Clinical Methods

20 Clinical Evaluation

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Presentation of Renal Disease in Children

Introduction

Renal disease in children may present with overt abnormalities clearly associated with the urinary tract, such as the development of macroscopic haematuria or profound oliguria. However, in many instances symptoms may be very non specific or seemingly mild. Children with chronic renal failure present with a wide variety of symptoms including enuresis, failure to thrive, short stature, lethargy and pallor. The onset may be silent and the progress insidious, with symptoms only developing late in its course. Urinary tract infection in infants and small children may, in contrast to older children, present with non-specific manifestations including poor feeding, vomiting, irritability, abdominal pain, failure to thrive, lethargy and restlessness. The possibility of renal disease should therefore be considered in the differential diagnosis of any child presenting to hospital with acute or chronic symptoms.

Antenatal Imaging

Since the first report of renal abnormalities being detected by antenatal ultrasonography in the 1970s (1), there have been major developments in the antenatal assessment of the urinary tract (2–4). In most countries, pregnant women undergo routine ultrasound assessment of the fetus at various stages throughout pregnancy, including a detailed scan performed at around 20 weeks gestation. Ultrasound is particularly informative with regard to renal abnormalities, which account for around 20% of all significant fetal abnormalities detected during gestation (5). Recent developments including 3D ultrasound and magnetic resonance imaging of the fetus will allow these anomalies to be studied in further detail. This has resulted in many significant congenital and inherited abnormalities of the urinary tract being detected antenatally, notably posterior urethral valves, the multicystic dysplastic kidney (MCDK), pelvi-ureteric junction obstruction and polycystic kidney diseases. In the case of posterior urethral valves, this has resulted in the possibility of antenatal therapy, currently the subject of an ongoing randomized controlled trial investigating vesico-amniotic shunting (www.pluto.bham.ac.uk). Large kidneys on antenatal imaging may suggest hydronephrosis, polycystic kidney disease (PKD), MCDK, congenital nephrotic syndrome or rarely a renal tumor whereas small kidneys may point to the presence of renal dysplasia or hypoplasia. PKD, cystic dysplasia and glomerulocystic disease are common causes of echobright kidneys. TCF2 gene mutations are found in almost a third of the children with antenatally diagnosed bilateral echogenic kidneys (6). The presence of renal macrocysts in the antenatal period should alert the physician towards a diagnosis of autosomal dominant PKD, PKD associated with tuberous sclerosis, MCDK or cystic dysplasia.

The sensitivity of ultrasound imaging does, however, result in the detection of many minor abnormalities, particularly unilateral renal pelvic dilatation, which appear to resolve spontaneously in later pregnancy or after birth and are of no long term significance. Their detection may be a source of significant maternal anxiety and multiple invasive investigations where appropriate protocols are not in operation.

Abnormalities of Appearance of Urine

Red or Dark Urine

The presence of blood in the urine causes it to develop a pink to red color. Only a relatively small amount of blood is necessary to produce discoloration. Prolonged contact between blood in the urinary tract and acidic urine causes the haem pigment to become oxidized to a methaem derivative, giving the urine a brown color. In general, the longer the contact and the more acidic the urine, the darker brown the urine becomes.

Contamination with blood from menstruation in older girls needs ruling out. There are a number of causes of false positive haematuria, where alternative substances produce red discoloration (*Table 20-1*). One of the most common of these is the pink discoloration seen in nappies caused by

Table 20-1

False positive haematuria; alternative causes of red urine

Foods e.g., beetroot, berries containing anthocyanins and food dyes
Haemoglobinuria e.g., in intravascular haemolysis
Myoglobinuria e.g., in rhabdomyolysis
Urate crystals (a cause of pink discoloration of nappies)
Drugs e.g., rifampicin, phenothiazines, desferroximine, phenindione
Inborn errors of metabolism e.g., porphyria and alkaptonuria

the precipitation of urate crystals. Urine microscopy is therefore mandatory following the detection of red or dark urine. It is important that this is performed on a fresh sample as red cell lysis occurs where samples are allowed to stand for prolonged periods prior to examination.

The passage of fresh red blood in the urine, with or without clots, is most likely to originate from the lower urinary tract, particularly where this is most marked at the beginning or the end of the urinary stream. This highlights the importance of obtaining a comprehensive clinical history in such children. Causes include urethritis, trauma, bladder calculus and schistosomiasis. Urological assessment and cystoscopy in indicated in most of these cases. More uncommon causes of bleeding from the upper tracts include trauma, arteriovenous malformations, tumors and angiomyolipoma associated with tuberous sclerosis.

Fabricated and induced illness by proxy, previously termed Munchausen syndrome by proxy is a very rare disorder, though falsification of urine samples by contamination with maternal or other blood is one of the more common modes of presentation (7). A high index of suspicion needs to be maintained to detect such cases. Absolute confirmation of contamination requires analysis of urinary red cells for differences in blood group type, or if required, DNA profiling.

Dark urine associated with jaundice in the neonate or older child should alert the physician to the presence of conjugated hyperbilirubinaemia, indicative of significant liver or biliary tract disease. Bilirubin and urobilinogen will be detected on dipstick testing the urine in such cases.

Cloudy Urine

The urine may become cloudy secondary to the presence of white blood cells (pyuria) associated with urinary infection, calcium phosphate crystals or a combination of calcium salts, uric acid, oxalate, cystine or struvite. These substances are normally present in the urine, though may be present in excess in various disease states. The precipitation of phosphates and urates is enhanced by refrigeration of the urine sample.

Frothy Urine

The presence of significant quantities of protein in the urine will result in it becoming frothy. Presentation with frothy urine should therefore prompt the physician to perform dipstick analysis followed by formal quantification of protein content.

Offensive or Unusual Smelling Urine

A number of factors may result in an alteration in the smell of urine. Infection with urea splitting organisms including *Ureaplasma urealyticum, Proteus, Staphylococcus, Klebsiella, Providentia* and *Pseudomonas* species may generate an ammonia-like smell, though the positive predictive value of offensive urine for bone fide urinary infection is very low. A number of the inborn errors of metabolism, including maple syrup urine disease, phenylketonuria and isovaleric acidaemia also produce characteristic odors. The change in urine odor following the ingestion of asparagus was first reported in the eighteenth century by a physician to the French royal family (8). This is thought to be due to the presence of S-methylthioacrylate and S-methyl-3-(methylthio)thiopropionate (9), though a combination of methyl mercaptan, dimethyl sulfide, and small amounts of sulfur-oxidized compounds could also be responsible (10).

Passage of Gravel or Stones

The passage of gravel or stones in the urine is an unusual, though recognized mode of presentation of urinary tract calculi. Stones are either metabolic or infective in origin (Chapter 58).

Abnormalities of Volume of Urine

Oliguria

The otherwise healthy neonate is oliguric for the first 2–3 days of life until the onset of the postnatal diuresis.

Ninety-two percent of neonates will pass urine within the first 24 h of life and almost all newborns will do so in the first 48 h (11). Beyond the immediate neonatal period, oliguria is defined a urine output of less than 500 ml/24 h/1.73 m^2; that which is sufficient to maintain homeostasis. The most common cause of oliguria in children is intravascular volume depletion. Where this has been excluded or adequately treated and volume depletion persists, a search for intrinsic or obstructive renal disease should be commenced.

Polyuria and Polydipsia

Of those children presenting to medical practitioners with symptoms of polyuria, only a very small proportion will have a significant renal or other pathology. A strict definition of polyuria does not exist, though a daily urine output exceeding 2 l in school-aged children is unusual. It is important to distinguish polyuria from frequency of micturition where small volumes of urine are passed frequently though the 24 h urine output is within normal limits.

Significant pathologies which result in polyuria are shown in *Table 20-2* and include excessive fluid intake, increased osmotic load, failure to produce or release antidiuretic hormone (ADH) and resistance to the actions of ADH in the kidney. The distinction between primary polydipsia and primary polyuria may be inferred from the relative osmolality of plasma and urine and the response to controlled water deprivation. The distinction between pituitary and renal causes of polyuria may be made by the plasma ADH concentration and the urinary response to D-amino-arginine vasopressine.

Table 20-2
Causes of polyuria in children

Increased fluid intake
Psychogenic/behavioral polydipsia
Hypothalamic polydipsia
Hyperreninaemia including Wilm's tumor
Increased osmotic load
Diabetes mellitus and other causes of hyperglycaemia
Chronic renal failure (urea)
Following mannitol infusion
Failure of ADH production
Cranial diabetes insipidus
Basal skull fracture
Cranial tumors
Post hypophysectomy
Infection; encephalitis, meningitis, tuberculosis
Vascular aneurysm or thrombosis
Failure of renal response to ADH
Nephrogenic diabetes insipidus (X-linked)
Acquired unresponsiveness to ADH
Obstructive uropathy
Hypokalaemia
Hypercalcaemia
Sickle cell disease
Chronic renal failure
Drugs e.g., amphotericin, methoxyflurane, tetracycline

Wetting and Abnormalities of the Passage of Urine

Wetting is the most common urinary tract disorder of childhood, though in most cases there is no organic pathology. The majority of children will achieve daytime bladder control between 3 and 4 years of age (12). The prevalence of nocturnal enuresis is 15–20% at age 5 years and up to 3% in young adults (13). Nocturnal enuresis has a strong genetic predisposition and on its own, is a benign self-limiting condition. Daytime wetting, which can occur as a result of a number of disorders including detrusor overactivity, dysfunctional voiding and, rarely, giggle incontinence which is more common in girls and usually resolves by the age of 9 years. Secondary enuresis, both diurnal and nocturnal raises the possibility of an organic cause (e.g., neuropathic bladder) especially in boys; however it is commonly associated with psychosocial disturbances such as parental separation, the birth of a new child or a death in the family. Diabetes mellitus should always be excluded. A careful voiding and wetting history along with a focused physical examination will help to identify any organic pathology. The presence of dysuria and frequency might suggest a diagnosis of urinary tract infection whereas poor urinary stream and an enlarged bladder would point to a diagnosis of a neuropathic bladder or an obstructive pathology such as posterior urethral valves. Examination of the urine for infection is essential in all children with wetting. In a child with persistent daytime wetting a pre and post-void ultrasound of the renal tract is useful to screen for urinary tract anomalies and to assess bladder emptying. Urodynamic assessment to identify abnormalities of bladder and sphincter function is indicated in children with a neuropathic bladder and in some children with

persistent and troublesome wetting who do not demonstrate a good response to conservative management.

Pollakiuria, a benign, self-limiting condition is characterized by the very frequent (every 5–20 min) passage of urine during the daytime hours. It most commonly presents in pre-school age children and is not associated with wetting.

Edema

Children with renal disease may present with edema, a major clinical manifestation of ECF volume expansion. Edema may occur in the acute nephritic syndrome and other causes of acute renal impairment as a result of failure of salt and water excretion. Here, peripheral edema is accompanied by intravascular volume expansion with hypertension and pulmonary edema. In the nephrotic syndrome, loss of plasma oncotic pressure secondary to hypoproteinaemia and increased vascular permeability result in the loss of fluid from the intravascular into the extravascular space. Here, edema is initially first evident as swelling of the periorbital region, which is often most marked in the morning. With progressive fluid retention, more generalized edema develops in a gravity dependent distribution, the ankle and sacral areas being the most severely affected. This may be associated with abdominal distension secondary to ascites.

Asymptomatic Presentation Following Screening or Routine Assessment

Whilst the universal routine testing of children's urine by dipstick examination is not performed in the large majority of countries, this has been undertaken in Japan, having been introduced by the Ministry of Education in 1973 with the aim of the early detection of asymptomatic renal disease (14). Outside of universal screening programs, children may have their urine tested at the time of attendance at hospital Emergency Departments and out-patient clinics or as part of a routine medical assessment for insurance or immigration purposes. Such testing may detect abnormalities in the urine (commonly microscopic haematuria) which results in referral for further assessment.

Children may have hypertension detected following a routine medical examination performed at school or for participation in particular sporting activities etc. In such instances it is firstly essential to rule out erroneously high blood pressure which has occurred as a result of the use of incorrect measuring equipment or white coat hypertension. Whilst renal disease is widely reported to be the commonest cause of hypertension in children, the rising tide of childhood obesity may soon see this become the predominant cause (15).

The screening of asymptomatic siblings of index cases of renal disease is a difficult area. Clearly where the detection of significant pathology necessitating the commencement of specific therapy is possible e.g., cystinosis, then appropriate testing should be performed. Siblings and close contacts of children presenting with diarrhea associated haemolytic uraemic syndrome are not infrequently found to have evidence of varying degrees of renal impairment and anemia in the absence of any significant symptoms and such detection will allow the commencement of appropriate therapy and follow-up. In contrast, in the asymptomatic siblings of children with autosomal dominant PKD, many authorities would recommend that ultrasound or genetic screening does not take place. Potentially affected individuals should undergo an annual check of blood pressure and urinalysis until they are able to make a fully informed decision about the relative merits of presymptomatic detection, bearing in mind the implications that this may have. There are a number of situations where medical opinion is divided, for instance whether newborn siblings of children with vesicoureteric reflux should undergo radiological assessment; definitive answers to these question are only likely to be obtained through the enrolment of such children in prospective randomized controlled trials.

Urinary Tract Infection

Urinary tract infection is common. Swedish data report a cumulative incidence by 2 years of age of 2.2% in boys and 2.1% in girls (16). In the northern United Kingdom, cumulative referral rates by 7 years of age are as high as 2.8% for boys and 8.2% for girls, rising to 3.6 and 11.3% respectively by 16 years of age (17). Whilst older children may present with classical symptoms of either lower urinary tract infection (dysuria, frequency, wetting) or upper urinary tract infection (systemic upset, fever, loin pain), these features are much less pronounced in the younger child; here nonspecific manifestations may include poor feeding, vomiting, irritability, failure to thrive, lethargy and abdominal pain.

Diagnosis of urinary tract infection is important, as aside from the acute morbidity associated with infection, the development of infection is an important marker of underlying congenital abnormalities of the urinary tract, in particular vesico-ureteric reflux. Furthermore, infection itself is an important cause of renal cortical scarring in those predisposed to this. Therefore a diagnosis of urinary tract infection should always result in

consideration being given to radiological assessment of the urinary tract. Previous guidelines recommended that all children be investigated after a single infection, though more recent guidelines, for instance those produced by the UK National Institute for Health and Clinical Excellence, have recommended radiological investigations are only performed on the very young and those with recurrent or difficult to treat infections (http://www.nice.org.uk/guidance/index.jsp?action=byID&o=11819).

Clinical History

Antenatal History

A record should be made of the results of antenatal imaging studies, particularly the detailed scan performed at around 20 weeks gestation. Abnormalities of liquor volume should be recorded. In the absence of rupture of the amniotic membranes, oligohydramnios or anhydramnios after 16 weeks' gestation represents failure of urine excretion due to obstruction to urine flow or inability of the kidneys to produce urine. Polyuric states including neonatal Bartter's syndrome and congenital nephrotic syndrome are associated with polyhydramnios; it should be remembered, however, that only a small proportion of cases of polyhydramnios are caused by renal disease.

A raised maternal serum alpha-fetoprotein level between 15 and 20 weeks gestation is associated with spinal cord defects and the congenital nephrotic syndromes and is an indication for a detailed antenatal ultrasound scan and amniocentesis.

Close attention should be paid to drug history. Maternal intake of medications such as COX-2 inhibitors, angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers in the second and third trimester is associated with renal failure in the neonatal period. First trimester exposure to ACEi can lead to major cardiovascular, central nervous system and renal malformations (18).

Other aspects of maternal medical history should be noted. Previous recurrent miscarriages should alert the physician to the possibility of a chromosomal abnormality. There is an increased risk of MCDK among infants of mothers with gestational diabetes. Maternal obesity is associated with increased risk of neural tube defects (19).

Birth History

An enlarged placenta (greater than 25% of the child's birth weight) is a feature of congenital nephrotic syndrome. The presence of hematuria following perinatal asphyxia may be due to renal venous thrombosis. Umbilical arterial catheterization is associated with vascular damage and is the commonest cause of hypertension in the neonatal period (20). The presence of a single umbilical artery in an infant is associated with an increased risk of a variety of renal anomalies including vesicoureteric reflux, MCDK and renal aplasia and dysplasia (21). It is debatable as to whether these infants merit further imaging unless the antenatal scan has demonstrated any abnormality; in such cases an ultrasound scan of the renal tract will provide useful initial information and guide further evaluation.

Family History

A detailed family history forms an essential component of the clinical evaluation and may often provide important clues to the diagnosis. It is considered good practice to document the family tree in the case records. A variety of renal diseases including PKD, familial glomerulonephritis and tubular disorders e.g., Bartter's and Gitelmann's syndromes are inherited. An increasing number of hereditary renal disorders can now be diagnosed by DNA analysis and it is therefore essential that the family is provided with detailed counseling with regard to the potential future implications.

Parental consanguinity is common in a number of societies including the Muslim Middle Eastern countries and the UK Pakistani community, where up to 55% are married to a first cousin (22). This should raise the possibility of conditions which are transmitted in an autosomal recessive manner such as autosomal recessive PKD, juvenile nephronophthisis and cystinosis. End stage renal failure of all causes is also more prevalent in this population (23).

Deafness and renal failure in a male relative may suggest a diagnosis of Alport's syndrome which is most commonly inherited in an X-linked manner. The inheritance of isolated vesicoureteric reflux is felt to be consistent with multifactorial or autosomal dominant with reduced penetrance and has a sibling recurrence rate of 30–50% (24).

General Medical History

Renal disease may be feature of a number of childhood disorders. A Pediatric Nephrologist working in a tertiary centre will often be asked to see children under the care of other specialists and must therefore be familiar with the

renal manifestations of systemic disorders and iatrogenic problems. Renal involvement may be a part of a multisystem disorder such as Henoch Schönlein purpura or systemic lupus erythematosus. Hyponatraemia due to cerebral salt wasting or syndrome of inappropriate ADH secretion is a common problem on the neurosurgical ward. A diagnosis of retinitis pigmentosa should alert to the possibility of juvenile nephronophthisis. Tubulopathy is often seen in children on the pediatric oncology ward following chemotherapy with agents such as adriamycin or ifosfamide. Asymptomatic renal calculi are known to occur after a short course of ceftriaxone and nephrocalcinosis is associated with prolonged use of furosemide.

Urine and Micturition

The clinical history should record information regarding daytime and night-time wetting (see above) and abnormalities of micturition, including the nature of the urinary stream (e.g., hesitancy, staccato micturition, terminal dribbling, the need to stand to void etc). Poor urinary stream should raise the possibility of posterior urethral valves in a male infant, though following the introduction of routine ultrasound scanning, the majority of such cases would be detected in the antenatal period. By 3 years of age most children have some conscious control over micturition and achieve daytime control, but enuresis and daytime accidents can continue to occur. In an older child, the voiding frequency and an estimate of the urinary volume should be documented (25).

Dietary History

The fluid and dietary restrictions in renal disease depend on the type and stage of disease. For instance, while salt and fluid restriction is not necessary in polyuric states such as proximal renal tubular disorders and Bartter's syndrome, anephric children on dialysis will require tight control of their salt and fluid intake. Most children with advanced renal failure will be on a restricted potassium, phosphorus and protein diet. Anorexia associated with renal failure means that these children are often malnourished and input from an experienced pediatric dietician is mandatory.

One of the consequences of the obesity epidemic has been the increasing numbers of overweight children with hypertension, disturbed glucose metabolism and hyperlipidaemia (26). Excessive salt intake may be associated with hypercalciuria.

Psychosocial History

The impact of the disease on the child, for example the amount of school missed, body image, limitations on lifestyle, self-esteem and peer reactions should be assessed. There is a wealth of evidence supporting the view that chronic physical illness and disability are risk factors for mental health problems in children. Social disadvantage, poverty, poor housing, educational failure and family instability are other risk factors. Caring for a chronically ill child is a huge challenge for any family and parents often have to give up employment in order to achieve this. Impact on siblings should be given consideration. A skilled social worker and child psychiatrist or psychologist are therefore essential members of a multiprofessional pediatric nephrology team. The impact of the disease on the child's intellectual, emotional and social progress must be assessed. An awareness of the risk factors will help the physician identify those children who are at particularly high risk of developing mental health problems. Adherence with prescribed medications is a particular problem during adolescence and is the commonest cause of rejection and graft loss in this age group (27).

Clinical Examination

General Assessment (› *Fig. 20-1*)

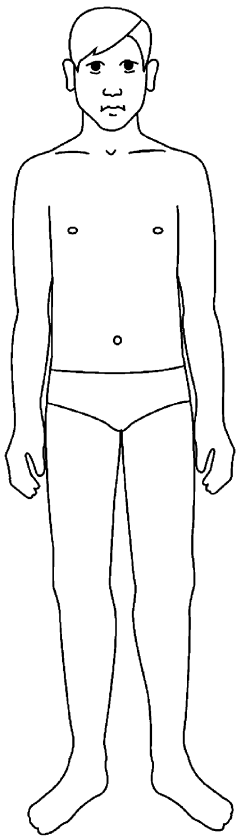
An initial rapid assessment of the level of consciousness, airway, breathing and circulation should be performed to determine how ill the child is. Any obvious dysmorphic features should be recorded. Pain can be a manifestation of renal disease and is often confused with back pain and other causes of abdominal pain in childhood. The state of the child (clothing and hygiene) should be noted. A record of the mood and demeanor of the child together with the family interaction is informative.

Growth

Growth is an invaluable measure of health during childhood and accurate measurement of height and weight along with the head circumference in younger children is therefore essential. Most growth charts express anthropometric measures in terms of percentiles, however not infrequently children with renal disease are significantly below the lowest percentile lines and therefore expressing height, weight and body mass index in terms of standard deviation score (SDS or Z score) is sometimes more

Figure 20-1

Assessment of the child with renal disease



1. **Airway**
   Breathing
   Circulation
   Ill or well child
2. **General assessment**
   Hydration
   Growth - centile charts
   Nutrition
   Dysmorphic features
   Tanner staging
3. **Skin**
   Sallow
   Pallor
   Jaundice
   Oedema
   Cushingoid features
   Scratch marks
   Rash
   Central venous/ haemodialysis catheter

   Eyes
   Face and oral cavity
   Ear deformity
4. **Cardiovascular system**
   Pulse including femorals
   BP
   JVP
   AV fistula
   Cardiomegaly
   Murmur
   Bruits
5. **Chest**
   Kussmaul breathing
   Rib rosary
   Harrison's sulcus
   Pleural effusion/pulmonary oedema
6. **Abdomen**
   Scars, PD catheter
   Distension, peritonitis
   Renal mass
   Bowel sounds
   Transplant kidney- tenderness/bruit
   Genitalia, urethral opening
   Anus
7. **Central nervous system**
   Mental status
   Cranial nerves
   Tone, power, reflexes
   Gait, coordination
8. **Musculoskeletal system**
   Muscle wasting, weakness
   Hemihypertrophy
   Joint swelling
   Spine, sacrum
   Linb deformity
   Wrist swelling
9. **Urine analysis**
   Microscopy
   Dipstick for blood, protein, nitrite and glucose

informative. Pubertal development (Tanner staging) should also be formally assessed.

Nutrition

Assessment of nutrition in children with renal disease can be a challenge; fluid overload and abnormalities in the distribution of fat and lean body tissue can lead to misinterpretation of the nutritional anthropometric measures (28). The commonly used nutritional markers are dietary assessment, height, estimated dry weight, body mass index, serum albumin and skin fold thickness. Tools for assessing body composition such as dual energy x-ray absorptiometry and bioelectrical impedance analysis can sometimes provide useful information.

Hydration/Volume Status

Assessment of the state of hydration and circulatory status is an important skill for all physicians dealing with children with kidney disease. An understanding of total body water and its distribution between the intravascular (plasma) and extracellular fluid (interstitial) compartments is essential. A child with nephrotic syndrome usually presents with a recent increase in weight and peripheral edema, reflecting an increase in ECF volume, though at the same time may exhibit signs of intravascular volume depletion such as reduced capillary refill time, cold extremities, tachycardia and oliguria. Occasionally, clinical signs may be subtle and measurement of urinary sodium, fractional excretion of sodium (FeNa) and urine osmolality

may provide additional information. In contrast, expansion of the intravascular volume, such as in nephritic states results in hypertension, raised jugular venous pulse, hepatomegaly and the development of pulmonary edema.

Cardiovascular System

Pulse

The rate, rhythm and volume of the pulse should be recorded. Tachycardia with a low volume pulse is a feature of intravascular volume depletion. The presence of a gallop rhythm suggests congestive cardiac failure. The femoral pulses should always be examined; coarctation of the aorta may present with hypertension and cardiac failure. The presence of bruits on auscultation over major arteries such as the carotid or renal arteries suggests extensive vascular disease or renal artery stenosis.

Blood Pressure

Measurement of the blood pressure is an integral part of the assessment of the child with renal disease. It is important to ensure that the right equipment and standards are used to ensure that hypertension is correctly diagnosed; a wrong diagnosis due to incorrect measurement can lead to a battery of unnecessary invasive tests. There is increasing use of ambulatory blood pressure monitoring in children, especially to diagnose essential and white coat hypertension (29). The investigation of hypertension is discussed in Chapter 62.

Precordium

Fluid overload, long standing hypertension and cardiomyopathy will give rise to cardiomegaly. Pericarditis with a rub may be a feature of severe uremia. A heart murmur may suggest a structural anomaly but can also be a feature of infective endocarditis or a hyperdynamic state as occurs in anemia.

Respiratory System

Hyperventilation with Kussmaul respiration suggests the presence of metabolic acidosis. Rachitic deformity of the ribs can be seen in longstanding chronic renal failure. Dullness on percussion over the lung fields might suggest pleural effusion in a child with nephrotic syndrome or a peritino-pleural leak in a patient on peritoneal dialysis. Fine crepitations over the lung bases may indicate the presence of pulmonary edema.

Abdomen

Abdominal Distension

Abdominal distension in renal disease may be due to ascites, bladder enlargement due to urinary retention and mass (see below) and the presence of peritoneal dialysis fluid. In children who have undergone previous abdominal surgery, for example urinary diversion procedures, one should be aware of the possibility of adhesions and obstruction presenting as an acute surgical abdomen. Tenderness with guarding and rigidity is highly suggestive of peritonitis and in these circumstances the opinion of a pediatric surgeon should be sought.

Abdominal Mass

Prior to the onset of routine antenatal imaging, the detection of an abdominal mass was a reasonably frequent mode of presentation of a variety of renal and urological disorders, including the MCDK, pelvi-ureteric junction obstruction and other causes of hydronephrosis. In the neonatal period, 55% of abdominal masses are renal in origin (hydronephrosis 25% and multicystic dysplastic kidney 15%). In later infancy and childhood, the proportion of abdominal masses which are renal in origin increases, largely due to the increased rate of malignant tumors in the age group (30).

Renal causes of an abdominal mass are shown in *Table 20-3*.

Features in the clinical history may help in ascertaining the likely cause of the mass. In the newborn period, the large majority of these lesions will have been identified antenatally, though additional clinical information may inform subsequent investigation and likely diagnosis i.e., the presence of oligohydramnios or polyhydramnios. Beyond the newborn period, a family history of severe hypertension may point to a diagnosis of PKD. Presentation with symptoms and signs of urinary tract infection may point to many of the anomalies associated with urinary obstruction or stasis.

Table 20-3

Causes of an abdominal mass of renal origin

Abnormality	Causes if unilateral	Causes if bilateral
Hydronephrosis (obstructive and non-obstructive)	PUJ obstruction	Causes of bladder outlet obstruction including posterior urethral valves
	VUJ obstruction	Eagle Barrett syndrome
	Primary megaureter	
Cystic mass	Multicystic dysplastic kidney	PKD (dominant and recessive)
	Simple cyst	Cystic disease associated with syndromal diagnosis
	Cystic dysplasia	Cystic dysplasia
Infection	Acute pyelonephritis	
	Xantogranulomatous pyelonephrtis	
	Perinephric abscess	
Vascular	Renal venous thrombosis	
	Arterial thrombosis	
	Acute cortical necrosis	
Tumors	Wilm's tumor	
	Mesoblastic nephroma	
	Leukaemic infiltrate	
Miscellaneous	Compensatory hypertrophy	Beckwith Weidemann syndrome
	Duplex kidney	Acute renal failure
	Fused crossed ectopia	Storage disorders
		Congenital nephrotic syndrome

Hepatosplenomegaly

Liver enlargement in association with renal disease can be seen in a number of conditions including glycogen storage disease type 1, tyrosinaemia and Fanconi-Bickel syndrome. Splenomegaly in a child with haematuria might suggest infective endocarditis. Autosomal recessive PKD may cause hypersplenism as a consequence of hepatic fibrosis. Hepatosplenomegaly in association with renal disease reflects a multi-system disorder which can be inflammatory such as systemic lupus erythematosus or a neoplastic process, for instance lymphoma presenting with acute renal impairment secondary to uric acid nephropathy.

Urinary Bladder

An enlarged urinary bladder can be detected by palpation and percussion and is characteristically associated with suprapubic pain. Gross constipation and local genital inflammation are the common causes of acute urinary retention in children and rarely require urethral catheterization. Lower urinary tract obstruction due to urological causes such as posterior urethral valves, pelvic tumors and the neuropathic bladder should be considered an emergency, immediate decompression of the urinary tract being indicated.

Genitalia

Clinical evaluation of the renal patient is incomplete without examination of the genitalia. The presence of vulvovaginitis, a common gynaecological problem in pre pubertal girls causing dysuria should be noted. In male children the state of the foreskin and the position of the urethral meatus should be recorded. Hypospadias is a common problem with an incidence of up to 1:130 live births; parents should be made aware that circumcision is contraindicated where this is present. Eagle Barratt syndrome is associated with bilateral cryptorchidism. The presence of male pseudohermaphroditism in association with proteinuria and renal impairment in an infant is suggestive of Denys Drash syndrome.

Anus

The presence of an imperforate anus in a neonate should alert the physician towards other associated anomalies such as sacral dysplasia, spinal dysraphism and vesicoureteric reflux.

Nervous System

Whilst a detailed neurological examination is often not required, it is important to record the level of consciousness,

mental status and examination of the cranial nerves, muscle tone, power and reflexes along with the gait and co-ordination. Hypertension can present with papilloedema and is the commonest cause of bilateral Bell's palsy. Seizures are associated with hyponatraemia, uremia, hypocalcaemia, hypertensive encephalopathy, vasculitis and haemolytic uremic syndrome. Blindness can result from rapid lowering of blood pressure in severe hypertension and is also known to occur in association with the use of immunosuppressive agents including methylprednisolone (31) and tacrolimus following renal transplantation (32). In a child with continence issues, careful examination of the peripheral sensory and motor functions together with the assessment of the anal tone is essential.

Skin

SLE can present with the characteristic fixed erythematous malar rash. The presence of a palpable purpura over the extensor surfaces and buttocks suggests Henoch Schönlein purpura. Multiple café au lait spots are seen in neurofibromatosis, which can give rise to hypertension secondary to renal artery stenosis. Tuberous sclerosis is characterized by typical dermatological lesions including facial adenofibromas (adenoma sebaceum), shagreen patches over the lower back and hypopigmented ash leaf macules which may be present anywhere in the body. Icthyosis is a recognized feature of the arthrogryposis, renal Fanconi syndrome and cholestasis (ARC) syndrome. Dystrophic nails should raise the possibility of nail patella syndrome.

Face

Examination of the face can provide valuable clues to the underlying clinical problem. Any obvious dysmorphic features such as Down's or William's syndrome should be noted. Long-term ciclosporin use is associated with hypertrichosis, particularly in the Asian population. Hirsutism is a well recognized feature of steroid toxicity and Cushing's syndrome. Nephrotic syndrome often presents with early morning periorbital swelling and is frequently misdiagnosed as allergic rhinitis. Examination of the oral cavity is important and may reveal gingival overgrowth as a consequence of ciclosporin therapy. Asking the child to smile may reveal a facial expression resembling crying in the child with Ochoa syndrome, which is associated with the presence of a neuropathic bladder.

Eyes

The eyes are affected in a number of renal diseases and therefore input from an experienced pediatric ophthalmologist is invaluable. Coloboma of the eyelid is seen in Goldenhar syndrome. Uncontrolled renal osteodystrophy can lead to scleral calcification. The presence of hypercalcaemia may cause redness of the eyes secondary to the metastatic crystallization of calcium, phosphate and hydroxyapatite in the conjunctiva (33). Slit lamp examination may reveal characteristic crystal deposits in the cornea in cystinosis. In a child with unexplained acute renal failure, examination of the eyes may clinch the diagnosis; for example in tubulointerstitial nephritis and uveitis (TINU) syndrome. Uveitis is also a feature of systemic diseases such as juvenile rheumatoid arthritis. Aniridia is associated with an increased risk of Wilm's tumor. Presence of anterior lenticonus, which is a conical protrusion in the anterior aspect of the lens (seen almost exclusively in males) along with macular changes, is a characteristic feature of Alport's syndrome. Cataracts are seen in Lowe's syndrome and galactosaemia, but can also be a consequence of steroid therapy.

Not infrequently, a child with severe hypertension is referred by an optician with papilloedema and retinal hemorrhages and exudates. Diabetic retinopathy, which parallels nephropathy is rare in childhood and correlates with the duration and control of disease. Nephronophthisis is associated with several characteristic eye lesions; retinitis pigmentosa in Senior Loken syndrome, tapetoretinal degeneration in juvenile nephronophthisis and oculomotor apraxia in children with Cogan syndrome. Retinitis pigmentosa is a feature of Bardet-Biedl syndrome.

Ears

Minor external ear malformations such as preauricular skin tags and pits are found in 0.5–1% of newborns and do not warrant renal evaluation unless accompanied by other systemic malformations (34). Branchial fistulae are a feature of branchio-oto-renal syndrome. Alport's syndrome is characterized by the insidious onset of high tone sensorineural deafness. Sensorineural deafness is also a feature of type 4 Bartter's syndrome which is the most severe phenotype presenting in the neonatal period with life-threatening volume depletion and chronic renal failure. Deafness can be a consequence of aminoglycoside toxicity and is also seen following rapid administration of a large dose of furosemide.

Musculoskeletal System

Muscles

Muscle wasting is a feature of chronic uremia. Myopathy can also be secondary to rickets and renal osteodystrophy which may improve following vitamin D therapy. One of the recognized side-effects of steroid therapy is proximal myopathy, demonstrated by eliciting Gower's maneuver. Up to half of children with mitochondrial disorders will have renal involvement with tubular dysfunction being the commonest pathology.

Skeletal System

Florid skeletal deformities of the weight bearing limbs, such as genu varum or valgum can be seen in infants with rickets. Rachitic rosary and swelling of the wrists and ankles due to epiphyseal swelling are the other well recognized features of rickets. Slipped femoral capital epiphysis is a feature of renal osteodystrophy, and a vascular necrosis of the head of the femur may complicate corticosteroid therapy, particularly following renal transplantation.

Whilst polydactyly is a recognized feature of syndromes such as Bardet Biedl and Meckel Gruber syndrome, isolated polydactyly is usually associated with a favorable outcome. Hemihypertrophy and Beckwith Wiedeman syndrome are associated with an increased risk of Wilm's tumor. Spinal dysraphism should be suspected in infants with a lower midline back lesion such as a subcutaneous mass, dermal vascular malformation, hypertrichosis, a midline dimple or sinus tract, a skin tag or an asymmetric gluteal cleft. Sacral agenesis is seen in infants of insulin dependent diabetic mothers but may also be part of the familial Currarino triad syndrome (presacral mass, sacral agenesis and anorectal malformation) (35).

Joints

Arthropathy is a characteristic feature of Henoch Schönlein purpura and SLE. It is also seen in systemic onset juvenile idiopathic arthritis, which if poorly controlled can lead to renal amyloidosis. Arthralgia and arthritis affect almost half of children with sarcoidosis. Metabolic disorders such as Lowe's syndrome and Lesch-Nyhan syndrome may present with arthropathy. Although hyperuricemia is common in pediatric transplant recipients, gouty arthritis is rare.

Examination of the Urine

Macroscopic Examination

The usual yellow color or urine is due to the presence of a number of pigments, some of which are derived from food (i.e., riboflavine) and others produced endogenously. The intensity of the coloration depends upon the urinary flow rate; where large quantities of urine are produced e.g., following high fluid intake, the urine is paler in color though darker in color at times of reduced urine production.

Where the urine is abnormally red or dark in color, dipstick testing and microscopy examination of the sample should be performed.

Dipstick Examination of Urine

Dipsticks

It is important that urine dipsticks are kept dry in their container with the lid on and that the manufacturer's expiry date is adhered to. A number of automated devices are available. These ensure that the stick is read at the correct time, thus reducing interobserver variability. Most will produce a printout which can be attached to the patient's medical record.

Specific Gravity

Most modern urine dipsticks measure urinary specific gravity, though this information is rarely utilized in clinical practice. Specific gravity is a measure of the mass of individual solutes present per unit volume of urine, as opposed to osmolality, which is the measure of the total particle concentrations, irrespective of the mass of the individual particles. Low values of specific gravity (less than 1.010) are found at times of maximal water excretion and high values (greater than 1.025) at time of maximal urinary concentration.

pH

The pH of healthy urine varies between 4.5 and 8.0. Fasting produces low values and the highest pH measurements are seen following meals. pH values are low where acidaemia is present, except for where this is secondary to renal tubular acidosis.

Blood

Urine dipsticks detect the presence of hemoglobin in the urine through its ability to catalyze a reaction between hydrogen peroxide and o-tolidine. Spotted positivity indicates intact red cells, whereas uniform positivity indicates free hemoglobin (e.g., in intravascular haemolysis or red cell lysis in the urinary tract).

There are a number of causes of false positivity, including the presence of myoglobinuria, oxidizing agents in the urine and heavy bacterial contamination. The presence of reducing agents, such as ascorbic acid in the urine may cause a false negative result. These highlight the importance of confirmation of the presence of red blood cells by microscopy of a fresh sample of urine.

Protein

Urine dipsticks undergo color change from yellow to green following binding with proteins. Albumin is better detected than other urinary proteins including globulins, tubular proteins etc. There are a number of causes of false negative and false positive results (*Table 20-4*). Dipstick analysis is not a good quantitative test because of the effect of urinary concentration; more concentrated urine will show higher protein content, and where proteinuria is detected, formal quantification with a urinary protein/creatinine or albumin/creatinine ratio is indicated.

It is well recognized that urinary protein excretion increases throughout the daytime with prolonged duration in the upright position, and first morning samples should be assessed to rule out any element of orthostatic proteinuria. Transient proteinuria may occur following exertion, fever or acute illness and is of no significance with regard to long term renal outcome.

Table 20-4
Causes of false positive and false negative proteinuria on dipstick testing

False positive proteinuria	False negative proteinuria
Concentrated urine	Dilute urine
Alkaline urine	Acidic urine
Gross haematuria, pyuria, bacteriuria	
Dipstick left in urine too long or delay in reading	
Contamination and drugs	
Antiseptics: chlorhexidine, benzalkonium	

Glucose

Glucose is a small molecule which is freely filtered in the glomerulus. In health, the proximal tubule reabsorbs all of the filtered glucose by an active process., which has an upper rate limit or transport maximum (T_M). Certain normal individuals have a lower T_M for glucose and will have glycosuria at normal or only slightly increased plasma glucose concentrations (so called renal glycosuria). Glycosuria also occurs where overt hyperglycaemia is present, e.g., in diabetes mellitus and in a number of tubular abnormalities, including Fanconi syndrome. The lower limit of detection for glucose in the urine is 0.5 mmol/l.

Leucocytes

A number of routinely available urine testing sticks will detect the presence of leucocyte esterase, indicating the presence of pyuria. Where testing is positive, urine microscopy should be used to confirm this finding.

Nitrites

A number of routinely available urine testing sticks will also detect the presence of nitrites. These are produced by the majority of pathogenic bacteria and their detection provides further screening data to assist in the diagnosis of urinary tract infection. The test has a high specificity but a low sensitivity for the diagnosis of UTI. As such, as a standalone test, it is of limited usefulness. Where UTI is suspected or needs to be excluded, a urine culture is necessary to determine the bacteriological cause and antibiotic sensitivities or to confidently rule out UTI.

Microscopy of Urine

There are many who advocate the routine bedside microscopy of urine in all children who present with suspected renal disease or urinary tract infection. This is not, however, widely performed for a variety of reasons including unfamiliarity with the technique and availability of appropriate microscopes in clinical areas.

Casts

Casts are produced by the aggregation of Tamm-Horsfall protein with cells or cellular debris in the renal tubule. They are best seen in unspun urine as centrifugation may damage casts. Where urine has centrifuged for other reasons, casts are most frequently seen at the edge of the coverslip.

Hyaline casts are present in proteinuric states, though may be found in concentrated specimens of urine from normal individuals. These may appear waxy if lipid droplets are present.

Cellular casts contain cellular material, the source of which may provide some clues regarding the underlying pathology. Red blood cell casts are always pathological and indicate glomerular bleeding. White blood cell casts indicate renal inflammation secondary to pyelonephritis or immunologically mediated disease. Epithelial cell casts (often present with red and white blood cell casts) are produced from shed tubular epithelial cells and may be seen during recovery from acute tubular necrosis.

Red Blood Cells

The excretion of a small number of red cells is a normal phenomenon, which increases with increasing age and following vigorous exercise. Children with febrile illness may develop a transient increase in red cell excretion. However, the persistent presence of greater than 5 red cells/mm^3 in uncentrifuged urine is abnormal. Urine microscopy can distinguish anatomically normal RBCs of lower urinary tract origin from dysmorphic RBCs of glomerular origin which have been distorted during their passage through the filtration barrier. This is best performed using phase contract microscopy, though possible with ordinary light microscopy. In its purest form the distinction is useful, though often a mixture of abnormal and normal cells is present and interpretation is difficult. Acanthocytes are red blood cells with thorn-like projections of varying lengths distributed over the surface due to an increase in membrane cholesterol:lethicin ratio. Where acanthocytes constitute greater than 5% of the urinary red cell population, this may indicate the presence of a glomerulonephritis.

White Blood Cells

The presence of greater than 10 white cells/mm^3 in a midstream sample of urine is considered abnormal. Neutrophils are detected in urinary tract infection, but are also seen in contaminated urine samples, proliferative glomerulonephritis and interstitial nephritis. The presence of osinophils in the urine is a sensitive and specific sign of acute interstitial nephritis.

Bacteria and Other Organisms

Urinary bacteria may be clearly visible without Gram staining. Their detection may be enhanced by the use of phase contrast microscopy. Fungi e.g., *Candida* and *Schistosoma* species (a rare cause of haematuria) may also be detected.

Epithelial Cells

The presence of epithelial cells in the urine may represent desquamation from the urinary tract. Tubular cells may be seen following tubular injury (acute tubular necrosis, acute transplant rejection). Squamous cells are commonly exfoliated from urethra and are a normal finding.

Crystals

Normal urine contains crystals of calcium phosphate and oxalate. Other crystals may be cystine, uric acid or dihydroxyadenine.

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