WHAT'S HOT WHAT'S NEW - AN UPDATE FROM THE IPNA 2016 MEETING

Inherited and structural kidney diseases

1) This study has shown an increase in urinary excretion of lipid metabolism/transport- related proteins in non-obese children with nephrolithiasis and hypercalciuria compared with healthy controls. This result indicates a possible key role of the lipid metabolism nephrolithiasis.

FP-S12-3: - Significant Increase in Urinary Excretion of Apolipoproteins and Fatty Acid-Binding Protein in Children with Nephrolithiasis and Hypercalciuria

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Objectives: Using a proteomic model and pooled samples, we have recently identified several urinary proteins involved in lipid transport and metabolism in children with nephrolithiasis and hypercalciuria (CAL). In the current study, we aimed (1) to confirm these results in individual samples by performing enzyme-linked immunosorbent assay (ELISA), and (2) to examine the relationship between the urinary excretion of selected proteins with demographic, dietary, blood, and urinary parameters.

Methods: Prospective, controlled, pilot study comparing the urinary excretion of Apolipoprotein A4 (ApoA4), Apolipoprotein C3 (ApoC3), and Fatty Acid-Binding Protein 1 (FABP1) between CAL (N=16, 9 females, mean age 11.8+/-4.1 years), and their age- and gender-matched healthy controls (HC) (N=14) (ttest). Exclusion criteria included obese children (BMI>/= the 95th percentile for children of the same age and sex).

Results: Statistically significant increase in the urinary excretion of ApoA4, ApoC3 and FABP1 in CAL group vs HC was found. ApoA4 and ApoC3 levels were higher in boys compared to girls. In the CAL group, urinary ApoA4 was positively correlated with urinary ApoC3 ($r=0.68$, $p<0.001$), and intake of meat ($r=0.65$, $p<0.011$). 24-hour urinary calcium excretion significantly correlated with concentrations of ApoC3 ($r=0.77$, $p<0.001$), and FABP1 ($r=0.80$, $p=0.005$).

Conclusions: We found marked increase in urinary excretion of lipid metabolism/transport- related proteins in non-obese children with nephrolithiasis and hypercalciuria. These findings suggest that abnormalities in lipid metabolism may play an important role in nephrolithiasis. Targeting these proteins may have preventive and therapeutic benefits.

2) These data from the Eunefron cohort show the importance of registries. Over the past decades, a progressive improvement in renal function was observed, together with an improved linear growth. The use of cysteamine, of indomethacin and of growth hormone were associated with an improved outcome.

FP-S24-1: - Outcome and prognostic factors of nephropathic cystinosis: data from the Eunefron cohort

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Objectives: To evaluate the outcome of nephropathic cystinosis over the past decades and to identify factors that have improved the outcome over time.

Methods: Renal function, linear growth and treatment data from 307 patients with nephropathic cystinosis were collected in the UK, France, The Netherlands and Belgium, Italy and Spain over a period spanning 1970 to 2010.

Results: Overall, a progressive improvement in renal function was observed over the past decades with an increase in the median age at dialysis from 11.2 years in the 1970's, to 13.2 years in the 1980's and to 17.1 years in the 1990's and 2000's. By Mantel-Cox univariate analysis, gender, homozygous or heterozygous 57 kb CTNS deletion or the use of ACE inhibitors were not associated with renal outcome. A significant association was observed when data were compared by decade of birth (Hazard ratio (HR): 0.61 [0.48-0.77], p<0.001), with the use of indomethacin for >50% of the follow-up (HR: 0.62[0.42-0.91], p=0.015), and with the age (years) at which cysteamine was started (HR: 1.33 [1.19-1.49], p=0.001). A weak, statistically non-significant association was observed with leucocyte cysteine levels (HR: 1.20 [0.98-1.46], p=0.078). After modelling the HR, a nearly linear relationship was observed with the age at which cysteamine was started from 0.5 to 3.5 years and the risk of dialysis; correcting for leucocyte cysteine levels did not change significantly this relationship. Over the same period of time, linear growth has improved. Factors associated with improved outcome were the use of cysteamine, of indomethacin and of growth hormone.

Conclusions: This study represents one of the largest cohorts of nephropathic cystinosis patients assembled to date, and shows a gain of approximately 6 years in the median age to reach dialysis over a period of 30 years. Early treatment with cysteamine and the use of indomethacin influenced positively renal outcome.

3) This study has shown that patients diagnosed with primary hyperoxaluria through family screening have significant disease, similar compared with those diagnosed conventionally. Therefore, the authors suggest screening in the family of patients with primary hyperoxaluria.

FP-S36-3:- Do patients diagnosed with primary hyperoxaluria through family screening have different characteristics compared with those diagnosed conventionally?

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Objectives: Primary hyperoxaluria (PH) is an inherited disease characterized by excessive production of oxalate leading to recurrent nephrolithiasis, nephrocalcinosis and progressive kidney damage. Most PH patients are diagnosed through evaluation initiated for clinical suspicion (CS) based on signs or symptoms. However, some are detected by family screening (FS) once an affected family member has been identified. We sought to characterize differences between these two groups.

Methods: Patients with PH types 1,2, and 3 enrolled in the Rare Kidney Stone Consortium PH registry who have not reached ESRD are the subject of this report. Clinical and laboratory results including serum creatinine, plasma oxalate, 24-hour urine calcium, citrate and oxalate were obtained from the registry database.

Results: Among 426 PH patients in the registry, 40 (13.5%) were FS. After excluding 129 patients with ESRD at diagnosis, 257 CS and 40 FS remained for further analysis. Compared to CS, FS had fewer stones at diagnosis (mean 1.60 vs. 4.57, p=0.036), although their initial symptoms occurred at a similar age (median age 3.7 vs. 4.4 years, p=0.54). Follow-up was 7.98 and 11.23 years in CS and FS, respectively (p=0.058). eGFR at diagnosis and decline over time were also similar between the two groups. Urinary oxalate, calcium, citrate, and volume were similar between groups. Altogether, 12.5% (5/40) of FS patients and 23.0% (59/257) of CS developed ESRD at last follow-up (p=0.135).

Conclusions: Patients with PH diagnosed through family screening have significant disease despite no outward clinical suspicion for PH. Our findings suggest that genetic screening of family members of PH patients is warranted.

4) This study showed the feasibility to have adequate TKV measurements from 3D US method in ADPKD children. However, compared to MR TKV as the golden standard, these are prone to underestimation.

FP-S08-2: - 3D-US with a correction factor is a good alternative in estimating total kidney volume in children with Autosomal Dominant Polycystic Kidney Disease

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Objectives: Total kidney volume (TKV) has been shown in adult Autosomal Dominant Polycystic Kidney Disease (ADPKD) to be an independent and strong predictor for disease progression. In the current interventional clinical trials, TKV measurement by magnetic resonance (MR) imaging has been shown to be more accurate, reproducible and able to detect small changes over a short period of time compared to ultrasound (US). Since future therapies in ADPKD could be extended to include children, we aimed to examine whether the high-resolution 3D-US TKV measurements might be used as an alternative method to MR measurements in ADPKD children.

Methods: Prospective evaluations of renal MR, 2D- and 3D-US were performed, whereby TKV was calculated by means of manual delineations (MR, 3D-US) or by the ellipsoid method (2D-US). Correlations and differences between parameters were evaluated using Pearson r and Wilcoxon signed rank tests. After correction using the optimal linear regression, the variability of the measurements was examined using Bland-Altman plots.

Results: We studied 29 patients (17 male, 12 female) with a median age (SD) of 14.0 (3.4) years and eGFR 111 (17) ml/min/1.71m2 leading to 58 evaluated kidneys. Although both US methods showed significantly lower TKV compared to MR (In ml, 3D-US: 181 (111); 2D-US 158 (101); MR 205 (132); all $p<0.001$), both showed a strong correlation to the MR TKV (2D-US: $r=0.963$; 3D-US: $r=0.941$). After correcting for the lower values in US, Bland-Altman plots showed slightly lower variability and error in 3D-US measurements compared to 2D-US in kidneys with a TKV below 200 ml (on average 15.5 ml error on 2D-US compared to 12.9 ml on 3D-US), although not reaching significance ($p=0.23$)

Conclusions: In children, 3D-US represents a good alternative for MR to measure TKV in ADPKD. Compared with MR, US TKV was prone to underestimation. After correcting for these, 3D-US tended to be slightly more comparable to MR in small TKV(<200 ml) than 2D-US.