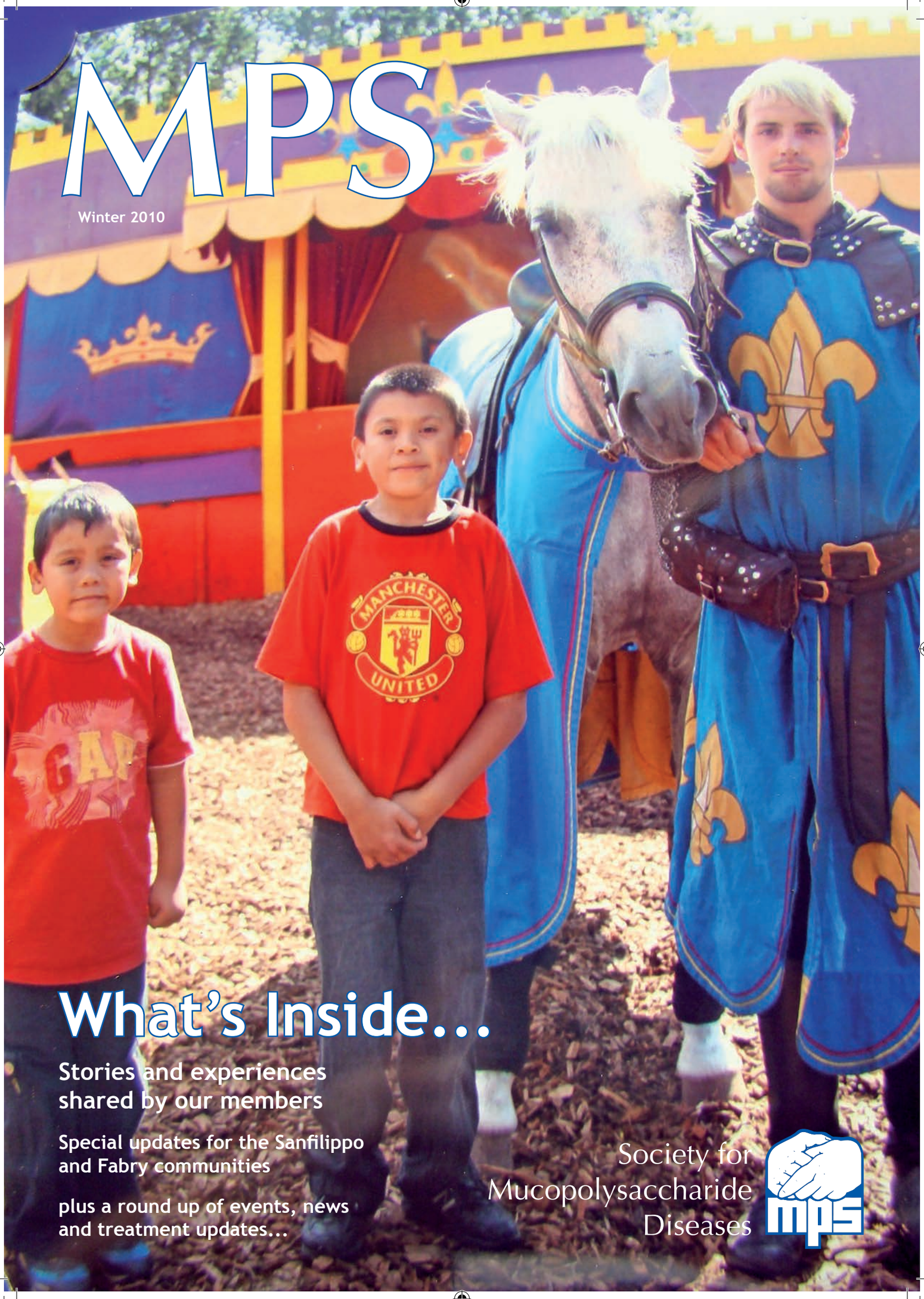
MPS

Winter 2010



What's Inside...

Stories and experiences shared by our members

Special updates for the Sanfilippo and Fabry communities

plus a round up of events, news and treatment updates...

Society for Mucopolysaccharide Diseases

mps

Please donate to
www.mpssociety.co.uk,
phone 0845 389 9901
or post your donation
to our office, MPS House.

The MPS Society

Founded in 1982, the Society for Mucopolysaccharide Diseases (the MPS Society) is the only national charity specialising in MPS and Related Diseases in the UK, representing and supporting over 1200 affected children and adults, their families, carers and professionals. The MPS Society:

Acts as a **support network** for those affected by MPS and Related Diseases

Brings about more **public awareness** of MPS and Related Diseases

Promotes and supports **research** into MPS and Related Diseases

MPS & Related Diseases

Mucopolysaccharide (MPS) and Related Diseases affect 1:25,000 live births in the United Kingdom. One baby born every eight days in the UK is diagnosed with an MPS or Related Disease.

These multi-organ storage diseases cause progressive physical disability and in many cases, severe degenerative mental deterioration resulting in death in childhood.

At present there is no cure for these devastating diseases, only treatment for the symptoms as they arise.

Where does your money go?

A donation of *£2 per month* could help us to offer so much more support in so many ways:

Access to clinical management and palliative care

MPS Regional Specialist clinics

Support with disability benefits

Paving a child's way in accessing education

Upholding rights in employment

Advising on home adaptations

Bereavement support

Front cover photo: Sam Jamil (ML III) and his brother Ed at the MPS Camelot Weekend 2010.
For their full story please see page 16.

Society for Mucopolysaccharide Diseases

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Magazine Deadlines

Spring	1 Mar 2011	Summer	1 Jun 2011
Autumn	1 Sep 2011	Winter	1 Dec 2011

Friend of MPS

Become a Friend of MPS to receive the Society's magazine and fundraising newsletter plus a range of other benefits. Contact us for more information.

IN THIS ISSUE...

Winter 2010

MPS Children's Newsletter

Enclosed with this magazine is the Winter 2010 edition of the MPS Children's Newsletter. We are so pleased to have heard from everyone who sent us their articles.

Eliza who tells us what life is like living with her brother Isaac who has Hurler.

Zack has written in to tell us all about what he's been up to over the past few months...and he's been very busy!

Aaryanna and Jasmine's mum Helen wrote in to tell us how the girls loved their sparkling reindeer food and George Bell's Mum tells us what her little boy and his friend Charlie did to raise money for the MPS Society.

In this edition you can also find out how you can help us celebrate MPS Awareness Day on 15th May 2011.

We love reading your articles so get in touch and tell us all about you! You could write an article about you and your brother or sister, tell us all about what you're doing at school or about your after school clubs and hobbies. Why don't you do a drawing of you and your brother or sister and send it in to us? You could also write a poem about what it's like for you or your brother or sister to have MPS or a related disease.

Whatever you want to share with us you can send it to:
MPS Society, MPS House, Repton Place, White Lion Road, Amersham, HP7 9LP or you could email us at:
newsletter@mpssociety.co.uk. Please remember to get permission from your parents or guardian first!
We can't wait to hear from you all!

A message from the Chief Executive

Winter came early to most in the United Kingdom but it did not stop the MPS Society, as part of the UK Lysosomal Storage Disease (LSD) Patient Collaborative, being in the European Parliament in Brussels on 2 December to co-host the 'Rare Neurological Diseases in Childhood' meeting. The aim of the meeting was to acknowledge the growing interest of the European Commission in both rare and neurological diseases and demonstrating the unity of intent of the LSD Patient Associations, the pharmaceutical industry and the scientific community. The message was clear – that lessons learned from in-depth research conducted into Lysosomal Storage Diseases will provide important information for the treatment of more common neurological disorders.

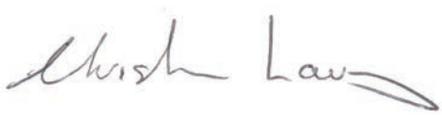
This collaborative effort is all part of the MPS Society's determination to find the answers for the MPS and related diseases with progressive neurological disease. The University of Manchester MPS Stem Cell Group are continuing to make significant progress in understanding the role of substrate inhibitors principally Genistein. Further on in the MPS Magazine is the paper just published by Dr Brian Bigger et al 'Genistein Improves Neuropathy and Corrects Behaviour in a Mouse Model of Neurodegenerative Metabolic Disease (Sanfilippo)'. The UK MPS Society funded the first three years and in a global collaborative spirit ten MPS Societies jointly funded the fourth year.

Where does this lead us? Well the work does not stop here. The MPS Society has been most fortunate to have received a grant of nearly half a million pounds from a high net donor to fund the next three years of Sanfilippo research pursuing a preclinical research project focused on evaluation of combined enzyme and substrate reduction therapy and evaluate new surrogate and clinical outcome measures. These will be used in the application to develop genistein as a clinical therapy and perform a clinical trial of this compound in patients with Sanfilippo A, B and C disease.

Going into 2011 this is where we need your help. The clinical trial will cost in the region of £500,000 to £800,000. The MPS Society needs to raise at least £300,000 and is turning to Sanfilippo families and supporters not just in the UK but around the world to help us. When donating to the 'Genistein Clinical Trial Fund' please make sure your communication clearly states Genistein Research.

Thank you to everyone who sent in suggestions for the content of the 'MPS Weekend Conference' to be held 24 – 26 June 2011 at the Hilton Hotel, Northampton. The programme is enclosed with this Magazine and I hope you will agree there is something for everyone whether you be at the beginning of your MPS journey, someway down the route as a parent, or an adult with MPS or a bereaved family. Apart from the one Fabry and two MPS Symposia on Saturday, for bereaved families there is a lunch out followed by a visit to the Childhood Wood returning to join everyone for the MPS 30th Anniversary Gala Dinner. On Sunday, as well as the three half day symposia for Fabry and MPS, we are offering two workshops, one on Palliative Care and End of Life and the other for bereaved families. The children and vulnerable adults take centre stage with their own amazing activity programme cared for by a huge team of dedicated volunteers.

As we move into the New Year our thoughts are with all our members and their families, the doctors, nurses who care for them and all those making a difference for those affected by Fabry, MPS and related diseases.



Christine Lavery
Chief Executive

Winter 2010

Management Committee Update

The Society's Board of Trustees meet regularly. Here is a summary of the key issues that were discussed and agreed at the Management Committee Meeting held 3-4 September 2010.

The Trustees reviewed and approved 23 policies and agreed that the Society's policy on Human Embryo Research is no longer needed. The Trustees approved the Charity Commission Annual Return document. The Chief Executive reported that there is one place available on the Board for co-option and that a Fabry member had expressed an interest in joining the Board. It was agreed to invite the individual to attend the February 2011 Management Committee as an observer.

PERSONNEL
Trustees were advised that the two new advocacy support officers have settled in well and found their exposure at the MPS III Expert Meeting very beneficial to their working practice.

RISK MANAGEMENT
The Trustees agreed that there should be no changes to the Risk Management Register at this time. The Trustees were also advised that the four senior managers all have remote working access. Sue Cotterell spoke to her Health and Safety report and explained the steps in place to ensure the management of health and safety continues to run smoothly whilst she is on maternity leave. Trustees were advised that the Events and Office Administrator will take on the role of managing health and safety during this time.

JEANS FOR GENES
The CEO appraised Trustees of the current situation with regards to Jeans for Genes. The legal advice sought following the last Management Committee and the transition offer from the trademark holders CGDRT would result in the Society benefiting from the 2011-2013 Jeans for Genes campaigns in a small way.

CLINICAL MANAGEMENT
The Chief Executive reported that the Henry Smith Charitable Trust has awarded a three year grant for a transition worker and that Qidis funding from the National Commissioning Group has also been awarded to the MPS Society to work collaboratively with the other UK lysosomal disease groups to develop a national model of transition.

The Trustees congratulated Dr Atul Mehta and Dr Lionel Ginsburg, specialists in Fabry disease at the Royal Free Hospital London, on both being made Professors.

The Chief Executive advised Trustees that Alison Wilson had been appointed to the All Ireland Advocacy Support Officer post shared with the Primary Immunodeficiency Association (PIA). Alison will be based at Belfast City Hospital and works closely with the MPS specialists throughout the whole of Ireland.

The Trustees received advice from the CEO and Prof. Bryan Winchester on the proposal to provide advocacy support to families affected by Metachromatic Leukodystrophy (MLD). MLD is related to the mucopolysaccharide diseases and currently these patients have no dedicated patient organisation to meet their needs. It was agreed unanimously that as of 1 January 2011 the Society would offer the same services to this group of patients as it does to those with the other 23 MPS and related disorders.

NO MORE RESEARCH AND SUPPORT MONEY FROM JEANS FOR GENES

On 31st March 2011 the partnership agreement between the MPS Society, the Primary Immunodeficiency Association (PIA), Great Ormond Street Children's Charity (GOSHCC) and the Chronic Granulomatous Disease Research Trust (CGDRT) comes to an end. The partnership has been together for 15 years and it was immensely disappointing that the trademark holders CGDRT have withdrawn the use of the Jeans for Genes trademark and plan to run Jeans for Genes for themselves. The Trademark holder, CGDRT, initially offered MPS, PIA and GOSHCC a three year transition agreement that meant we would each receive a small percentage of the income raised from the 2011, 2012 and 2013 campaigns but at the eleventh hour just as the agreement was about to be signed CGDRT, the trademark holder, withdrew the offer of the transition agreement.

This means MPS has to find new avenues to raise significant funds for research and advocacy support. Not an easy task in this financial climate. If, as an MPS family or supporter you, your child's school, business or friends have raised funds for Jeans for Genes in the past you may like to tell them that ***MPS DOES NOT BENEFIT FROM JEANS FOR GENES ANY MORE***. Clearly we need to find new sources to raise the funds we used to receive from Jeans for Genes so if you, your friends, your business or your child's school wants to support MPS please let us know. They may also be reassured to know that compared to Jeans for Genes' where in excess of 75% is spent in administrative costs, the MPS Society spends over 85p in the pound in direct charitable costs supporting our members.
Please spread the word and think MPS.

New faces at MPS

SASKIA SANTOS

I joined MPS in October 2010 to cover for Sue Cotterell's maternity leave, working as Personal Assistant to the Chief Executive. I'm certainly enjoying this very busy and varied role supporting Christine with her diary commitments, travel and general workload. I often wonder where Christine gets her endless energy from and hope it will rub off on me!

I have worked as a PA for nearly 20 years, (gosh that makes me sound old!) but from all types of industries from Software Companies, Car Dealerships to Educational Publishers so it is a refreshing change to work for MPS.

Outside of MPS I am a single mum with a gorgeous 10 year old daughter Eliscia, who makes me very proud to be her mum. When I get the chance I love to go ceroc dancing, get down the gym and in warmer weather go waterskiing.

I feel honoured to work for MPS and am so inspired hearing members' stories and am looking forward to meeting some of you during my time here.
Saskia Santos s.santos@mpssociety.co.uk

New service offered by the MPS Society to those affected by Metachromatic Leukodystrophy

With immediate effect the Society for Mucopolysaccharide Diseases is delighted to welcome members with Metachromatic Leukodystrophy (MLD). We invite anyone who is affected by this disease, or professionals working with those affected, to contact us. We have a new Advocacy Support Officer who will be dedicated to supporting individuals and their families affected by MLD and so this will not affect the current service already provided by the MPS Advocacy Team to those affected by MPS and Related Diseases.

For further information
please contact the MPS Advocacy Team by phone on **0845 389 9901** or email **advocacy@mpssociety.co.uk**

TINA BOUGH

I joined the Society at the end of November as an Advocacy Support Officer, specialising in Palliative Care and Bereavement, I will be working closely with MPS lll and ML ll.

I have recently worked for the ambulance service as part of a frontline crew. Prior to this I took a career break in order to bring up three children, two of which suffered an undiagnosed neuro-degenerative disease. I feel I have some understanding of the unique challenges and complexities that families and affected individuals face and have come to enjoy overturning poor practice and policy decisions!

I enjoy travel and have a long list of countries still to visit, I am also a keen rugby fan and enjoy days out at Twickenham and Adams Park to see Wasps play. I enjoy listening to anything from Genesis and Aerosmith to David Grey.

I am really looking forward to working for MPS and having the chance to meet with you all, learn from you and support you in as many ways as I can.
Tina Bough t.bough@mpssociety.co.uk

This post is part funded with thanks to Roald Dahl's Marvellous Children's Charity.

Congratulations to Sue and Steve Cotterell
on the birth of their baby daughter, Celeste, weighing 7lb 12oz on 13 November 2010

All Ireland Advocacy Service

In August 2010 the MPS Society, as part joint venture with the Primary Immunodeficiency Assocation (PiA), expanded their Advocacy Support Team (AST) to include a dedicated All Ireland Advocacy Support Officer. Through this venture we have also strengthened our links with the Irish MPS Society as we work to provide support to individuals with MPS and related diseases in Southern Ireland.

Alison Wilson is based in Belfast City Hospital and works jointly for the MPS Society and the Primary Immunodeficiency Association; as well as providing one day per week of genetic counselling for the Belfast City Hospital Trust.

The aim of setting up this service was to ensure that MPS Society members living in Ireland would have access to a Advocacy Support Officer with specialist local knowledge and the ability to carry out home visits when required. So far the service has been welcomed by the members who have got in touch.

Please look out for an extended report on the All Ireland Advocacy Support Service in the next MPS Magazine, including some testimonials from members who have made use of the service; an update on the newly established Fabry Clinic in Belfast; a report on the latest MPS regional clinic; and a word from Alison about the future plans for the All Ireland Service.

ALISON WILSON

I am a new member of the MPS Society's Advocacy Support Team.

I am based in Belfast City Hospital (Northern Ireland) and my role is to provide an Advocacy Support Service to MPS Society members in Northern Ireland. I also work closely with the Irish MPS Society in providing Advocacy Support to individuals diagnosed with MPS and related conditions in Southern Ireland.

As I am sure you are all aware, the MPS Society have an established Advocacy Support Team whose aim is to meet the needs of their members throughout the UK. It was however felt that our Northern Ireland members might benefit from having a locally based Advocacy Support Officer who is more readily available for home visits and attendance at important meetings and clinic appointments.

As a new-comer to the MPS Society I have been delighted to witness the care and support shown by the other members of the Advocacy Support Team to the MPS Society members. I only hope that I can mirror this level of care and support in this new role; and I trust that having a locally based Advocacy Support Officer will be of benefit to the MPS Society members in Ireland.

Do you need help or advice from the MPS Advocacy Team? Phone us on 0845 389 9901 or email **advocacy@mpssociety.co.uk**

Congratulations to Alison and Andy Wilson on their marriage on 15 November 2010

WHAT'S ON 2011!

REGIONAL

Post Christmas blues Party, Scotland
23 January

CONFERENCE EVENTS

MPS National Weekend Conference
24 - 26 June
(Please see enclosed booking form)

AWARENESS EVENTS

MPS Awareness Day
Sunday 15 May
Whipsnade Zoo
(Please see enclosed booking form)

For more information about how you can help us celebrate MPS Awareness Day, please visit **www.mpssociety.co.uk**

MPS REGIONAL CLINICS

Birmingham clinic: 18 February, 17 June, 18 November

Bone Marrow Transplant clinic (under 6's): 14 January, 15 April, 29 July, 14 October

Bone Marrow Transplant clinic (over 6's): 21 January, 1 April, 22 July, 21 October

Bone Marrow Transplant Teenage Transition clinic: 17 June

Bristol clinic: 18 January

Cardiff clinic: 20 January

The MPS Society invites you to apply for a family trip to Lapland

The trip will take place in December 2011 for a limited number of MPS families, consisting of up to 2x Adults and 2x Children, (aged 2 - 14 years).

This trip of a lifetime includes return flights from Gatwick Airport to Kittila Airport in Finland, 3 nights hotel accommodation (including Breakfast and Evening meals), sleigh rides, tobogganing, sledging through the winter wonderland, a visit to Santa Claus' workshop and sorting office with the opportunity to give Santa your letters in person (subject to change at time of booking), and much more.

This trip promises to be a magical experience, remembered forever by all.

Look out for the application form in this issue of the MPS Magazine or contact Fiona Hopson at the MPS Society for more information
f.hopson@mpssociety.co.uk

ANNOUNCEMENTS

New Members

Ms Tranter has recently been in contact with the Society. Rosalind has a diagnosis of Fabry disease. She lives in London.

Mr Gareth Evans has recently been in contact with the Society. Gareth has a diagnosis of Fabry disease. The family live in Wales.

Ms Laycock has recently been in contact with the Society. Amanda has a diagnosis of Fabry disease after two strokes at the age of 38 and 42 years and is so grateful for the medical support she has received from the NHS throughout. She lives in the South East.

Ms Tandy has recently been in contact with the Society. Ms Tandy has a diagnosis of Fabry disease. Ms Tandy lives in the North West.

Deaths

We wish to extend our deepest sympathies to the family and friends of:

Helen O'Toole who suffered from Morquio disease and who passed away on 3 October 2010 aged 33 years.

Masuud Wais who suffered from Hunter disease and who passed away on 11 October 2010 aged 8 years.

Michael Megoran who suffered from Hunter disease and who passed away on 30 November 2010 aged 12 years.

CONGRATULATIONS TO EMMA SLATER (MPS I BMT). EMMA RECENTLY PASSED HER DRIVING TEST AND SHE HAS AN ADAPTED CAR FROM MOTABILITY

Congratulations to Barbara Wedehase, Executive Director of the National MPS Society, on her 60th birthday on 31 October 2010

CONGRATULATIONS TO GAIL & MARTIN MALCOLM

on the safe arrival of baby Oliver on 22 September 2010, weighing 9lb 7.5oz. He was poorly after the birth and had to stay in hospital for 6 days but he's doing great now and looks a lot like Jack (photo right).

Oliver is brother to Jack who sadly passed away after his Bone Marrow Transplant on 25 November 2008.

Congratulations to Myles and Sarah Broughton
on their marriage on 11 September 2010

In the photo above, on the left is Derek Broughton, Myles' father, in front of him is Joanne Lewis, Myles' sister, the little girl at the front is Joanne's daughter Sophie Jane Lewis, behind Sophie in the pretty dress is Sarah. Myles has MPS IHS

Archie's Story

Geraldine Rudham's little boy, Archie, has MPS II Hunter Disease. Geraldine shares her family's experience of life since receiving Archie's diagnosis

Archie was born in 2000, when his older sister Emily was two. We had lots of trips to hospitals and appointments with doctors in his first year or two. There always seemed to be something the matter with him – frequent ear, chest and urine infections, funny-shaped head, etc. By the time he turned 3, we noticed his fingers were becoming quite clawed.

He was referred to a paediatrician, who asked me lots of seemingly unrelated questions such as does he look like other members of the family? They then wrote on a urine sample form the word 'Mucopolysaccharidosis', which we immediately looked up on the internet when we got home. I couldn't sleep or eat for days after that.

We went to see Dr Wraith in Manchester a week or so after the diagnosis had been confirmed and we felt a bit better after he told us about the ERT trial that was about to begin. Archie, however, was too young to be eligible for the trial but at least it gave us some much-needed hope for the future.

He continued to be the same happy boisterous little boy, started school aged 4 and in his first term he managed to count to twenty and write an 'A' for his name. He loved singing nursery rhymes, playing with his beloved cars and also spending time with his Year 6 friends who helped to look after him at lunchtimes.

When he was 5 his youngest sister Bella was born. Archie decided to call her 'Roy' – no idea why!

After he turned 6 we realised he needed to be moved to a different school as he was finding the constraints of a mainstream school a bit much. His intellectual capabilities had plateaued; he was very hyperactive and was also back in nappies all the time.

Archie settled well into his new school and by June 2007 we were delighted that he started receiving his first dose of ERT. We noticed some positive changes after he started on the ERT, the pebbly bumps on his skin were disappearing and he seemed to have lots of energy.

In 2009 we transferred Archie's care from the Royal Manchester Children's Hospital to Birmingham Children's Hospital as it's much closer for us, living in Nottingham. It was around this time that we began to see some deterioration in Archie's condition. He wasn't moving around very well and started having more chest infections. He had also lost all of his speech and had begun to have seizures. Then we were told in early 2010 that there was the possibility that Archie was developing antibodies to the ERT, so at the moment we are not sure how well the treatment is working.

By autumn 2010 we had finished the home adaptations (the whole process took two and a half years) to give Archie a downstairs bedroom and bathroom – which was timely as he can't get up and down the stairs any longer.

Despite these setbacks and all the difficulties he has to contend with, Archie remains such a loving and gentle boy, his smiles and hugs never fail to make everyone around him happy too. **Geraldine Rudham**

Do you have a story to share?
Email **newsletter@mpssociety.co.uk** or phone **0845 389 9901**

Becoming a Mum, Hannah's Story

Hannah Holt has Morquio. She is 19 years old and recently became a Mum to baby Ollie. Hannah shares her story with us...

My name is Hannah Holt; some people may remember me as Hannah Booty. I am 19 years young and thought I'd write a bit about my journey so far.

I was diagnosed with Morquio at the age of 4 ½. I was small for my age and my mum had noticed changes in me that, when investigated, were found to be as a result of this rare disorder.

I was referred to Dr Velodi at Great Ormond Street Hospital where I had my cervical fusion when I was 5. Wearing the halo for 3 months was a challenge but me and mum dealt with it as best we could. Again, at the age of 7 I had a lower spinal fusion as I had rather a large curve in my spine. This was a harder operation to overcome and I had to wear a brace for 6 months. I grew by 2 inches after that operation so I was really pleased!

I continued to grow until I was around 14 years of age and am now a healthy 4 feet 5 inches, which is rather good I think. I am still mobile; although my hips are becoming more and more stiff… I just hope they don't give up yet. I have always tried to live my life as "normal" as possible, giving my parents the usual headaches of being a teenager and causing trouble. I didn't really enjoy academics at school so I left at 16 and started work at Sainsbury's who have been a fab employer and have always tried to help where they can.

When I was 18 I had been seeing my boyfriend for around 18 months and had to break the news to my parents that I was pregnant. They were rather shocked but supported me enormously. I have always had difficulty with contraception, the pill didn't suit me nor did the implant, maybe it has something to do with my size!

I went to see my doctor to confirm the pregnancy, who was great. They referred me to every consultant you could think of… and a few more besides!

No doctors had experience of a Morquio pregnancy before and so I was a learning curve for them. They monitored me every 2 weeks with scans and tests, and to everyone's delight the pregnancy was text book, once I had got over the sickness which many women will know is horrid. I enjoyed being pregnant very much. Growing this life inside me was amazing and something I was afraid that I may never be able to do, although it did get pretty heavy towards the end!

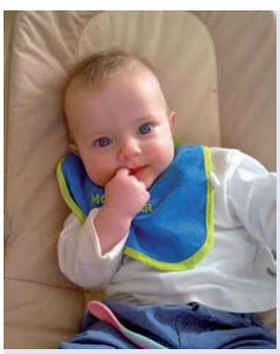
The doctors decided that I would not be able to carry full term and so I was booked in for a caesarean at 34 weeks. This was scary as I wanted to be awake for the birth and so opted for a spinal section. On the day this did not work so they reluctantly gave me a full anaesthetic. Looking back now I wish I had done that to start with as all the drugs they had given me made me quite poorly for a few days.

I became a very proud mum to baby boy Ollie who weighed 4lbs 8oz, a good weight for 34 weeks.

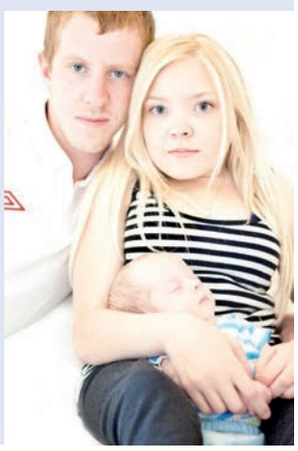
He was only in the special care baby unit for 2 weeks where he grew strong enough to breathe and feed on his own before coming home, which I think is amazing after such a short stay.

Now 7 months on, me and my partner Scott have a gorgeous baby boy who is getting rather heavy! We decided not to have Ollie tested as this would alter the way we will raise him, what will be will be, he is a very precious gift.

I hope that both parents and individuals that are affected by Morquio read my story and are able to gain some inspiration from me. You can achieve whatever you wish for in life if you want it badly enough and I have a perfect little family to prove it! I love every minute and I can't wait to add to it… but perhaps not quite yet!



Ollie
born 4lbs 8oz



Proud parents
Scott and Hannah

On a Hunter's Journey

Caleb, the meaning behind the name: pronounced KAY-leb. It is of Hebrew origin, and the meaning of Caleb is "faith, devotion, whole hearted". Biblical: Caleb, a companion of Moses and Joshua, was noted for his astute powers of observation and fearlessness in the face of overwhelming odds.

My name is Daniella Vandepeer, my husband is called Mark, and we have one son - Caleb. Caleb is 3 and a half years old and was diagnosed with Hunter Disease (MPS type II) in May 2010 exactly one month before his third birthday.

Caleb was born almost 2 weeks overdue, and I guess it would be fair to say that as a mother, instinctively I knew that there was something a little different about my boy.

Caleb, like many other children born with Hunter's did not display immediate signs straight away. He was crawling at 7 months, walking at 11 and even said his first words by the age of one. He, like most other babies, was perfect!

Yet as a first time mum, I couldn't help but worry. In the early days, Caleb had the "Colic" and Reflux, he had just about every cold, virus and ear infection going.

But each time I saw our GP, I was told he just had a low immune system and asked the usual questions, "how long did you breast feed for?" "does he eat well?"

At 18 months it was established Caleb had severe Glue Ear and enlarged tonsils, again a very common problem in toddlers. Really, there was no reason for me to worry but I couldn't help think that something was wrong.

After his Grommet insertion and adenoid removal, one doctor noticed that Caleb had a possible sub mucous cleft palate and something called a bifid uvula (a bifid uvula is the little piece of skin at the back of our throats shaped like a U, but in Caleb's case it was shaped like a fork in two. Confused, I certainly was. I tried researching these terms but I still was not getting the answers I needed. Caleb was getting very frustrated, I was on edge, he wasn't sleeping and neither were we.

The first time I came across the word Mucopolysaccharidosis was in a paediatrician's office in February 2010. It was a routine appointment and the paediatrician I am sorry to say was very unsympathetic. His first observation was that he thought Caleb did not bear much resemblance to myself or his father. We explained in vain that Caleb came from a very diverse cultural background which included African, Irish and Dutch origins. All of these varied qualities were the reason for our handsome boy's caramel skin, and his cute little button nose and cherry lips, thick curly hair, and his stocky build.

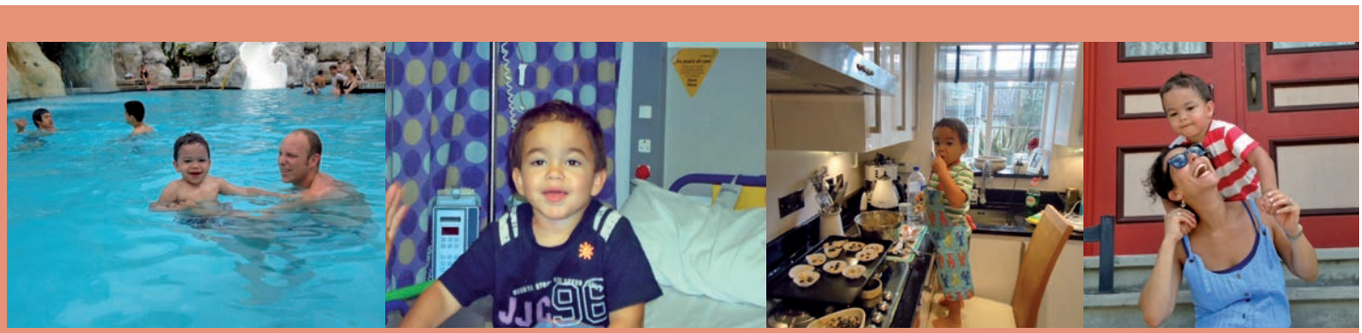
This doctor did not offer us genetic tests to determine his initial thought of MPS, he just very casually said Caleb may have a genetic disease but he doubted it as it was "incredibly rare." We were astonished, only hearing the word once made it stick in my mind and I did the thing most parents do, I googled it.

I panicked, I needed answers, I needed clarification. Everything I was reading just did not make sense.

I called Caleb's ENT consultant after the appointment with the unsympathetic paediatrician, he listened to my concerns and put me in touch with a geneticist called Dr Saggar.

Dr Saggar became our saviour, he seemed to have all the answers, reassurance and sensitivity that we needed. I remember watching Dr Saggar interact with Caleb and take photos of his hands, feet and face - that's when I first realised how serious things were.

Despite the bad experience with the paediatrician, I feel as if he did us a favour. If it wasn't for him mentioning MPS who knows what may have happened to Caleb.



Dr Saggar was almost certain that Caleb had Hunter's just by that first meeting. He immediately undertook tests, and never stopped reassuring us that we had been incredibly astute parents and we had hopefully established the condition early enough to get treatment.

We were referred to the Metabolic Team at Great Ormond Street, who have all been a constant source of support and information since day one.

That was 9 months ago, and things have been fantastic. Just weeks after Caleb was diagnosed he was offered Enzyme Replacement Therapy.

Although we were told that the ERT would not cure the disease, we were reassured that it would provide a way of Caleb's body to deal with the build-up of GAGs and help reduce the symptoms of Hunter's.

Caleb started his ERT on 18th September, and we instantly saw results. His tummy was always swollen and he always seemed to be grazing at his food, his sleep was erratic and generally he was just very sluggish. All these things changed after just 3 weeks of treatment! His tummy is much less swollen now, and boy does he have an appetite! He has much more energy although Caleb has always been a very lively little bean. He just seems more switched on and less burdened.

Life seems to have changed since ERT. Caleb is more comfortable around groups of people, he interacts more, and I don't know if it's the treatment, or if Caleb is just growing up and becoming himself. Each day is a new day for Caleb, and for us as parents.

Accepting Hunter's has been hard for Mark and I, and like all parents we have good days and bad. I guess

this is just part of our new life, we will always go through the ifs, whys, whens and hows, but this IS our life now so we have to embrace it, face it and take it each day at a time.

Hunter's has brought our family closer together, and also brought us a whole new circle of friends from Surrey, to Washington USA! I am so grateful for all the support us Hunter mums give one another from near and far, and also for the instant friendships our boys have.

There are many negatives the condition brings to our life, but there are also many many positives. The spirit of my friends and family help me through the bad times, and assist me with the good.

Caleb has always been known as the little lord in our family, and seems to walk around the house with a royal grace! He is such a character and has his dad's sense of humor. We think he is a bit of a budding artist and is very handy with a pen and paper, we have found numerous faces around the house complete with eyes, ears nose and mouth, on the bed sheets, leather sofa and a wall here and there! Caleb has also recently learned to write his name… Something I am immensely proud of!

Mark and I cherish each and every moment we have with Caleb.
Daniella Vandepeer

Living with Fabry, from a partner's perspective

When Darrin told me that he may have an adult inherited illness, I must admit to being a little bewildered. Fabry? What, who, and how were just a few of the questions I asked. Confused… you bet I was.

Even right up to him having the tests that proved he had the same genetic mutation as his brother, I was still basically in the dark.

Darrin explained things to me with the aid of a few information pamphlets and I began to understand the basic problems of the illness. Obviously I knew about certain ailments he already had, but when you read things like 'A shortened life span' and 'the possibility of liver failure, heart attacks and strokes' all from one illness, it became really scary.

At this point I still felt rather distant from it all, but then it dawned on me, an inherited disease? What about our kids? This put an even worse perspective on the whole situation.

Now, both our children have been in very good health throughout their childhoods. They never had colds or the flu, they brushed off mumps, measles and chicken pox quicker than you could blink an eye. It was soon established that Perry, my youngest could not get the disease but my daughter on the other hand could.

After having her referred for tests they came back positive. This was a double whammy, but fortunately she had no ailments or any indication of problems caused by the disease and she has no need to have any infusions, which she is thankful about. In her opinion, she hasn't got time for an illness because it interferes with her social life. Young adults eh, we've all been there.

It took a while to get my head around the problems, but as each day passed and Darrin started his infusions, I became more confident about the future. Although he had nothing major that was obvious, it was interesting to know what was happening inside his body.

On one occasion when I had a few days off work, I went with Darrin to Hope Hospital, met Laura the infusion nurse and saw how the infusion was done. I also met Dr Waldek. It was reassuring visiting the hospital and seeing firsthand what was happening (and there's always the added bonus of being able to do some shopping in Manchester). (You can't beat some retail therapy!). This was when I began to realise that positives could be taken from him having the illness.

Shortly after his final infusion in Salford, the first of the two Homecare Nurses visited our house and I began to take an interest on how the infusion was carried out.
I remember thinking "I could do that".

In the meantime, Darrin was no longer having any side effects from the Fabrazyme and he was generally feeling much better. After a discussion with Nurse Christine, I asked if it was possible for me to be trained up to do the infusions myself. This was my way of becoming more involved and to be truthful I loved the idea of doing it. It was quickly agreed that I could do the infusions and I was trained every fortnight for about six months and found it quite a pleasing role to do.

I was signed off by Healthcare at Home as being competent and have been doing Darrin's infusions for over a year now. The responsibility of doing this has now changed my way of thinking. I had always taken any old job for the sake of providing for my family and to be honest I never really liked any of them. I was always wondering what job role/career path I would like to take and all of a sudden I knew. I was now determined to do this sort of job as my career… another positive I have been able to take from all of this.

After several attempts to get a job at the local hospital, I eventually obtained a position as a Technical Assistant in the Sterilising Services Unit and it has been the best career move ever. Although I initially wanted to obtain a position as a phlebotomist, I decided to apply for any suitable position, and my persistence paid off.

I now have a reasonable understanding of the illness and I can tell when Darrin is not having a good day. Little things that you wouldn't normally notice in everyday life stand out when you know what you're looking for.

I know as time passes that the possibility of the illness getting worse is always there because it is a progressive disease, but on the positive side, more scientific research is being undertaken to find better or improved medication. Hopefully, in time, medical advances will provide us with the best result… a cure.

I do keep an eye on my daughter, because she doesn't take care of herself as much as she should do. By this I mean she is not eating a good balanced diet and she doesn't tell us how she is feeling or talk about the illness in general. But we have to respect her privacy.

So as you can see, we as a family have tried to turn all the negatives into positives and we all carry on as normal.

With that I would like to wish everyone that has any connections with Fabry Disease all the very best luck. **Sharon Minett**

Do you have a story to share?
Please email
newsletter@mpssociety.co.uk
or phone **0845 389 9901**

Ian's column

Ian continues his series of articles written for the MPS Magazine sharing his experiences of living with Fabry

This is just a short paragraph this edition due to the fact that I'm completing my tenth week in hospital after another stroke. I've lots to tell you but it will have to wait. Just before my stroke I was away in France and I found out alot of useful information for disabled travellers in and around Paris.

Hopefully next time I'll be able to write an article. I hope to be out of hospital in the next couple of weeks to carry on recuperating at home. It's just a small hiccup in life that will be overcome. Take care everybody, until next time. **Ian Hedgecock**

Our journey to discovering ML III

Sam is 8 years old. He was diagnosed with ML III in September 2008.

Sam was born in 2002, a healthy little boy, with a couple of 'anomalies' to his health - talipes in his right foot, a Mongolian blue spot, and a deep sacral dimple, and his teeth were showing through his gums. Dr Rupert Smith, the Consultant Paedtrician at Rochdale Infirmary was called to give Sam the 'once over' before he could be discharged to go home. The dimple was safe, the foot could be massaged back into position, and the Mongolian Blue spot was typical as I,(mum) was of Oriental origin, and dad was a mix of Bengal and Scottish. Dr Smith said Sam was fine and healthy, but would like to keep an eye on him to make sure he developed normally. He looked at me and my husband and said 'Sam was a mongrel'. The way he held Sam in his hands, like Rafiki held Simba up at Pride Rock, we knew he meant well, and cared for children. He explained that because our gene pools were so far removed, the chances of Sam having any genetic problems would be rare. We, as a family prefer to refer to Sam and his brother, Edward, as 'Banoffee Boys'.

We massaged Sam's foot back into the correct position, and Sam developed normally. Sam had various hospital check ups which didn't amount to anything being amiss with his development. Sam was also seen by geneticist Prof Clayton Smith, who apart from noticing Sam had Camptodactyly (where the small finger bends inwards slightly) everything else appeared fine. The Camptodactyly was inherited from me, and a couple of my siblings and my mother had the same condition. It didn't cause a problem with us, so there was no reason to think it would cause a problem to Sam.

During an assessment, it was noted that Sam's right leg was slightly longer than his left leg, and that there was a little dullness in his hearing in his left ear. We dutifully went along with all the extra hospital appointments, but nothing negative was said, plus, to us, Sam was a happy, healthy little boy. We weren't worried about his development at all.

Sam was late to start walking, just two weeks off his second birthday, but he learned to steady himself and walk and run. Sam was never keen on jumping or climbing, and took his time climbing the stairs.

When Sam was three, his little brother, Edward arrived. Sam was still at nursery, when the carers pointed out that Sam was having difficulty with his grip, holding crayons, cups and cutlery. His handprints were never legible enough to distinguish palms and fingers. Sam was upset that he couldn't clap along to songs with his friends. We had noticed this also, but put it down to the Camptodactyly.

On our next visit to Dr Smith, I mentioned Sam's fingers were stiff and bending inwards like a claw. We were referred to OT, and plastic surgery at Wythenshawe. Sam was given hand splints to wear at night. Over a short time, Sam's fingers began to stretch out, and Sam had full motor movements in his hands. We were told that Sam would have to wear splints until his late teens when he stopped growing. As Sam seemed to be developing normally, Sam was discharged from Dr Smith's clinic.

As Sam was our first child, we had no one else to measure his development against. Edward walked soon after his first birthday, and soon began climbing, jumping and running everywhere, at times, overtaking Sam. Sam still seemed to be moving at a slower pace, but we just dismissed it as every child being different. If Sam did jump or fall, he would fall heavily, and seemed unable to cushion his fall. He seemed to stumble and trip up a lot too.

Around Sam's sixth birthday, he developed a bad chest infection. This was unusual for Sam as he rarely suffered from coughs or colds. The GP prescribed antibiotics, but these didn't clear the infection. On the second visit within a week, the GP asked me if I was aware that Sam had a heart murmur. As Sam had been seen regularly by various doctors, I said it was probably due to his chest infection. The GP asked us to come back in a couple of weeks, just to make sure it was just the chest infection. When we returned, the heart murmur was still there. I asked to be referred back to Dr Smith, as he knew Sam's history.

When Dr Smith examined Sam, he detected the heart murmur and said that Sam should be referred to Cardio at Pendlebury Children's Hospital for verification. He admitted that he had not noticed the murmur before, probably because he was looking at Sam's hands and legs previously. I asked if Dr Smith could check Sam's shoulders and legs, as I didn't think Sam had full range in his shoulders, and he was beginning to limp a bit. Sam also seemed very stiff when he got up after sitting down for a while. He looked like an old man slowly levering himself up. Dr Smith checked Sam and agreed that there wasn't full range of movement. I was also concerned that since his chest infection, some six months prior, Sam seemed to be constantly full of mucous, and couldn't breathe properly. He was constantly getting ear infections. Dr Smith asked me if I was trying to ask or tell him something about Sam. In the back of my mind, little anomalies were cropping up with Sam's development, especially his movement. I didn't want to appear a neurotic mother, but I also didn't want to ignore all the signs. Dr Smith said he would refer Sam back to Prof Clayton Smith to see if she could find a genetic link between the hands, heart and joints.

The cardio appointment came up showing that Sam had 'Mitral valve regurgitation' where some of the blood was leaking back into the chamber through a weak valve. Sam didn't need surgery, but may have to have some medication in the future.

During Sam's appointment with Prof Clayton Smith, blood and urine samples were taken. Shortly after, me and my husband were asked to attend a meeting with Prof Clayton Smith. The samples taken had shown that Sam had a rare genetic condition called ML III. We were to attend St Mary's Hospital to meet Prof Ed Wraith who was a specialist regarding the condition. He would explain what the condition was, and how it would affect Sam in the future. We were asked if we were planning on having any more children, as we would be advised to take genetic counselling. From our description of Edward and his antics, they didn't think he had the condition, although he may be a carrier.

We met with Prof Wraith, and he examined Sam first before explaining things to my husband and me. He said Sam was at the lower end of the spectrum of MLIII, which was probably why it hadn't been diagnosed earlier. He explained the characteristics and symptoms of the condition, many of which corresponded to Sam's symptoms. Sam is doing well at school, and keeping up with his peers. He was quite proud to tell Prof Wraith that he was one of the tallest in his class. We had a long list of questions to ask, and Prof Wraith explained all the answers. Both my husband, and me, unknowingly were carriers of the ML III gene, and had passed this onto Sam. Everything was starting to fall into place. The reasons why Sam didn't like to jump, or why he was limping were due to the pain in his hips and legs. Sam also struggled to dress himself, especially his top half. He would struggle putting his head and arms in, or undressing. I put it down to my laundry techniques, or lack of them. Sam managed to adapt to dressing in his own way.

The ML III over time had caused the Mitral Valve Regurgitation, which is why the murmur had probably not been detected previously. The fact that I had Camptodactyly had thrown everyone to believe that Sam just had the same condition in his hands, only a worse case. As previously mentioned, my husband's gene pools and mine were so far removed, the chances of something like this happening were slim. Some things are just meant to be. That's nature for you.

I felt a kind of sense of relief that I wasn't imagining things, and that I wasn't just a neurotic mother. It was now time to start thinking of the future, and what we could do for Sam. My husband took it badly at first, wondering 'Why us?, why Sam?' We both have our low moments at times, but luckily not at the same time, as we always seem to be there for each other and supportive when the lows hit.

Sam still runs around to his best ability, and loves to play football and cricket. He has swimming lessons, which help him to keep his joints moving. He loves playing on the Wii. We make sure he's playing the games with plenty of movement. He and Edward are always singing and dancing, and when they are having a race, Sam waits till he gets half way, then tells Ed it's time to turn back, so he's got a head start. He joins in PE at school, unless it's Maypole dancing, then he says his legs are aching. We don't rush Sam along as much now when we're out, and if he wants to jump, we hold his hands, and help cushion his fall. Sam has tried to ride a bike, but can't get the speed up as it causes him pain. Sam has never liked speed, whether it be on the motorway, or fairground rides. He gets upset and loses control. We can only put this down to his heart, so we don't force him? Sam is like any other boy his age, but with a slight disadvantage. He and his brother still drive us crazy when they are squabbling, like all other siblings do.

We've tried to explain to Sam about his condition, and what may happen in the future. He kind of understands, but often asks why Edward isn't the same, as he is his brother. How can we explain this?

Sam is currently on Enalapril for his heart, Loratadine for the mucous build up, and Brufen for his pain relief. As I am an Holistic therapist, I believe in trying to help Sam and his symptoms by using complementary therapies alongside his medicine. I often massage Sam or try some Reflexology, when he lets me. Reiki comes in handy to help calm him down in general, and helps him cope with the pain. As we are quite concerned about the amounts of pain relief Sam is having daily, I am currently studying 'The Bowen technique' in an attempt to help Sam deal with the progression of pain he will encounter. I have a friend who uses this technique to help her son who has paraplegia, and the results are always positive. I will keep you posted on the results with Sam.

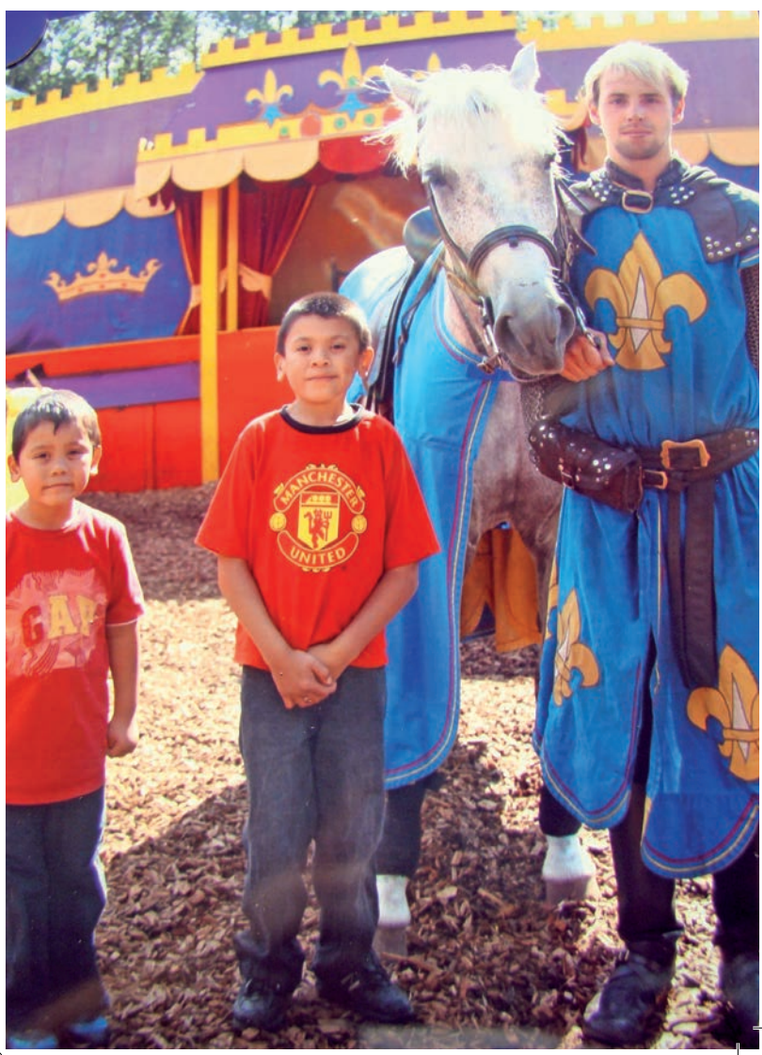
Although Sam is at the lower end of the spectrum for ML III, it still poses an uncertainty for his future. We don't know if a cure will be found, but we are happy that Sam is under the care of Prof Wraith and his team. For questions nearer to home, we know Dr Smith will always be there to listen, explain and direct Sam towards the best care available. Between us all, Sam doesn't need to worry about the amount of care and attention he will receive.

Sam has recently had MRI scans for his neck and spine, and x rays on his hips and knees. We are currently awaiting the results on these.

We recently won tickets to Camelot through a prize draw with the MPS Society. We all had a great time, and here is a photo of Sam and Ed having fun.

To end on an upbeat note, we sometimes have a giggle saying, with all the hospital appointments Sam has across the different hospitals in the North West, if Sam was ever to turn to a life of crime, they'd catch him within minutes, as it would be easy tracking him from his DNA.

Thank you MPS for a great day out, and 'Thank you' all for listening to our story.
Shirley, Shamim, Sam & Edward Jamil



Bristol MPS Clinic

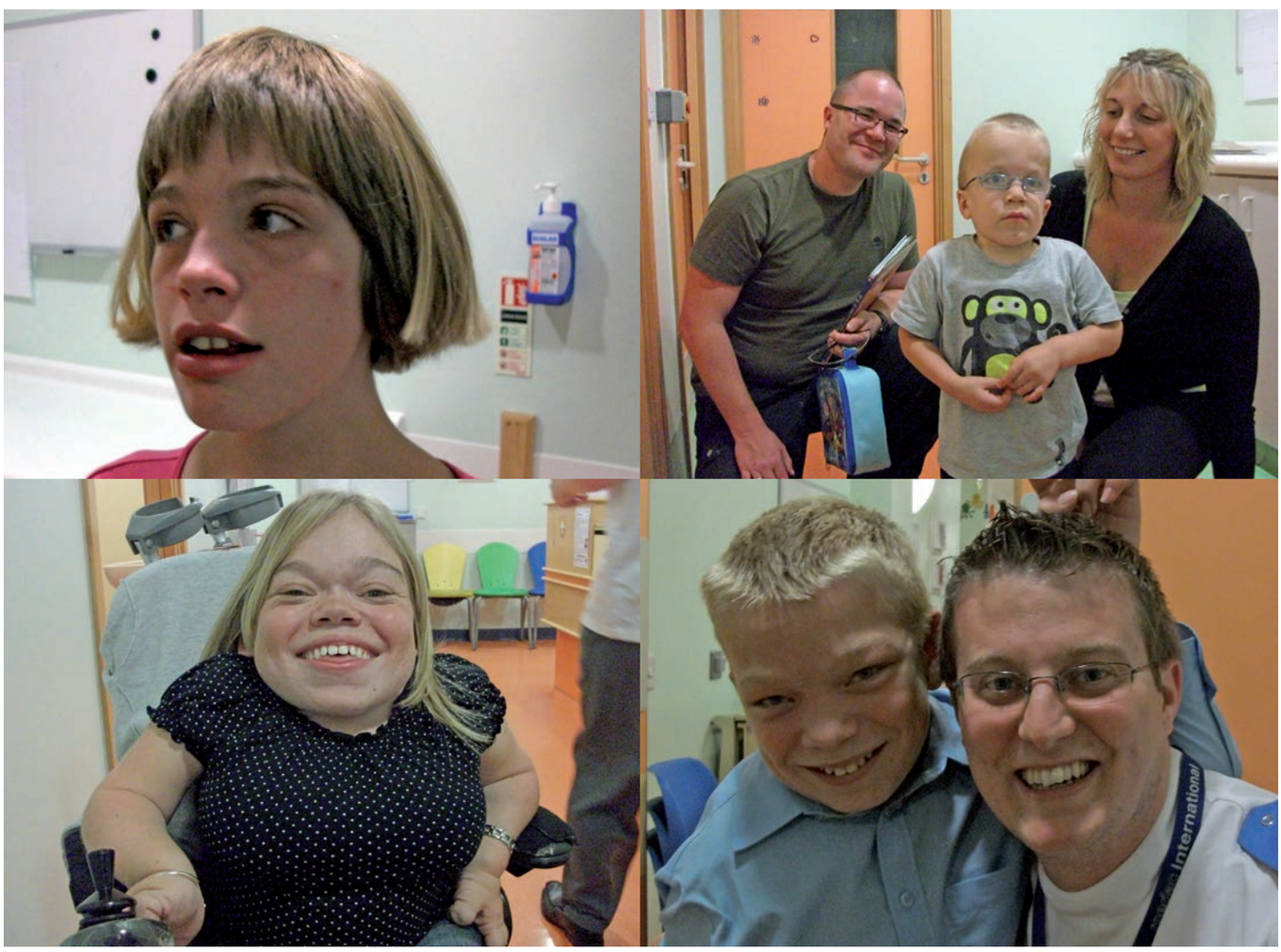
8th September 2010

One month into my new job, Jolanta and I set off from Buckinghamshire early in the morning to attend the Bristol MPS Clinic. We were delighted to find a parking space and the time to buy a coffee to start the day. This was my first clinic and I was eager to begin meeting the families.

We found the clinic room and met Professor Wraith, Dr Pierre and Dr Jardine and waited in the corridor to meet our families.

It was a fabulous experience to meet with so many smiling faces, wonderful parents and their wonderful children. Everyone's strength and upbeat outlook made the hours in the day speed by, and it felt too soon to leave Bristol at the end of the day.

Lindsey Wingate l.wingate@mpssociety.co.uk



Photos clockwise from top left:
Sophie Clarke (MPS III), Archie Pearson (MPS VI), Terry Butler (MPS I), Faye Longley (MPS IVA)

Manchester BMT Clinic

15th October 2010

There I was again in Manchester to meet with parents, children and the great Manchester team. I don't remember what the weather was like but I'm assuming it was raining, as it often does in Manchester!

The first to meet me was Aiden, who told me straight away that he spent the last night on the ward. I did not know that then but there was the pattern established for the rest of the clinic. As more families arrived I learnt that almost all of them spent their night on the ward. You could tell that by looking at the parents but not so much from the children, who were full of energy.

It was great to meet Aiden for the first time and to see Sonny, Ethan, Demi-Leigh and Harvey again! The clinic ran smoothly and almost everybody turned up.

I am looking forward to seeing you all in a New Year!
Jolanta Turz j.turz@mpssociety.co.uk

Photos clockwise from top left:
Aiden Brown (MPS I), Sonny Gibbard (MPS I), Ethan Greening (MPS I), Demi-Leigh Rodden (MPS I)

Manchester BMT Clinic

22nd October 2010

It was a bright and early start to the day to attend my first Manchester Clinic, with Jolanta.

First customer through the doors was Isaac, with his Superman shirt. Wanting to know what time we got up, how we got there etc. Fashion expert in the making after commenting on both mine and Jolanta's boots, although he asked Jolanta why she was wearing her wellies (they were black patent leather)

Little Melissa was getting ready for Halloween with little pumpkin hair accessories. Cody came with her monkey and we enjoyed building a very large wall out of bricks with monkey sitting on top.

Rachel and Charlie arrived, carrying, what looked like spiky cucumbers with hair. They could be pulled in all directions, great fun. Rachel looked very trendy in her jacket and hair swept to the side in a pony tail. Charlie, well, after trying to get in the play house with him, (the entrance is a bit tight for curvy women), proceeded to build a tower out of the building blocks and thought it was great fun when it fell over on top of me!

Keira, the quiet one with her lovely red hair, came with her mum and did some lovely pictures.

Matthew arrived with some very trendy trainers, which he designed himself, with his name and age on them. Perhaps he should join forces with Isaac and start up their own business in shoes and boots.

Thomas arrived with the family and immediately wanted his photo taken, (with granddad this time). Then he and Matthew had a little chat about how many football shirts they had and which footballers they had met. All they needed was a pint in front of them…

Holly arrived in her school uniform and couldn't wait to leave wanting to get back to school, even though it was finished, rushing mum to hurry up.

Thank you to Jean, Ed and the team for looking after us and the families for making my first clinic an enjoyable one.

Rebecca Brandon & Jolanta Turz
r.brandon@mpssociety.co.uk and j.turz@mpssociety.co.uk

Photos clockwise from top left:
Isaac Turner, Melissa McKie, Cody Taylor, Thomas Mett and granddad, Rachel Rothwell, Charlie Escalonilla (all MPS I)

Birmingham MPS Clinic

26th November 2010

On a cold and frosty morning, before all the snow, Lindsey and I met at the station to travel to Birmingham for the MPS clinic. We arrived at the hospital before two of the first families. We met with the Team who were prepared and ready to see 17 children. However, not all of them at the same time!

Families were arriving on time and Lindsey and I, between us, managed to have a chat with almost everybody who attended the clinic. We were shown the place where the Enzyme Replacement Therapy (ERT) infusions take place to meet with a new MPS Society member. I also was taken to the isolation room, where children are placed following their Bone Morrow Transplant, to see Emily and her mum.

Although it was a very busy clinic the energies of everyone we met were upbeat and cheerful. We are looking forward to coming to the next Birmingham clinic and wish Emily a speedy recovery!

Lindsey Wingate & Jolanta Turz
l.wingate@mpssociety.co.uk and j.turz@mpssociety.co.uk

Photos clockwise from top left: From Manchester Clinic on 22 October - Kiera O'Neill, Matthew Ingram and the trainers he designed (both MPS I); From the Birmingham Clinic - Archie Rudham (MPS II), Natasha Pace (MPS III), Anya Bhatti (MPS III)

Childhood Wood Planting

Nine children and adults who lost their loves to MPS and related diseases in the last 12 months were remembered in the Childhood Wood on 22 October 2010.

After lunch at the Clumber Park Hotel the families made their way to Sherwood Pines where they were able to see their loved one's names on the new Remembrance Boards as well as some new children's activity areas. After a short remembrance ceremony blue and white balloons were realeased followed by the planting of an oak tree sapling.

A tree was also planted in memory of Chloe Walker, sister of Jordan Walker who died from Sanfilippo disease in 2007. Chloe lost her life in the school bus crash in Keswick, Cumbria on 24 May 2010. On this page are a selection of photos from the day.

REMEMBERED

Shujah Altaf
Daniel Ellis
Josephine Kembrey
Helen O'Toole
Nicole Pickard
Catherine Scott
Faiza Shaikh
Samuel Sparkes
Chloe Walker

"I am afraid this is rather late but I would be very pleased if you could convey to Christine Lavery our grateful thanks for all MPS did to make the tree planting at Sherwood Pines such a moving experience.

The organisation was superb, even arranging wonderful autumn weather. We were very grateful to the Mayor and Mayoress for giving us a lift to the forest as John is not able to walk far, and we enjoyed meeting the other members at the table."

We are so glad we were able to come, and will remember it for always. We will hope to visit the Wood in the next few years as our grandaughter is at Sheffield University, and we can combine the trip to see her as well. With best wishes and many thanks." ***Sue Scott***

MPS Events

Thank you from the Dickersons

We have just enjoyed two trips arranged by the MPS Society. We travelled to Birmingham in September to visit Cadbury World. It was a glorious day and perfect for exploring the whole site which included gardens and a play area.

The exhibition was full of interesting facts about cocoa beans, the origins of chocolate and its later development by the Cadbury family.

We didn't know about the social history surrounding the village of Bourneville and how the Cadbury family sought to improve the lives of their Victorian employees and their families. So we learned something! The only thing we didn't see which we wanted to was the actual making of the sweets and chocolate bars. There was a display of wrapping and decorating chocolate novelties. This disappointment disappeared as we ate the freebie chocolate bars and the small pot of warm chocolate and marshmallows.

Our second outing was to the Science Museum in London. Another glorious day, MPS can you arrange this for next June?! As with these events, the venues are so interesting there isn't a lot of time to rub shoulders with other MPS families.

As with London, the start of the day had some British Rail inactivity and also some at the end for us. Signals... whatever!

The museum is, well, full of science stuff and of course the IMAX 3D cinema which was AMAZING and to be thoroughly recommended. We also had entry to the 3D Red Arrows show.

A good time was had by all.
Thank you!
Alan, Heather and Callum Dickerson

MPS Awareness Day

15 May 2011

One baby every eight days in the UK will be born with an MPS or related disease

Each year the Society celebrates International MPS Awareness Day on 15 May. This is a day devoted to raising awareness of MPS and Related Diseases

Help us celebrate International MPS Awareness Day on Saturday 15 May 2011

In 2011 we're asking all our members, Friends and supporters to do something, big or small, to mark MPS Awareness Day

Visit **www.mpssociety.co.uk** for more information or give us a call on **0845 389 9901** to find out how you can support us...

Rare neurological diseases of childhood:

2 December 2010
The European Parliament, Brussels

This meeting was organised by the Brains for Brain Foundation, the European Brain Council, the UK Lysosomal Storage Disease (LSD) Patient Collaborative and the Veneto Region, and sponsored by MEP Mrs Amalia Sartori (Veneto, Italy). The meeting was moderated by Dr Michael D Rogers. The aim of the meeting was to acknowledge the growing interest of the European Commission in both rare and neurological diseases and demonstrating the unity of intent of the LSD Patient Associations, the pharmaceutical industry and the scientific community. The message was clear – that lessons learned from in depth research conducted into Lysosomal Storage Diseases will inform treatment of more common neurological disorders.

Brain, rare neurological diseases and European healthcare systems

"We are here to build a partnership for rare diseases and for the children, in particular, who live with them," said Mr John Bowis OBE previously a British MP and MEP. He applauded the European Commission for their willingness to listen and respond. John Bowis went on to say that for children with neurological disorders we need research into the various causes and the impact of these conditions, as well as potential treatments. This is expensive. "It has never been a more difficult time to promote investment in health as a priority for governments, and yet never has there been a more important time to do so." The number of patients affected by rare neurological diseases during childhood makes it clear that these conditions should figure in the mainstream economic argument. "If governments and directorates, and international and national agencies, and health services do nothing, the cost of such inaction will be immense. If they invest in research, prevention, treatment and care now, then the future economic benefits can also be immense for individuals, families and economists." He concluded that we have to educate the public about these rare disorders and recruit them to the battle to persuade governments and international agencies that child brain research deserves a higher priority and greater investment.

Brain and rare diseases – the patients' perspective

This session was opened with a dialogue between Dr Mary Baker MBE and Christine Lavery MBE (MPS Society, UK) about the life-changing experience of being the mother of a son who had a rare neurological disease.

Christine described how her first child was diagnosed with Hunter syndrome in 1976 at the age of 18 months. At the time when her son was born, she was told that everything was alright, but gradually it became obvious that this was not the case. Fortunately, Simon, was able to lead a relatively normal childhood; however, his condition progressively deteriorated and sadly he died in 1981 aged 7 years. Mrs Lavery recalled how she was desperate to meet another parent who had a child with this disorder and so wrote a letter to the Mencap magazine. As a result, she found 40 other parents who had a child with a mucopolysaccharide disease. At this point, only weeks before her own son died, Mrs Lavery decided to organise a Society for patients and families with these rare diseases. She has been Chief Executive of the Society for Mucopolysaccharide and Related Diseases (the MPS Society) since 1993.

we treat the child to treat the adult

Christine Lavery told those present that today the MPS Society looks after over 1000 individuals suffering from MPS or related diseases in the UK. “Based on the knowledge of how much help you really want when you have a child with such a rare progressive neurological disease, we have built up an advocacy team,” said Mrs Lavery. “This team provides support to patients and families in a range of areas, including helping to gain access to clinical centres, specialist education, disability benefits and respite care, as well as providing support for siblings and carers and for dealing with issues such as bereavement.”

Dr Baker noted the importance for patients and families of having information from clinicians and the pharmaceutical industry, as well as having support following diagnosis. “Life is a journey,” said Dr Baker. “And you need the fellow travellers – those people who make you feel that you are not alone.”

Christine Lavery then explained that the MPS society had played a key role 20 years ago in establishing a specialist centre for MPS disorders in Manchester under the guidance of Professor Ed Wraith to lead the field in the management of MPS diseases. “What we wanted to do is to try and inspire other regional professionals and centres to become interested in these diseases,” commented Mrs Lavery. In recent years the Society has also worked alongside the Department of Health National Specialist Commissioning Advisory Group (NSCAG) in order to provide patients with access to expert centres. For the five conditions for which there are currently therapies, this also gives access to treatment that is appropriately funded.

The main research priority for the MPS Society is now overcoming the challenge of the blood brain barrier and the brain itself.

Dr Baker highlighted that it is imperative that this research is shared with research into other more common neurological disorders such as Parkinson’s disease. Mrs Lavery explained how the MPS Society has worked collaboratively with other patient organisations in Europe to raise funds to support scientific and clinical research in this and other areas. However, patient organisations alone cannot provide funding for such initiatives. Mrs Lavery explained that collaboration with government, the European Parliament and Industry are needed to support further advances in research.

Despite the arctic conditions in the UK and across Europe over 80 clinicians, scientists, patient organisation representatives and MEPs attended the meeting and signed the declaration of principles.

The declaration of principles follows this article on the next page.

Christine Lavery ***Chief Executive***
c.lavery@mpssociety.co.uk

Press release and declaration of principles

The following parties support this initiative: the Brains for Brain Foundation and Research Consortium, the European Brain Council, the LSD Patient Organisation Collaborative, the Veneto Region and members of the pharmaceutical industry.

We have entered a new golden age in which science is increasingly able to inform the treatment and care of patients with rare neurological conditions. Neurological disorders affect the brain, spinal cord and nerves of the central and peripheral nervous systems. While many neurological disorders are common, others are recognised as rare disorders. Rare neurological diseases, the focus of this document, are mainly inherited conditions, the vast majority of which are fatal during childhood. The time is right for a new initiative.

We propose a new initiative to coordinate the efforts of existing groups in Europe with the shared goal of improving the treatment and care of patients with rare neurological disorders. This initiative will unite all interested parties, who are working:

- to increase the visibility, recognition and awareness of rare neurological disorders in order to facilitate early diagnosis of these conditions
- to promote and facilitate partnership and collaboration between physicians, researchers, patient advocates, carers, policy- and decision-makers and industry
- to encourage and support research and the translation of scientific breakthroughs into clinical practice
- to contribute to the establishment of a standard of care for patients with rare neurological disorders which is agreed across Europe, and to ensure equity of access to diagnosis, treatment and care.

We hope that you will join us in this important initiative by adding your signature to those below.

Background

- According to the World Health Organisation (WHO), an estimated 1 in 10 people will be diagnosed with a severe and sometimes rare neurological disorder during their lifetime. Brain disease is responsible for 35% of the total disease burden in Europe and is associated with an overall cost of €386 billion. For many such disorders, early intervention can prevent or reduce long-term morbidity and the associated healthcare costs.
- Today, over 6000 disease-causing genes have been identified, including many that are associated with rare disorders. Although individually uncommon, collectively there are thousands of rare diseases, making them an important group of disorders that affect a large number of patients throughout Europe. Most are genetically inherited. In the European Union (EU), a rare disease is defined as one that affects fewer than 5 people per 10,000. In the context that we have so far identified somewhere in the region of 5000–8000 distinct rare diseases, between 27 and 36 million people in the EU could be affected (6–8% of the population), making the management of these conditions an important issue. The socioeconomic burden of rare diseases has not yet been quantified.
- For these reasons, the EU takes the position that rare diseases are a serious public health concern and should be a priority in EU health and research programmes. The overall EU strategy is to support member states in diagnosing, treating and caring for up to 36 million EU citizens with rare diseases.
- This year we celebrate the 10th anniversary of the introduction of the Orphan Drug Regulation in Europe. This legislation provides incentives to industry to invest in the development of treatments for rare disorders and has had a positive impact on the care of patients with these conditions. The 2008 European Commission Communication and the 2009 Council Recommendations, which called on EU member states to develop and implement comprehensive national plans to address rare diseases by 2013, reflect the growing momentum associated with rare diseases at the EU level.
- The recent announcement by the European Commission and the US National Institutes of Health (part of the US Department of Health and Human Services) of their plan to join forces to focus on research into rare diseases is another sign of Europe's willingness to tackle these diseases seriously. As part of the commitment made by these two institutions, the European Commission announced that it will earmark more than €100 million for research and innovation on rare diseases in 2011. This will be the largest single investment in this research field by the European Commission so far.
- At present, however, there is an imbalance in the funding allocated to research into different types of disease. In the UK, for example, based on data from 2008–2009, it was estimated that rare diseases affect more individuals than cancer, cardiac disease, Alzheimer's disease or diabetes, but receive less research funding than these other disorders. Research funding for rare diseases, which were estimated to affect 3.5 million individuals in the UK, was £3.6 million during this period – about £1 per affected individual, which is considerably lower than the spending of £185 for each of the 2 million individuals with cancer.

Diagnosis

- Diagnosis of rare neurological diseases is made difficult by the lack of knowledge and awareness of these conditions within the general medical community. This leads to delayed diagnosis and often misdiagnosis, as was highlighted in a book on rare diseases produced in 2009 by the European Organisation for Rare Diseases (EURORDIS) and co-funded by the European Commission. This publication also notes that patients with rare conditions experience difficulties in accessing services, often as a result of a lack of referral. Raising the awareness of these disorders and increasing their visibility is therefore paramount to speed up diagnosis and to give affected families access to appropriate counselling.

Treatment and care

- The management of diseases and the provision of therapy also represent a social and economic burden. Treatment options for patients with neurological conditions remain limited. Although representing a third of the burden of all diseases in Europe, brain disorders account for only 15% of the direct healthcare costs. This discrepancy is due in part to the fewer available treatments for brain disorders compared with other types of diseases. It may also be due to a shortfall in healthcare provision, which may reflect both suboptimal training of clinicians in brain-related disorders and a shortage of material resources. Although there have been major advances in treatment, for the majority of disorders this is not curative. Management needs to be holistic, multidisciplinary and to include palliative and supportive care. This means that there are benefits in establishing centres of expertise that specialise in the diagnosis, treatment and care of patients with rare neurological diseases.

Research

- The EU is already committed to supporting research into neurological problems and has awarded major grants to study neurological disorders under the FP6 programme. An even stronger effort has been realised under the FP7 programme. We know that by studying the neurological disorders of well-defined, rare, monogenic diseases affecting children we will be able to discover information and develop techniques that will help us to generate new therapies for more common adult disorders, such as Parkinson's and Alzheimer's diseases.
- One particularly important group of rare disorders that impact on the brain during childhood is the lysosomal storage diseases, which affect approximately 1 in every 7000 newborns. There is already a strong community supporting research and scientific developments in this area, which includes physicians, researchers, patient advocates and industry. Our understanding of these conditions has grown dramatically over the past 10–20 years thanks to advances in cell and molecular biology, and we are moving closer to being able to provide therapies for neurological signs and symptoms in these patients. Further research is needed to increase our understanding of the brain and to drive the development of treatments.

Join us in this new initiative

- We advocate working together with the European Commission and other interested stakeholders to promote the diagnosis, treatment and care of patients with rare neurological diseases throughout Europe, and to support and encourage scientific research in this field.
- We invite you to join us in supporting this new initiative.

10th INTERNATIONAL WORKSHOP ON LYSOSOMAL STORAGE DISEASES

Improving LSD patient care in a new decade
3-4 December 2010, Prague, Czech Republic

The meeting began with an overall review of progress across the field of LSDs and then focussed specifically on the latest thinking in the management of patients with Gaucher, Hunter and Fabry disease. The plenary sessions offered practical considerations in the management of LSDs as well as looking forward to what the future of treatment in this area holds.

I was privileged to attend this impressive meeting as a member of the faculty where I was invited to present the patient organisation perspective in treatment decision-making in Fabry disease. This piece of the puzzle session was led by Dr Derralynn Hughes and each of the speakers formed a panel sharing individual perspectives on the management of Fabry disease. The session demonstrated a multidisciplinary approach in Fabry disease.
Christine Lavery *CEO* c.lavery@mpssociety.co.uk

Position Statement on the use of genistein to treat Sanfilippo disease (Mucopolysaccharidosis type IIIA-D)

Released 3rd December 2010

MPS Stem Cell Research Group, Department of Biomedicine, University of Manchester
Genetic Medicine, St Mary's Hospital, Central Manchester University Hospitals NHS Foundation Trust

The Manchester team have recently published preclinical data in the mouse model of Sanfilippo disease IIIB (MPSIIIB) showing significant delay in neurodegeneration and behavioural correction following high daily doses of the drug genistein aglycone delivered over a 9 month period.

The mouse model of MPSIIIB is affected by increasing pathological heparan sulphate storage in the brain and other organs, neuroinflammation, progressive neurodegenerative decline, abnormal behaviour and hyperactivity with a shortened lifespan and as such shows many similarities with patients with the disease.

Following 9 months of high daily doses (160 mg/kg/day) of genistein aglycone we have shown a 31-34% reduction in lysosomal compartment size in the brain and 37% reduction in brain levels of pathological heparan sulphate in the mouse model of MPSIIIB. Neuroinflammation was reduced by 12-19% whilst most behavioural abnormalities observed at 8 months including the lack of a sense of danger and hyperactivity were corrected by drug treatment.

We are aware that many parents already give their affected children different forms of genistein and other supplements and thus feel that it is important to offer interim advice prior to a clinical trial due to the widespread availability of genistein as a dietary supplement.

Genistein may have several modes of action including blocking protein tyrosine kinase receptor function and is also a mild oestrogen analogue. It has undergone significant safety testing in rodents and dogs but has only been tested in humans at low doses for its use as a food supplement or for treatment of osteopenia and menopausal flushes in the USA.

Genistein used in the preclinical study was synthetically produced and is the pure aglycone form of the drug. Genistein can also be purified from soy extract but this is not necessarily the same product and we would advise against its use since the naturally occurring form of genistein may not be absorbed as effectively by the digestive system.

Whilst genistein is available as a dietary supplement at lower doses, there is not yet any clear clinical data to suggest that it is effective at these doses in Sanfilippo.

Synthetic genistein aglycone is not widely available and has not been tested in a clinically controlled manner in humans at the effective and very high doses used in mice. The use of genistein in this disease at high doses is considered to be an Investigational Medicinal Product by European regulatory agencies, thus we would caution against its use by families with affected children.

We intend to run a placebo controlled clinical trial using high doses of pharmaceutical grade genistein aglycone in patients with MPSIIIA, B and C in the near future in Manchester subject to appropriate regulatory approval.

It is important that we are able to run a clinical trial comparing genistein at high doses to a placebo control as this is the only way that we can be sure if it really has an effect or not. We are currently evaluating the appropriate dose for human use as this is often relatively lower than those used in mice and again would advise against the use of high doses of genistein until we have concluded this work.

We will update this bulletin and make a formal trial announcement when we have further information in due course. The preclinical genistein publication is available for free from PLoSONE at the following link:
http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0014192

For further information please contact Dr Simon Jones or Dr Brian Bigger. Simon.Jones@cmft.nhs.uk
Brian.Bigger@manchester.ac.uk

MPS III C Mouse Model

During the Expert Meeting on Sanfilippo Disease held in Northampton in August 2010 the question was raised as to whether there is a mouse model for Sanfilippo Type C disease. It is recognised that these mouse models play a very important role in pre-clinical research and without this model research may be severely hampered. On further investigation Professor Bryan Winchester and Dr Brian Bigger of the University of Manchester MPS Stem Cell Group have identified a research group in Canada that have the MPS III C mouse model. Dr Bigger is now in touch with Alexei Pcheietski from the University of Montreal to understand the nature of his mouse model and the current research initiatives.

Sanfilippo families provide a helping hand in diagnosing their disease

Dr Brian Bigger MPS Stem Cell Research Group, University of Manchester

This summer, at the Sanfilippo Expert Meeting in Northampton, UK, we asked families and children suffering from Sanfilippo disease to donate blood samples to allow us to search for disease biomarkers.

These are extremely valuable samples that will enable the development of new biomarkers so that we can accurately diagnose Sanfilippo disease and determine if new treatments being developed for patients are effective or not. Together with help from the consultants and nurse specialists at the Genetic Medicine unit at St Mary's Hospital in Manchester, we are now able to report our preliminary findings to you.

Although we have yet to perform an in depth study on these samples, we have so far been able to show that an existing biomarker, developed originally in Canada, that is effective for diagnosis and treatment monitoring in other kinds of mucopolysaccharide disease, is also an effective biomarker for Sanfilippo types IIIA, IIIB and IIIC.

Sanfilippo disease is caused by a genetic defect in the breakdown of heparan sulphate which leads to a build up of this complex sugar in cells and in the bloodstream, resulting in a neurodegenerative disease of childhood. An excess of heparan sulphate in the blood promotes the formation of the Heparan cofactor II/thrombin complex. Detection of this complex in blood of patients compared to unaffected relatives has allowed us to clearly distinguish between patients with MPSIIIA, MPSIIIB, MPSIIIC and unaffected individuals and will appear shortly in the Journal of Metabolic Diseases.

This biomarker is the first step in developing ways of monitoring treatments in Sanfilippo, and hopefully the first in a series of new biomarker and treatment developments that we are planning in the MPS Stem Cell Research group at the University of Manchester for these diseases.

We only exist as a group because of donations from you via the UK Society for Mucopolysaccharide Diseases and many other MPS charities, so I would like to take this opportunity to thank you for your continued support.

Our website provides a good introduction to our group's activities on the following link

http://www.medicine.manchester.ac.uk/geneticmedicine/research/genetics/biochemical

If you have any questions on MPS III research or any other issue related to the MPS and related diseases, please email us your question at newsletter@mpssociety.co.uk

Soya beans could hold clue to treating fatal childhood disease

Scientists from The University of Manchester say a naturally occurring chemical found in soy could prove to be an effective new treatment for a fatal genetic disease that affects children.

Dr Brian Bigger, from the University's MPS Stem Cell Research Laboratory, found that genistein – derived from soya beans and licensed in the US as an osteoporosis drug – had a dramatic effect on mice suffering from the human childhood disease Sanfilippo.

"Sanfilippo is an untreatable mucopolysaccharide (MPS) disease affecting one in 89,000 children in the United Kingdom," said Dr Bigger, who is based in the School of Biomedicine.

"Children with Sanfilippo disease experience progressive deterioration of mental function, similar to dementia, in early childhood, with other symptoms including severe behavioural problems, hyperactivity and ultimately death in early teens."

In the study, published in the journal Public Library of Science One today, mice with Sanfilippo disease were fed with high doses of genistein over a nine-month period. Treated mice showed a significant delay in their mental decline, including a third reduction in the amount of excess sugars found in the brain as a result of the disease, and a sixth reduction in inflammation in the brain.

Importantly, the research, carried out with colleagues at St Mary's Hospital in Manchester, also showed that the hyperactivity and other abnormal behaviour normally seen in Sanfilippo mice were fully corrected by genistein treatment.

Professor Wraith, a co-author on this study and consultant paediatrician from Genetic Medicine in St Mary's Hospital, said "Sanfilippo is a disease where the genetic lack of an enzyme leads to a fault in the breakdown of complex sugars in the cell."

"This leads to storage of these undegraded complex sugars in cells, disturbances in brain function and ultimately to this profound mental deterioration that we see in the children with this condition. Manchester is a specialist centre for this type of genetic disease and as such we look after more than 100 patients from all over the UK and beyond."

The Manchester team, supported by the UK Society for Mucopolysaccharide Diseases and the Manchester Biomedical Research Centre, hope to announce a placebo controlled clinical trial for patients with Sanfilippo disease in the near future.

The UK MPS Society considers this paper to be so important for the Sanfilippo Community that we have taken the unusual step of publishing the paper at the back of this MPS Magazine.

Supply situation for Fabrazyme and Replagal

As some members of the Fabry community know only too well the supply shortage of Fabrazyme continues and we are advised that this will continue until Genzyme's new manufacturing plant opens at the end of 2011. Members have been contacting the Society with concerns over delayed deliveries, continuing low doses and deterioration in health and quality of life.

The Society has been working closely with the Fabry International Network (FIN), and Eurordis to advocate for Fabry patients. In October 2010 two Fabrazyme Concensus Meetings were held in Amsterdam to discuss the ongoing Fabrazyme shortage. I participated in the Consensus meeting held on 4 October along with Erica Schenke from FIN and Lut De Baere and Erica attended the meeting on 9 October. Shortly afterwards a Concensus document was agreed. The patient organisations' concerns are not essentially around clinical decisions but transparency of terminology. On this matter we have voiced our concerns to the European Medicines Agency (EMA) who adopted the Concensus document.

So what is the terminology that concerns us and as Fabry patients do you know the difference?

Licenced dose or Authorised dose - This denotes that the dose has been robustly clinically trialled and the dose is approved by the regulatory authorities

Low dose - This refers to a dose that is below that of the approved dose and has not been robustly clinically trialled and approved by the regulatory authorities

The Fabry patient organisations are keen to ensure that during these challenging times, patients' views are properly understood and are reflected in the decisions being made on their behalf. The complete Fabry concensus statement can be found on the EMA website www.ema.europa.eu/ema. If as a patient you want to know more about your current Fabrazyme dosage please speak to your Fabry specialist who prescribes your drug.

The good news is that Shire have advised the patient organisations that they have ample supplies of Replagal.

Christine Lavery c.lavery@mpssociety.co.uk

European Medicines Agency reviews treatment recommendations for Fabrazyme

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has reviewed its previous recommendations on the use of Fabrazyme (agalsidase beta) during the ongoing supply shortage.
This was triggered by an increase in reported adverse events in patients treated with the lower dose of Fabrazyme that has been introduced during the shortage.

Fabrazyme is used to treat the rare, inherited enzyme-deficiency disorder Fabry disease. Temporary treatment recommendations to manage patients relying on this medicine have been in place since the start of the supply shortage and have been regularly updated.

The CHMP is now recommending that physicians switch back to prescribing the full dose of Fabrazyme according to the authorised product information, depending on the availability of enzyme replacement therapy and the severity of the disease.

In making their recommendation, the Committee took the outcome of a consensus group of experts in Fabry disease into account. The group met twice in October 2010, and included physicians with experience in Fabry disease and patient representatives working together to prioritise patients with Fabry disease during the ongoing supply shortage. The Committee also looked at spontaneous reports of adverse events and data from the Fabry registry.

The CHMP noted that since the introduction of a lower dose of Fabrazyme in June 2009, there has been a steady increase in the number of reported adverse events, matching the increase in the number of patients on the lower dose. At first, most of the events were pain-related, soon followed by reports of events affecting the heart, the central nervous system and the kidneys. This pattern suggests a progression of Fabry disease. Recently, a decrease in number of reported adverse events has been observed, which reflects the fact that more patients have either been switched to Replagal or have started receiving a full dose of Fabrazyme again. Despite this, the Committee observed that a subgroup of patients seems to be doing well on the lower Fabrazyme dose.

The CHMP also noted that monitoring plasma or urine GL-3 levels does not appear to add value to the clinical management of the patients while on a lower dose.

The updated CHMP temporary treatment recommendations for Fabrazyme are as follows:

- Patients who require enzyme replacement therapy for Fabry disease should be prescribed the authorised dose of either Fabrazyme (1.0 mg/kg once every two weeks) or Replagal (0.2 mg/kg once every two weeks).
- Low doses of Fabrazyme should be limited to those patients who are stable and prefer to remain on a low dose.
- Patients and prescribers are advised that a deterioration of the condition has been observed in patients on the lower dose. Pain, cardiac manifestations and deafness are the usual manifestations of Fabry disease progression.

These recommendations do not change the currently approved product information for Fabrazyme.

The supply shortage of Fabrazyme began in June 2009 and was caused by a series of manufacturing problems at the production site in Allston Landing, in the United States of America. Because the current productivity at Allston Landing is still lower than expected, supply of Fabrazyme will not return to normal before the second half of 2011, according to Genzyme.

The CHMP remains concerned about the continued supply shortages of Genzyme's medicines and is closely monitoring the implementation of their improvement measures to prevent similar manufacturing and quality problems in the future.

The Agency will make further updates as appropriate.

GSK and Amicus Therapeutics Enter Exclusive Worldwide Agreement to Develop and Commercialise Amigal™ for Fabry Disease

Amicus to receive $60M in upfront license payment and equity investment and eligible for approximately $170M million in future potential milestone payments.

LONDON, UK & CRANBURY, NJ, US, October 29, 2010 – GlaxoSmithKline PLC (GSK) and Amicus Therapeutics today announced a definitive agreement to develop and commercialise Amigal™ (migalastat HCl), currently in Phase 3 for the treatment of Fabry disease, a rare inherited disorder. Under the terms of the agreement, GSK will receive an exclusive worldwide license to develop, manufacture and commercialise migalastat HCl. Additionally, as part of the agreement GSK and Amicus also intend to advance clinical studies exploring the co-administration of migalastat HCl with enzyme replacement therapy (ERT) for the treatment of Fabry disease.

"This strategic collaboration is another significant milestone in delivering our vision for GSK Rare Diseases. Amicus' scientific and clinical expertise in human genetic diseases is among the best in the industry, and we are pleased to be collaborators and investors in this exceptional company" said Marc Dunoyer, Global Head of GSK Rare Diseases and a member of the GSK Corporate Executive Team. "Our focus now is to continue to advance Amigal for Fabry disease and it is our hope to deliver a first-in-class, oral medicine to the thousands of people worldwide living with this devastating rare disease."

John F. Crowley, Chairman and Chief Executive Officer of Amicus Therapeutics said, "The completion of this agreement with GSK is a transformational event for Amicus. It provides a strong validation of the potential for Amigal to become an important new treatment option for people living with Fabry disease and for our pharmacological chaperone technology broadly. GSK has extremely impressive global clinical, regulatory and commercial expertise and a strong commitment to the development of treatments for rare diseases. We look forward to working in close partnership with them." Crowley continued, "With this key strategic alliance with GSK and the added financial strength it provides, Amicus is now uniquely positioned to build shareholder value through our expertise in rare disease drug development."

About Amigal™ (migalastat HCl) for the Treatment of Fabry Disease

Migalastat HCl is an investigational treatment for Fabry disease and has the potential to be the first in a new class of oral, small molecule medicines called pharmacological chaperones. It is designed to selectively bind to and stabilise the target enzyme α-galactosidase A (α-Gal A), which facilitates proper trafficking of the enzyme to the lysosomes, where it is needed to break down the target substrate globotriaosylceramide (GL-3).

Results from Phase 2 studies of migalastat HCl, which has orphan designation in both the US and EU, demonstrated that in subjects identified as responders to migalastat HCl treatment resulted in increased levels of α-Gal A, reduced levels of GL-3 as measured in renal interstitial capillary cells from kidney biopsies and in urine, and a potential positive impact on renal function. Treatment with migalastat HCl has been generally well-tolerated, with no drug-related serious adverse events. The most common adverse events were headache, arthralgia and diarrhea.

A Phase 3 study (Study 011) commenced in the second quarter of 2009 and treatment of the first patient began in the fourth quarter of 2009. This ongoing study is a 6-month, randomized, double-blind trial comparing migalastat HCl to placebo in 60 subjects in approximately 40 investigational sites worldwide. The surrogate primary endpoint is the change in the amount of kidney interstitial capillary GL-3. Subjects being enrolled are Fabry patients who have never received enzyme replacement therapy (ERT), or who have not received ERT for at least 6 months, and who have a mutation responsive to migalastat HCl.

GSK and Amicus today provided an update to the enrollment timeline for Study 011. Enrollment is now expected to be completed in the first quarter of 2011 and preliminary results are expected to be announced in the second half of 2011.

Furthermore, a separate Phase 3 study (Study 012) is expected to commence before the year end. The study will be an 18-month, randomised, open-label study comparing migalastat HCl to ERT in approximately 60 subjects. The primary outcome of efficacy will be renal function as measured by glomerular filtration rate (GFR).

Articles appear courtesy of Amicus Therapeutics **www.amicustherapeutics.com**

Update on the MPS Society's Information Resources

The MPS Society is committed to providing current and accessible support to the MPS community and as part of this service we strive to ensure that we do our part to equip our members, their families and carers with relevant information resources.

These resources, which include the *Guide to Understanding...* series provide information on MPS and related diseases, their causes and affects and a general understanding of how the various diseases are managed. We are also dedicated to providing sources of informative support to the extended family such as Grandparents and Siblings.

Until recently many of our information materials have been available in a booklet format, however, we are now in the process of revising and transferring these into fact sheets that are available to download from our website as PDF documents.

We are aware that transferring the majority of our information resources into an electronic format is a significant change for some of our members, their families and carers; however, in doing so, the MPS Society is able to instantly update the information as and when necessary without having to use vital funding for the costly reprinting of literature.

The other added benefit of having these vitally important sources of information available online is how accessible they are to the individuals that need them. If a child with an MPS or related disease moves school or a family are newly diagnosed, they have the information instantly at their fingertips instead of waiting for the literature to be posted out to them.

There are, however, certain materials that we produce that are better suited to print. These include the booklets that are specifically designed for children in a way that they can sit with their parents, guardians, grandparent and/or siblings and learn from age appropriate information and pictures. These booklets are also an invaluable tool for use in schools to support children in understanding more about these diseases.

For more information, please phone us on 0845 389 9901 or email mps@mpssociety.co.uk.

New Fabry DVD resource

The MPS Society is pleased to introduce a new resource for individuals with Fabry. Supported by an unrestricted educational grant from Genzyme, a new DVD, Fabry: A Family Story has been developed. Two families, one from the UK and the other from the USA, talk to Dr Rob Hicks about living with Fabry and share their family experiences. The Society has copies available free of charge. If you would like one, please email mps@mpssociety.co.uk or phone 0845 389 9901.

Suggestions from our members

I wanted to share something which I think will be helpful to others.

I know it was a very extravagant moment but a while ago I purchased an alpaca duvet. The web details are listed below. They also make the duvet to the size you require. In the recent bouts of very cold weather and having been buried under piles of duvet, blankets etc, pinned down, and still not feeling my feet, I needed a solution. I am amazed, it is so worth it! This duvet regulates my temperature and I am warm, something I struggle with. It is also very light so easy for me to get into bed, more comfortable as I am not squashed and so I am in less pain. My sleep is also improved. I also think the fact that dust mite will not inhabit alpaca has helped my breathing. I can't wait to get home some days at the moment to warm up!

I just thought it was something you may find helpful for others not a cheap option but so worth it, particularly on the bad days as it's such an amazing comfort! **Sarah Long, MPS IVA**

www.farrlacey.co.uk

I was impressed with a drinking aid shown to me by the Gremo Family (MPS III). It is a straw named the Pat Saunders Straw. The straw has a clip which can attach the straw to the side of a thin walled beaker or cup. The unique part of the straw is the one way valve it has at the bottom. The valve stops the liquid from running back down the straw into the drink again thus can help users to not swallow too much air with their drinks.

Robert Gremo demonstrated how to make a curve towards the end of a straw as this could help stop users from gagging on too much straw in their mouths. A hairdryer could be aimed onto the straw about 3 to 4 inches from the mouth end and the straw could be curved while warm and held until cooled in the shape wanted.

I had a look online and found many sites selling Pat Saunders straws. Here are two I have chosen to increase your choices:
Living Aids Online, *found at www.livingaidsonline.co.uk/ then "About the house" then "drinking"*

Living Made Easy, *found at www.livingmadeeasy.org.uk/ then "Eating and Drinking" then "Drinking equipment" then "Drinking straws and straw holders"*
Lindsey Wingate l.wingate@mpssociety.co.uk

Obtaining Travel Insurance

Fiona Macrae, founder of *Insurancewith* explains how she became involved in specialist travel insurance following her own experiences and how she hopes to help others affected by long term conditions in accessing travel insurance policies.

In 2010 the erupting volcano in Iceland brought travel insurance under the microscope, and what has become clear from the scrutiny is that you should check your travel insurance policy documents carefully to ensure that the cover provided meets your requirements.

Insurance is one of those things that everyone needs but nobody wants to pay for and unfortunately you only realise the benefit of a good comprehensive travel insurance policy when things go wrong and then they are worth their weight in gold.

If you have a pre-existing medical condition, it is always advisable to use a specialist travel insurance adviser like *Insurancewith*, that way if you need to make a claim you will not get any nasty surprises.

Insurancewith is the brain child of Fiona Macrae who was diagnosed with breast cancer in 2005. Fiona was horrified, not only at the cost of travel insurance after her diagnosis but with the questions that she was asked and the way in which she was spoken to in the process of obtaining quotes.

Before Fiona's diagnosis she was a Lloyd's insurance broker and she thought that there must be a better way to do this. There was, and the result is *Insurancewith*.

The travel insurance market for people with pre-existing medical conditions was seriously lacking, the policies on offer seemed to be rated on the perceived risk of the condition rather than the actual risk. Because of Fiona's experience with cancer and her career in the insurance industry, she and the Underwriters, Travel Insurance Facilities (TIF) were in the unique position of being able to look at the problems from both sides.

One of the main issues Fiona found was discussing personal medical information with strangers. She found it very distressing, which is why at *Insurancewith* you can do everything online, even the medical screening. They do, however, have a call centre if you prefer to talk to someone. Everyone in the call centre is fully trained to deal sensitively and empathically with the callers.

Insurancewith also fully understands the risk; they are not insuring your life, just your holiday, so they look at the risk in the short term. You may have a life limiting condition, however at present you are well and stable, therefore why should you not be offered a reasonably priced travel insurance policy?

It is by taking this attitude to rating travel insurance policies that enables *Insurancewith* to offer lower premiums than most.

At *Insurancewith* we have a very good understanding of breast cancer, and we are building up our understanding of other conditions.

Working with the Genetic Alliance UK has enabled *Insurancewith* to work with a wide range of charities and conditions. The company has started to build specific medical screening questions for individual conditions as they recognise that different aspects of conditions can cause different risks, this is what helps keep the premiums at affordable levels for the majority.

Flexibility is also a key. The medical screening questions that *Insurancewith* depend on to rate the policies need to be up to date and relevant to the consumer.

Because everything is in house, *Insurancewith* are able to react quickly to changes in treatment regimes and medication.

Insurancewith's medical screening system is updated on a daily basis.

If you are having trouble obtaining travel insurance because of your condition then take a look at the *Insurancewith* website: **www.insurancewith.com/GIG** or email them at **Insurancewith@infinityinsurance/co.uk**

Insurancewith want to work with as many charities as possible so they can understand as many conditions as possible, enabling them to offer affordable travel insurance to the majority of people with pre-existing medical conditions.

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Genetic Alliance UK
Supporting. Campaigning. Uniting.

Getting legal authority to make decisions about money, property and welfare: a new information sheet from the Challenging Behaviour Foundation

Are you a family carer?
Do you support a family member aged 16 years or above?
Does your family member have severe learning disabilities?
Do they live in England or Wales?

If the answer is yes to all these questions, then read on.

If you have a relative with severe learning disabilities they may not be able to make all of their own decisions e.g. choosing where to live. In some circumstances you may need to get legal authority to make decisions on behalf of your family member by applying to the Court of Protection to be appointed as a 'deputy'.

One example is applying to be a deputy to get legal authority to sign a tenancy agreement on behalf of your relative so they can rent their own property.

Our new information sheet has been written for family carers who wish to gain legal authority to make decisions about money, property and/or welfare on behalf of a family member who has severe learning disabilities. It provides a practical step by step guide to the application process.

The information sheet can be downloaded free of charge: www.challengingbehaviour.org.uk

Alternatively a hard copy can be ordered from the Challenging Behaviour Foundation. Cost: £1; free to family carers supporting an individual with severe learning disabilities.

Helen Marron
The Challenging Behaviour Foundation
Email: info@thecbf.org.uk

www.challengingbehaviour.org.uk
General Enquiries: Tel. 01634 838739
Family Support Worker: Tel. 0845 602 7885 (individual telephone support for families at the cost of a local call)

The Challenging Behaviour Foundation is a registered charity (no. 1060714) supporting families caring for individuals with severe learning disabilities.

If any MPS families would like to receive hard copies of the Challenging Behaviour Foundation newsletter please contact the Foundation. They also have a range of information sheets available to download free of charge from their website and resources which are all available free to family carers.

Contact a Family and the Children's Trust are campaigning for changes to rules regarding DLA when under 16s receive it or claim for it

• A child under 16 who receives DLA stops receiving it once they have spent 84+ days in hospital. These days do not need to be consecutive, they are added up.
• When a child first becomes eligible for DLA while in a hospital or medical establishment, they cannot receive the money until they are discharged.

If a child's DLA is suspended, the parents Carers Allowance is jeopardised too even if the parent is providing a substantial amount of care for the child in hospital.

If Carers Allowance is stopped this can affect other benefits the parents receive.

Many parents have additional costs when their child is in hospital.

Many parents have to take unpaid leave from work or give up work to care for the child in hospital.

There are additional costs for parents, which will affect them financially and emotionally, additional travel costs incurred due to child's hospitalisation (many families have funds for a certain amount of miles per week fuel, or certain bus/train journeys and the budget is not negotiable), car parking, meals away from home (will cost more than the family food budget), alternative childcare for siblings. Something has to give, the pressure caused to parents over added financial pressure could prevent them being able to cope in many ways, and cause them to stop being able to take in and comprehend vital medical advice and treatment as well as stop them being able to manage their own health needs.

Lindsey Wingate l.wingate@mpssociety.co.uk

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PLoS one

Genistein Improves Neuropathology and Corrects Behaviour in a Mouse Model of Neurodegenerative Metabolic Disease

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Abstract

Background: Neurodegenerative metabolic disorders such as mucopolysaccharidosis IIIB (MPSIIIB or Sanfilippo disease) accumulate undegraded substrates in the brain and are often unresponsive to enzyme replacement treatments due to the impermeability of the blood brain barrier to enzyme. MPSIIIB is characterised by behavioural difficulties, cognitive and later motor decline, with death in the second decade of life. Most of these neurodegenerative lysosomal storage diseases lack effective treatments. We recently described significant reductions of accumulated heparan sulphate substrate in liver of a mouse model of MPSIIIB using the tyrosine kinase inhibitor genistein.

Methodology/Principal Findings: We report here that high doses of genistein aglycone, given continuously over a 9 month period to MPSIIIB mice, significantly reduce lysosomal storage, heparan sulphate substrate and neuroinflammation in the cerebral cortex and hippocampus, resulting in correction of the behavioural defects observed. Improvements in synaptic vesicle protein expression and secondary storage in the cerebral cortex were also observed.

Conclusions/Significance: Genistein may prove useful as a substrate reduction agent to delay clinical onset of MPSIIIB and, due to its multimodal action, may provide a treatment adjunct for several other neurodegenerative metabolic diseases.

Citation: Malinowska M, Wilkinson FL, Langford-Smith KJ, Langford-Smith A, Brown JR, et al. (2010) Genistein Improves Neuropathology and Corrects Behaviour in a Mouse Model of Neurodegenerative Metabolic Disease. PLoS ONE 5(12): e14192. doi:10.1371/journal.pone.0014192

Editor: Maria A. Deli, Hungarian Academy of Sciences, Hungary

Received July 14, 2010; **Accepted** November 8, 2010; **Published** December 1, 2010

Funding: This work was funded by the UK Society for Mucopolysaccharide Diseases (J4G/25/04), with contributions from the Japanese Society of the Patients and Families with MPS, MPS Schweiz, Gesellschaft fur Mukopolysaccharidosen, Asociacion MPS Espana, The Irish Society for Mucopolysaccharide Diseases, the Canadian Society for Mucopolysaccharide and Related Diseases, the National MPS Society, the Swedish MPS Society, Gesellschaft fur MPS e.V., VKS, with partial support by Ministry of Science and Higher Education (Poland) (N302 046 32/3603) and Foundation for Polish Science Team Programme, co-financed by the EU European Regional Development Fund (TEAM/2008-2/7). Support from the Polish MPS Society and the Manchester Biomedical Research Centre is also acknowledged. MM was supported by the InnoDoktorant, scholarships for PhD students from the European Social Fund, and by the Program of Introduction of Modern Education Elements at University of Gdansk. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. Also as Jillian R. Brown and Brett E. Crawford are affiliated to Zacharon Pharmaceuticals Inc, Zacharon Pharmaceuticals Inc did play a role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: Jillian R. Brown and Brett E. Crawford are affiliated to Zacharon Pharmaceuticals Inc. It could be reasonably perceived by an outside party that Zacharon Parmaceuticals could have interfered with objective analysis of the data they produced. However, all samples from the University of Manchester were blinded before sending to Zacharon Pharmaceuticals for biochemical analysis. Therefore Zacharon Pharmaceuticals had no control over the interpretation of the data produced. This does not alter the authors' adherence to the PLoS policy on data sharing.

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☯ These authors contributed equally to this work.

Introduction

There are over 50 described lysosomal storage disorders (LSDs), affecting approximately 1/7000 live births [1]. Many of these are caused by defects in lysosomal enzyme function, leading to the accumulation of uncatabolised substrates, often resulting in progressive neurodegeneration, neuroinflammation and death in childhood [2]. Enzyme replacement therapies are limited to attenuated LSDs or those affecting visceral organs alone due to an inability of lysosomal enzymes to traffic across the adult blood brain barrier [3]. Haematopoietic stem cell transplantation is an efficient treatment for a very small subset of these disorders [4], but substrate reduction therapy (SRT) which relies on inhibition of substrate anabolism, or substrate clearance via alternative catabolic pathways, is emerging as an effective alternative for some glycosphingolipid LSDs [5]. SRTs are limited by the lack of

agents able to effectively reduce substrate without significant toxic side effects.

The tyrosine kinase inhibitor genistein aglycone [6] reduces glycosaminoglycan (GAG) substrate accumulation in fibroblasts of several mucopolysaccharide LSDs [7] has low oral toxicity in mammals [8,9] and around 10% blood brain barrier permeability [10]. Genistein in a supplement form has been given to patients with MPSIIIA and IIIB, GAG storing LSDs with no effective treatments [11], at 5 mg/kg/day, but efficacy, although encouraging, remains unclear [12]. We have recently shown that short-term administration of genistein significantly reduces liver lysosomal storage in mice with MPSIIIB [13]. Genistein has also been shown to inhibit lipopolysaccharide (LPS) induced TNF-alpha, IL1-alpha and IL6 production in mixed glial and astrocytic cultures [14] and inhibit microglial activation in mixed neuron-glial and microglial enriched cultures [15], suggesting a possible role in attenuating neuroinflammation. We tested the hypothesis that high doses of genistein given long-term could reduce brain storage of primary GAG substrates, secondary glycosphingolipids and reduce neuroinflammation, a common feature of many neurodegenerative diseases.

Results

Genistein reduces lysosomal size and storage of heparan sulphate in brain and liver

MPSIIIB and control wild-type (WT) mice of both sexes were treated from 8 weeks of age for 9 months with a soy free diet or diet containing 160 mg/kg/day of genistein aglycone. Four coronal sections from each brain were stained and two fields of view for each section quantified (Figure 1A). Cells throughout the brains of MPSIIIB mice have an enlarged lysosomal compartment size as measured by the intensity of LAMP2 (lysosomal associated membrane protein 2) staining [16], and increased storage of the GAG, heparan sulphate. Following genistein treatment, highly significant 31% reductions in LAMP2 staining were observed in the cortex (Figure 1B,C,F), 34% in the hippocampus (Figure 1D) as well as a significant 37% reduction in the pathogenic heparan sulphate stored in the brains of MPSIIIB mice (Figure 1E). No changes in LAMP2 or heparan sulphate were seen in WT mice.

LAMP2 staining and total GAGs were also significantly reduced by 64% and 35% respectively in the livers of MPSIIIB mice receiving genistein (Figure 1G,H), whilst genistein treated WT mice showed significantly decreased liver GAGs (Figure 1H).

Genistein reduces neuroinflammation in MPSIIIB mice

To determine if genistein could reduce neuroinflammation in MPSIIIB, we counted the number of GFAP-positive astrocytes (Figure 2A,B) and Isolectin B4-positive microglial cells (Figure 2C,D) in the cerebral cortex. MPSIIIB mice exhibit a marked increase in neuroinflammatory astrocytes and microglial cells [13,16] concomitant with activation of several neuroinflammatory mediators [17,18,19] compared to WTs. Genistein significantly reduced both GFAP-positive astrocytes (12%) and Isolectin B4-positive microglial cells (19%) in the cerebral cortex of MPSIIIB mice whilst no change was seen in WT mice (Figure 2A–D). Furthermore, some microglia in the genistein treated MPSIIIB mice appear to be smaller and less intensely stained suggesting that they are less activated than microglia in untreated MPSIIIB mice.

Genistein may reduce secondary metabolites and improves synaptic function

In many LSDs, including MPSIIIB, secondary metabolites such as GM2 and GM3 gangliosides, as well as cholesterol, are accumulated [20,21] as a result of the primary catabolic block. Immunohistochemistry showed significant GM2 ganglioside storage, particularly in layer II, III and V of the cortex in MPSIIIB mice that was significantly reduced by genistein (25%) (Figure 3A,B). In WT mice, GM2 was virtually undetectable in the cortex as previously shown [20]. The proportion of GM2 and GM3 measured biochemically and expressed as percentage of total gangliosides also showed clear pathologic elevation in untreated MPSIIIB mice (Figure 3C). However a minor reduction of GM2 was only observed in genistein treated MPSIIIB female mice (6.2% vs $7.4\pm0.5\%$) while GM3 remained unchanged in all mutants ($12.5\pm0.1\%$). Because pooled brain sections were used for analysis, we cannot be confident that this small GM2 reduction is mediated by genistein. Histology reflects cerebral cortical GM2 between 0.26 to -1.94 mm relative to bregma, whilst biochemistry reflects ganglioside storage from -2.5 to -4.5 mm relative to bregma.

We observed a significant reduction of the pre-synaptic vesicle associated membrane protein, VAMP2 in the cerebral cortex (Figure 3D,E) and hippocampus (not shown) of MPSIIIB mice in agreement with our previous findings [16]. VAMP2 is part of the SNAP/SNARE complex involved in synaptic transmission, the loss of which has been shown to result in a dramatic reduction in synaptic function [22]. Genistein significantly improved VAMP2 staining in cortex but not in hippocampus of MPSIIIB mice.

Genistein corrects behaviour of MPSIIIB mice

Locomotor activity, anxiety and exploratory behaviour were monitored automatically in the open field test [23] over a 1 hour period, as well as frequency and duration of very rapid exploratory behaviour (speed>90 mm/s) and immobility (speed<0.05 mm/s) at 8 months of age. MPSIIIB mice showed a highly significant increase in the frequency with which they cross into or out of a central area (Figure 4A), their speed in this area or the side area (Figure 4B,C), the total distance travelled (Figure 4D), and frequency and duration of travelling at more than 90 mm/s (Figure 4E,F), indicating increased exploration. All of these parameters were fully normalised by genistein treatment. MPSIIIB mice showed significantly reduced frequency (Figure 4G) and duration of immobility (Figure 4H) which were also normalised by genistein treatment.

Significant gender*genotype effects were observed in centre and side speed, distance travelled, frequency of speed over 90 mm/s, immobility frequency and duration. Untreated female MPSIIIB mice performed significantly worse than male MPSIIIB mice on these tasks, however when genders were analysed separately, significant correction of MPSIIIB mice by genistein was observed in all cases except total distance travelled ($p = 0.06$) and frequency of immobility ($p = 0.07$) for untreated vs treated male MPSIIIB mice.

The hanging bar test measures motor co-ordination and has an element of memory and learning due to a training period [24]. MPSIIIB mice performed significantly worse than WT mice at 10 months (Figure 4I). In contrast, genistein treated MPSIIIB mice were completely corrected at 10 months and could not be distinguished from WT mice suggesting retention of motor function.

Discussion

We have shown a significant reduction in lysosomal size in the cerebral cortex and hippocampus and in total brain storage of pathological heparan sulphate in MPSIIIB mice treated with genistein aglycone for 9 months. The fact that WT mice do not show a reduction in brain substrate and the lack of any obvious

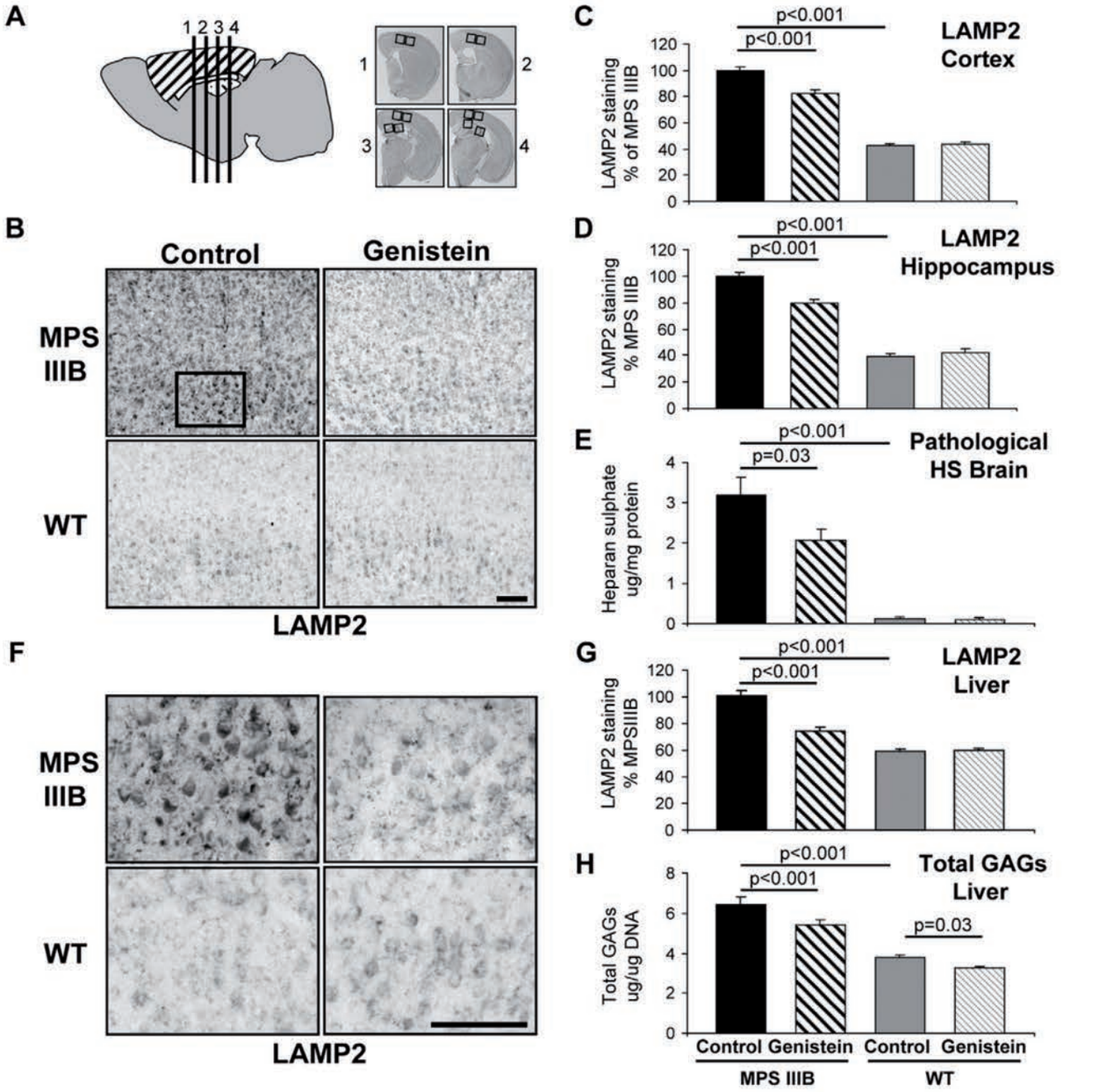

Figure 1. Primary storage substrates are reduced in brains of MPSIIIB mice after genistein treatment. (**A**) 11 month old MPSIIIB and WT, male and female mice with and without long-term genistein treatment were sacrificed and 30 μm coronal sections (numbered 1–4) were cut from each mouse at positions 0.26, −0.46, −1.18 and −1.94 relative to bregma. For cerebral cortex (hatched), two low power fields of view for each section (boxed) were quantified or positive cells counted (8 fields total), whilst for hippocampus (spots), two low power fields from sections 3–4 (boxed) were quantified (4 fields total). All sections were stained together and blinded to ensure consistency. (**B**) Representative Lysosomal Associated Membrane Protein (LAMP2) staining of cerebral cortex of 11 month old MPSIIIB and WT, male and female mice with and without long-term genistein treatment. This indicates the size of the lysosomal compartment and hence stored material in cells in layers II/III-V/VI of the cerebral cortex. The images correspond to section 2 shown in Figure 1A. Bar = 100 μm. (**C**) Quantification of mean LAMP2 staining in cerebral cortex is expressed as a percentage of staining in untreated MPSIIIB mice. (**D**) Quantification of mean LAMP2 staining of hippocampus. (**E**) Mean weight of pathological heparan sulphate in the brain per mg protein, measured using the SensiPro assay. (**F**) High power view of cerebral cortex layer V - box from (**B**). Bar = 100 μm. (**G**) Quantification of mean LAMP2 staining of 2 fields of view from 3 liver sections (6 fields total) is expressed as a percentage of staining in untreated MPSIIIB mice. (**H**) Mean weight of total glycosaminoglycans in the liver per μg DNA, measured using the Blyscan assay. For all graphs genders were pooled, thus n = 12 mice per group, error bars represent SEM, p values are for Tukey's multiple comparisons test.
doi:10.1371/journal.pone.0014192.g001

toxicity, suggests that genistein at these doses in the brain only weakly inhibits tyrosine kinases and this is borne out by chronic studies in the rat and dog suggesting low oral toxicity [8,9].

We did see liver GAG reductions in WT mice treated with genistein which could reflect higher bioavailability in the liver [10], coupled with the high metabolic activity of this organ. We

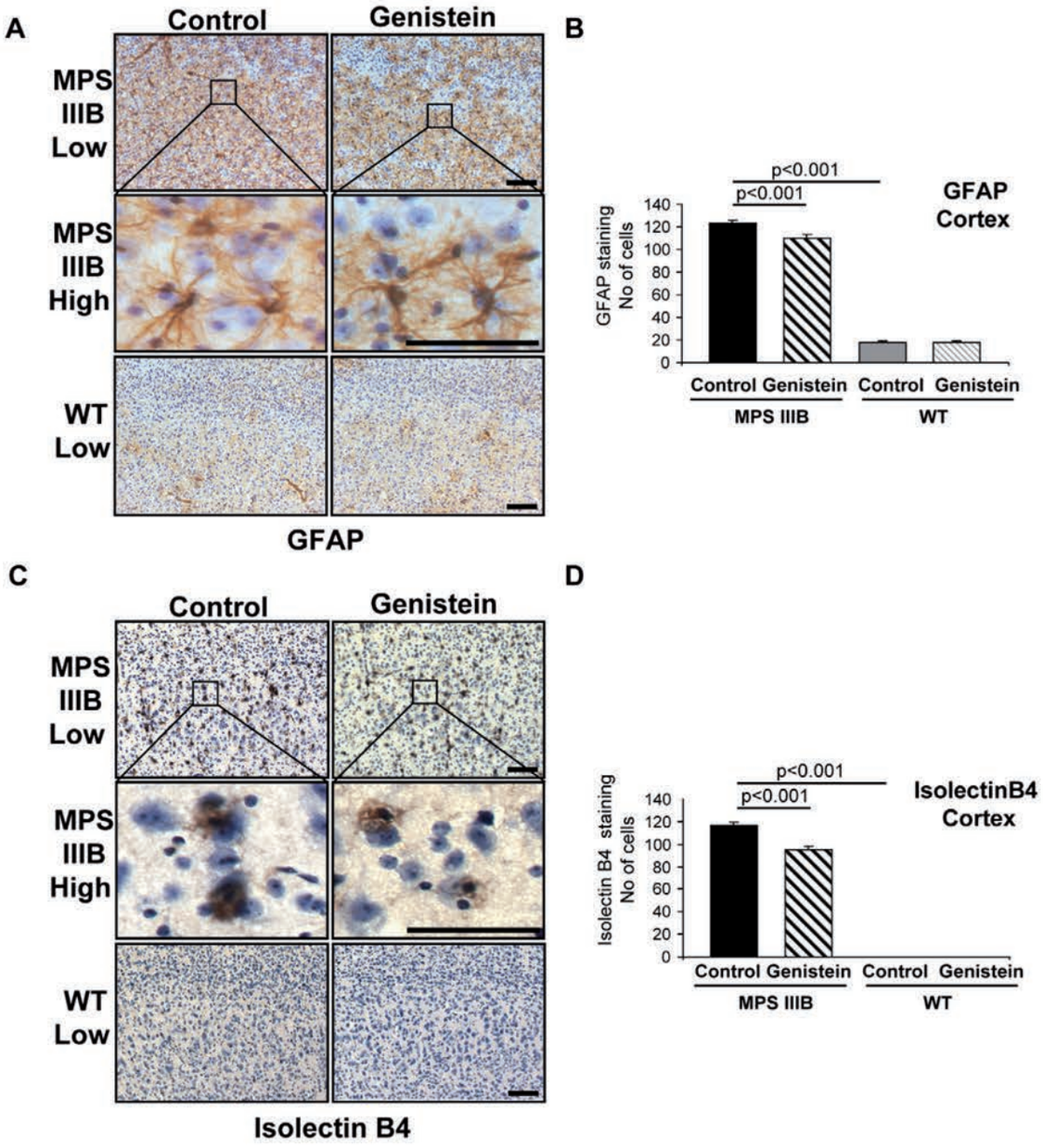

Figure 2. Neuroinflammatory markers are reduced in brains of MPSIIIB mice after genistein treatment. (**A**) Representative Glial Fibrillary Associated Protein (GFAP) staining of astrocytes (brown) in the cerebral cortex of 11 month old MPSIIIB and WT mice with and without long-term genistein treatment. Sections have been counterstained with haematoxylin to highlight nuclei (blue). The images correspond to section 2 shown in Figure 1A. Boxed areas are enlarged to show individual astrocyte cell bodies. Bar = 100 μm for low power images and 50 μm for enlargements. (**B**) The mean number of GFAP positive cells in the cerebral cortex per low power field of view were counted as described in Figure 1. (**C**) Representative Isolectin B4 staining of microglial cells (brown) in the cerebral cortex. Sections have been counterstained with haematoxylin to highlight nuclei (blue). The images correspond to section 2 shown in Figure 1A. Boxed areas are enlarged to show individual microglial cells. Bar = 100 μm for low power images and 50 μm for enlargements. (**D**) The mean number of Isolectin B4 positive cells in the cerebral cortex per low power field of view were counted. For all graphs genders were pooled, thus n = 12 mice per group, error bars represent SEM, p values are for Tukey's multiple comparisons test.

doi:10.1371/journal.pone.0014192.g002

found a significant gender effect in total liver GAGs as observed previously [13], with male mice storing more GAGs than females. Genistein still significantly reduced storage in male and female MPSIIIB mice. No gender or gender*genotype effects were seen in the brain. Gender specific differences in GAG storage have not been reported to our knowledge in patients with MPSIIIB and may just reflect metabolic gender differences in inbred murine strains.

Our observation that genistein was able to reduce the number of microglial and astrocytic cells in MPSIIIB mice could have a dual explanation. Genistein has been reported to reduce LPS induced inflammatory cytokine production [14], and to inhibit microglial

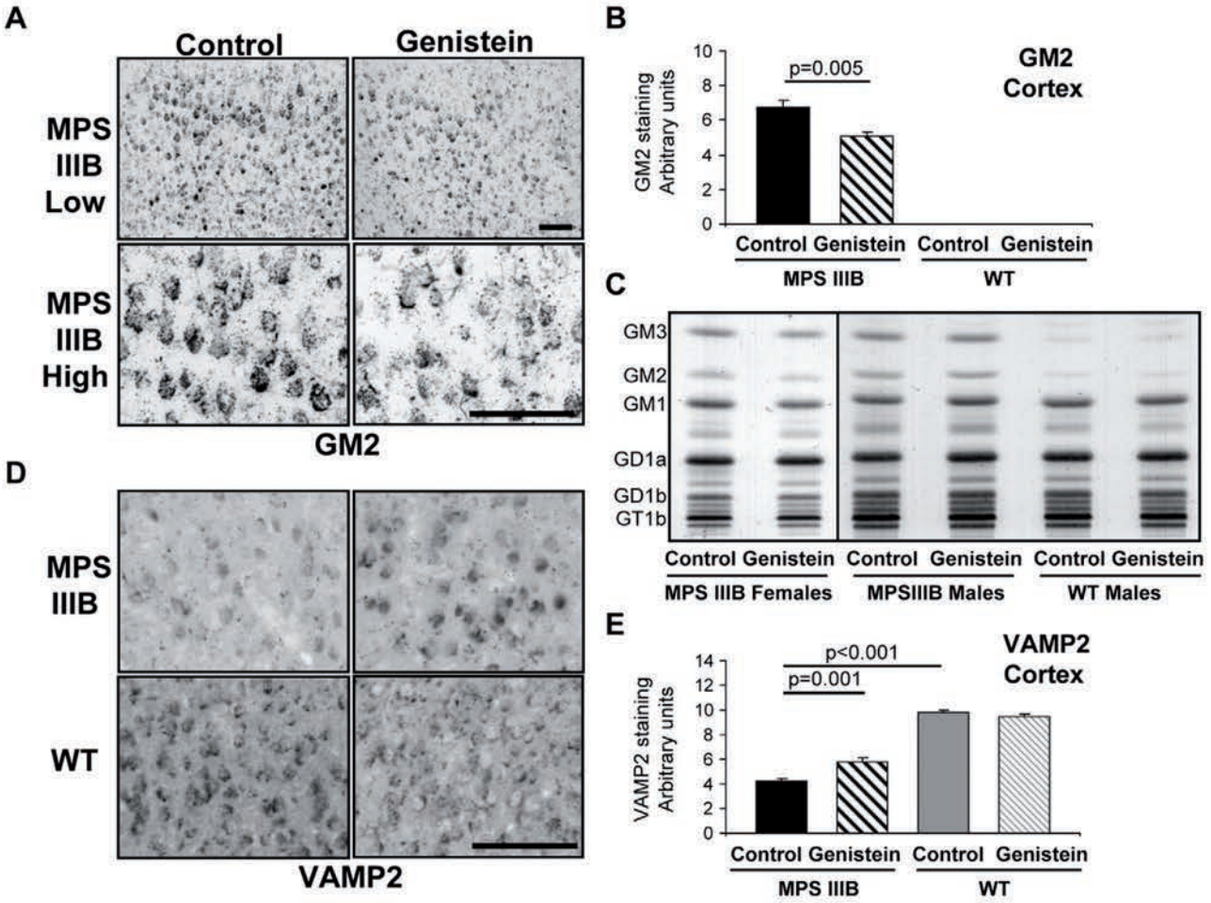

Figure 3. Some improvements were seen in secondary metabolite storage and markers of synaptic transmission in brains of MPSIIIB mice after genistein treatment. (A) Representative GM2 ganglioside staining in the cerebral cortex of 11 month old MPSIIIB mice with and without long-term genistein treatment at low (layers II/III-V/VI) and high power (layer V). The images correspond to section 2 shown in Figure 1A. Bar = 100 μm. WT mice have no GM2 staining in the cortex and are not shown. (B) Quantification of mean GM2 staining of cerebral cortex in arbitrary units. (C) Chromatographic profiles of total gangliosides from the fourth brain hemicoronal fifth (rostral to caudal). Each lane represents 3mg wet weight of pooled sections from 4 mice. (D) Representative Vesicle Associated Membrane Protein (VAMP2) staining in the cerebral cortex. VAMP2 is a synaptic vesicle marker required for effective synaptic transmission. The images correspond to section 2 shown in Figure 1A. Bar = 100 μm. (E) Quantification of mean VAMP2 staining of cerebral cortex in arbitrary units. For all graphs genders were pooled, thus n = 12 mice per group, error bars represent SEM, p values are for Tukey's multiple comparisons test.
doi:10.1371/journal.pone.0014192.g003

activation [15] *in vitro*, but it would be difficult to separate a role for genistein in direct modulation of neuroinflammation from that of reduced heparan sulphate storage, as reduction of heparan sulphate oligosaccharides ameliorates inflammation, although the converse may not be true [25]. Despite this apparent disconnect, further investigation of the role of genistein in neuroinflammation in other neurodegenerative diseases is warranted, since anti-inflammatories have been shown to reduce microglial cells in mouse models of Alzheimer disease [26,27] and reduce neuroinflammation and prolong life in models of Sandhoff disease [28]. Thus although a reduction in inflammation is unlikely to reduce primary storage, it may help to improve behavioural manifestations of disease.

There was some evidence to suggest that genistein was also able to change other downstream neuropathological events. Although it was unclear if genistein was able to mediate changes in minor monosialogangliosides, the data was more clear cut for improvements in synaptic organisation as shown by VAMP2 staining [16]. This is unlikely to reflect a gain in function, instead it is more likely that genistein is able to delay loss of synaptic transmission, which would be important if this effect can be replicated in other neurodegenerative diseases.

Finally, behaviour of MPSIIIB mice was fully corrected to WT levels by genistein treatment. The hyperactive and increased exploratory locomotor behaviour of MPSIIIB mice is similar to that of MPSIIIB patients and is consistent with changes reported previously by us and others [16,23]. We found the 60 minute open field test to be an equally good measure of abnormal locomotor activity in these mice as our circadian locomotor test, with the advantage of being much shorter [16,23]. Interestingly, the duration spent in the centre of the cage was virtually unchanged in MPSIIIB or WT mice in our hands (not shown) suggesting a normal prey response to danger in these mice. This is in contrast to decreased responses to danger in MPSIIIB mice observed in the elevated plus maze [23], although the small size of our arenas could have reduced these responses [29] and may explain why we did not observe these differences. Males also showed reduced responses compared to females in several of these locomotor tests.

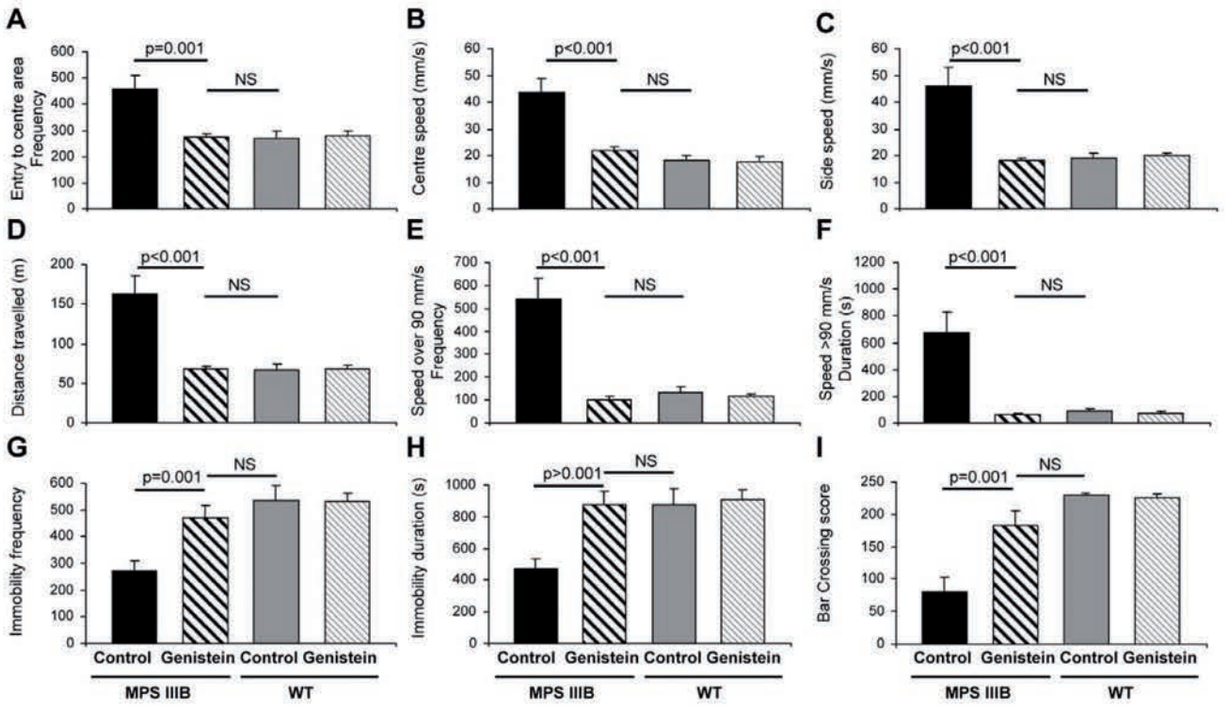

Figure 4. Genistein treatment corrects behavioural abnormalities seen in MPSIIIB mice. (**A**) 8 month old MPSIIIB and WT, male and female mice with and without long-term genistein treatment were monitored in the open field test of locomotor and exploratory activity for 60 minutes. The arena was divided into 12 squares and the frequency of entry (and total duration- not shown) to the central 4 squares measured to determine responses to danger and thigmotaxis. (**B**) The average speed in the central area and (**C**) side squares was also measured, as was (**D**) total distance travelled, to give an indication of abnormal locomotor activity. (**E**) Rapid exploratory behaviour was measured by frequency and (**F**) duration of speed more than 90 mm/s. (**G**) The number of times and (**H**) the duration of time spent immobile was also measured as speed under 0.05 mm/s. (**I**) Latency to cross or fall from a hanging bar is a measure of locomotor activity with some element of cognitive function due to a training period and was tested at 10 months of age. Significant gender*genotype effects were seen in centre and side speed, distance travelled, frequency of speed over 90 mm/s, immobility frequency and duration reflecting greater pathological effect in female MPSIIIB mice. For all graphs genders were pooled, thus n = 12–14 mice per group, error bars represent SEM, p values are for Tukey's multiple comparisons test.
doi:10.1371/journal.pone.0014192.g004

MPSIIIB mice start to retain urine at 4–6 months of age (not shown), often leading to hydronephrosis or uremia, which may reflect autonomic control of urinary sphincter function or more likely, blockage of the urinary tract [30]. This manifestation of disease appears earlier in males than females, leads to gait abnormalities and is often the humane endpoint. This may limit male MPSIIIB mice in their locomotor activity giving the illusion of less pathology in these tasks. Given that urinary retention is not reported in humans with MPSIIIB, extended studies of lifespan in MPSIIIB mice where urinary retention is the primary endpoint have limited value in indicating improvements in neuropathology.

Genistein is widely available as a food supplement, occurring naturally within soy foods predominantly in a glycoside form (genistin) [31] and can also be synthesised or purified in its aglycone form. A concentrated form of soy extract has been used in clinical trial for patients with MPSIIIA and IIIB at 5–10 mg/kg/day, doses that we would predict from our previous data [13] would not be effective in the brain but may clear peripheral storage. This open label study was not designed to study neurological outcomes but did show small reductions in urinary GAGs [12]. Although genistein has been widely tested for safety and efficacy at reducing incidence of various forms of cancer [32] its only approved clinical indication to our knowledge is for osteopenia using relatively low doses [33]. Our use of genistein aglycone, which is reported to be less susceptible to degradation by gut flora than genistin [31], has high plasma bioavailability [34] and delivery of high doses to ensure sufficient blood brain barrier diffusion [10] may explain why our approach was effective.

In conclusion, genistein aglycone significantly reduces brain lysosomal storage, and neuroinflammation, delays synaptic loss and corrects behaviour in mice with MPSIIIB. Due to its multimodal actions, genistein may prove applicable in delaying clinical onset of disease and neuroinflammation in MPSIIIB and similar neurodegenerative metabolic diseases.

Materials and Methods

Mouse maintenance and drug administration

Animal procedures were ethically approved and carried out in accordance with UK Home Office regulations under project licence PPL 40/3056. The MPSIIIB knock-out mouse [35] was maintained as a heterozygote line on an inbred C57BL/6J background at the University of Manchester, UK as previously described [16]. Eight week old male and female MPSIIIB and WT mice (n = 6–7 per group) received a soy free diet (2014 Teklad Global Rodent Diet, Harlan, England) or the same diet containing 160 mg/kg/day genistein aglycone (Pharmaceutical Research Institute, Warsaw, Poland). 2 mice from the MPSIIIB untreated and 2 from the MPSIIIB treated groups were found dead at 9–10 months of age and excluded from biochemical or histological analysis.

Behavioural testing

All animals had access *ad libitum* to food and water. Behavioural testing was performed between 8:00 and 10:00 A.M. on naïve mice, standardizing as many environmental parameters as possible [29]. The tester was blinded to genotype.

Open field test

8 month old mice were placed in the centre of one of 4 opaque arenas (480×375×210 mm) and monitored for 60 minutes by digital camera. Arenas were cleaned between sessions. Videos were analyzed and scored in an unbiased fashion using TopScan Suite (Clever Sys. Inc, Virginia, USA) and random videos were checked for consistency of automated scoring. Locomotor measures included total distance travelled, duration and frequency of immobility (speed less than 0.05 mm/s), duration and frequency of rapid exploration (speed over 60 mm/s and 90 mm/s). The arena was divided into 12 squares and frequency and duration of crossover to or from the 4 central squares was used to measure locomotor activity and response to danger. Frequency and duration of rearing was not found to be consistent using Topscan suite.

Hanging bar test

Mice were tested individually with randomization. The test was modified from [24]. Briefly, a metal bar 25 cm long was located horizontally between 2 wooden columns. The animal was held by the tail and allowed to grasp the centre of the bar with forepaws only before release. Latency to cross or fall was scored as described [24]. Each animal had 3 training trials with a 10 min rest before the final scored trial. Results are presented as an average of 3 trials, and the test was performed at 10 months of age.

Tissue preparation

Mice were sacrificed by dislocation of the cervical vertebrae. Brains were divided into two hemispheres. One hemisphere was fixed (4% paraformaldehyde/PBS) for 24 hours followed by cryoprotection with 30%sucrose/PBS/2mMgCl_2 for 48 hours at 4°C and stored at −80°C for histological analysis. The entire fixed hemisphere was cut into coronal sections (30 µm) using a sledge microtome (Hyrax S30, Zeiss, Germany) and each section stored in sequential wells of a 96 well plate. Staining was performed on free-floating sections before mounting on superfrost slides (Fisher Scientific, USA). The other hemisphere was divided into hemicoronal fifths, snap frozen, and stored at −80°C for biochemistry. For liver, half a lobe was fixed (4% paraformaldehyde/PBS) and embedded in paraffin for histology. 6 µm-thick sections were mounted on superfrost slides before staining. The other half was snap frozen for biochemistry.

Immunohistochemistry

For staining to be quantifiable and comparable, 4 brain sections were taken from positions 0.26, −0.46 −1.18 and −1.94 mm relative to bregma [36], from every mouse (n = 6–7), in all 8 groups and all 192 sections stained concurrently for each marker and developed for exactly the same period of time. Each marker used the next adjacent set of comparative sections from positions 0.26, −0.46 −1.18 and −1.94 mm relative to bregma. For brains, LAMP2, GFAP, VAMP2, and Isolectin B4 staining was performed as previously described [13,16]. The anti-GM2 antibody (a gift from Dr Kostantin Dobrenis and Prof Walkley) was diluted 1/40 and the staining was performed as previously described [20]. Sections were visualised with diaminobenzidine (DAB substrate kit, Vector Labs Inc.). For quantification analysis, nickel was added to the DAB substrate to obtain black staining for easier quantification. Isolectin B4 and GFAP sections were counter-stained with Mayer's haematoxylin. Liver sections were stained for LAMP2 as previously described [13].

Image analysis

Two non-overlapping low power (x20 objective) fields of view were digitally photographed from each of the 4 sections, as shown in Figure 1A, using an Axioscope light microscope and Axiocam color CCD with Axiovision software (Figure 1A).

The first field of view was taken with the left edge of the field of view in line with the apex of the cingulum and at a right angle to the fibres of the corpus callosum and positioned so that cerebral cortical laminas II/III-V/VI were photographed. The second non-overlapping field of view was taken adjacent to the first field of view covering cerebral cortical laminas II/III-V/VI. This ensured that the same fields of view were taken for each section for each mouse (total 8 non-overlapping fields per mouse [n = 6–7/group]). For the hippocampus, two non-overlapping low power (x20 objective) fields of view were digitally photographed from the third and fourth sections (relative to Bregma −1.18 and 1.94) with the first field of view covering the CA1 region and the second covering the CA2 and CA3 regions of the hippocampus as shown in Figure 1A (total of 4 non-overlapping fields per mouse [n = 6–7/group]). Identical exposure settings were used for each stain and all photographs taken in one session. Images were transformed to eight bits of grey resolution and stored in TIFF format. To quantify LAMP2, VAMP2, GM2 staining, Image J software (NIH, USA) was used. Each entire unmanipulated field of view was blinded and quantified for the stain, whilst an unstained area was used to determine (and subtract) background staining for each section. An average of the levels of optical density for each section and each mouse was calculated. These were then averaged to give a group mean for cerebral cortex or hippocampus for each mouse. To quantify Isolectin B4 or GFAP staining, the number of positive cells per non-overlapping cortical field (as described above) was counted and all 8 fields averaged for each mouse. We have also included examples of full sized high quality images of GFAP staining that were used for counting astrocytes as supplementary data to show that individual astrocytes are easily distinguishable at this magnification (See Figures S1, S2, S3, and S4). These images correspond to the first field of view on section 2 as shown in Figure 1A, and to the images presented in Figure 2A.

Biochemical assays

All samples were analyzed in blinded fashion. Liver samples were prepared as previously described. Total sulphated glycosaminoglycans in livers were measured using the Blyscan kit (Biocolor Ltd.,UK), standardized against DNA using PicoGreen ® dsDNA Kit (Invitrogen Ltd, UK) as previously described [13]. The final values were the mean of three tissue samples. High performance liquid chromatography (HPLC) was used to quantify the presence of pathological GAGs which have accumulated due to reduced enzyme activity in the brain from the second hemicoronal fifth (rostral to caudal) (SensiPro assay, Zacharon Pharmaceuticals Inc., data on file). Tissue GAG was extracted as previously described [37]. Samples were prepared by normalizing each to equivalent volumes using phosphate buffered saline followed by purification using reagents to extract impurities and isolate pathogenic GAG (pGAG). The pGAG were tagged with fluorescent dye, analyzed by HPLC [37] and this was standardized against total protein in each sample (Bradford assay). Tissue lipid extraction, isolation and quantitative densitometric studies of

gangliosides after separation on silica gel 60 HPTLC plates were performed as previously described [23,25].

Statistics

For statistical analysis, extreme outliers in biochemical and immunohistochemical data were formally removed using the boxplot tool in SPSS (Those more than 3x the interquartile range outside of the end of the interquartile box). None were removed from behavioural data due to the possibility of excluding erratic phenotypes. Data were analysed using 3 way ANOVA for gender (Male/Female), genotype (MPSIIIB/WT), drug (Untreated/Genistein) and Tukey's multiple comparisons test used to determine differences between groups using JMP software (SAS Ltd, UK).

Supporting Information

Figure S1 WT control GFAP stain x20.tif. The full sized TIFF image of GFAP (brown) stained cerebral cortex from an untreated 11 month old WT mouse. This image corresponds to the first field of view on section 2 as shown in Figure 1A, to the image presented in Figure 2A and was used to count the number of GFAP-positive cells. The section was counterstained with Mayer's haematoxylin (blue) to highlight the nuclei of cells.
Found at: doi:10.1371/journal.pone.0014192.s001 (36.15 MB TIF)

Figure S2 MPS IIIB control GFAP stain x20.tif. The full sized TIFF image of GFAP (brown) stained cerebral cortex from an untreated 11 month old MPSIIIB mouse. This image corresponds to the first field of view on section 2 as shown in Figure 1A, to the image presented in Figure 2A and was used to count the number of GFAP-positive cells. The section was counterstained with Mayer's haematoxylin (blue) to highlight the nuclei of cells.
Found at: doi:10.1371/journal.pone.0014192.s002 (36.15 MB TIF)

Figure S3 WT genistein treated GFAP stain x20.tif. The full sized TIFF image of GFAP (brown) stained cerebral cortex from a genistein treated 11 month old WT mouse. This image corresponds to the first field of view on section 2 as shown in Figure 1A, to the image presented in Figure 2A and was used to count the number of GFAP-positive cells. The section was counterstained with Mayer's haematoxylin (blue) to highlight the nuclei of cells.
Found at: doi:10.1371/journal.pone.0014192.s003 (36.15 MB TIF)

Figure S4 MPS IIIB genistein treated GFAP stain x20.tif. The full sized TIFF image of GFAP (brown) stained cerebral cortex from a genistein treated 11 month old MPSIIIB mouse. This image corresponds to the first field of view on section 2 as shown in Figure 1A, to the image presented in Figure 2A and was used to count the number of GFAP-positive cells. The section was counterstained with Mayer's haematoxylin (blue) to highlight the nuclei of cells.
Found at: doi:10.1371/journal.pone.0014192.s004 (36.15 MB TIF)

Acknowledgments

The authors gratefully acknowledge the help and assistance of the staff of the Manchester BSU, Dr Richard Preziosi for statistical advice, the Bioimaging Facility at the University of Manchester, Dr Kostantin Dobrenis and Prof. Steve Walkley for providing GM2 antibody and Dr Joanna Jakobkiewicz-Banecka.

Author Contributions

Conceived and designed the experiments: MM FLW KJLS ALS JRB BEC MTV GW BB. Performed the experiments: MM FLW KJLS ALS JRB BEC MTV. Analyzed the data: MM FLW KJLS ALS BEC MTV GW BB. Contributed reagents/materials/analysis tools: GG. Wrote the paper: MM FLW KJLS ALS MTV RFW JEW GW BB. Critically appraised the manuscript: MM FLW KJLS ALS JRB BEC MTV GG RFW JEW GW.

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MPS Awareness Day

15 May 2011

One baby every eight days in the UK will be born with an MPS or related disease

Each year the Society celebrates International MPS Awareness Day on 15 May. This is a day devoted to raising awareness of MPS and Related Diseases

Help us celebrate International MPS Awareness Day on Sunday 15 May 2011

This year we're asking all our members, Friends and supporters to do something, big or small, to mark MPS Awareness Day

Visit our website **www.mpssociety.co.uk**
or give us a call on **0845 389 9901** to find out more.

How your money helps...

More professional support for more MPS Families

MPS Advocacy Workers offer a whole range of services to help children and adults living with Fabry, Mucopolysaccharide and related diseases and support their families. We are there at the time of diagnosis and offer support for as long as we are needed. A donation of £2 per month could help us to offer so much more support in so many ways.

Access to expert clinical management & palliative care
MPS Regional Specialist clinics
Support with disability benefits
Paving a child's way in accessing education
Upholding rights in employment
Advising on home adaptations
Bereavement support

More MPS advocacy workers

You'll be helping to fund more advocacy workers that are so crucial to empowering children and adults living with MPS and related diseases and their families through the information, advice and advocacy they provide.

More vital information

Your donation could help us to have more trained advisors running our MPS Helpline at the MPS Society's national resource centre. One child born every eight days in the United Kingdom will be diagnosed with an MPS or related disease.

More help to cope with the isolation of a rare disease

The chances are you have never heard of Mucopolysaccharide diseases, Mucolipidosis or Fabry disease. The truth is most of the families we support had never heard of these diseases either. That is why they need your help to enable MPS to provide national and regional family conferences, activity weekends for siblings, young adult weekends for those affected and run the MPS befriending scheme.

More noise to force through change

The MPS Society is already recognised for punching above its weight to achieve improved clinical care for all those affected, over half of whom will lose their lives in childhood. We campaign for change, we fight to eradicate discrimination and we aim to ensure that all affected children and adults get the health and social care whoever and wherever they are.

More help

Even if you don't know anyone living or dying with Fabry disease, a Mucopolysaccharide or a related lysosomal disease, your help is vital and enables us to help over 1200 affected families in the United Kingdom.

For more information, to seek support and advice from our advocacy team, or to help raise funds so we can continue our work, contact us now!

0845 389 9901 **mps@mpssociety.co.uk**