National Study Day
Update on Care of Patients with Cystinosis

Postgraduate Medical Centre
Queen Elizabeth Hospital
Birmingham
Tuesday, 1 October, 2013

A non-promotional meeting in partnership with Orphan Europe (UK) Limited
Welcome to the First National Study day on Cystinosis!

It gives me great pleasure to welcome you all here to the New Queen Elizabeth Hospital Birmingham.

Following the first description of the disease by Emil Abderhalden in 1903 there were many subsequent descriptions of the clinical effects. However, it was not until 1967 that Schneider described the presence of intracellular cystine and then Schulman in 1969 showed that it this was a lysosomal storage disease. Despite all this, and many subsequent reports, there is still so much more to learn about the pathophysiology and the clinical course of the disease in both children and especially in adults as the children increasingly survive into adulthood.

We have assembled an expert faculty to cover most of the clinical aspects of the disease and I hope that you will enjoy their presentations and go away able to translate what you learn into improved care for the cystinotic patient.

While there is a very full and varied programme, there will be enough time for “networking” and make new contacts.

Finally, I would like to thank you all for coming and Sara Elgott from Orphan Europe for making this all possible.

Graham Lipkin

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Dr. Graham Lipkin

Consultant Nephrologist
Current Positions Held:
- Consultant Nephrologist, University Hospital Birmingham NHS Foundation Trust and Honorary Senior Lecturer University Of Birmingham, UK (appointed 1996)
- Chair British Renal Association Clinical Services Committee
- Vice-President Elect of British Renal Association
- Chair Transplant Renal Forum-Wmids, UK

Specific Clinical Areas of Interest:
1. Renal Transplantation (Director of Live Donor transplantation at UHBFT)
2. Rare Renal Metabolic Disease (Coordinator of Renal association Rare Disease Initiative-Cystinosis)
3. Pregnancy in women with Kidney disease (Runs large Regional Renal/Obstetric service at Birmingham Women’s Hospital NHS Trust) over 15 years.
4. Renovascular Disease (Steering group member of ASTRAL trial-largest trial of real revascularisation)
5. Acute Kidney injury.

Research Interests:
1. Contraception in women with Renal Disease
2. Founding member of Collaboration in Obstetric Renal disease (CORD)-Registry of pregnancy outcomes in women with Renal disease.
3. Factors predictive of pre-eclampsia in women with Kidney disease.
4. Obstetric outcomes in women with Renal disease in Ghana (in collaboration with Korle Bu Hospital, Accra, Ghana).
5. Transplant Renal artery Stenosis
6. Renal function outcomes in patient with Non-Renal transplants

Abstract
The challenges of caring for patients with Cystinosis in the adult world will be discussed. This includes an outline of transfer, models of care, renal transplant care in adults with cystinosis and issues of reproductive health.
Dr. Stephen Waldek M.B., B Ch., F.R.C.P.

He qualified in medicine from the Welsh National School of Medicine, Cardiff, in 1971.

He then acquired a broad training in general internal medicine in South Wales and 12 months of specialist neurology in London.

He was then appointed clinical lecturer in general and renal medicine at the University of Manchester based at Salford in 1975. This provided extensive further experience in acute general medicine and renal medicine including the setting up of an acute dialysis service.

In 1978 he moved to Sheffield as senior registrar in renal and general medicine gaining further extensive experience.

During this time he established one of the first chronic ambulatory peritoneal dialysis services in Europe.

1980 saw him appointed as renal and general consultant physician at Hope Hospital (University of Manchester) now known as Salford Royal Hospital. There he was responsible for the development of a full renal service, (but not acute transplantation). Special interests were in metabolic aspects and the management of renal failure, including dialysis—especially CAPD. The CAPD programme grew successfully and the outcome results were some of the best in Europe. Coupled with his clinical work he was involved on clinical research—especially in the field of dialysis technology. As such he was responsible for the development and introduction of continuous haemofiltration for acute renal impairment within the ICU and the use of prostacyclin.

Ever since a research studentship with the late Prof Robert Mahler in Cardiff had an interest in metabolic and genetic diseases. In Salford he continued this interest by managing these disease as far as the kidney was concerned. However, in 1999 was introduced to the world lysosomal storage disease through his involvement with the phase 3 trial of enzyme replacement therapy for Fabry disease. With the help and encouragement of the late, and sorely missed, Prof Ed Wraith and his colleagues he became involved with all the other LSDs in adult patients. A few years later he also took on adults with the whole range of inherited metabolic diseases. As a result of these new interests, in 2004 left full time renal medicine for metabolic diseases. Subsequently he built up a large LSD practice (one of the original 4 national centres for the management of LSD) that included over 300 patients with a wide variety of LSDs. In addition, the general IMD work rapidly increased. Coupled with this he established a successful R and D programme in the area of LSDs. In November 2011 Dr Waldek retired from clinical practice and now works as an independent medical consultant working mostly in the LSD, metabolic and renal fields.

Abstract

Cystinosis is a rare lysosomal storage disease caused by mutations in the gene encoding cystinosin the putative transporter of cysteine. It is a multi-systemic disease requiring a multi-disciplinary and multi-professional team to ensure that patients get the best possible management. While the disease nearly always starts in childhood, now that effective treatment is available most of the complications do not occur till the teenage years and beyond into adulthood.

The presentation will give an introduction to cystinosis and then outline the various issues faced by the patients at will then be covered in more detail by the speakers that follow. However, my presentation will focus on the adult patient.
Abstract

The infant with cystinosis appears normal at birth and will develop appropriately up to 6 months of age before presenting with polyuria and polydipsia, unexplained fever, anorexia, constipation, vomiting with resultant dehydration and failure to thrive, and signs of rickets. The key presenting features are hypokalemia, hyponatraemia, hypophosphatemia, acidosis, generalised amino aciduria and glycosuria. Caucasian infants typically have blond hair and blue eyes. At presentation the GFR in these children is normal. Cystine accumulation in the proximal tubular cells impairs oxidative phosphorylation and decreases the activity of Na-K-ATPase which reduces the gradient for sodium entry into the cells with decrease in sodium coupled transport of other solutes, leading to the clinical presentation of Fanconi syndrome. The diagnosis is made by the white blood cell cystine assay which is typically 10–100 times above the normal range, and with genetic confirmation. Antenatal testing of chorionic villi for specific mutations is available from 8 weeks gestation in suitable families or through measurement of cystine content in the amniotic fluid. In early life the importance of adequate correction of hydration and electrolyte imbalances are of paramount importance to improve growth. Regular review of electrolytes and phosphate supplementation is required to prevent constipation from hypokalemia and rickets from hypophosphatemia. To maintain adequate nutritional intake, gastrostomy or nasogastric feeding is required. Growth hormone therapy is beneficial once nutritional intake is optimised. Carnitine supplementation has not been proven to have specific benefits except for restoring normal plasma concentrations. Indomethacin (1-3 mg/kg/day in 2 to 3 divided doses) is very useful in improving general wellbeing as well as reducing polyuria and may be given as a single dose at night to assist nocturia. Cysteamine, the main drug therapy for cystinosis, is effective in circumventing the defective lysosomal cystine carrier system, thereby reducing the cystine content of the lysosomes. Cysteamine is administered orally at a dose of 60–90 mg/kg/day given every 6 hours. At commencement of therapy, the Cysteamine dose must be commenced at a quarter of the final intended dose and increased gradually over the first 2-3 weeks of therapy, to avoid nausea and neurological complications. The leukocyte cystine measurements are used to gauge the compliance and adequacy of dosing. The leukocyte cystine measurements are taken as a trough level 5½ to 6 hours after the previous dose of medication, aiming for the white cell cystine level to be less than 2 nmol ½-cystine/mg protein. Cysteamine has no effect on the Fanconi syndrome but it does retard the rate of renal glomerular deterioration and improve linear growth in children. Oral Cysteamine does not improve the effects in the eye but topically administered Cysteamine 0.55% eye drops given 6-12 times per day are extremely useful. The optimal care of patients with cystinosis requires a multi-professional team approach with referral and advice to centres specialising in the disorder.
Abstract

The eye has been known to be involved in patients with cystinosis for many years, although the earliest age at which crystals are seen within the eye is unknown. The cystine crystals can be found in all parts of the eye – the conjunctiva, the cornea, the ciliary body, the iris, the sclera, the retina, the choroid and the optic nerve. Interestingly the crystals in the cornea are morphologically distinctive and are uniform needle shaped structures whereas elsewhere in the eye the crystals are similar to those elsewhere in the body. The crystals are most abundant in the cornea and rare in the optic nerve with variable prominence in other parts of the eye.

Many patients are asymptomatic despite having lots of crystals within their cornea. However common symptoms are photophobia and even sneezing in bright light due to the massive diffraction caused by the crystals. Recurrent corneal erosions with peripheral corneal degeneration can occur. The crystals are found in the trabecular meshwork and patients with cystinosis have narrower angles and shallower anterior chambers than controls predisposing them to glaucoma later in life.

Studies in the 1980’s showed crystals in the retina sometimes associated with abnormal retinal electrophysiology but this work has not been repeated.

Treatment of the eye is with regular 0.55% cysteamine (mercaptine) drops which may not be well tolerated and ocular lubricants to minimize the corneal symptoms. Laser refractive surgery is not recommended for these patients.
Mr. Steven Wise

Current Position:
• Renal Metabolic Disease Nurse Specialist, Queen Elizabeth Hospital Birmingham.
• Member of the Cystinosis Rare Disease Working Group.

Academic History:
• BSc Hons – Professional Practice, Long Term Conditions
• DipHE – Adult Nursing

Steven Wise is a nurse specialist in renal metabolic diseases at Queen Elizabeth Hospital Birmingham. He qualified from Coventry University with a diploma in Adult Nursing and had since gained a BSc 1st Class honours degree in long term conditions and is currently studying for an MSc in advanced practice. He came in to post in 2011 and has developed patient pathways, protocols and information for patients with rare renal metabolic disorders. Prior to this he worked on the haemodialysis unit a University Hospital Coventry and Warwickshire and became a charge nurse on the unit in 2010. He took a keen interest in patient empowerment and coordinated the home haemodialysis training programme.

Steven supports the Cystinosis clinic at QEHB and coordinates the one stop cystinosis clinic which sees patients attending from all over the country. He has presented at national conferences, local forums and training sessions. He has plays an active role in raising the profile of rare renal metabolic diseases through arranging education days, and has had articles published in leading nursing journals. Other activities include taking an active role in the rare disease nurse forum at QEHB.

Abstract

Title: Patient Transition and the Birmingham Model
The presentation will present the model of care at the Queen Elizabeth Hospital Birmingham for patients with Cystinosis.

Patients with rare conditions, such as cystinosis, often spend a significant amount of time attending multiple hospital appointments. This has the potential to significantly impact on a patient’s education, career, and social activities which can affect quality of life.

The annual review clinic and care coordination at Queen Elizabeth Hospital offers a one stop annual review in which multiple diagnostics and clinic review take place on the same day. This allows for the multisystemic nature of cystinosis to be regularly assessed and significantly reduces hospital visits.
Dr. Mark Bradbury

Mark is a consultant paediatric nephrologist at the Royal Manchester Childrens’ Hospital. He studied medicine in London and first started working with children with Cystinosis in London and then in Leeds working with Trevor Brocklebank and Mick Henderson. In Manchester he looks after one of the largest group of patients with cystinosis outside of London.

Abstract

Swallowing and nutritional problems are often not immediately apparent in cystinotic patients. They are not present in all patients, but when they do occur they are not always easily diagnosed and can lead to major problems. Not only can poor nutrition affect the general health of the patient, it can also aggravate the other cystinosis complications. These issues will be addressed by reference to a difficult case that was managed in our department.
Dr. Nick Davies

I have a broad experience of general neurological disorders gained through specialist training both in Birmingham and at the National Hospital for Neurology and Neurosurgery, Queen Square, London. Birmingham has a long tradition as a centre of excellence for metabolic medicine and I run combined Neurometabolic clinics with other physicians experienced in the management of patients with such disorders. In the past I undertook 4 years of research under the auspices of UCL and the National Hospital for Neurology and Neurosurgery, Queen Square, London. This included setting up a genetic diagnostic service for skeletal muscle ion channel disorders including myotonia, paramyotonia and periodic paralysis.

Abstract

Although rare, metabolic disorders such as cystinosis represent a potentially treatable group of conditions with various presentations. Although predominantly a renal disorder, cystinosis can result in a number of neurological complications, The discussion will focus on the central and peripheral nervous system complaints that occur 1) prior to the advent of therapy for cystinosis 2) during therapy and 3) relating to the drug therapy.
Professor Roz Anderson

Roz is a professor at University of Sunderland, where she teaches pharmaceutical and medicinal chemistry to pharmacy students and leads a small research group. She is a chemist by training and her research focuses on the application of chemistry to the solution of medicinal problems. There are two main strands to research into cystinosis in Roz’s group: the development of new medicines for the improved treatment of cystinosis, and the proteomic investigation of cystinotic cells and how protein expression changes after treatment with cysteamine.

The research into cysteamine prodrugs for oral administration is funded by the Cystinosis Foundation UK and has resulted in one candidate being chosen for further investigation; all results so far show this candidate to have optimal potential for clinical development. In the near future, this candidate will be evaluated for its efficacy in treating cystinotic mice. A related project, following a similar process of investigation, is at an earlier stage, but has already shown potential for enhancing the delivery of cysteamine to the eyes to improve the treatment of ocular cystinosis.

The study of protein expression in cystinotic cells is funded by Cystinosis Research Foundation and is investigating the changes in cellular proteins as a result of the disease. The results are helping us to understand more about the processes that are not fully functional as a result of cystine accumulation. We are now investigating how treatment with cysteamine changes the levels and identities of cellular proteins and whether this information allows new medicines to be identified or new tests to be designed.

Besides her research on cystinosis, Roz leads a research collaboration with industry on improving the detection and identification of bacteria in clinical samples and has two patents on new agents designed for the treatment of psoriasis. She leads the science research at the University of Sunderland, mentors less experienced research staff, and chairs the department’s Athena Swan group.

Abstract

If we were designing a better treatment for cystinosis, what would it be? Having written a list of requirements, we designed cysteamine prodrugs for the improved treatment of cystinosis and subjected them to a range of in vitro tests (cytotoxicity, uptake into cells, release of cysteamine, depletion of cystine) to identify those with the best profile. Two prodrugs have been further tested for acute toxicity and gastrointestinal damage; one of these will progress to efficacy testing for its ability to treat cystinotic mice.

Using cystinotic cell lines (fibroblasts and PTECs) and isotopic labelling, we are conducting a study to identify proteins that are differentially expressed in cystinotic cells. More than 3500 proteins have been identified and about 60% quantified; of these >700 have significantly altered expression. Analysis of these results is helping to identify the cellular pathways that are affected in this disease.

This presentation will summarise the key findings of the research being carried out into cystinosis at the University of Sunderland and future directions; other approaches will be highlighted.
Cystinosis: Endocrine and bone problems and their management
Dr Jeremy Kirk, Consultant Paediatric Endocrinologist, Birmingham Children’s Hospital

Abstract
Growth retardation is more pronounced in cystinosis than in other chronic kidney diseases and is mostly not corrected by cysteamine treatment. The growth retardation is multifactorial in origin, and due to a combination of decreased renal function, poor metabolic status secondary to renal Fanconi syndrome, feeding difficulties, and possibly cystine accumulation in the bone. Some data also indicates abnormalities in quantitative and qualitative secretion of growth hormone.
Growth can be partly improved by the correction of metabolic and nutritional deficits, but children with cystinosis and poor renal function in whom poor growth continues are eligible for treatment of growth hormone under the chronic renal failure licence, which has been ratified by NICE in 2002 and also in 2010. Long-term GH treatment appears to be safe and effective in young children with cystinosis, and there is no evidence that GH therapy is associated with worsening of renal failure.
Cystine crystal accumulation also leads to other endocrinopathies, including primary hypogonadism, diabetes and thyroid dysfunction. These complications are only partially prevented or improved with cysteamine treatment.
Many of the end-organ effects of cystinosis are also known to be risk factors for osteopenia; these include deposition of cystine crystals in bone, hypothyroidism, diabetes mellitus, primary hypogonadism, urinary phosphate wasting, and chronic renal failure. DEXA scanning often does not reveal any evidence of reduced bone mineral density, despite an apparent increased fracture risk.
Abstract

This talk will provide an introduction to understanding the range of ways, in which patients perceive their illness and their treatment. First, it will describe the nature of illness beliefs and show how they can have strong effects on coping and a wide range of outcomes, including mood, quality of life and level of functioning. Next, it will outline the importance of treatment beliefs in influencing the uptake of and adherence to treatment and other medical advice. Finally some preliminary recent data from patients with cystinosis will be presented.
Ami Froehlich

I was born in 1985 and I have nephropathic cystinosis. Thanks to the development of cysteamine therapy in the 80s I did not have my kidney transplant until 2009, which I received from my mum. I obtained a BSc degree in psychology in 2007 and since then have pursued a career in mental health. I currently work as a Senior Psychological Wellbeing Practitioner for Lancashire Care NHS trust, which involves facilitating guided self help interventions for patients with anxiety and depression, as well as managing the service in West Lancashire as the locality lead. I became a trustee for the Cystinosis Foundation UK in 2012, and hope to represent the growing adult population of patients with cystinosis.

Abstract

The Patient’s Perspective and the Role of the Cystinosis Foundation UK
Ami Froehlich, Secretary, Cystinosis Foundation UK
I was born 10th October 1985 and diagnosed with nephropathic cystinosis aged 22 months, after my parents struggled to find a diagnosis for over a year.
I believe that being compliant with cysteamine treatment has made a significant positive impact on my health, it increased my native kidneys lifespan, and at the age of 27 I do not have any other complications commonly associated with adults with cystinosis. Considering the prognosis of my condition when I was diagnosed I consider myself to be healthy and I am able to lead a normal life, with a career in mental health, and an active social life outside of work.
The Cystinosis Foundation UK was founded in 1998 by Jonathan Terry, and charity status was achieved in March 1999. The aims of the Cystinosis Foundation UK are to provide support and information to children and adults with cystinosis, and their families, participate in conferences, and to support research in cystinosis.