Nephrology and clinical genetics joint session

G72 ARE MUTATIONS OF *PLCE1* SUFFICIENT TO CAUSE DIFFUSE MESANGIAL SCLEROSIS?

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Aim: We present the first report of an individual homozygous for an apparently pathogenic mutation of *PLCE1* who has no clinical renal disease.
Method: Three children from a consanguineous kindred of Pakistani origin with diffuse mesangial sclerosis (DMS) presented with congenital or infantile nephrotic syndrome. Genome-wide single nucleotide polymorphism (SNP) mapping was carried out in the three affected and four of the unaffected individuals. Direct sequencing of the *PLCE1* gene was undertaken. In one individual results were confirmed with two additional primer sets. Multiplex ligation-dependent probe amplification (MLPA) analysis was also performed and methylation analysis of an imprinted site on chromosome 10. Microsatellite analysis was carried out by PCR amplification of DNA using primers for polymorphic (CA)n repeat sequences in the region of the *PLCE1* gene. Analysis was repeated on DNA samples from repeated blood and saliva samples.
Results: SNP analysis revealed two long regions of homozygosity on chromosomes 10 and 13. One of these contained the *PLCE1* gene (sometimes known as *KIAA1516*, *PLCE* or *NPHS3*) recently described as a cause of DMS. All affected children were homozygous for a four base-pair deletion in exon 3, which creates a premature translational stop codon. However, analysis of the asymptomatic father of two of the children revealed that he was homozygous for the same mutation. This result was confirmed using a variety of PCR primers and MLPA. Methylation analysis revealed normal biparental inheritance of chromosome 10. Microsatellite analysis confirmed homozygosity for (CA)n repeat polymorphisms in the region of *PLCE1*.
Conclusion: We conclude that this observed non-penetrance is either due to compensatory mutations at a second locus or that mutations of *PLCE1* by themselves are not sufficient to cause DMS.

G73 THE SMARTNET CLINICAL NETWORK: CREATION OF A NATIONAL STANDARDISED NATURAL HISTORY DATABASE FOR SPINAL MUSCULAR ATROPHY

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Aims: To develop a standard neuromuscular measurement tool for the assessment of children and adults with spinal muscular atrophy (SMA) in order to optimise their management and to create a national database to collect natural history data on type II and type III SMA.
Background: The Smartnet Clinical Network UK was established in 2006 following the appointment of a project coordinator and collaboration between the major paediatric neuromuscular centres and some adult-based centres. A similar initiative had already been successfully established in the UK through North Star, a network designed to establish standardised assessment procedures in ambulant Duchenne muscular dystrophy boys. Increasingly, there has been a need to establish standardised assessment procedures as clinical trials become more likely and regulatory authorities require more comprehensive measures of progress.
Methods: To establish the optimum motor function scales, existing scales were reviewed by an expert group and consensus was achieved on the choice of three measures, as follows: For non-ambulant children, the Hammersmith functional motor scale, this has been used in clinical trials already and has been used by clinicians overseas fairly extensively. For ambulant children and adults, the slightly modified North Star ambulatory assessment, which was originally designed for use in Duchenne muscular dystrophy, but has now been adapted for the use in SMA. For non-ambulant children, teenagers and adults, Egen Klassifikation for SMA, which is a robust functional questionnaire highly relevant to individuals.
Results: Through the activities of the project coordinator and the network a web-based national clinical database has been developed in order to review the natural history of SMA, facilitate multicentre clinical audit and review services. The database is hosted on a joint website with the North Star project and is due to go live in February 2009.
Discussion: It is hoped that with further funding the work can be extended to cover the adult population more comprehensively, and new outcome measures can be evaluated and correlations between measures assessed.
Funding: The authors gratefully acknowledge the financial support of the Jennifer Trust for Spinal Muscular Atrophy and the muscular dystrophy campaign.

G74 A NOVEL INTERACTION BETWEEN KIDNEY ANION EXCHANGER (KAE1) AND NEPHRIN IN GLOMERULAR PODOCYTES EXPLAINS PROTEINURIA IN DISTAL RENAL TUBULAR ACIDOSIS

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Patients with distal renal tubular acidosis (dRTA) frequently develop proteinuria and ongoing renal damage. Protein filtration in the kidney is controlled at the level of the podocyte, in the glomerulus. Nephrin (NPHS1) is a podocyte junctional slit diaphragm (SD) protein, providing a physical framework for the glomerular filter, connecting the SD to the cell cytoskeleton and participates in cellular signalling. The tubular-cell membrane protein kidney AE1 (kAE1) is a HCO_3/Cl^- exchanger crucial for distal tubular urinary acidification, mutations in which result in recessive dRTA. The presence of kAE1 in the glomerulus has not previously been reported. The N-terminus was recently shown to bind integrin-linked kinase (ILK). We report a novel interaction between the kAE1 cytoplasmic C-terminus and nephrin by yeast two-hybrid assay and study the functional significance of this interaction.

Glomerular kAE1 expression was confirmed by Western analysis and confocal imaging of the human kidney. Protein interaction with nephrin was demonstrated by immunoprecipitation. In normal glomeruli, kAE1 staining partly co-localised with that of nephrin. Strikingly, kAE1 protein was absent in glomeruli homozygous for the human nephrin ($NPHS1_{FinMaj}$) mutation, but distal tubular expression was unaffected. In wild-type human conditionally immortalised podocytes, kAE1 localised to the cytoplasm and the plasma membrane; its expression was absent in $NPHS1_{FinMaj}$ cultured podocytes. The reintroduction of wild-type nephrin into mutant podocytes by stable expression rescued kAE1 expression and localisation.

In AE1 knockout mice, nephrin protein expression was unchanged compared with wild-type littermates, but albuminuria was detected in the majority of mice studied. Scanning electron microscopy showed abnormalities in all three layers of the glomerulus, including foot process effacement and fusion, irregular glomerular basement membrane (GBM) thickening, subendothelial expansion and arcade formation.

We propose kAE1 as a novel podocyte protein that via interactions with nephrin, contributes to the structure or signalling of the SD and also via ILK connects to the GBM. This also introduces a mechanism to explain the proteinuria and glomerulosclerosis seen in patients with dRTA.

G75 CHILD PRESENTING WITH FEATURES OF DOWN'S SYNDROME BUT NORMAL KARYOTYPE: IS THIS 9Q34 DELETION SYNDROME?

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Introduction: 9q34 deletion syndrome is an emerging micro deletion syndrome with a distinctive facial appearance and learning difficulties. The facial gestalt is similar to Down's syndrome and may cause a diagnostic dilemma especially when the chromosome testing is normal.

Abstract: The chromosome 9q subtelomere deletion syndrome is among the first and most common clinically recognisable syndromes to arise from widespread testing by fluorescent in situ hybridisation (FISH) of subtelomere deletions. There are approximately 50 reported cases worldwide. Affected individuals invariably have severe hypotonia with speech and gross motor delay. The facial appearance is distinct and includes relative microcephaly or brachycephaly, hypertelorism, synophrys, and/or arched eyebrows, mid-face hypoplasia, a short nose with upturned nares, a protruding tongue with everted lower lip and down-turned corners of the mouth. Approximately half of affected individuals have congenital heart defects (primarily atrial septal defect or ventricular septal defect). A significant minority have epilepsy and/or behavioural and sleep disturbances. A variety of eye, ear, genital and limb anomalies has been reported. It is also said to cause an increased incidence of obesity and respiratory failure. Several reports have described ''autistic'' traits including unusual behaviour and interests. Most patients have sub-microscopic deletions of the subtelomere region of chromosome 9q34.3. The clinical phenotype is caused by haploinsufficiency of the *EHMT1* gene. The key take-home message is that in a patient that looks like Down's syndrome, but there is no trisomy 21, consider a 9q34 deletion, which is usually only detectable on telomeric FISH. With advanced genetic testing it is now possible specifically to test the *EHMT1* gene mutation. We discuss the varying presentation of the 9q34 deletion and present several cases seen in our centre that should highlight the facial appearance and associated clinical features. This condition is being diagnosed more frequently with the increased use of FISH and making the diagnosis early helps in patient management. It also aids in appropriate genetic counselling of patients and providing accurate recurrence risk.

G76 GENE EXPRESSION PROFILING IN NEONATAL URETERIC OBSTRUCTION IMPLICATES UNSUSPECTED MOLECULES IN CONGENITAL OBSTRUCTIVE UROPATHY

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Background and Aims: Fetal urinary flow impairment, accompanied by renal dysplasia and hypoplasia, is implicated in 20% of children needing dialysis and renal transplantation. Developmental genes may play an important role in the pathogenesis of congenital obstructive uropathy and the aim of this study was to investigate changes in gene expression involved in nephrogenesis and renal epithelial differentiation in a model of congenital obstructive uropathy.

Methods: To model the disorder, we surgically induced unilateral ureteric obstruction in wild-type 48-h old neonatal mice; in this species, 90% of nephrons form in the first postnatal week. Obstructed and sham-operated kidneys were harvested at 1 and 12 days after surgery and were analysed by histology and for gene expression for which we designed and used a super array reverse transcription profiler PCR array system plate, allowing simultaneous quantitated PCR of 80 genes implicated in nephrogenesis and renal epithelial differentiation. Experimental groups were compared with paired t tests (with Bonferroni correction, $p<0.0005$).

Results: After just one day of ureteric obstruction, kidneys were hydronephrotic, with widespread dilatation of tubules and small cysts in the nephrogenic zone. At this stage, there was a significant upregulation of smooth muscle actin and downregulation of both Ift88/Polaris and Invs. The latter two transcripts encode proteins implicated in primary ciliary function and the maintenance of planar cell polarity. Furthermore, mutation of Ift88 causes polycystic kidneys in mice, whereas mutation of the human homologue of Invs causes nephronophthisis, a disease associated with renal cysts and fibrosis. At 12 days, kidney histology is dominated by intense fibrosis and loss of normal tubules. We found further upregulation of smooth muscle actin and downregulation of aquaporin-2 and γ-glutamyl transferase: markers of collecting ducts and proximal tubules, respectively. Transcripts for two growth factors were deregulated: epidermal growth factor (15-fold downregulated) and leukaemia inhibitory factor (eightfold upregulated). Prox1, a transcription factor implicated in renal hypoplasia caused by a maternal low protein diet, was downregulated.

Conclusion: Gene expression profiling in this model thus implicates several nephrogenic and epithelial differentiation molecules hitherto unsuspected in congenital obstructive nephropathy; these insights could lead to novel therapeutic strategies.

G77 COORDINATING CARE FOR NEUROFIBROMATOSIS TYPE 1: A NURSE-LED SERVICE

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Aims: An advanced nurse practitioner (ANP)-led neurofibromatosis type 1 (NF1) service has been developed since 2006 with the aim of identifying the paediatric population with NF1 in Bolton. A local care pathway has been developed, which addresses the physical, emotional and intellectual needs of the children locally (when possible) in line with the recommendations of the National Service Framework for Children, Young People and Maternity Services, Department of Health (2004). We report our experience.

Methods: All cases of NF1 in children under 16 years of age were identified by accessing the NF1 genetics register held at the regional genetics centre, by direct referral from local paediatricians and by identifying such children and their families while undertaking other non-related medical examinations. Children identified with NF1 have been seen every 6 months by the ANP or earlier if problems arise. The local care pathway has been designed as a ''spoke service'', which is in direct contact with the expertise at the ''hub'', the specialist clinic at the regional genetics centre.

Results: Twenty-four children have so far been identified with NF1, out of a paediatric population of 59 520 children aged from birth to 16 years (incidence 1 : 2480 live births). The children are from both the indigenous population and the ethnic minority communities. The severity of their physical, emotional and intellectual problems varies from mild stigmata to serious neurological, nephrological and orthopaedic problems.

Conclusions: This is the first NF1 study in which disease prevalence has equalled the predicted birth incidence; in previous prevalence studies there was evidence of an underascertainment of mildly affected sporadic cases (Huson *et al* 1989). With appropriate

training routine NF1 healthcare can be led by an ANP. The clinical benefits of subspecialisation are an increasing ability to recognise NF1-related problems, particularly the learning and behaviour issues but also to distinguish severe from mild NF1 phenotypes. For the families the advantage is that the ANP can see the children at home/school or clinic and knows when to encourage affected parents to seek review. The ANP and NF1 specialist hold a 6-monthly clinic in Bolton for all ages.

G78 FATHERS AND MOTHERS OF CHILDREN WITH LONG-TERM KIDNEY CONDITIONS: A QUALITATIVE STUDY OF THEIR CONTRIBUTIONS TO THEIR CHILD'S HEALTHCARE

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Objectives: Parents are expected to contribute to the expert/medical management of chronic disease in their children in many ways, including medication administration, feeding regimens, injections and home dialysis at the same time as being ''normal'' parents. Their involvement is well documented to be very important and the quality of it may affect the clinical outcome. Since previous research has focussed on mothers as the main respondents, fathers' views are underrepresented. Our objective was to explore/compare parents' individual and joint accounts of their contributions to care.
Methods: As this was a previously unexplored area of clinical practice, a qualitative design based on the principles of grounded theory was used. Parents were selected from one UK children's kidney unit using a purposive sampling approach based on their child's age, gender and level of clinical intervention needed. Mothers and fathers of 59 children each received postal invitations to participate. Confidentiality and anonymity were assured. The resulting sample involved 14 couples (the parents of 15 children with a long-term kidney condition) who represented a range of educational backgrounds, social circumstances and occupations. Data were obtained through 28 individual and 14 joint, semistructured interviews, tape-recorded/transcribed/analysed using a process of constant comparison. Individual and joint datasets were compared and contrasted.
Results: Parents generally shared the management role but had different ways of coping with this. Analysis revealed five themes that we called: Developing skills; Impact of the condition on daily life; Mutual support; Coping and Things that help. Emotional/physiological effects were reported by some when managing care at home (even parents who were health professionals). Fathers sometimes coped by ''disengaging'' from the situation, they needed to understand the ''bigger picture'', what might happen in the future and be reassured that professionals ''know what they are doing''. Mothers' coping was facilitated by remaining close to the situation. They were more likely to consider the impact on family life and how they could adapt to it.
Conclusions: Although fathers' and mothers' healthcare roles are similar, they may deal differently with the consequences, and their emotional and practical support requirements may need to be addressed differently.

G79 INVESTIGATING PAEDIATRIC URINARY TRACT INFECTIONS: IS NICE GUIDANCE ENOUGH?

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Background: Recent National Institute for Health and Clinical Excellence (NICE) guidance has recommended a controversial reduction in imaging following a urinary tract infection, and concern has been raised that children with specific renal tract abnormalities (vesicoureteric reflux in particular) will remain undiagnosed as a result. Consequently, paediatricians may be missing opportunities for rapid treatment and appropriate secondary prevention.
Aims: To determine whether implementation of NICE guidance would result in cases of significant renal tract abnormalities being missed. To compare predicted imaging rates between current local and NICE guidance.
Methods: A retrospective case note audit of 100 paediatric patients with a diagnosis of urinary tract infection was performed. Data were collected on the results of investigations performed under the local imaging strategy, which pre-dates the latest NICE guidance. Basic demographic data were used to predict the number of investigations required under the NICE guidance for the audit population. The two imaging strategies were compared for each case, allowing the identification of potentially missed significant renal abnormalities had NICE guidance been used alone.
Results: 100 patients aged 0–15 years (65% female) were included in the audit. 27 patients were identified as having a significant renal abnormality during the investigations performed under the local imaging strategy. Crucially, eight of these patients had either high-grade vesicoureteric reflux or renal scarring, which would not have been detected using NICE guidance alone. Over one quarter of the 159 ultrasound, micturating cystourethrogram (MCUG) and dimercaptosuccinic acid (DMSA) scans performed on the audit population demonstrated some form of renal tract abnormality. In comparison, only 93 scans would have been performed using NICE guidance, with the most notable reduction occurring in the number of MCUG being undertaken.
Conclusion: Although NICE guidance reduces the burden of follow-up investigations, it is clear that a substantial percentage of children with renal tract abnormalities will either be missed completely or picked up at a later stage when renal damage has already occurred.

G80 LONG-TERM USE OF CINACALCET IN PAEDIATRIC DIALYSIS PATIENTS IS AN EFFECTIVE ADDITIONAL TREATMENT OPTION

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The calcium-sensing receptor is thought to be the prime regulator of parathyroid hormone (PTH) secretion. It is the target of the calcimimetic drug, cinacalcet, which acts by increasing the sensitivity of this receptor to extracellular calcium ions, thereby diminishing PTH secretion.
Aims: To describe the long-term effects of cinacalcet in children with uncontrolled hyperparathyroidism in the context of end-stage renal disease. Current literature regarding the use of this drug in paediatric practice is limited.
Methods: The effects of the calcimimetic drug cinacalcet were assessed in six children with uncontrolled hyperparathyroidism secondary to stage 5 chronic kidney disease. Data regarding bone biochemistry, medications, longitudinal growth and adverse events were collected over a period of time from the initial commencement of cinacalcet to the present (July 2007), or earlier if the drug was discontinued for any reason.
Results: Patients were between the ages of 11 months and 14 years on commencing cinacalcet at initial doses of 0.4–1.4 mg/kg. Treatment, which has been well tolerated and is still ongoing in five of six patients, has been for periods ranging between 3 months and 3 years, with a maximum dose of 2.6 mg/kg used. Five of six cases have seen at least an 85% reduction in serum PTH. Hypophosphataemia and/or hypocalcaemia were observed in three of six cases. Overall, the achievement of National Kidney Fundation disease outcomes quality initiative targets was unaffected and there

was no reduction in the number of medications required to control bone biochemistry during the study period.
Conclusions: We conclude that cinacalcet is an effective treatment for correcting and sustaining correction of the biochemical derangement seen in these patients. Importantly, it has allowed the avoidance of parathyroidectomy for a significant time period in at least two of six cases. There remain concerns about the effect of Cincalcet on linear growth and future studies should aim to address this in more detail.

G81 BK VIRAEMIA AND NEPHROPATHY IN A PAEDIATRIC RENAL TRANSPLANTATION POPULATION

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Aims: To evaluate the incidence of BK viraemia and associated nephropathy in a single-centre paediatric renal transplantation population.
Methods: Children who received renal transplants between 1993 and 2007 were monitored during the period May 2007 to June 2008. Plasma BK PCR DNA was measured weekly in those who had a renal transplant during this screening period. Those who received a renal transplant before this period had routine BK screening at clinic reviews or if there was any concern about graft dysfunction. A renal biopsy was performed if there was any evidence of graft dysfunction.
Results: 729 blood samples from 130 patients were screened during this study period, with BK PCR DNA positivity detected in 8.5% (11) of patients with 100% patient and graft survival. BK PCR DNA was only detected in patients who received transplants after 2003 and the incidence increased significantly to 24% (9/37) during the period 2006–7. BK viral-associated nephropathy (BKVAN) was diagnosed in 2.3% (3/130) of all patients. 27.2% (3/11) BK PCR DNA-positive patients developed BKVAN and had become viraemic at day 18–56 posttransplant on triple immunosuppression (with corticosteroids, mycophenolate mofitil and tacrolimus) and had the highest viral loads, greater than 50 000 copies/ml at the time of first detection. 64% (7/11) BK PCR DNA-positive patients received their transplants from live related donors and 36% (4/11) had a significant rise of more than 10% from baseline of plasma creatinine at time of BK PCR DNA detection (of these, two had BKVAN). 45% (5/11) of BK PCR DNA-positive patients received monoclonal antibodies at induction (of these patients, one had confirmed BKVAN).
Conclusion: Despite BK viraemia being common in our renal transplant population, the incidence of BKVAN is rarer than other paediatric reports in the literature. Viral complications are commoner after transplantation due to increasing immunosuppression in order to reduce acute rejection rates. Paediatric renal transplant recipients should be screened for BK viraemia in order to manage patients with a reduction of immunosuppression to avoid BKVAN.

G82 RENAL DISEASE IN CHILDREN WITH IMMUNE DYSREGULATION

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Aims: To describe the development and spectrum of renal disease in children with known complex immunodeficiencies and/or autoimmune disease.
Methods: A comprehensive chart review of patients with complex immunodeficiencies and renal involvement who were under the care of paediatric immunologists and latterly paediatric nephrologists.
Results: Six patients (50% male) presented at 0.2–10.3 years (median 7.3) with common variable immunodeficiency (n = 2), autoimmune enteropathy (n = 1), recurrent infections and bronchiectasis (subsequent diagnosis systemic lupus erythematosus) (n = 1), erythroderma, eosinophilic enteropathy, recurrent infection (n = 1), failure to thrive and recurrent infections (n = 1). Renal involvement was noted at a median of 4.0 years after immunological presentation, with 50% each of nephrotic and nephritic syndrome. All patients had renal biopsies demonstrating membranous nephropathy (n = 2), lupus nephritis (n = 2), minimal change disease (n = 1) and renal vasculitis (n = 1). Initial treatments before renal diagnosis included nil (n = 3), IVIg (n = 1), ciclosporin and infliximab (n = 1), cyclophosphamide and corticosteroids (n = 1). Only one case had urine dipstick at presentation (3+ proteinuria and haematuria). None of the other cases had blood pressure or urine dipstick recorded until the realisation of renal dysfunction or hypoalbuminaemia. 50% of cases had evidence of renal dysfunction with elevated plasma creatinine and/or hypoalbuminaemia in the months before nephrological referral. Patient and renal survival rates were 100% and 67%, respectively (two children have successfully received renal transplants) with the remaining four patients having estimated glomerular filtration rates of 76–140 ml/minute per 1.73m^2 (median 89), urine albumin : creatinine ratios of 1.4 to 101.6 mg/mmol (median 2.9) and median blood pressure at the 90th centile.
Conclusion: Children with complex immunodeficiencies and autoimmune disease should have renal screening as part of their ongoing assessments to ensure the early detection of associated renal disease.

G83 THE EFFICACY OF RITUXIMAB IN IDIOPATHIC NEPHROTIC SYNDROME: A MULTICENTRE RETROSPECTIVE STUDY

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Aims: The aim of this study was to establish the efficacy of rituximab in idiopathic nephrotic syndrome (NS) and in treatment of the posttransplant recurrence of NS.
Methods: The members of the International Society of Paediatric Nephrology were contacted and asked to fill in a questionnaire retrospectively with details of the use of rituximab in their centres. We then divided the data into three groups: group 1 with steroid-dependent and frequently relapsing NS (SDNS and FRNS); group 2 with steroid-resistant NS (SRNS) and group 3 with patients treated for a posttransplant recurrence of NS.
Results: We have received 52 questionnaires back. We have included 17 patients with SDNS or FRNS, 22 with SRNS and 13 with posttransplant recurrence of NS. In group 1, 88% (n = 15) of patients had a good initial response with 70% (n = 12) of patients achieving a complete remission. In group 2, 47% (n = 10) of patients had a good initial response with 19% (n = 4) achieving full remission, whereas 24% (n = 5) of children did not show any response to rituximab. In the posttransplant recurrence group, 89% (n = 10) of patients showed a good initial response with 62% (n = 7) entering full remission. Twenty-five per cent of patients had side effects. These were most frequently acute reactions.
Conclusion: There is a significant difference between the initial response rate in the SDNS/FRNS and SRNS groups. The good initial response in the posttransplant recurrence group can be biased by the accompanying treatments, which were administered at the same time as rituximab. A controlled prospective trial is required to establish the value of rituximab in idiopathic NS.