Nephrology

LAPAROSCOPIC-ASSISTED PLACEMENT OF PERITONEAL DIALYSIS CATHETERS: EXPERIENCE OF A NOVEL TECHNIQUE


Aims: To review early and medium-term outcome and survival of peritoneal dialysis (PD) catheters placed using a novel technique under laparoscopic visualisation.

Methods: A retrospective case-note and clinical review of catheters placed in 18 children during a 2 year period.

Results: 18 patients underwent 19 operations to place PD catheters between January 2000 and December 2001, using a technique of omentectomy via a supraumbilical incision, and guidance under vision of a ‘peel-away’ sheath. The PD catheter was threaded to a long tunnel, 1 of the 19 operations was an emergency for haemolytic uraemic syndrome. 4 of 19 were redo procedures.

The median age was 11 years (0.5 - 17). Median theatre time was 87.5 minutes (60 - 135) with 7/19 operations involving additional procedures. The median time to 1 of possible effects on growth.

C-PTH antagonizes the biological action of 1-84 PTH. A new IRMA (CAP-IRMA) that is specific for 1-84 PTH allows estimation of the C-PTH ratio. A ratio of >3.6% of these children had abnormal renal scars. There was no significant difference (p>0.05) in age, gender, infecting organism, presence of any degree of vesicoureteric reflux (VUR), duration of symptoms before treatment commenced, temperature and C-reactive protein (CRP) concentration on initial assessment, urinalysis, and antibiotic use between controls and cases.

Results: 124 children were identified. 23 patients (18.5%) had evidence of renal scarring on DMSA scan. 26 (21%) children were infected with a trimethoprim resistant organism, of which 18 were initially treated with trimethoprim. The other 8 were treated with norfloxacin and ceftriaxone. There were 44 (35%) children with adenovirus associated renal scars.

S.C. Waller1, D. Ridout2, T. Cantor3, P. Gao3, L. Rees1. 1Neuro-Urology Unit, Paediatric Nephrology and Biochemistry Unit, Institute of Child Health and Great Ormond Street Hospital for Children NHS Trust, 30 Guilford Street, London, WC1N 1EH; 2Scantibodies Laboratory, Inc., Santee, California, USA

PARATHYROID HORMONE IN CHILDREN WITH CHRONIC RENAL FAILURE; CHARACTERISATION OF THE 1-84 PTH: C-PTH RATIO

Background: Immunoradiometric [‘intact’IRMA] parathyroid hormone (PTH) assays cross-react with long carboxy-terminal PTH (C-PTH) molecules. C-PTH antagonizes the biological action of 1-84 PTH. A new IRMA (CAP-IRMA) that is specific for 1-84 PTH allows estimation of C-PTH levels. As the 1-84 PTH: C-PTH ratio maybe related to bone turnover, it is likely to be of particular importance in children because of possible effects on growth.

Aims: To investigate differences in and characterize the ratio 1-84 PTH: C-PTH in children with varying severity of CRF and levels of PTH.

Methods: 241 patients were recruited. There were 156 children with a GFR < 60 ml/min/1.73m2 managed conservatively (CRF group); 49 renal transplant patients with a GFR < 60 (transplant group); 26 patients maintained on peritoneal dialysis and 10 on haemodialysis (dialysis group). In addition 53 patients with normal renal function were recruited (control group). All had samples taken for ‘intact’IRMA and CAP-IRMA.

Results: Correlation between assays was excellent: r=0.98. However, mean values were significantly different from each other (p<0.001). Mean ‘intact’IRMA values were, as expected, greater than CAP-IRMA values. The ratio 1-84 PTH: C-PTH was significantly lower in dialysis patients than any other patient group and controls. The ratio was also significantly (p=0.003) lower in those with the most severe CRF (GFR<30). In those with normal range PTH levels the 1-84 PTH: C-PTH ratio was not significantly different between renal patients and controls. However, this ratio was significantly (p<0.01) lower when PTH levels were outside the normal range.

Conclusions: CAP-IRMA is more specific for detecting 1-84 PTH than current ‘intact’IRMA. The ratio between two biologically antagonistic forms of PTH, 1-84 PTH and C-PTH, is lower in children on dialysis, as renal function worsens and with PTH levels outside the normal range. Maintenance of normal PTH levels may be appropriate.

RISK FACTORS FOR RENAL SCARRING IN CHILDREN WITH URINARY TRACT INFECTION—A RETROSPECTIVE CASE CONTROL STUDY

M. Eisenhut, F. El Masri, P. Murphy, C.A. Jones. Royal Liverpool Childrens Hospital NHS Trust, Alder Hey

Aims: To identify risk factors for renal scarring in clinical course and management of urinary tract infections (UTI) in early childhood; to examine the contribution of trimethoprim resistance of infecting organisms to the risk of renal scarring in patients treated with trimethoprim as the first line antibiotic.

Methods: Records of children, aged 0 to 2 years, who were treated at Royal Liverpool Childrens NHS Trust (Alder Hey) for a UTI from April 2000 to April 2002 were identified. Patients with a single proven UTI (>105 of pure growth of a significant organism) and a history of lower urinary tract symptoms in the month before presentation were included. Cases with renal scarring on DMSA scan were compared to controls without scarring with regards to age, gender, infecting organism, presence of any degree of vesicoureteric reflux (VUR), duration of symptoms before treatment commenced, temperature and C-reactive protein (CRP) concentration on initial assessment, urinalysis, and antibiotic use between controls and cases.

Results: 124 children were identified. 23 patients (18.5%) had evidence of renal scarring on DMSA scan. 26 (21%) children were infected with a trimethoprim resistant organism, of which 18 were initially treated with trimethoprim. The other 8 were treated with norfloxacin and ceftriaxone. There were 44 (35%) children with adenovirus associated renal scars.

S.D. Marks, M.P. Massicotte, B.T. Steele, D.G. Matesell, G. Filler, P. Shah, M. Perlman, N.D. Rosenblum, V.S. Shah. Divisions of Nephrology and Neonatology, Department of Paediatrics, The Hospital for Sick Children and University of Toronto, Ontario, Canada

NEONATAL RENAL VENOUS THROMBOSIS (RVT): LONG-TERM OUTCOMES AND PREVALENCE OF PRO-THROMBOTIC CONDITIONS

Aims: To establish long-term outcomes and prevalence of pro-thrombotic conditions in renal venous thrombosis during the neonatal period.

Methods: A retrospective review of 47 children who had clinical and radiological diagnosis of RVT during the neonatal period and were referred to the four paediatric centres of Toronto, Ottawa, London and Hamilton in the Province of Ontario, Canada, between 1980 and 2001. The prospective component of the study involved follow-up of survivors, including work-up for pro-thrombotic abnormalities to determine the prevalence of genetically predisposed thrombophilic disorders in this group of patients.

Results: There were 28 males and 19 females (1.5:1). The range of gestational age was 24-42 (median 38) weeks with birth weights of 753-5680 (median 3040) grams. The clinical presentation was renal failure in 23 (53%), thrombocytopenia and/or anaemia in 23 (49%), abdominal mass in 10 (21%), hypoglycaemia in 9 (19%), infection in 8 (17%), peritoneal dialysis in 2 (4%) and unilateral nephrectomy in 4 (9%) and antenatal diagnosis in 3 (6%). The RVT was unilateral in 24 (51%), bilateral in 23 (49%) and associated with other thrombi in 30 (64%) infants. The specific neonatal treatments included low molecular weight heparin in 15 (32%), systemic heparin in 9 (19%), systemic tisseinogen activator in 5 (11%) and warfarin in 1 (2%). The other neonatal treatments included antihypertensive medications in 8 (17%), peritoneal dialysis in 2 (4%) and unilateral nephrectomy in 2 (4%). The follow-up period ranged from 0.5-20.2 (mean 5.6) years and revealed 16 (34%) children with hypertension, 12 (26%) with chronic renal failure, 3 (6%) with end-stage renal failure and 4 (9%) unrelated deaths. There were no further thrombotic events outside the neonatal period but 4 (9%) positive family histories of thrombotic conditions. 33 cases (70% of all patients and 77% of survivors) were recalled with abnormal pro-thrombotic results in 19 (58%).
Conclusions: The results of this study demonstrate substantial renal morbidity in a large group of RVT patients with a high prevalence of thrombotic disorders, which necessitate investigation at time of diagnosis and may direct therapy.

**HYPOMAGNESIEMIA, DYSLIPIDEMIA AND HYPERTENSION IN PAEDIATRIC RENAL TRANSPLANT PATIENTS**

A. Doulah, D. Geary, D. Hebert. Division of Paediatric Nephrology and Academic Department of Multiorgan Transplantation, University of Toronto, Hospital for Sick Children, Toronto, Canada; Department of Paediatrics and Child Health, St James University Hospital, Leeds, LS9 7TF

**Background:** Adult renal patients show an increased risk of cardiovascular disease and there is concern that the risk factors of the paediatric patient will manifest in later life as cardiovascular morbidity and mortality. Low plasma levels of magnesium have been associated with raised lipids and hypertension, both from animal studies and epidemiological data.

**Aim:** To determine prevalence of hypomagnesaemia in stable paediatric renal transplant patients and to see if there was any correlation with GFR, hypertension, time from transplantation, age, sex, lipid levels, type of graft and immuno-suppression regime.

**Methods:** 47 clinically stable patients, more than six months post transplant, attending the paediatric renal transplant clinic were identified. Records were reviewed to determine their demographics, median magnesium, lipid, blood pressure and GFR for the previous three months. Exclusion criteria included the presence of diabetes, sirolimus therapy, a documented acute rejection episode diagnosed within the previous 6 months and a >10% change in serum creatinine documented within the preceding 3 months.

**Results:** 54% of the patients were hypomagnesaemic. 74% of the hypomagnesaemic children were hypertensive compared to 36% in the normomagnesaemia group (p=0.022). This hypertensive tendency was seen whether the patient was on tacrolimus or cyclosporin and independent of their drug levels. There were no significant correlations between magnesium levels and cholesterol, triglyceride, steroid dose, time from transplant, body mass index and GFR. Magnesium levels were significantly lower in the tacrolimus treated group compared to patients on cyclosporin (p=0.004). The lack of correlation of magnesium levels with dyslipidaemia may have been due to the strong association of dyslipidaemia with steroid dose (p=0.004).

**Conclusion:** The results demonstrate low plasma magnesium levels are associated with hypertension in stable paediatric renal transplant patients and thus potentially an important and treatable cardiovascular risk factor.

**REFLUX NEPHROPATHY, PLASMA RENIN ACTIVITY AND BLOOD PRESSURE—24 YEAR FOLLOW UP STUDY**

S.E. Stephens, V. Shah, M.J. Dillon. Institute of Child Health, 30 Guilford St, London, UK

**Aims:** This study was commenced in 1978 to determine whether plasma renin activity (PRA) was predictive of development of hypertension in patients with reflux nephropathy (RN)

**Methods:** The original study recruited 100 normotensive children, between the ages of 2 and 15 years, with RN who had a history of urinary tract infection and surgical correction of vesicoureteric reflux. The degree of scarring was noted, and PRA measured. There have been reviews at 5, 10, 15, and now 24 years. On this occasion 42 patients were reviewed. Blood pressure was measured on three occasions with the average taken and PRA measured after 2 hours supine rest. A brief medical questionnaire was also completed for each patient.

**Results:** No significant predictive factor for the development of hypertension was found, including PRA, degree of scarring, laterality of scars or family history of hypertension. However, PRA standard deviation scores previously found to be high, have remained so. During the 24 year study period 26% of patients have developed hypertension.

**Conclusions:** PRA is not predictive of the development of hypertension in RN, however the renin-angiotensin system continues to be implicated in the hypertension associated with the condition, and an increasing number of patients become hypertensive with time.

**THE ALPORT NEPHROPATHY—CLINICOPATHOLOGICAL CORRELATIONS**

R.H.R. White, F. Raafat, D.V. Milford, N.E. Maghali, F. Komianou. Department of Nephrology and Histopathology, Birmingham Children’s Hospital

Recent observations reveal diffuse glomerular basement membrane (GBM) attenuation forms a component of the ultrastructural complex of Alport Syndrome (AS). Impressions of its greater frequency in very young children and females led to the suggestion that it might be the primary lesion. We carried out a "blind" review of 130 renal biopsy specimens obtained from 100 patients with AS, with special emphasis on the electron microscopy changes, and related the findings to the clinical presentation and outcome. Biopsies not showing typical GBM changes were only included if obtained from first degree relatives of classical cases. The extents of thickened, attenuated and normal GBM were assessed semi-quantitatively as: >50% (grade 3), 25–50% (grade 2), <25% (grade 1) and nil (grade 0). Deafness was defined as persistent bilateral hearing loss of >30 dBs. Proteinuria was measured as protein/creatinine ratios in early morning urine (normal <20 mg/mmol; heavy proteinuria =200 mg/mmol).

Heavy proteinuria correlated significantly with both segmental and global glomerulosclerosis, and interstitial foam cells. Immunofluorescence and immunoperoxidase stains were essentially negative. There was a correlation between grade of GBM thickening and proteinuria (p=0.002). The grade of both thickening and attenuation of the GBM failed to correlate with either age at biopsy or sex. In 30 repeat biopsies there was a trend towards increasing GBM thickening with age. There was no clear relationship between grade of GBM thickening and age at which end-stage renal failure developed.

Our data do not support the concept that GBM thinning is the primary lesion of AS.

**INDIVIDUALLY TAILORED PLASMA EXCHANGE TREATMENT FOR PRIMARY AND RECURRENT FOCAL SEGMENTAL GLOMERULOSCLEROSIS**


**Introduction:** Focal segmental glomerulosclerosis (FSGS), a cause of childhood nephrotic syndrome, results in end stage renal failure in over 50% of affected children and is a condition that can recur in the transplant kidney. Plasma exchange, usually with additional immunosuppression, is well described as a treatment option in post transplant recurrent disease. Reports of the use of plasma exchange for FSGS of the native kidney are scarce.

**Aims:** We describe our experience of individually tailored treatment regimes for FSGS in the native kidney and in post transplant recurrent disease.

**Methods:** 6 children: 3 with FSGS in the native kidney and 3 with post transplant recurrent disease were treated with plasma exchange and immunosuppression. The duration of plasma exchange and the additional immunosuppressive treatments were individually tailored depending on clinical response. Each patient initially received at least 6 single volume plasma exchanges over a 1-4 day period.

**Results:** A total of 146 sessions of plasma exchange, combined with immunosuppression, were administered over 25 patient months. 4 children, including all with post transplant recurrence, achieved full remission [resolution of proteinuria], 1 partial remission [reduced proteinuria and improvement in oedema], and 1 showed no clinically significant response. Three children had further recurrences, all of which responded [resolution of proteinuria] to a further induction course of exchange and have subsequently received ongoing maintenance plasma exchange combined with immunosuppression. The frequency and duration of these sessions were then adapted accordingly to response.

**Conclusions:** This single centre experience provides further evidence of a role for plasma exchange in the treatment of post transplant recurrent FSGS and adds to the paucity of reports of its use in EGS in the native kidney.
THE MATURE GLOMERULAR PODOCYTE DISPLAYS A MODIFIED SMOOTH MUSCLE PHENOTYPE

M. Saleem1, J. Sanday1, I. Witherden1, J. Zavadil2, P. Mundel2, E. Bottinger2, L. Ni3, P. Mathieson1. 1Academic and Children’s Renal Unit, University of Bristol, Bristol, UK; 2Albert Einstein College of Medicine, Bronx, New York, USA.

The podocyte is traditionally described as an epithelial cell, though little is known about its true differentiated phenotype. We studied a conditionally immortalised human podocyte cell line, with the ability to mature from proliferating cobblestoned epithelial cells to growth-arrested differentiated podocytes over a period of 14 days. To compare gene expression at different time points along this differentiation pathway, RNA was collected at day 0 (proliferating, undifferentiated); day 3; day 9 and day 12 of the differentiation pathway, and was hybridised to cDNA microarrays containing 9,216 unique human clones. Of the genes that were significantly regulated, there was a preponderance of genes whose expression increased early (day 3), and subsequently either diminished (most genes) or showed a static profile or only gradual increase over time. This indicated that the gene expression profile of podocytes responsible for phenotypic maturation is determined early in differentiation. Of these genes there were at least 25 genes involved in epithelial-mesenchymal transition (EMT). Of these, 18 were involved in matrix turnover. This included early upregulation of several collagen and laminin genes, matrix metalloproteinases and proteoglycans. There were also genes involved in smooth muscle differentiation, and we confirmed the expression in differentiated cells and in vivo of two proteins specifically associated with differentiated, contractile smooth muscle, calponin and smoothelin. Finally there was a striking upregulation at day 3 of cytokines or cytokine induced genes. This included 8 interferon-associated genes, 3 tumor necrosis factor related genes and several other inducible cytokines. These data imply that the mature podocyte has a modified myofibroblastic phenotype, which may partially be maintained by its cytokine environment. Hence podocyte transdifferentiation in response to a deregulation of the external cytokine environment may be a cause of foot process loss in nephrotic syndrome.

PAMIDRONATE THERAPY IN HYPERPARATHYROID BONE DISEASE WITH SEVERE HYPERCALCAEMIA

S.C. Waller, W. van’t Hoff. Nephro-Urology Unit, Institute of Child Health and Great Ormond Street Hospital for Children NHS Trust, 30 Guilford Street, London, WC1N 1EH

Background: Paediatric experience with bisphosphonates is limited. There is growing, case report, evidence of their efficacy and safety in the treatment of hypercalcaemia; mode of action is via inhibition of osteoclast mediated bone resorption. Neonatal severe hyperparathyroidism (NSHPT) characterised by marked hypercalcaemia, bone demineralisation and parathyroid gland hyperplasia with marked hyperparathyroidism can be life threatening; patients are homozygous for inactivating calcium sensing receptor (CaSR) gene mutations.

Aims: To explain the rationale for and describe, for the first time, the use of pamidronate in NSHPT, for the treatment of 1) severe hypercalcaemia and 2) life threatening hyperparathyroid bone disease.

Methods: Case note review of two related patients, homozygous for a CaSR gene point mutation (Q164X), who were both treated with pamidronate.

Results: Case 1: Severe hypercalcaemic (serum Ca 6.3 mmol/L) episode not responding to hyperhydration and frusemide was successfully treated with i.v. pamidronate (1mg/kg). Serum Ca 2.2 mmol/L and 2.5 mmol/L at 2 weeks and 2 months post-therapy, respectively. Case 2: An infant with marked hyperparathyroid skeletal demineralisation, with consequent multiple fractures and respiratory compromise resulting in ventilator dependence, was treated with i.v. pamidronate (total of 2.5mg/kg in 3 doses over six days). Hypercalcaemia was controlled allowing improved dietary calcium manipulation. Hyperparathyroid bone resorption was inhibited, leading to stabilisation and clinical improvement of the patient, permitting definitive total parathyroidectomy to be performed. Both patients suffered from acute phase reactions following initial pamidronate infusion.

Conclusions: Pamidronate is efficacious and safe in the treatment of severe hypercalcaemia in NSHPT. Pamidronate may halt the hyperparathyroid skeletal demineralisation process that occurs in NSHPT.