Predicting Risk of Chronic Kidney Disease in Infants and Young Children at Diagnosis of Posterior Urethral Valves: Initial Ultrasound Kidney Characteristics and Validation of Parenchymal Area as Forecasters of Renal Reserve

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Abbreviations and Acronyms

CKD = chronic kidney disease
CKD5 = stage 5 chronic kidney disease
CMD = corticomedullary differentiation
eGFR = estimated glomerular filtration rate
ESRD = end-stage renal disease
PUV = posterior urethral valves
RE = renal echogenicity
RRT = renal replacement therapy
tRPA = total renal parenchymal area
US = ultrasound
UTI = urinary tract infection

Purpose: There is paucity of validated objective early imaging markers to help predict future renal deterioration in infants with posterior urethral valves. We evaluated the prognostic value of total renal parenchymal area, renal echogenicity and corticomedullary differentiation regarding future development of chronic kidney disease.

Materials and Methods: We analyzed initial postnatal ultrasonographic images from serial posterior urethral valve cases seen at a single tertiary referral center using National Institutes of Health sponsored image processing software. Echogenicity and corticomedullary differentiation were objectively measured as ratios relative to the adjacent liver or spleen and between cortex and medulla. The primary study outcome, renal function at last followup, was dichotomized based on glomerular filtration rate and/or need for renal replacement therapy (dialysis or renal transplantation, stage 5 chronic kidney disease).

Results: A total of 75 patients were evaluated, of whom 16 had progression to stage 5 chronic kidney disease after a mean ± SD followup of 64.2 ± 38.9 months. Mean renal parenchymal area was 21.41 cm^2 in patients without and 16 cm^2 in patients with stage 5 chronic kidney disease ($p < 0.001$), and mean corticomedullary differentiation was 1.77 and 1.21, respectively ($p < 0.001$). Bilateral echogenic kidneys were significantly associated with development of stage 5 chronic kidney disease ($p = 0.004$). The performance of corticomedullary differentiation in predicting stage 5 chronic kidney disease was statistically significant (AUROC 0.881, 95% CI 0.776–0.987, $p < 0.001$).

Conclusions: Estimates of renal parenchyma quantity (total renal parenchymal area) and quality (corticomedullary differentiation and renal echogenicity)

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measured on initial postnatal ultrasound carry prognostic value in determining future risk of stage 5 chronic kidney disease in patients with posterior urethral valves. These data are promising for developing tools to risk stratify patients, counsel parents and customize monitoring protocols.

Key Words: kidney cortex; kidney medulla; renal insufficiency, chronic; renal replacement therapy; urethra

Posterior urethral valves are a relatively common etiology of chronic kidney disease in children and adolescents. With the widespread use of prenatal ultrasound early diagnosis is the norm in many parts of the world, allowing timely intervention and close monitoring aimed at minimizing further upper tract deterioration and delaying the need for renal replacement therapy.

Acquired damage aside, ultimate kidney function is clearly impacted by renal reserve at diagnosis, which is a reflection of the quantity and quality of the nephron mass. Theoretically noninvasive assessment of these parenchymal attributes can help stratify patients as being at low or high risk for renal failure, aid in counseling parents, assist with monitoring plans and allow exposure to putative nephron protective agents.[1] Although firmly establishing the presence and degree of dysplasia would serve as a useful marker, tissue sampling for this diagnosis can be overtly invasive and potentially deleterious in a child already at risk for CKD.

Previous work provides insight into the value of US as a noninvasive, widely available, accessible imaging modality. US is routinely used in infants with suspected obstructive uropathy and can generate parameters that hold prognostic value. A landmark study estimating the amount of renal mass by measuring tRPA presents compelling predictive data that depart from previously used ellipsoid volume estimates,[2] which can be inaccurate due to the impact of hydronephrosis and irregularity of the renal contour. To our knowledge these important single institution findings have not been validated. In addition, other studies have examined RE and CMD as indicators of parenchymal quality.[3,4] However, these analyses were based on subjective assessment of images and classification within broad categories.

To further evaluate and refine our knowledge regarding the value of objective US parameters gathered during initial assessment of patients with obstructive uropathy secondary to PUV, we present objective data systematically gathered from US studies correlated with known predictive factors and long-term renal function assessment. The main study outcome, development of renal failure or need for chronic replacement therapy, is contrasted with a priori defined variables, testing the hypothesis that tRPA, in conjunction with objective assessment of RE and CMD at diagnosis, provides complementary value in estimating risk of renal deterioration.

MATERIALS AND METHODS

Patient Population

Following research ethics board approval we retrospectively evaluated consecutive patients diagnosed with posterior urethral valves between 2003 and 2013. Data capture was censored in 2013 to allow a minimum followup of 2 years.

Inclusion and Exclusion Criteria

We identified serial infants with a confirmed diagnosis of PUV evaluated and followed at a single tertiary care referral center with available US results at presentation. Patients with incomplete studies (4 patients) and lack of followup after treatment in first year of life (3) were subsequently excluded.

Study Design

We performed a retrospective review of imaging studies, laboratory evaluations and patient records. Analysis and data extraction from US image files were performed blinded to clinical data, and parameters were verified by 10% random audit conducted by an independent second investigator. Interrater agreement to ensure consistency and reproducibility of all quantitative measurements was estimated with the intraclass correlation coefficient. Variables were further analyzed only if a high level of concordance was present, arbitrarily defined as ICC greater than 0.95.

Hypothesis, Primary Outcome, Secondary Outcomes

Based on our conceptual framework, we hypothesized that US estimates of renal mass (quantified based on parenchymal area) and quality (indirectly measured with echogenicity and CMD indices) would help distinguish patients at risk for end-stage renal disease (CKD5, the primary study outcome). CKD5 was strictly defined based on glomerular filtration rate less than 15 ml/minute/1.73 m^2 and/or need for permanent RRT (dialysis or renal transplantation). Secondary outcomes included creatinine levels at age 1 year and last followup, and development of other stages of renal insufficiency (stage 1 to 4 CKD based on eGFR calculated with widely used validated formulas).[5] Duration of followup was individually captured to perform time to event analyses, censoring data at last assessment, initiation of dialysis or renal transplantation date (if preemptive). For patients with