper back as these were restricted and also affect breathing.

After a thorough consultation and muscle tests I created a treatment plan and gave my patient 4 massage treatments of approximately 60-80 minutes in length each over a 2 week period. During the four treatments I worked mainly on massage of these muscles with a view to continuing treatment of other muscle groups later on as this is a particularly unique and complicated patient. My patient made use of his non-invasive ventilator throughout the treatments.

In addition to my massage techniques I used Muscle Energy Techniques aka MET.

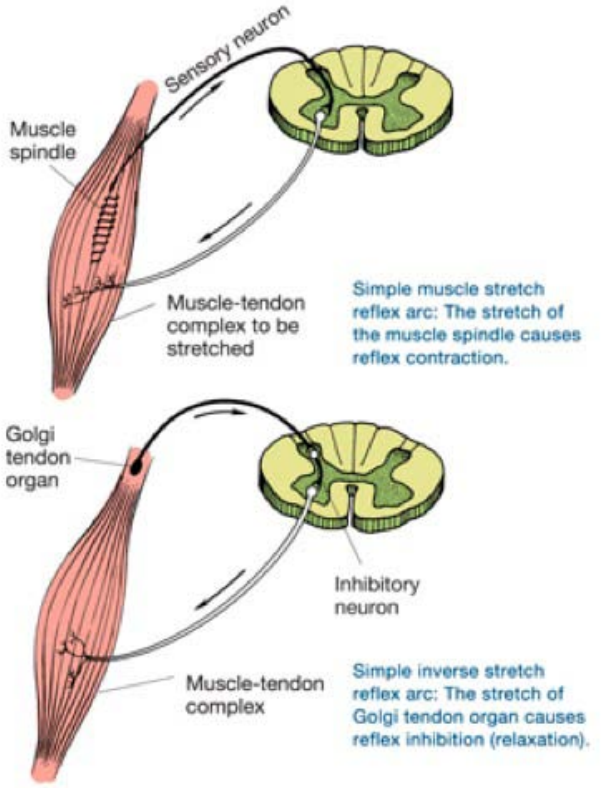
MET is a manual therapy that uses the gentle muscle contractions of the patient to relax and lengthen muscles and normalize joint motion. This process of lengthening shortened or spastic muscles to improve weakened ligament and muscle strength, aims to directly improve range of motion. This procedure is performed when a patient is asked to contract a muscle for approximately 5 seconds against a resistant force applied by the massage therapist. The muscle contraction is performed by the patient 3 to 5 times in a row with a view to stretching the muscle further each time.

The main aims of the treatment in this case:

- Relieve acute and chronic muscle pain,
- Improve lung capacity by relaxing any tightness in the respiratory muscles
- To slow down the rate of respiration due to the reduced stimulation of the sympathetic nervous system.
- Improve the range of motion and flexibility,
- Increase energy and stamina,
- to treat muscular imbalance and damage in deep tissues minimising the risk of further damage.

To aid to the massage effectiveness the patient was given homecare advice with adapted stretches and resistance exercises using an elastic band.

During research of the patient's condition, I realised that some of my initial aims (for example, slowing rate of respiration and increasing range of motion) were perhaps a



little optimistic and that the considered wisdom on this rare progressive condition is that the best outcome is often to maintain the patient's current ability and prevent further muscle damage. This can often mean that specific test results don't seem to improve much, especially over a short

period of time such as the 4 treatments that were available for this case study. I intend however to continue treating the patient as we both feel that a longer-term treatment plan will be of benefit. Generally massage improves muscle tightness and aching and enables the patient to have a more comfortable quality of life.

Although I wasn't expecting a great improvement in any one area I was pleasantly surprised that the Range of Motion and Quality of Motion retest showed a 5% increase in the neck.

As the client has severe muscular problems in every area of the body, I intend to continue the work I have already done on the muscle groups mentioned above but combine this with work on the arms and legs as these are particularly stiff and I feel that sports massage, MET and gentle exercise will actually help to improve the patient's mobility and quality of life going forward.

The patient is continuing his Enzyme Replacement Therapy but he feels that the right combination of massage, exercise and diet is of as much benefit as his ERT. We are finding ways of managing his exercise so that he can maintain a level of activity that is on-going and not too tiring in combination with his daily activities.

Listening to the individual in this case was paramount as in addition to Pompe Disease being extremely rare each Pompe patient is different due to the nature of muscle wasting. Moreover, there is next to no research or writing on the subject of Sports Massage for Pompe Disease. The patient felt that a combination of hands on therapy, traditional physio and ERT are of great benefit.

Due to the patient's fatigue I feel that a shorter less tiring treatment, given more often, is of more benefit to this particular condition than the normal routine. The aim of treatment ended up being to help the patient feel more able to move and use his muscles, therefore preventing the vicious cycle of underuse, tightness and fatigue.

Patient's Feedback:

"After the treatment my muscles felt more relaxed and looser than normal, as they are normally tight and achy feeling. I performed all of the stretches 3 times a week. These took around 15 minutes. After stretching generally I felt looser and more relaxed than before, although actively these are hard work for me. As long as I work within my limitations and don't overuse my muscles, this is of benefit to me.

I found some of the exercises difficult to do alone as my muscles are too weak by themselves to get the limbs into the positions needed. Also once in those positions sometimes it didn't feel like a stretch in the correct place probably because my muscles are very small or imbalanced. I felt the MET was of much more benefit to me because having someone else to resist against makes things a lot easier.

Generally my muscles feel achy by the evening, after a day of sitting without moving that much, and the MET is a good way of using the muscle to stop it aching without overworking it and it being counter-productive.

After the treatment my muscles feel like they have been used in a good way and that the aching perhaps due to toxins or underuse has subsided. They feel a lot looser and it was easier to move afterwards."

GIVE AS YOU LIVE

Donations to AGSD-UK from online shopping

Give as You Live

Did you know you can raise free funds for us every time you shop online? Simply shop via “Give as you Live” and each purchase you make will raise money for AGSD-UK!

www.giveasyoulive.com/join/agsd-uk

Already signed up?

Check that the Give as you Live extension is enabled in your browser; its bar should appear at the top of shopping pages. If its missing, you may need to reload it by visiting:

www.giveasyoulive.com

AMAZON SMILE

AmazonSmile is an alternativeway for you to collect donations for AGSD-UK every time you shop, at no cost to you.

To shop at AmazonSmile simply go to smile.amazon.co.uk from the web browser on your computer or mobile device.

You use the same account on Amazon.co.uk and AmazonSmile. Your shopping cart, Wish List, wedding or baby registry, and other account settings are also the same.

On your first visit to AmazonSmile, you need to select AGSD-UK to receive donations from eligible purchases before you begin shopping. Amazon will remember your selection, and then every eligible purchase you make will result in a donation.

LEGACIES

Leaving a legacy

A legacy is a wonderful way to ensure that we can continue our vital work. It can also be a valuable way of reducing inheritance-tax liability on your estate, because a legacy to a registered charity such as AGSD-UK is tax-free.

Whatever their size, bequests can make a big difference. Thanks to the kind support of our legacy givers, we can plan our future work and provide support to persons affected by Glycogen Storage Disease and their families in the UK.

For more information please contact our Droxford office.

FUNDRAISING IDEAS

www.agsd.org.uk/help-us-help/fundraise-for-us/

Our website has a list of organised fundraising events for which AGSD-UK has places. Notably we have 22 places in the annual cycling event in London and Surrey Hills on August 4th. Places are still available so please contact the office if you know a willing cyclist; we need to sign them up before the end of May.

There are also many fun runs around the UK for which we can provide places; look for the Big Fun Run on our website.

Of course, you may have your own fundraising ideas, and we can help you by providing T-shirts, leaflets and collection tins or buckets.

Facebook Donations

We are aware that people are inviting a growing number of donations to AGSD-UK through Facebook, instead of receiving birthday gifts or other reasons. Unfortunately, due to privacy restrictions, we don't always know who created the event, so we can't thank them as we would like. So, I would like you all to know that we really do appreciate your wonderful support for the Association.

Halloween Cones

A great example of raising funds at work was brought to my attention by Lydia Parmenter who joined with colleagues at the Nationwide Building Society to sell Halloween Sweet Cones on behalf of a boy with GSD. £226 was donated to AGSD-UK as a result of their efforts.

AGSD-UK Calendar Sales

Many thanks to Gemma Seyfang for organising our calendars, and everybody who helped to sell them. We made a very nice profit of £500. We still have a few copies left over with nine months of the year left to enjoy them.

Jeans for Genes Day

20th September 2019

If your school or workplace has not held a J4G Day in the last 3 years, AGSD-UK may be able to sign them up, as we are a Charity Partner in the scheme. If that results in your school or workplace raising funds on Jeans for Genes Day, AGSD-UK will be awarded 50% of the total raised.

Please contact the Droxford office, or email info@agsd.org.uk, for information about how you can approach schools or organisations to take part. More details about the scheme are on the Genetic Disorders UK website:

www.geneticdisordersuk.org/partnershipnetwork/

https://www.jeansforgenesday.org/sign-up

Dress Down for GSD

There are often other opportunities for schools and workplaces to raise funds for AGSD-UK directly, for example by holding a special casual dress day for the charity or by nominating AGSD-UK as their “Charity of the Year”. Please do ask head-teachers or businesses on our behalf, if you get the chance.

CONTACTS

The AGSD-UK Ltd is managed by a Board of Trustees elected by its members at the AGM held each year during our Annual Conference.

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If you have anything interesting for the newsletter we'd be very pleased to hear from you.

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Glisten

Glycogen Storage News

AGSD UK
Association for Glycogen Storage Disease

SPRING 2019