Research Awards Report

BSPGHAN/CORE: 2011 – 2017

Details of Joint Guts/BSPGHAN awards can be seen on https://gutscharity.org.uk/research/our-research-partners/gutsuk-bspghan-collaboration/

Title: An exploration of perceptions and views of the key stakeholders about what constitutes successful transition for young people with liver transplants.

Professor Deirdre Kelly

2010 BSPGHAN/Guts UK Development Award Winner

Project Start Date: April 2011 **Completion Date**: September 2013

Summary:

Twenty years ago, most infants and children with liver disease had little chance of survival. The successful development of liver transplantation (LT) means that up to 80% of children survive more than 20 years to become adults. Many young people and their parents find leaving paediatric units difficult especially because adult units are not familiar with managing young people who have survived chronic illness. In the past many of these young people do not do well following transfer to adult units as there has been a high rate of graft loss (loss of the transplanted liver) due to not taking their medication or not coming regularly to clinics. There have been few studies to find out exactly what the risk factors are for an unsuccessful transfer to adult care or how preparation for transition (transition readiness) in paediatric centres and management in adult centres influence long term health.

For this project Professor Kelly and her team asked patients and their parents (if possible) what they thought about the transfer process and whether or not they were well prepared and felt ready to move to adult services. They did this by interviewing individual young people and their parents before and after the transfer.

In addition they looked at the case records of over 100 liver transplant survivors who transferred from paediatric to adult services in two national liver units to find out how young people managed in the past. The researchers collected information 1 year before and up to 5 years post transfer about how often they kept their clinic appointments, whether they developed complications, what medicines they were taking, and how many died or required another transplant because their transplanted liver failed (graft loss).

The analysis of the case notes highlighted that the median age at transfer to adult care was 18.6 years and the main reason for liver transplant was biliary atresia, a liver disease detected in infancy. Ten (9%) patients died following transfer to adult care. The median time to death was 2.3 years (range 0.6-5.5). The case notes also showed that missing appointments, not taking anti-rejection medications regularly, and psychosocial issues (such as low mood, anxiety, social issues or excessive alcohol use) occurred more frequently among the deceased patients compared to the living patients.

The interviews yielded a wealth of information. Four main themes were identified from interviews with patients as being important factors in their lives and also for successful transitional care. These were:

- being different from their peers (e.g. social or visible differences),
- coping (adopting different coping strategies to manage their liver transplant),
- social support (the benefit of various types of social support) and relationships with health care professionals,
- and continuity of care.

Three main themes were identified from interviews with parents. These were:

- impact on life (the impact that having a child with a liver transplant has upon everyday life),
- protection vs. independence (striving for the balance between protecting their child and allowing them to be independent as they near adulthood),
- and relationships with health care professionals.

The researchers also analysed the interviews with health care professionals.

This project's findings highlight the need for care that is appropriate for the developmental stage of the patients and that focuses on all aspects of being a young person with a liver transplant, and not just transition in isolation. Transitional care needs to be individually tailored to take into account the psychological needs of young people with a liver transplant. In addition, the impact that having a child with a liver transplant and transition to adult care has upon parents must be considered and support provided.

The researchers hope that the information from this pilot study will help set up a future study to measure the factors identified, to find out when young people are ready to move to adult services (transition readiness) and how best to look them so we can improve their long-term future.

Scientific publications from this research

"Are these adult doctors gonna know me?" Experiences of transition for young people with a liver transplant

'It's hard but you've just gotta get on with it' – The experiences of growing-up with a liver transplant

Parents in transition: Experiences of parents of young people with a liver transplant transferring to adult services

Healthcare transition in pediatric liver transplantation: The perspectives of pediatric and adult healthcare professionals

---

Title: Treatment of Iron Deficiency Anaemia in Adolescents with Inflammatory Bowel Disease: Tolerance and Effects on Haemoglobin, Disease Activity, Mood, Quality of Life and Autonomic Nervous System Activity.

Professor Ian Sanderson

2010 BSPGHAN/Guts UK Development Award Winner

Project Start Date: 1 October 2010 **Completion Date**: April 2015

Summary:

Iron deficiency anaemia (IDA), largely as a consequence of intestinal blood loss, is common in inflammatory bowel disease (IBD). IBD in young people is increasing, and their disease tends to be more extensive than in adults. It is not surprising therefore that IDA seems to be commoner in young people than adults with IBD. Under-treatment with oral iron tablets may be a contributory factor, possibly due to a perceived lack of benefit of iron supplementation or gastroenterologists' concerns about possible side effects.

IBD in adolescence impairs growth, education, employment and sexual development. Adolescents with IBD suffer more psychological distress than their peers, but whether being anaemic affects mood is unknown. Quality of life (QOL) scores in anaemic adults with IBD resemble those recorded in malignancy. Iron supplementation and correction of anaemia in adults improves QOL, implying that IBD patients when anaemic adapt their behaviour to their symptoms, including a degree of fatigue and reduced exercise tolerance, which may conceivably contribute to a depressed mood. Behavioural adaptation to anaemia causes activation of the autonomic nervous system, a state recently implicated in relapse of IBD.

The research team set out to test the following ideas:

1. that adolescents with IBD can benefit as much as adults do from oral iron supplementation, in terms of improvement to their anaemia;
2. that oral iron does not worsen symptoms of IBD or level of inflammation of the disease;
3. that correction of anaemia improves quality of life, mood and fatigue in patients with IBD.

The researchers also investigated the role of hepcidin, a molecule that is involved in how the body regulates iron levels and absorption. The researchers hoped to be able to use levels of hepcidin to predict how patients with IBD and anaemia would respond to oral iron supplementation.

To test these ideas, the researchers carried out a study. They provided oral iron supplementation for 6 weeks to 43 adolescents and 46 adults with iron-deficient anaemia in IBD. To help them understand the effect of the iron supplementation, the researchers measured a set of factors in study participants both before and after providing iron treatment. These factors measured were:

- the levels of iron in the blood of the study participants (specifically levels of haemoglobin, a molecule that carries iron in the blood);
- whether study participants' IBD symptoms and level of inflammation changed;
- how well the study participant tolerated the iron supplements;
- quality of life, perceived stress, mood and fatigue (measured using psychometric questionnaires);
- how the body processes the iron, including levels in the blood of the molecule hepcidin.

When the researchers compared the differences in the above factors before and after iron supplementation of the study participants, they found that:

1. the improvement in anaemia status (represented by levels of haemoglobin in the blood) was similar in adolescents and adults study participants.
2. intolerance of oral iron occurred as often in adolescents as in adults, about 20% of patients developing non-specific symptoms such as abdominal pain and changes in bowel habit (as reported in many previous studies of people with and without IBD taking iron orally). Importantly, however, there was no evidence in either group of patients that oral iron increased the amount of inflammation in the bowel as measured by special blood (C-reactive protein, CRP) and stool (calprotectin) tests done before and at the end of treatment with iron.
3. the small improvement in anaemia status produced by oral iron did not significantly improve quality of life, mood or fatigue scores in adolescent or adult patients with IBD.

The researchers also found that patients who had low levels of the molecule hepcidin before receiving iron supplementation subsequently had a bigger rise in their haemoglobin concentration than those with high hepcidin levels at the outset.

These results should reassure paediatricians (as well as adult gastroenterologists) about the effectiveness and safety of oral iron for the treatment of anaemia in IBD. Additionally, the researcher's finding that the level of the molecule hepcidin affects the response to oral iron supplementation could signify a change in clinical practice, provided the finding is replicated by other research teams, to confirm its validity. It shows that it may become sensible practice to check the serum hepcidin level of patients before deciding whether to give the iron by mouth (if the baseline hepcidin is low) or intravenously (if the hepcidin is high).

The lack of improvement in quality of life, mood or fatigue could be because the improvement in anaemia status induced by oral iron supplementation for only 6 weeks was too small to influence those factors. Another explanation might be that study participants did not complete the questionnaire with sufficient detail to allow the researchers to analyse that information with sufficient accurately.

The next step for the researchers is to analyse, in a separate study, the stools that were collected before and after iron supplementation. This will allow them to assess whether oral iron alters the bacterial populations of the large intestine. This is a key question to answer given the important role of gut bacteria in a range of human disorders, including not only IBD but also, for example, obesity.

Scientific publications from this research

Prevalence and Management of Anemia in Children, Adolescents, and Adults with Inflammatory Bowel Disease

Oral Iron Treatment Response and Predictors in Anaemic Adolescents and Adults with IBD: A Prospective Controlled Open-Label Trial

Efficacy and tolerability of intravenous iron dextran and oral iron in inflammatory bowel disease: a case-matched study in clinical practice

---

Title: Genetic association studies in chronic liver disease and chronic obstructive pulmonary disease secondary to PiZ alpha-1-antitrypsin deficiency

Prof Nedim Hadzic

2012 BSPGHAN/Guts UK Development Award Winner

Project Start Date: 1 January 2013 **Completion Date**: September 2015

Summary:

Alpha-1-antitrypsin (A1AT) deficiency is a relatively common genetic disorder, with 1 in 2,000 people in Northern Europe carrying the genetic defect responsible for the disorder. The condition leads to chronic liver disease (CLD) in children and to chronic obstructive pulmonary disease (COPD) in young adults, particularly among smokers. However liver disease in people with A1AT deficiency presents in variable ways and with different outcomes, with some people affected showing no symptoms at all, some displaying intermediate stages of chronic liver disease, and some requiring a life-saving liver transplantation. The reasons why some people develop liver disease, some develop lung disease and some remain asymptomatic for life are unknown.

Additionally, at present it is not known whether children with liver disease due to A1AT deficiency will develop lung disease. This uncertainty represents one of the major problems in their long term management. Once patients who are at risk of developing lung disease in adulthood are identified, it will be possible to target them for early treatment. Currently this includes replacement therapy with the A1AT protein, in addition to lifestyle modifications such as avoidance of smoking and heavy alcohol use. In the future it may be possible to modify the condition by either changing the A1AT protein or giving medications before severe damage in the liver or lungs occurs. Furthermore, it is hoped that by analysing genetic markers in a minority of the children who required liver transplantation it would be possible to look for the same markers in adults and identify the ones who will need closer monitoring of liver function during their lifetime.

In this project Prof Hadzic and his colleagues tried to identify why individuals with seemingly identical defects in their gene responsible for A1AT deficiency develop liver or lung disease, by comparing genetic markers in large cohorts of children with chronic liver disease of different severity, and among adults with COPD from national referral centres. The researchers examined the full genetic material (DNA) of 384 patients with A1AT deficiency and lung disease but no obvious liver disease, and the

genetic material of 132 children who presented with early onset liver disease. The primary aim was to find additional genetic differences between the children with liver disease and adult respiratory patients. They identified a number of genetic differences between the groups, which they plan to explore in future work.

Title: Body composition and metabolic profile of children with end stage liver disease before and after liver transplant; relations with outcome and cell energy controlling metabolic pathways

Professor Anil Dhawan

2012 - BSPGHAN/Guts UK Award

Project Start Date: 14 February 2013 **Completion Date**: 31 January 2017

Summary:

Children who have end stage liver disease sometimes suffer from a form of wasting known as cachexia. These children can lose weight in the form of both fat and muscle mass. Cachexia is not just the result of poor appetite and malabsorption of nutrients caused by the disease: it is also caused by changes to the way the children's cells process energy from food (metabolism), resulting in an excess energy use by the cells and ensuing higher energy requirements in these children. The growth and development of these children can be compromised.

Children with cachexia tend to have more complications after their liver transplant. However we are not sure how changes to the body composition and to the energy requirements of children with liver disease affect their clinical outcomes. We are also not sure what changes take place in the cells of those children to cause the excess energy use and resulting fat and muscle loss.

Professor Dhawan and his team received funding from Guts UK and BSPGHAN to investigate these changes in children with end stage liver disease scheduled to receive a liver transplant. The team assessed how the body composition and energy requirements of children with end stage liver disease change before and after liver transplantation. They also compared how these factors differ from those of healthy children.

The team used a number of techniques to calculate the body composition of the children. These techniques (basic anthropometry, stable isotopes, bioelectrical impedance, DXA scan and air displacement plethysmography) can give an estimate of the percentage of fat mass, muscle mass and water content in the children's bodies. The amount of energy used by these children was assessed by another technique, known as indirect calorimetry. Finally, to understand what changes were taking place within the cells that causes changes in energy requirements, the team took biopsy samples of the liver, the muscle and the fat tissue of the children and examined the cells obtained from these samples.

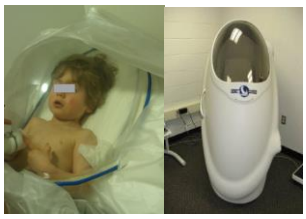
The body composition, growth and energy requirements of children enlisted in the study were assessed before and at 6 months after their liver transplant. Those children who still had high energy requirements at 6 months were assessed again 1 year after their transplant. Additionally, these factors were compared between children with liver disease and healthy children, who acted as controls in the study.

The researchers also examined the liver, muscle and fat tissue obtained from the children at the time of their liver transplant. They measured the level of activity of genes involved in how cells process energy. In particular they were interested in genes involved in obtaining energy from nutrients such as fats and sugars, as well as genes involved in how muscle and fat tissue build up.

The analyses the researchers found that children awaiting liver transplantation show loss of muscle mass, as well as higher levels of water retention. However, their fat mass was relatively normal. This is important as the researchers also showed that children with more fat mass had a shorter stay in hospital after their transplant.

When the researchers examined the tissue samples from the liver, fat and muscle biopsies, they noted that a small group of children displayed changes in the activity of genes associated with the development of insulin resistance. Insulin resistance is a metabolic disturbance that can lead to diabetes and is linked to the preservation of fat mass. The researchers propose that in these children insulin resistance might be responsible for the maintenance of their fat stores and, arguably, could be a defence mechanism in children with liver disease. Their work shows the importance of ensuring children with end stage liver disease are adequately nourished before they receive their transplant.

This was a pilot study and the researchers plan to examine the tissue samples in more detail, to shed more light on the genetic and molecular mechanisms involved in the changes in body composition of these children. This might allow them to, in the future, manipulate these mechanisms in a way that is beneficial to the children.



Title: Anabolic resistance and abnormal muscle function across the nutritional spectrum: a pilot study in Crohn's disease

Dr Gordon Moran – 2015 Guts UK / BSPGHAN Development Award

Institution: University of Nottingham

Project Start Date: 1 December 2015 **Completion Date**: 1 March 2017

Summary:

Weight loss, including muscle loss, in Crohn's disease during childhood is a common problem. Even when the child is well, a large proportion of patients never grow their muscles back to normal. This is important as muscle loss has a negative effect on physical activity, patient wellbeing and quality of life. Moreover, physical activity plays a major role in normal growth development, physical fitness, bone strength, intellectual and social functions of children.

When inactive, the muscles tend to accumulate fat which stops the muscles from growing any further. This may lead to further physical inactivity and a further reduction in muscle mass and function. The inability of a muscle to grow is called anabolic resistance. Additionally, when muscles accumulate fat, they are less able to respond to insulin, the hormone that allows muscle to absorb glucose (a type of sugar). This is called insulin resistance, a problem often associated with diabetes.

It is not known what causes this loss of muscle mass and function. It is possible that general lack of appetite, problems absorbing food and low levels of physical activity are the key contributors.

However Dr Moran and his colleagues wanted to explore whether the gut inflammation that characterises Crohn's disease could itself be affecting muscle function. They thought it was possible that 'inflammatory signals' from the gut travel through the bloodstream to the muscles and cause them to suffer from anabolic and insulin resistance.

The researchers carried out a pilot study, co-funded by Guts UK and BSPGHAN, to investigate their idea that children with Crohn's disease (even when well) suffer from anabolic resistance. Children who participated in the study were asked to come into the laboratory to have an intravenous cannulae placed in the forearm and elbow of the non-dominant arm. The participants were given a meal in the form of a protein drink followed by an energy drink taken an hour afterwards. Blood samples were taken every

20 minutes during 3 hours. Information on the children's metabolic rate, total muscle mass (using an X-ray), habitual food intake (obtained via phone calls during that study week), quality of life and physical activity (wearing a sensewear arm band for a few days) were also collected.

When they analysed all the data, the researchers found out that, in contrast to healthy children, children with Crohn's disease do not have the capacity to build muscle after a meal. The muscles of children with Crohn's disease initially respond positively to the stimulus given by the meal i.e. they are not technically anabolically resistant. However, they cannot sustain this response and so overall do not make extra muscle protein after eating. This means the children are unable to build back up the muscle they have lost during the active phase of their disease and can only maintain what the muscles they have.

Understanding that children with Crohn's disease, even when well, are unable to build muscle protein after a meal means we now know why they can't grow their muscles back to normal size. We can now design further studies to test interventions that may be able to solve this problem.

Further analysis of the current data is needed to understand if there are differences within this group of children with Crohn's disease in terms of gender and / or treatment. Once this is complete a further intervention study will be designed to see if this problem can be overcome with, for example, medicines to reduce the breakdown by the body of muscle protein and/or with a high protein diet to boost the muscle's response to a meal.

If we are able to successfully test an intervention, we may be able to ensure children with Crohn's disease do fully regain lost muscle mass when well, and so reduce fatigue and improve quality of life.

The Guts UK/BSPGHAN fund has provided much need pump-priming funding to allow me to get pilot data and track record in this very competitive field. This will hopefully allow further detailed work investigating how exercise or pharmacological treatment altering fat content within the muscle might improve and normalise muscle physiology hence improving fatigue and quality of life in children with Crohn's disease.

Title: LiverMultiScanTM for the assessment of graft fibrosis in children post-liver transplant Dr Emer Fitzpatrick – 2015 Guts UK / BSPGHAN Development Award

https://gutscharity.org.uk/research/our-research-partners/gutsuk-bspghan-collaboration/dr-emer-fitzpatrick/

Institution: King's College London

Project Start Date: 9 November 2015 **Completion Date**: 8 May 2017

Summary:

Liver transplantation in children is a lifesaving procedure. Improvements in surgical techniques and post-transplant care have led to a survival of greater than 80% at 10 years following transplant. A number of recent studies have highlighted problems with the transplant at 5 and 10 years however, and inflammation and scarring are present in the vast majority of transplanted livers. The major concern is that this injury will progress and the organ will cease to function properly with time. If changes are made to immunosuppressive medication, progression of the injury can potentially be modified and even reversed. A liver biopsy is generally needed to detect this inflammation and scarring, as in the majority of cases the patient is otherwise well with normal blood tests. Liver biopsy is an invasive procedure and risks include bleeding and, rarely, death. Routine biopsies are done in some centres to assess the liver at intervals after transplant however this is not universally accepted, particularly in completely well children.

An alternative would be to use non-invasive methods to assess the transplanted organ. Routine blood tests and scans are not accurate enough for this purpose. A recent study using MRI to assess scarring

in adult patients with liver disease has found it to have excellent correlation with liver biopsy. The researchers' aim was to use this technique (which is quick, pain free and does not involve any radiation) in children who have had a transplant. MRI using this software system may have more promise than other non-invasive methods for this purpose.

The researchers investigated the use of MRI scans to detect the presence of scarring and inflammation in the transplanted liver, and assessed how effective that method was compared to using liver biopsies.

This particular study was designed as a pilot that would provide sufficient data to plan a larger multi-centre (European) study. As this type of study involving MRI has not been done before in the UK specifically on children who had received a liver transplant, the researchers wanted to check how feasible it was to carry out and what the likelihood was of recruiting sufficient patients in the 2 years planned for the larger study.

The pilot demonstrated that the larger study was feasible. The researchers showed it was possible to recruit children within the allocate time frame; they also showed children as young as 8 years old were capable of undergoing the MRI scan without sedation.

The pilot study also highlighted a number of alterations to the protocol (the steps followed by the study) that needed to be made before proceeding with the larger study. The logistics and timing of the MRI scans and other investigations were trialled in different ways and refined, resulting in a clearer protocol. The children and their families also made suggestions to make the protocol more user friendly.

The researchers also tested different ways to assess (score) the liver tissue samples obtained from the biopsies, to help them determine the best scoring system to use in the larger trial.

The researchers were able to obtained additional funds from the European Union (the Horizon 2020 funding scheme) to carry out the larger study, which has just started. This study will recruit 200 children from 4 centres across Europe. The UK centre, represented by King's College London, which is the institution where Dr Fitzpatrick is based, will be responsible for recruiting 50 children for the study. They will also be responsible for analysing all the tissue samples obtained from biopsies from all the 4 centres.

The researchers noted that the pilot study was fundamental in obtaining enough preliminary data to secure the funding for the larger study.

Ultimately the aim of this pilot and the planned larger study is to devise a test with the best diagnostic accuracy for monitoring livers after transplant, thus saving numerous liver biopsies and potentially maintaining good function of the transplanted liver beyond the 10 year mark.

The Joint Guts UK-BSPGHAN award has enabled us to investigate a very promising new MRI based technique that measures inflammation, scarring and fat in the liver without the need for liver biopsy. Children and young people who have had a liver transplant often need quite frequent liver biopsies to tell us what is going on in the liver and understand what we have to do to keep the liver healthy. We hope that this new type of MRI will allow us to detect any problems in the transplanted liver without the risks and discomfort associated with liver biopsy.

Chris Probert, Professor of Gastroenterology; Cellular and Molecular Physiology, Institute of Translational Medicine, University of Liverpool. "Characterization of the gut mycobiome in an inception cohort of paediatric inflammatory bowel disease"

http://corecharity.org.uk/research/current-active-research/professor-chris-probert/

Start Date: April 2018: Completion Date: 31st March 2019

Summary:
The cause of inflammatory bowel disease (Crohn's disease and ulcerative colitis) is unknown. For some time, we have known that some patients have signs of white cell reaction (immune response) to specific

yeasts. This was thought to be a result of intestine inflammation from Crohn's disease causing a leaky gut that allowed the yeasts into the body of the patient. Recent studies of the genes linked to the risk of inflammatory bowel disease suggest that some patients with Crohn's disease may have an impaired immune response allowing fungi and yeasts to live in the intestine more easily. This year, the ability of some yeast to damage the intestine leading to inflammation and a leaky gut was shown in laboratory mice. Several labs have looked for yeasts and fungi in the intestine of children with Crohn's disease, with conflicting results. In this study, we propose to look at children attending hospital with possible Crohn's disease: stool and blood samples will be taken at the first visit, before the diagnosis is made and treatment started. The children will be investigated and treated in the standard way. Some children will be found to have Crohn's disease, others will have other diagnoses. We will compare the samples from these two groups of children in order to understand the role of yeasts and fungi on the development and course of Crohn's disease.

We are collaborating with Prof Stephen Allen of Alder Hey Hospital who will lead the identification of patients and collection of samples with additional input from Dr Rafeeq Muhammed (Birmingham Children's Hospital) and Dr Chris Spray (Bristol Royal Hospital For Sick Children).

We have new tools to study fungi and we have access to samples from new patients: this is particularly important as we can study fungi before diet and drugs, used to treated IBD, have been started.

We will study samples from newly diagnosed children with IBD and from other children with gastrointestinal symptoms who do not have IBD. We will compare the fungi in their faeces using modern molecular techniques. The study of these samples will begin in April 2018 and will last for one year. We will report our findings to Guts UK in May 2019 and we aim to publish our finding in the medical research press later in 2019.

Our data will help to understand the role of yeasts and fungi on the risk of Crohn's disease and their influence on disease flares and response to treatment. We will be better able to talk to patients when they ask us about Candida (which is a common question) as well as other fungi. We will publish our findings and, depending on the results, seek additional funds to try to correct any imbalance in gut fungi that we discover.

There has been a great deal of interest in gut bacteria and the effect on Crohn's disease. However, fungi have been comparatively less well researched.

Future work will investigate how to modify yeasts and fungi by diet or specific (gentle) anti-fungal drugs. This could change the disease course in Crohn's disease.

What is the difference between the mycobiome and the microbiome?

The mycobiome is the collection of fungal species that live in the human body, including the gut. It's considered to be part of the microbiome, which also includes bacteria, viruses and other microorganisms.

Sarah Ennis, Professor of Genomics, Genomic Informatics Group Lead, University Hospital Southampton. "Metabolo-genomic interactions in paediatric Crohn's Disease"

http://corecharity.org.uk/research/current-active-research/professor-sarah-ennis/

Start Date: October 2017 Completion date: September 2019

Summary:
Crohn's disease (CD) is a lifelong inflammatory condition. We don't know the exact causes in individual patients but we do know that genes, the environment within the gut and diet can all interact in this condition. Unfortunately, this disease is sometimes diagnosed in children. We have recruited hundreds of patients diagnosed in childhood and will use their anonymised samples and clinical information in this study. We plan to identify genetic changes in hundreds of genes known to be important in this

disease. There is a new technology called next generation sequencing that allows us to do this efficiently. We also plan to detect all the products of metabolism – the biological pathways that help us get energy from fats, carbohydrates and proteins and use vitamins and minerals – in samples from the same patients using a very specialised machine called a nuclear magnetic resonance spectrometer! Both the genetic results and the metabolomics results generate enormous data sets. We need to use computer programs and mathematical models to help us interpret these data. We hope that by conducting both types of experiments in the same people and analysing the data together, that we will better understand any unusual findings. Our aim is always to help inform the clinical teams how to better diagnose and treat patients so they have a better quality of life. We want to help improve how children are treated so they grow properly, spend more time at school and less time in the clinic or hospital.

Sarah Ennis who is Professor of Genomics at the University of Southampton will lead the study and undertake the genetic analyses of the patients; Dr Sandrine Claus, Associate Professor in Integrative Metabolism in the Department of food and Nutritional Sciences at University of Reading will lead on the NMR analysis of metabolites and; Prof Mark Beattie is consultant Paediatric Gastroenterologist/Honorary Professor of Paediatric Gastroenterology and Nutrition is the clinical lead for the study.

We will take DNA and plasma samples from about 200 children diagnosed with Crohn's disease. We will analyse the two types of data (genetics and metabolomics) independently first and then merge all the important information together with details of how each child's disease is behaving (e.g. what part of the gut is affected, how inflamed is the gut, does the patient get well on certain drugs, is the child growing normally). We will work with colleagues in mathematics at the University of Southampton to identify patterns in the data. We expect to find that although all the children are diagnosed with the same disease, that not everybody's disease behaves the same. We want to identify key information that could help the medical team treat individual children differently according to how their own disease behaves.

We would love to identify very clear patterns in all of our first 200 children, but merging data in this way is a new field with lots of methods under development. We may only identify the strongest signals in a proportion of children. However, this would be a great start in getting experts from different disciplines coming together to make more sense out of the very sophisticated data they generate. Of course, we will need to follow up and confirm our findings in independent groups of patients to make sure they are real and robust. Because we have senior clinical staff on our team and we attend major national and international conferences about this disease, we will make sure the entire community treating these children get to hear about any important new breakthroughs.

I have been working in genetics for twenty years now. There have been enormous technological advances over the last decade and I want to see these used to the benefit of young patients diagnosed with IBD. There is lots we still don't understand about IBD but we now have better data than ever before. We do need to work across disciplines in order to best interpret this information and translate our findings back to clinicians as quickly as possible.

We hope this project will give a better understanding of what is happening at the molecular level in patients diagnosed with CD. We expect to gain insight into how metabolism is working in patients and how metabolic changes interact with genetic changes. The modelling we apply in this project will pave the way to integrate even more data types. Ultimately, we want to be able to take in all information about a specific patients' disease and use this to direct the best possible treatment.

Prof David Wilson

Start Date: June 2016 Completion: September 2018 Date of final report June 2020

Child Life and Health, University of Edinburgh; Paediatric Gastroenterology, Royal Hospital for Sick Children, Edinburgh "Health informatics research in paediatric gastroenterology: nationwide data-linkage exploration of perinatal risk factors for and consequences of paediatric-onset Inflammatory Bowel Disease"

https://gutscharity.org.uk/research/current-active-research/professor-david-wilson/

Project update August 2020

Professor Wilson has completed his project. A report of his work has been submitted and evaluated.

Here is a summary of his results.

Professor Wilson and his team have investigated a population of more than 2 million children born in Scotland between 1981 and 2017. This included almost 1,800 Paediatric Inflammatory bowel disease (PIBD) patients, diagnosed under 16 years of age. They have not identified any relationship between mode of delivery, gestational age or type of infant feeding that makes an infant more or less likely to develop PIBD in the future. This means that whether children are born vaginally or via caesarean section, whether they are born prematurely or at term and whether they are breast fed or bottle fed does not appear to impact on their **chance of being diagnosed with PIBD in the future. This is an important negative result given the suspected role of environmental factors in causing PIBD.**

Prof Wilson and his team are working on a scientific paper to publish these results. Prof David Wilson said "We have not shown any association of these 3 key perinatal factors with later development of PIBD in this very large population-based cohort study, but it remains possible that these factors contribute to risk of PIBD as environmental triggers within a multi-hit model, for example affecting the epigenome, the gut microbiome and the immune system".

Moreover, they have investigated this population for further health risks as their second aim. The risk of morbidity (ischaemic heart disease, stroke, and cancer in early adult life) and mortality related to active IBD and its treatment is a major concern to both patients and families as well as clinicians, especially when IBD is diagnosed in childhood. The research team are currently analysing these data obtained by a nested case-control study, and will send an update when this is completed.

BSPGHAN/CLDF 2016

Congenital porto-systemic shunts and the development of liver tumours; Professor Richard Thompson, King's College Hospital, London. *https://childliverdisease.org/congenital-portosystemic-shunts-and-the-development-of-liver-tumours/*

Congenital portosystemic shunts (CPS) occur when the blood vessels around the liver aren't formed properly so the blood doesn't flow through, in and around the liver as it should. In some cases of CPS, blood from the intestines, pancreas and spleen (called portal venous blood) bypasses the liver straight into the main blood circulation in the body. In other cases blood from the hepatic artery may take on the role of supplying nutrients to the liver instead of the portal vein. These changes can affect the chemical balance inside the liver. It isn't known exactly why, but people who have CPS are more likely to develop tumours. This study aimed to find out why this is.

This grant has taken the work a long way and has opened several new areas of investigation. Please view the abstract poster, kindly provided by Dr Athanasios Tyraskis, which explains the findings of this study: Congenital portosystemic shunts and the development of liver tumours

---

Association of stool microbial profile with short-term outcome in infants with biliary atresia; Professor Anil Dhawan and Dr Vandana Jain, King's College Hospital, London.
*https://childliverdisease.org/research/*What is this study looking at?
Biliary atresia (BA) is a disease in children where inflammation within the bile ducts lead to jaundice and liver inflammation. An operation called a "Kasai-Portoenterostomy" (Kasai) can be performed in the first two months of life to "re-plumb" the liver to the gut to restore bile flow between the liver and the gut. It is thought that microorganisms (such as bacteria, viruses, and fungi) within the gut may have an impact on how serious liver disease in children with BA becomes.

The research team will look at the microorganisms inside the guts of children who have had the Kasai at different ages. The team will then compare which microorganisms are present in the guts of children

who have BA but are healthy after the Kasai procedure, those with BA who have the procedure but need a liver transplant afterwards and healthy children without biliary atresia.

Why is this research important?

The impact of microorganisms in the gut has been studied in adults with liver disease and is believed to play a role in adult liver disease. Until now there has been little research into its potential role in biliary atresia.

This research will further our knowledge and understanding of whether microorganisms have a role in paediatric liver disease.

What about the future?

It is hoped that we will be able to find out if microorganisms inside the gut play a role in making liver disease worse in biliary atresia, and if so, which ones.

If microorganisms are identified the next step is to find out how to target these bacteria so we can reduce the number of harmful bacteria in the guts of biliary atresia patients. Potential treatments may include antibiotics, diet or probiotics.

BSPGHAN/CCUK

Investigating the use of CD8+ T-cell DNA methylation profiles as disease prognostic biomarkers in paediatrics with IBD

https://crohnsandcolitis.org.uk/research/projects/using-biomarkers-to-predict-disease-severity-in-children-with-ibd

Lead investigator: Dr Claire Lee, Cambridge
Project completed. Dr Marco Gasparetto is working on gene expression of CD8+ T-cells for his PhD and will utilise some of the results.

What is this research looking at?

More children are being diagnosed with Crohn's Disease and Ulcerative Colitis. In the absence of any cure, these children still face a lifetime of daily medication, and frequently require surgery, to help control symptoms. There is a substantial variation in severity of disease between individual children with IBD, ranging from mild, requiring minimal treatment to severe treatment resistant disease, requiring increasingly potent medications and surgery.

It is hard to predict disease severity for an individual child, which makes the choice of initial treatment very difficult. Recent research in adults has identified a highly promising measure that can predict the disease course in adults with IBD. This marker can be analysed in a specific blood cell type (i.e. CD8+ T cells).

We plan to see if we can use this biomarker to predict disease outcomes in a subset of children whose CD8+ T cells have been sampled.

What do the researchers think this could mean for people with IBD?

If successful, our disease predicting test would substantially improve current treatment practices for children suffering with IBD. Our test would allow us to personalise treatment for an individual child from the point of diagnosis, and as a result, improve both immediate quality of life, and long-term disease outcome for children with IBD.

Conclusions

The researchers were unable to develop a reliable biomarker (to predict disease outcomes) in a small group of children diagnosed with IBD. However, they have now recruited a larger group of children and received further funding for the project, allowing them to further explore this highly promising research area.

Who is leading this research? Ms Claire Lee & Dr Matthias Zilbauer, Addenbrooke's Hospital/University of Cambridge

---

Mechanisms of pain in paediatric IBD

https://crohnsandcolitis.org.uk/research/projects/cause-of-pain-in-children-with-ibd

Lead investigator: Professor Nick Croft, Barts/London

What the research looked at?

Gut pain is a major problem for children with Crohn's or Colitis and can be difficult to treat. But what causes this pain is not well understood, and many children experience pain even when they are in remission. This suggests that the causes of pain and gut inflammation are different.

Research has already shown that tissue samples from children with Crohn's or Colitis can stimulate pain sensing nerves. This study looked for the substances (mediators) in the gut tissue which leads to this activation of pain signals.

They compared tissue samples from people:

- newly diagnosed with Crohn's Disease
- with Crohn's Disease that had not responded to treatment
- with a healthy gut.

Several mediators were found to be involved in the cause of gut pain. This included specific enzymes known as MMPs (matrix metalloproteinases), activation of CXCR3 receptors for cytokines (chemicals produced in the inflammatory process) and mediators produced by neutrophils (a type of white blood cell). They also found a signal that draws T cells (a different type of white cell) into the gut may be a possible cause of pain.

The researchers were able to identify the causes of inflammation successfully treated by current drugs and those which are not.

Conclusion

Signals relating to the function of T cells are present in inflammation that does not respond well to current drug therapies. This suggests that targeting T cell function may improve disease treatment in the future.

What do the researchers think this could mean for people with IBD?

This study has further increased our understanding of pain in children with Crohn's and Colitis. Researchers now plan to build on these findings in further studies. They hope this will lead to the development of new therapies to control gut pain in children.

Exploring the inter-kingdom relationships of gut microbiota in Crohn's disease

https://crohnsandcolitis.org.uk/research/projects/does-gut-fungi-play-a-role-in-crohns-disease-in-children

Lead Investigator: Kostas Gerasimidis, Glasgow

What did this research look at?

Recent studies suggest that fungi which typically live in the gut (known as the mycobiome), play a role in Crohn's Disease. This study aimed to understand the role of the mycobiome. To do this the research team used stool samples to look at the mycobiome in children with and without Crohn's and explored how this changes with treatment with a liquid diet

They found there were significant differences between the types of fungi present in the two groups. They also found that after children with Crohn's were treated with a liquid diet, the fungi in their gut changed even further but this effect was not the same among the participants.

Conclusion

The study found that specific types of fungi were associated with CD and some of these species changed with a treatment based on a liquid diet It is possible that these fungi play an important role in the cause of Crohn's Disease but future research needs to confirm these findings.

What do the researchers think this could mean for people with IBD?

The researchers now want to find out whether the changes following treatment with a liquid diet are associated with the way that the treatment works. They hope that at the end of their studies they will better understand the cause of Crohn's disease. And that this will help towards the development of new treatments.

Early measurement of faecal calprotectin as a predictor of primary non-response to treatment on paediatric Crohn's disease: a pilot study

https://crohnsandcolitis.org.uk/research/projects/early-measurement-of-faecal-calprotectin-as-a-predictor-of-primary-non-resp

Lead investigator: Dr Astor Rodrigues, Oxford

What is this research looking at?

Testing stool for markers of inflammation has boosted our ability to diagnose Crohn's Disease early in children. While effective treatments exist, some children need to try several different types before they find the one that works for them. This has an adverse effect on their quality of life, and risks the development of complications. A simple test that could determine whether or not a treatment was working soon after it was started would allow clinicians to identify children that need to be put on stronger treatments earlier. We propose that the same tests for inflammation could be used for this purpose and that parents could collect samples at home.

What do the researchers think this could mean for people with IBD?

This research will hopefully enable faster and more personalised treatment for children with IBD.

BSPGHAN Innovation Grants

Decision tree for multi professional staff and families caring for patients with neuro-disabling conditions who develop severe gut dysmotility: Applicants: Dr Andrew Barclay and Dr Sue Protheroe on behalf of BSPGHAN NIFWG/ RCPCH Clinical Standards

Specialty area to be addressed

Children and Young People aged 0-18 years with neuro-disabling conditions with deteriorating gut motility, which is severe enough to lead to difficulties in maintaining nutrition and hydration.

Groups not covered- those who receive nutritional support without difficulties with provision of adequate nutrition or hydration.

Current stage of development

Scope written according to RCPCH guidance April 2015

2018

1. Systematic review (medical therapies) completed July 2017
2. Grant obtained to fund Delphi process from BSPGHAN 2017
3. Collaborator found to administer Delphi process 2017
4. Core group has met to decide on expert consensus statements and arrange Delphi process September 2018
5. Seeking support from RCPCH Clinical standards to recruit families and young people to contribute towards Delphi.
6. Seeking support from RCPCH Clinical Standards team to potentially conduct the Delphi process.

Progress to date

The Core group involved Professionals with expertise in gastroenterology & neurology and met face to face in 2017.

The work is supported by stakeholders from BSPGHAN, BACD, BPNA and BAPEN (British Association of Parenteral and Enteral Nutrition.

Subsequently, further key stakeholders with expertise in neuro-disability have been recruited during and an RCPCH representative and further BPNA colleague appointed in 2016 to aid with development of the guideline.

1. First Core Group meeting in London, Evelina Children's Hospital, July 2017. Set out aims and methods, roles and responsibilities. Identified relevant papers for SR and experts for Delphi process.
2. Colleagues supported by Dr Barclay in the Core Group undertook a systematic review.
3. Applied for Innovation Grant from BSPGHAN - funding to
   A] Pay for colleague, Mr Allin to administer the Delphi process (£1000)
   B] cover core group's travel expenses
   C] Pay for software.

   Successfully awarded £3,500 by BSPGHAN.

4. Recruited colleague experienced in running a Delphi Process to advice on setting up the Delphi and administration.
   Mr Benjamin Allin MBBS BSc MRCS |
   National Institute for Health Research Doctoral Research Fellow Paediatric Surgical Registrar, National Perinatal Epidemiology Unit **|** Nuffield Department of Population Health, University of Oxford. Nuffield Department of Surgical Sciences| University of Oxford

   Background

Mr Allin ran and designed the NETS1HD study based upon previously used methodology identified from protocols, and refined following discussions at COMET workshops.

Paula Williamson (NIHR Prof based in Liverpool, a UK leader in development of COS) has agreed to act as an advisor that we could discuss methodological questions/concerns with.

Mr Allin estimates that designing and implementing the Delphi processes will take about a year from completion of a systematic review to completion of the Delphi process. The Delphi process requires about one month per phase, from development of the questionnaire to finalisation of the phases results. Generally, each phase has taken a weeks' worth of full-time work, split over the month that the phase runs.

Steps

1. Refining the results of the systematic review/ expert consensus into the questions that we want to ask participants,
2. identifying the appropriate methodology for the particular study,
3. recruiting participants, and
4. Developing the text/educational material etc to go alongside the Delphi to explain the process and aim to people.
5. The actual collection of the data is (reasonably) automated now, and getting more so, each time we run one.
6. Online software to be purchased

   A] The COMET initiative provides software with outcomes into an excel file, and we can run the process There is however very little flexibility in their system, and may not be adaptable to creation of a consensus statement as opposed to a core outcome set. The presentation of feedback from each phase is also a bit clunky and difficult to interpret, with individual graphs, and then separate numerical results produced for each outcome for each stakeholder group. This results in one outcome being displayed per page, making it fairly laborious to complete the questionnaires. The DIY COMET package, without methodological support, costs approximately £2000.

   B] The second option for software is to use the program that we (B Allin) have developed in house. This is more flexible than the software provided by COMET, but does not come with a DIY option, as it is hosted on our secure servers, so can only be accessed by someone working within the NPEU. This software costs £4000, primarily because it is more adaptable, and as a result, requires more behind the scenes work. However, feedback from people who have used both systems is that the integrated nature of the different panel's graphical scores, numerical scores, and participants scores provided in our software makes it much easier to interpret the feedback, and much easier to complete the questionnaires.

Medical Therapies for the medical treatment of foregut dysmotility in children with neurodisability; A systematic review

N McConnell, LMB Beattie, AR Barclay
On behalf of the BSPGHAN/RCPCH core group

Conclusions

The evidence base for medical treatments in foregut dysmotility in children and young people with foregut is absent. This makes this construction of an evidence based guideline for treatment inappropriate, although this should remain an ultimate aspiration for invested health professionals. The development of best practice by the sharing of experience of highly specialised multidisciplinary teams could potentially be advanced by the development of consensus based guidelines by recognised experts in this field. Such a development would aid standardisation of practice and allow dissemination of personal experience, audit and clinical research to create the much needed evidence to inform future practice in this complex group of patients.

Progress 2018

Core Group meeting Edinburgh September 2018

Oral Presentation at national Intestinal failure and rehabilitation meeting.

Outcome

Consensus statements (expert panel) to be drafted September–October 2018

Sections for Delphi

1. Organisation of service
2. Early management for community based teams,
3. Nutritional assessment
4. Investigations
5. Medications
6. Indications and use of parenteral Nutrition
7. Ethics safeguarding and end of life

Next steps

1. Stakeholders who represent families with Children and Young People with neurodisabling conditions (eg Contact a Family, SCOPE, Dystonia society) and those receiving clinically assisted nutrition (eg Half PINNT) will be approached and a stakeholder meeting planned. We hope to receive support from RCPCH to recruit family and patient representatives.
2. Core group to meet (face to face meeting planned in London, RCPCH) to finalise statements and discuss Delphi process.

Issues to report

The Delphi advisor, Mr Ben Allin, has limitations on his time to support the Delphi process.

We are again seeking advice from the Clinical Standards team at the RCPCH, as to whether they can support the Delphi process and what cost this would entail. We have around £3,300 remaining from the BSPGHAN grant.

2019 Update

This project is designed to assist health professionals with a decision making framework for both clinical and ethical decisions for children with severe neurodisability who may require complex interventions to maintain nutrition and hydration, (now referred to as gastrointestinal dystonia (GID)). I will describe progress to date.

- A working group of interested professionals has been established drawing from Paediatric Gastroenterology, Surgery Neurology, Neurodisability and Allied Health professionals, we have met face to face on two occasions with additional teleconference. We have reached agreement on the need clear definitions for severe GI symptoms in the context of neurodisability to inform any such guideline; as part of initial draft of guideline a glossary of terms has been proposed
- A systematic review of the literature has been completed and presented for medical and surgical treatments for GID, and demonstrates the limited data in this area. McConnell N, Beattie LM, Richards CE, Protheroe S, Barclay AR, *Journ Pediatric Gastroenterol Nutr* 2018;66 (supp 2):1002;
- An agreement that a consensus based approached to constructing guidelines for GID is necessary in the absence of an evidence base
- We have sought agreement with the RCPCH, Quality improvement division for these guidelines to be developed with RCPCH endorsement, with tacit assistance from RCPCH for their production
- A methodology framework has been developed to meet RCPCH standards
- A series of test statements have been developed by the working group for use in an on-line Delphi consensus process

Although progress has been slower than anticipated we are now at a point to run on-line Delphi consensus with the assistance of the RCPCH next year. Provisional costs for RCPCH assistance are around £4500, whilst the majority of moneys from grant remain unspent, this cost will exceed initial grant, we will seek additional funding sources such as other interested societies. With the ongoing society support we would anticipate this project to be near completion/ public consultation by the next AGM January 2021.

Update January 2021

Funding secured to complete project.

Andy Barclay
Sue Protheroe

Digital Ulcerative Colitis Healthcare project. **(DUCH project): Applicants:** Dr Jonathan Hind; Dr Dhamyanthi Thangarah, Dr John Fell and Dr Mohammed Mutalib

All the gastroenterologists and gastro specialist nurses on each site have now met with Jonathan Hind and gone through the use of the app, the quality improvement protocol, and the data collection. The technology will now be provided to each doctor to trial on a personal level to learn how to use the app before becoming a professional service with patient involvement.

In the meantime, meetings are being set up in each Trust with IT governance and service managers, so that each Trust can agree the use of the app for the duration of the QI project. IT governance documents have been sent to C+W hospital and King's, and are ready to send to Evelina. A draft privacy impact assessment has been written and will be adapted for each centre according to their needs and the requirements of local IT governance

Update December 2019: Digital Pucai system has been built, working with IG in the Trusts involved

---

Paed eBANS administrator: Applicants: Dr Akshay Batra (eBANS); Dr Andrew Barclay (NIFWG); Dr Anthony Wiskin (eBANS): Dr Jutta Koeglmeier (NIFWG): Dr Julian Thomas (eBANS)

The grant was used to appoint a Band 5 administrator providing funding for 7.5 hours per week. The post was filled in February 2018 to organise the conduction of a complete survey of children receiving parenteral nutrition in England and Wales.

The funding the appointment of the administrator has made it possible to achieve the engagement from centres across the country to improve data collected recording the demographics and outcome. We aim to continue moving forward by standardising the processes of recording information in England, Wales, Scotland and Northern Ireland.

Vulnerability of the dataset as it is not as well supported as the adult database and work has been started with NHS England in trying to secure commitment for the patient. Having a database of these patients makes it easier to negotiate with them.

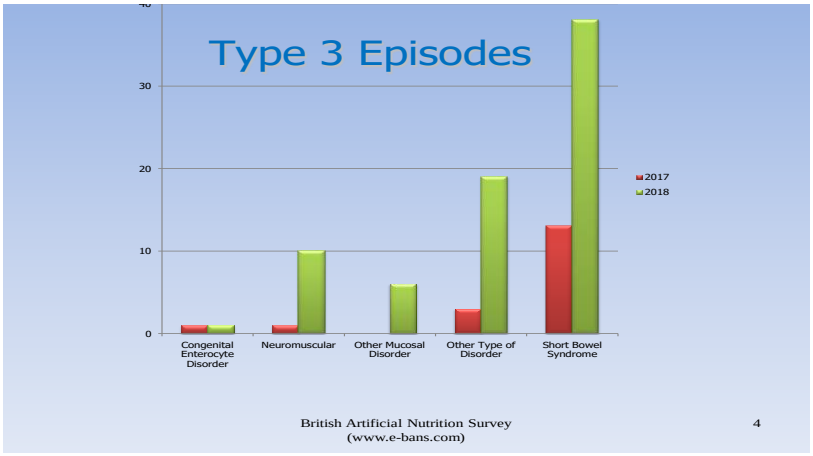
The formation of the eBANS working group and support from nutrition and intestinal failure working group has been instrumental in developing this platform and we are grateful for the continued support from BSPGHAN. The aim would be to obtain robust national outcome data making us the first country with a complete national registry for patients with type II and III intestinal failure.

The key achievements are

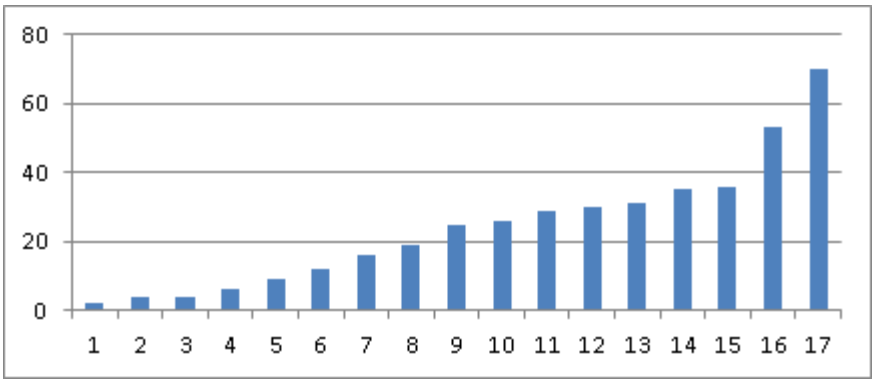
1. We have been able to establish a contemporaneous database of patients on Home parenteral nutrition. The prevalence was reported in 2018 and 2019. There were 381 patients registered on the database on home PN in 2018 which increased to 420 in 2019. There are further few patients in Wales, Scotland and Northern Ireland but not registered on the database.

2. Over the last year there has been further improvement in engagement and and 73% patient records were updated over the last 12 months.
3. A designated lead for entering data has been identified in all centres and there is now an up to date mailing list for all centres in England, Scotland, Wales and Northern Ireland.

Yearly comparison of patients on HPN based on their etiological diagnosis.



Distribution of patients across the recording centres



The aim moving forward with the currently available funding would be to

1. Reliably cross check the available data from other sources including home care providers and individual centres.

2. Maintain the current engagement by providing regular feedback to reporting centres, to ensure that the data recorded is up to date and accurate.

3. Continue to improve the usability of database and include some outcome data.

Innovation Grants Awarded October 2018 - £5,000 each

Using the Gastroesophageal Reflux Disease Symptom and Quality of Life Questionnaire (PGSQ) in children with cerebral palsy: a preliminary validation study'

Dr Mark Tighe, Consultant Paediatrician, Poole Hospital

December 2019: Ethical approval now granted. Project to start in 2020

January update 2021

We've just opened last week and are recruiting our first parent Friday. Hopefully will have finished the 1st phase in 2m.

We had to do a substantive amendment to allow us to do this via Teams which held us up by a month over Xmas.

Dr Mark Tighe, Consultant Paediatrician, Poole Hospital

Role of Vascular adhesion protein 1 in the pathogenesis of chronic graft hepatitis and fibrosis after paediatric liver transplantation

Professor Deirdre A Kelly, CBE, Consultant Paediatric Hepatologist, Birmingham Women's and Children's Hospital, Birmingham. Dr Steffen Hartleif, Groningen, Germany; Chris Weston, University Hospital of Birmingham

BSPGHAN Innovation Grant 2018: The role of vascular adhesion protein-1 in the pathogenesis of chronic graft hepatitis and fibrosis after paediatric liver transplantation

Steffen Hartleif[1,2,] Chris Weston[3], Stefan Hübscher[4], Deirdre Kelly[1,5]
[1]Graft Injury Group
[2]University Hospital for Children and Adolescents Tübingen, Germany
[3] Birmingham Liver Biomedical Research Centre, Institute of Immunology and Immunotherapy, University of Birmingham, Birmingham, United Kingdom
[4]Queen Elisabeth Hospital, Hepatic Pathology, University of Birmingham, Birmingham, United Kingdom
[5] Birmingham Women's and Children's Hospital, Birmingham, United Kingdom

Corresponding author: steffen.hartleif@med.uni-tuebingen.de

Progress Report

We selected 40 patients and 60 protocol biopsies from our registry and included these patients to our study. First, we established an assay for immunohistochemistry using the anti-VAP-1 antibody. We assessed the chromogenic stained biopsies for VAP-1 intensity and distribution of VAP-1 antibodies. We detected a sinusoidal and perivascular staining. Protocol biopsies were scored for inflammation and fibrosis using standard stainings. We found a typical pattern of anti-VAP1 staining in normal and disease biopsies. Expression of VAP-1 was mainly associated with perivenular fibrosis and central perivenulitis. Additionally, we performed quantitative RT-PCR of AOC3 RNA expression in protocol biopsies, which encoded the VAP-1 protein. Preliminary analysis showed an association of VAP-1 RNA expression with graft hepatitis, which was not statistically significant (***figure 1***). For better quantification and differentiation of VAP-1 in graft fibrosis, we will perform quantitative staining using immunofluorescence and confocal microscopy aiming VAP-1, α-SMA and CD31 antigen.

The key objectives for the coming year:

 Completion of VAP1 immunofluorescence staining and correlation with fibrosis and inflammation.

 Completion of quantitative reverse transcriptase PCR to quantify VAP1 RNA expression in protocol biopsies

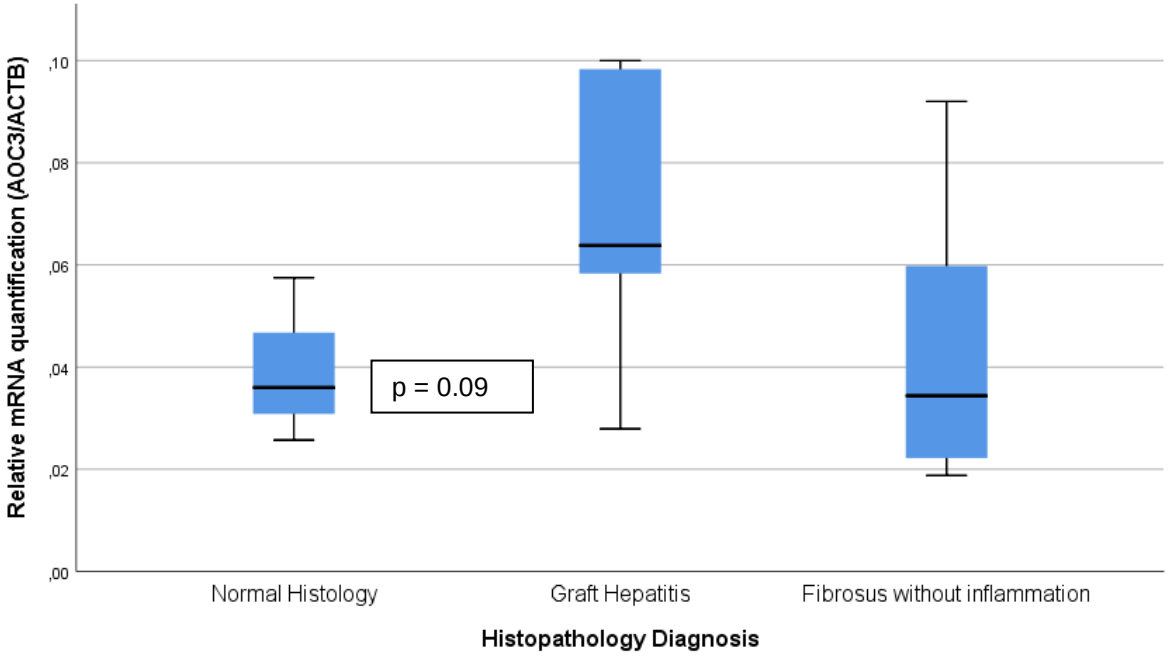


Figure 1: *Trend towards higher VAP-1 expression in patients with Graft Hepatitis* (N=17) Assessment of more samples!

Special Projects Grant: £6,000 matched with £6,000 from BAPS

In response to Coroner's request BSPGHAN and BAPS will be undertaking an Upper GI Bleeding Survey.

Professor Nick Croft, Consultant Gastroenterologist, Barts; Mr Michael Stanton, Consultant Paediatric Surgeon, London

Funding is being used to fund salary of data manager/statistician working at Barts. He has compiled a data base and set up a Red Cap Survey to capture information from centres

---

Awards 2019:

Two Joint CLDF/BSPGHAN awards: £10,000 contribution from each – project details can be viewed on CLDF website https://childliverdisease.org/research/#Current-Research-Projects

Lysophospholipid profiling of Fibrolamellar hepatocellular carcinoma (FLHCC) and identification of novel therapeutic targets

Dr Gary Reynolds, Liver Labs, University Hospital of Birmingham

https://childliverdisease.org/lysophospholipid-profiling-of-fibrolamellar-hepatocellular-carcinoma-flhcc-and-identification-of-novel-therapeutic-targets/

Dr Gary Reynolds of Queen Elizabeth Hospital Birmingham discusses his research and what it means for the future of treating childhood liver disease. This research is co-funded by BSPGHAN and Children's Liver Disease Foundation (CLDF).

What is this study looking at?

Fibrolamellar hepatocellular carcinoma is a liver cancer that affects adolescents. Bio-active lipids (fat-like substances) are key molecules in the blood and cells for normal development and function that can become unbalanced leading to similar effects in cancer. This research will target one of these groups of bio-active lipids (lysophospholipids) to understand more about the tumours biology and identify potential drug treatments.

Why is this research important?

Fibrolamellar hepatocellular carcinoma is a very rare type of primary liver cancer and therefore very little is known about it. There are no proven or effective treatment options other than radical surgery or transplantation. Because of this and as it is usually discovered at a late stage, the option of surgery or transplant is only possible for 70% of patients and recurrence of the cancer as well as treatment is a big problem.

What about the future?

The results from this study will provide much needed information into this cancer and data for a more substantial grant, moving towards clinical trials for new future treatments.

In vivo liver genome editing for the treatment of Alpha-1 antitrypsin deficiency

Professor Deborah Gill at John Radcliffe Hospital, University of Oxford

https://childliverdisease.org/in-vivo-liver-genome-editing-for-the-treatment-of-alpha-1-antitrypsin-deficiency/

Professor Deborah Gill of John Radcliffe Hospital, University of Oxford discusses her research and what it means for the future of treating childhood liver disease. This research is co-funded by BSPGHAN and Children's Liver Disease Foundation (CLDF).

What is this study looking at?

Gene therapy holds the promise of a curative treatment for genetic diseases by delivering a functional copy of a gene into cells to compensate for non-functional (defective) versions. This is called 'gene addition'. However, the liver grows in paediatric patients, which means that the gene addition approach may only have a short-term impact.

This study is proposing a new strategy called genome editing to precisely insert a functional copy of the gene into the genome (complete set of genes or genetic material present in a cell or organism) of the patient's liver cells, so that it could continue to function for the life-time of the patient. It will test the genome editing strategy on a mouse model of alpha-1 antitrypsin (A1AT) deficiency, in the hope it will replicate findings of tests with liver cells grown in culture and artificial 'mini livers' (organoids). The study hopes to evaluate the safety and therapeutic applicability before clinical trials can begin.

Why is this research important?

There is currently no definitive cure for AAT deficiency, however, genome editing provides an opportunity to address this unmet need. While this study focuses on AAT deficiency, it hopes to open the platform for exploration of other genetic liver diseases where genome editing may be beneficial.

There has been no previous paediatric study, to our knowledge, exploring the association of sarcopenia with increased fibrosis and/or inflammation in the context of NAFLD. No study in children with NAFLD has investigated the various myokines (products released by muscle cells) and adipokines (protein secreted by body fat) in relation to muscle mass.

What about the future?

If the strategy is successful in demonstrating genome editing of the A1AT gene in mice, the results will help progress this approach for clinical development. These results will also support further funding applications to use this approach for the treatment of other genetic liver diseases.

Joint CLDF/BSPGAN award: £4,000 from each partner

Using single cell sequencing to determine how bile ducts form; understanding the mechanisms to fight Biliary Atresia

Dr Luke Boulter, Institute of Genetic and Molecular Medicine, Edinburgh

https://childliverdisease.org/using-single-cell-sequencing-to-determine-how-bile-ducts-form-understanding-the-mechanisms-to-fight-biliary-atresia/

Dr Luke Boulter of the Institute of Genetics and Molecular Medicine, Edinburgh discusses his research and what it means for the future of treating childhood liver disease. This research is co-funded by BSPGHAN and Children's Liver Disease Foundation (CLDF).

What is this study looking at?

Bile ducts (tubes that carry bile from the liver in to the intestine) fail to form normally in biliary atresia and currently, children require surgery or liver transplantation as treatment. What we don't understand is how normally bile ducts form when the liver grows in the foetus.

Understanding this process will be essential for understanding what goes wrong in biliary atresia. A mouse mutant has been developed where biliary cells form in the foetal liver but then fail to form bile ducts. This research aims to investigate what factors cause biliary cells to form ducts in the foetal liver and ask how these factors change in our mutant mouse model of biliary atresia.

Why is this research important?

The process by which the ductal plate (cells that make up the building blocks for bile ducts) changes into a bile duct is unclear. By understanding the processes by which bile ducts form will help to identify the causes of biliary atresia leading to development of therapies to stimulate growth and repair the bile duct.

What about the future?

The aim of this preliminary study is to provide data to contribute to a subsequent larger research grant proposal and support applications for greater levels of funding to investigate further.

Two Joint GUTS UK/BSPGHAN Awards - £40,000 total award for each project

Dr Paul Henderson (IBD)

Institution: University of Edinburgh
Title: The PINPOINT study -The Prospective Incidence of Paediatric-Onset Inflammatory bowel disease in the United Kingdom

Project Start Date: 1 April 2021
Completion Date: 30 June 2022

The aim of this study involves coordinating 38 centres UK-wide to determine the incidence of paediatric IBD (PIBD) to help inform future epidemiological studies and NHS service design, as well as to create the first traceable UK-wide prospective PIBD cohort and give every paediatric IBD access to IBD registry.

The PINPOINT study -The Prospective Incidence of Paediatric-Onset Inflammatory bowel disease in the United Kingdom, University of Edinburgh, £39,936.

Update January 2021:

The process to get ethical approval was progressing well before the pandemic. Unfortunately, due to prioritisation of Covid-19 trials, this was halted for many months. However, progress continues to be made. Full ethics approval was granted (Scotland) in November 2020 and the final step is securing HRA approval (England/Wales) which is likely in late January/early February. Virtual Site Initiation Visit presentations will be scheduled immediately following HRA approval and site files have already been created. The changes to the IBD Registry needed for the study are also now in place so it is hoped that recruitment will commence in March/April 2021 for a 15-month period.

Professor Matthias Zilbauer (IBD)

Institution: University of Cambridge
Title: Stratification of inflammatory bowel disease treatment in children using human intestinal organoid derived epigenetic signatures
Project Start Date: 1 October 2019
Completion Date: 30 September 2020

This project is running slower than expected with the organoid study. COVID has slowed up work due to staff having limited access to the lab and isolation. Project has been granted a 6 month extension already.

Update January 2021

Stratification of inflammatory bowel disease treatment in children using human intestinal organoid derived epigenetic signatures, University of Cambridge, £40,000

The aim of this study is to analyse mini-guts generated from children diagnosed with IBD and matching controls to find out how patients with IBD differ from children without the disease. These can be used to develop new drugs, test existing drugs, and find out why these cells don't function properly in children with IBD. This project will apply world-leading, novel research technology to a large collection of existing patient samples. The results have a great potential to impact on patient's health by being able to identify novel ways to enable a tailored treatment approach.

Project update January 2020: Professor Matthias Zilbauer has submitted an interim/annual report, that has been evaluated and approved last December by our Research Trustee Professor John Mclaughlin for Guts UK and by Dr David Campbell for BSPGHAN.

Main findings: Their findings suggest that cells forming the most inner lining of our intestine may be malfunctioning in children diagnosed with IBD. The degree to which their function is impaired or altered could explain why some children suffer from a mild while others from severe disease. Also, identification of specific functions that are altered may help the researchers to develop novel treatments.

A manuscript reporting these findings is currently under review at Stem Cell Report. The funding from Guts UK and BSPGHAN has been acknowledged.