Adolescent nephro-urology

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Adolescents warrant specialist effort. With increasing autonomy, their own decisions and behaviour determine their health and hence progression of their disease. How they are managed through this phase will have considerable impact on the outcome. As the prospects for children with renal disease improve, adult physicians will see such patients more frequently.

Renal insufficiency

The causes of end-stage renal failure (ESRF) in children receiving first cadaver grafts are shown in Table 1.

Recognising renal insufficiency

As with adults, new renal disease is most commonly found by:

- routine examination
- blood or protein in the urine
- hypertension
- raised blood urea and creatinine, or
- investigation of urinary tract infection (UTI), poor growth or delay in puberty.

Management of renal insufficiency

Even with mild renal insufficiency, acidosis, hypocalcaemia and hyperphosphataemia are common, and growth retardation is a consistent feature. Regular follow-up in a specialist centre with a multidisciplinary approach is important to provide the opportunity for maximum growth and normal development.

Biochemical control. Renal function is assessed from plasma creatinine and, ideally, a yearly isotopic measurement of glomerular filtration rate (GFR). Until the patient has stopped growing, GFR can be estimated using the Schwartz formula (height in cm x 40/creatinine μmol/l). GFR increases rapidly in the first two years of life to adult values, provided that it is adjusted for body surface area. Plasma creatinine is proportional to muscle mass; most serious misappreciations of renal insufficiency occur because the creatinine value, although raised for that individual, is still within the 'normal' adult range.

Serum bicarbonate must be kept above 20 mmol/l, as acidosis is associated both with increased protein catabolism and growth failure, and with bone disease due to bone buffering of H+ ion. Supplementation is with oral sodium bicarbonate. Correcting acidosis will help control hyperkalaemia.

Unlike adults, adolescents with chronic renal failure (CRF) are often salt losers as tubular abnormalities are common, so sodium chloride supplementation may be required to avoid hypotension and hypovolaemia (serum sodium will be normal). Patients with obstructive uropathy are often unable to concentrate their urine; this results in polyuria, so access to fluids is necessary at all times.

Height and weight. Height and weight charts are essential. Good biochemical control will allow growth but some youngsters will not reach their genetic potential. A fall in height velocity greater than minus two standard deviations is an indication for intervention in the form of dietary advice or better biochemical control. If this has no effect, growth hormone supplementation is considered. Close monitoring of growth during the teenage years is particularly important: adolescents with CRF show both delayed and reduced pubertal growth spurt, resulting in a 50% reduction in height gain.

Blood pressure. Blood pressure is measured supine and standing to assess for hypovolaemia (postural hypotension) as well as hypertension. Controlling hypertension will reduce the

Table 1. Primary renal disease of first cadaver grafts in children in UK and Ireland since 1990 (data kindly supplied by UK Transplant Support Service Authority (TSSA)).

| Primary renal disease | % |
|-----------------------|---|
| Primary glomerulonephritis | 11 |
| Focal segmental glomerulosclerosis (6.5%) | 11 |
| Secondary glomerulonephritis | 6 |
| Henoch-Schönlein purpura (2%) | 6 |
| Haemolytic uraemic syndrome (2.6%) | 6 |
| Scarred kidneys, with or without hydronephrosis | 37 |
| Reflux nephropathy (6.7%) | 37 |
| Other interstitial nephritis/pyelonephritis (4.3%) | 37 |
| Congenital (26%) | 37 |
| Other hereditary/congenital | 11 |
| Polycystic (2%) | 11 |
| Medullary cystic (2.4%) | 11 |
| Miscellaneous | 9 |
| Cortical necrosis (1%) | 9 |
| Vascular (1%) | 9 |
| Uncertain/unknown | 19 |
| Missing data | 7 |
rate of progression of renal failure (Fig 1). In the presence of proteinuria, angiotensin-converting enzyme (ACE) inhibitors are the drugs of choice.

Proteinuria. It is almost impossible to get an adolescent to co-operate with a 24-hour urine collection, so a single (spot) urine sample for the albumin (or protein) to creatinine ratio is taken. ACE inhibitors lower intraglomerular pressure, and hence reduce proteinuria and the rate of disease progression.

Bone disease (Table 2). Phosphate control is imperative to prevent hyperparathyroidism and bone disease, but this is difficult as patients are often unwilling to limit phosphate intake and to take the phosphate binders which are large and unpalatable. (Aluminium-containing binders are not recommended in the growing child.) Calcitriol analogues should be considered once the GFR is less than 50% or the parathyroid hormone level rises. Iatrogenic hypercalcaemia must be avoided as this can lead to a worsening of renal function.

Anaemia. Normochromic, normocytic anaemia is predominantly due to failure of erythropoietin production. Once other treatment for anaemia has been checked, replacement therapy can be given in the form of recombinant human erythropoietin.

Nutrition. The total recommended daily intake is prescribed unless there is loss of height or weight velocity when it is increased to 120%. Energy supplements

Table 2. Management of bone disease.

- Early dietary restriction of phosphate
- Phosphate binders (calcium carbonate or acetate) when serum phosphate rises above normal range
- Correct acidosis with oral sodium bicarbonate
- Early use of calcitriol analogues. Supplementation should be considered once the glomerular filtration rate is less than 50%, at which point parathyroid hormone starts to rise.
are often provided in the form of polyunsaturated corn oil. Protein prescription is at the recommended daily intake, and provides adequate nitrogen for growth.

Uropathies

Causes

Causes of hydrenephrosis and renal scarring are shown in Table 3. Rarely, patients with posterior urethral valves may first present in adolescence with voiding or sexual dysfunction.

General management

The urological patient with renal insufficiency should be managed jointly by a nephrologist and a urologist. Although the urinary tract should no longer be obstructed, this must be kept under regular review.

Compliance is a particular problem, and the patient, family and primary care physician must have a complete understanding of the consultant's aims and goals. The first issue to make clear is the necessity of long-term follow-up, at no less than annual intervals. ESRF commonly occurs when a patient is lost to follow-up and presents later with accelerated hypertension and rapid loss of renal function.

As in any other renal condition, the remnant kidney function may decline inexorably; this is associated with increasing proteinuria and hypertension. Function is usually stable when there is little or no proteinuria. Deterioration of function in the absence of proteinuria must alert the physician to the likelihood of obstruction, or some other cause of acute-on-chronic renal failure, such as a nephrotoxic drug.

UTI is common, and must be treated promptly. Increase in frequency or severity of infections must lead to investigations to find the cause. The blood pressure must be monitored regularly and kept normal.

A number of routine investigations should be performed to document the current situation and to act as a reference point in the future (Table 4). If

| Table 3. Hydrenephrosis and renal scarring. |
|-------------------------------------------|
| **Without megaureter**                   |
| Pelvi-ureteric junction obstruction      |
| Primary vesico-ureteric reflux           |
| **With megaureter:**                     |
| non-obstructed                           |
| Primary renal and ureteric dysplasia     |
| (including prune belly syndrome)         |
| obstructed                               |
| Secondary to bladder outflow obstruction |
| • neuropathic bladder                   |
| • posterior urethral valves              |
| • urethral and bladder neck obstruction  |
| • ureteric stricture                     |

the bladder empties completely with an adequate flow rate (>15 ml/sec), it should not cause problems. If there is any doubt about the condition of the bladder, urodynamic investigations are necessary. If the clinical situation changes, further investigations are required. An increase in UTIs might suggest a stone or an increase in residual urine. If there is an unexpected decline in renal function, obstruction has again to be excluded.

Specific treatment

Treatment will depend on aetiology, but is aimed towards maintaining a low pressure, continent, sterile system with preservation of renal function. Intermittent clean self-catheterisation (ICSC) is commonly used to achieve this, and may also be used in association with urinary diversion with a continent stoma. Self-catheterisation may appear stigmatising and therefore be avoided by a self-conscious adolescent. Every effort should be made to educate the child and to facilitate treatment.

With posterior urethral valves, the prognosis correlates with the best creatinine value. Despite adequate early treatment, many children develop CRF due to renal dysplasia, hyperfiltration injury, and abnormal bladder function. Boys with substantial residual volumes can be managed by ICSC. However, there is often poor compliance with this, and poor prognosis correlates with poor bladder function.

Infections and scarring

UTI is common among children. Urinary tract pathology is found in 2% of girls and 10% of boys, and 25% of these children will have ureteric reflux.
Table 5. Indications for investigation of urinary tract infection (UTI).

- UTI in a male at any age
- UTI in an infant (<2 years)
- Pyelonephritis in a female
- Recurrent UTI in a female

Indications for further investigation are shown in Table 5, and are required to identify renal scarring and to investigate bladder function and ureteric reflux. Further investigations are:

- ultrasound scan of the kidneys, and bladder after voiding
- dimercaptosuccinic acid (DMSA) scan for scarring
- micturating cystourethrogram, direct or indirect depending on child’s age and sex (the urethra is not visualised on indirect).

Reflux nephropathy. This term is used to describe the renal scarring associated with vesicoureteric reflux. Ureteric reflux may be:

- primary and exist in isolation
- in association with complex syndromes of renal dysplasia such as Bardet-Biedl, or
- secondary to bladder outflow obstruction.

Reflux may itself be associated with primary renal dysplasia (ie the scarring is not secondary to reflux). Milder forms of reflux usually disappear in adolescence and, even with severe forms causing intrarenal dilatation, reflux ceases in 40% of patients.

The aim is to prevent pyelonephritis and preserve renal function by:

- regular clinic attendance, with monitoring of blood pressure and biochemical parameters
- prophylactic antibiotics for chronic infection
- assessment of siblings and parents (because of high familial incidence)
- consideration of anti-reflux surgery, if necessary.

Symptomatic UTI must be treated. Asymptomatic colonisation is usually left untreated. Infants presenting with symptomatic UTI and renal scarring are treated with prophylactic antibiotics for their first 4–5 years of life. Thereafter, new renal scarring is uncommon. In adolescents, recurrent UTIs in complicated patients with renal scarring should be prevented. As usual, all treatable causes must be excluded. The choice of antibiotic must be guided by known sensitivity of current bacteria. Nitrofurantoin is contraindicated if the GFR is below 50 ml/min, and is not effective for parenchymal renal infection. Prophylactic antibiotics can be tried, but, if breakthrough infections are common or organisms become highly resistant, it may be easier for the patient to have a supply of antibiotics at home and self-treat symptomatic infection as soon as symptoms start.

Nocturnal enuresis

Enuresis still occurs in 20% of children at the age of five years and in 1–2% of 15 year olds. It is predominantly primary, but secondary causes must be excluded, such as neurogenic bladder (eg spinal cord abnormalities), UTI, posterior urethral valves in boys and ectopic ureters in girls. Enuresis is the emptying of the bladder while asleep, and should be differentiated from involuntary incontinence during the day or night.

The teenager with nocturnal enuresis will suffer the stigma of bed-wetting more than the younger child, so warrants intervention that offers a quick and safe response. A careful history and examination together with urinalysis should be sufficient to make the diagnosis. Psychological and family histories are essential. There is a genetic predisposition: if one parent was affected, the children have a 45% probability of enuresis, while if both were affected the probability is 77%.

Treatment

Non-pharmacological:

- simple measures, such as improved access to lavatory, avoiding excessive fluids and emptying bladder before bedtime
- motivational therapy (20% success), such as positive reinforcement and reassurance, removing feelings of guilt, and providing emotional support
- behavioural conditioning with signal alarm devices (70% success);
- bladder training exercises (19% success);
- diet therapy (50% success);
- hypnotherapy (successful, but trials limited).

Pharmacological:

- tricyclic antidepressants: weak anticholinergic effect and possible effect on secretion of antidiuretic hormone
- anticholinergic therapy: direct effect on bladder smooth muscle
- desmopressin: reduces nocturnal urine production.

Pharmacological methods are not cures, but a temporary measure until patients are able to wake to void.
The majority of patients diagnosed in childhood with tubular disorders will survive into adulthood. The renal prognosis is worse in patients with complex rather than isolated tubular defects. Bone disease often precedes chronic renal insufficiency. Growth retardation is an important feature of this group, requiring continuing close supervision as patients enter adulthood.

### Glomerular disease

#### Systemic disease

Glomerular disease can be due to systemic disease; appropriate antibody tests and immunological examination of renal biopsy specimens should yield the diagnosis. Systemic lupus erythematosus is as common in boys as girls until puberty. Henoch-Schönlein purpura remains a clinical diagnosis until it can be confirmed by finding immunoglobulin A deposits in the glomerular mesangium. Anti-neutrophil cytoplasmic antibody-positive systemic vasculitis can occur in adolescents.

#### Steroid-sensitive nephrotic syndrome

Nephrotic syndrome is the triad of proteinuria (>3 g/day), hypoalbuminemia and oedema. It is unusual for this to present first in adolescence, with 60% of cases presenting in children under six years. In children, this is commonly primary and characterised by minimal histological change on light microscopy and by response to steroids. The most common cause of nephrotic syndrome which does not respond to steroids is focal segmental glomerulosclerosis. Notable clinical features of steroid-sensitive nephrotic syndrome are shown in Table 7.

**Table 6. Hereditary tubular disorders (from Ref 6).**

|                      | Nephrocalcinosis/ nephrolithiasis | Bone disease | Renal insufficiency |
|----------------------|-----------------------------------|--------------|---------------------|
| **Isolated tubular disorders:** |                                   |              |                     |
| cystinuria           | +                                 |              | ++                  |
| Barter’s, Gitelman syndrome | +                                 |              |                     |
| hypomagnesaemia-hypercalciuria | +                                 |              | ++                  |
| idiopathic hypercalciuria | +                                 |              |                     |
| X-linked hypophosphataemic rickets | +                                 | +           | –                   |
| nephrogenic diabetes insipidus | –                                 | +           | –                   |
| distal and other forms of RTA | +                                 |              | –                   |
| Dent’s disease       | +                                 |              | ++                  |
| unclassified nephrocalcinosis, RTA | +                                 |              | +                   |
| **Complex tubular disorders:** |                                   |              |                     |
| primary Fanconi syndrome | +                                 | +           | ++                  |
| cystinosis           | +                                 | +           | ++                  |
| primary hyperoxaluria | +                                 | +           | ++                  |
| Wilson’s disease     | –                                 |              | +                   |
| methylmalonic aciduria, galactosaemia, hereditary fructose intolerance | –                                 | +           | ++                  |

**Notes:**
- Bone disease: conspicuous and associated with growth retardation and rickets
- Renal insufficiency occurs (+): progresses to end-stage renal failure (++)
- RTA = Renal tubular acidosis.

### Hereditary tubular disorders

Many hereditary tubular disorders are insidious and slowly progressive, and can present with advanced renal insufficiency (Table 6). They probably account for a significant proportion of cases of renal failure of unknown origin in young patients, and can be overlooked because little or no proteinuria is present. A physician who has not heard of Dent’s disease (familial Fanconi syndrome, nephrocalcinosis and renal failure) will not diagnose it.

**Table 7. Clinical features of nephrotic syndrome.**

| Feature                      | Description                                                                 |
|-----------------------------|-----------------------------------------------------------------------------|
| Oedema                      | Periorbital followed by legs, ascites and pleural effusions                 |
| Hypovolaemia                | Abdominal pain and cool periphery                                           |
| Bacterial infection         | Primary peritonitis with *Streptococcus pneumonia*.                          |
|                             | Susceptibility due to low IgG levels from urinary loss, impaired lymphocyte function, impaired complement activation and immunosuppressive drugs |
| Thrombosis                  | Increased risk of venous thrombosis and a small risk of arterial thrombosis |
|                             | Increased fibrinogen concentration and anti-thrombin III levels are low due to urinary losses |
| Protein depletion           | Leads to muscle wasting, osteoporosis and poor growth                       |
| Acute renal failure         | Usually in the older patient                                                |
|                            | Due to acute tubular necrosis secondary to hypovolaemia                      |
| Hyperlipidaemia             | Hypercholesterolaemia                                                        |
| Haematuria                  | Often transient                                                             |
| Hypertension                | Uncommon                                                                    |
| Serum complement            | Characteristically normal                                                    |

Ig = Immunoglobulin.
Table 8. Indications for renal biopsy.

- Macroscopic haematuria
- Persistent proteinuria and microscopic haematuria
- Persistent hypertension
- Low complement (C3)
- Steroid resistance
- Frequent relapse
  
  - diuretic therapy and salt restriction
  - if hypovolaemic, 20% albumin (salt poor) infusions with boluses of frusemide
  - prednisolone 60 mg/m²/day until urine is protein free for five days, followed by 40 mg/m² on alternate days and gradual withdrawal over 8–12 weeks; if no response after four weeks, the patient is considered to be steroid resistant⁷.

Up to two-thirds of patients relapse within 12 months of first treatment, possibly spontaneously in a quarter but the rest usually follow infection. Frequent relapses require further maintenance therapy with the minimum steroid dose required to maintain remission. Relapse on this regimen requires treatment with other agents (cyclophosphamide, levamisole or cyclosporin). Steroids may often produce growth failure and delayed puberty which can be minimised with alternate day dosing. Transformation to steroid resistance is rare, with 30% of these progressing to ESRF (more common amongst black American children than Caucasians⁸).

**Indications for renal biopsy**

Renal biopsy should be performed according to the indications shown in Table 8. In practice, the histology matters less than the response to treatment which is a better predictor of outcome.

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**Adolescent medicine**

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