

COMMON ACQUIRED KIDNEY DISEASES IN CHILDREN

Examination of the urine is probably the most important investigation when acquired renal disease is suspected in children.

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The most commonly acquired kidney diseases in children are post-infectious glomerulonephritis, nephrotic syndrome and diarrhoea-associated haemolytic uraemic syndrome. In all of the above cases examination of the urine is of critical importance.

'When the patient dies the kidneys may go to the pathologist, but while he lives, the urine is ours ... the examination of the urine is the most essential part of the physical examination of any patient ...' — Thomas Addis, 1948.

A less well-recognised renal condition that usually only manifests in adulthood is oligomeganephronia. It is in fact congenital renal hypoplasia characterised by a reduced number and hypertrophy of nephrons.^[1] Oligomeganephronia is a common feature in small-for-gestational-age babies. Research has shown that the latter condition plays an important role in the epidemiology of essential hypertension and metabolic syndrome in adults and contributes to the increasing number of young adults with chronic kidney disease (CKD).^[2,3]

Acute post-streptococcal glomerulonephritis (APSGN)

Acute post-streptococcal glomerulonephritis (APSGN) is a non-suppurative, immunologically mediated complication of group A beta-haemolytic streptococcal infections. Certain strains of group A streptococci are either rheumatogenic or nephritogenic, while others are neither.^[4] Thus, acute rheumatic fever and APSGN should not result from the same streptococcal infection. The exact pathogenesis of the disease remains unknown.^[5,6]

Clinical manifestations

APSGN usually develops 10 - 14 days after a skin or throat infection with a nephritogenic strain of group A streptococcus. The median age at presentation is 6 - 8 years. It is rare before the age of 2 years. Typical characteristics of APSGN are oedema, oliguria, abrupt onset



Fig. 1. Macroscopic haematuria in a child with acute post-streptococcal glomerulonephritis.

of painless macroscopic haematuria (black-tea- or coke-coloured urine) (Fig. 1) and hypertension. Hypertension occurs in almost 80 - 90% of children, 30% of whom will present with complications of hypertension, including seizures or visual disturbances. Hypertension is caused by salt and water retention. Volume overload may also cause acute left-heart failure and pulmonary oedema. Atypical presentations of APSGN include those with subclinical disease and those presenting with acute complications of hypertension in the absence of overtly abnormal urine.

Special investigations

- Urine dipstick test reveals haematuria and 1 - 3+ proteinuria.
- Urine microscopy shows dysmorphic red blood cells, red cell casts, leukocytes and leukocyte casts.
- Serum-UKe must be done to monitor renal function. Hyperkalaemia and acidosis and elevated levels of s-urea and creatinine are often present during the acute phase of the disease. Renal function needs to be monitored until it normalises.
- APSGN is confirmed serologically by a positive anti-streptolysin O titre (ASOT) and/or a positive anti-strepDNase B titre.

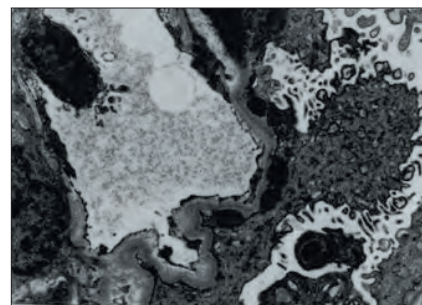


Fig. 2. Electron microscopy photo of APSGN showing subepithelial 'humps' that represent subepithelial immune complex deposition.

- Complement C3 is typically decreased in the acute phase and usually normalises within 6 - 12 weeks after the onset of the disease. A normal C3 level does not exclude the diagnosis of APSGN.^[7] C4 is normal.
- Kidney biopsy is done only when the diagnosis is in doubt. Indications for a kidney biopsy are declining renal function, persistent hypertension or persistent macroscopic haematuria and persistent hypocomplementaemia. The hallmark lesion of APSGN is subepithelial 'humps' that represent subepithelial immune complex deposition (Fig. 2).

Treatment

Treatment is supportive.

- Oral penicillin is given for 5 days to prevent spread of the infection but will not have any effect on the glomerulonephritis.
- Salt and water restriction in combination with furosemide are the first-line treatments for fluid overload and hypertension.
- Another effective and safe antihypertensive drug is amlodipine, while ACEIs should be avoided because of the risk of precipitating kidney failure and hyperkalaemia.

Differential diagnosis

- IgA glomerulonephritis (which is the commonest cause of acute glomerulonephritis in adults and children elsewhere in the world)
- Henoch-Schönlein purpura
- Other post-infectious causes, e.g. *Staphylococcus aureus*, *Mycoplasma pneumoniae*

- Epstein-Barr virus (EBV)
- Haemolytic uraemic syndrome
- Auto-immune diseases, e.g. systemic lupus erythematosus (SLE).

Prognosis

- APSGN has a good prognosis, with complete recovery of renal function in 90% of cases.
- Blood pressure usually normalises after diuresis has occurred and fluid overload has resolved, which in most cases happens within 2 - 3 weeks.
- Microscopic haematuria may persist for 1 - 4 years and proteinuria for 6 months - 3 years after the onset of nephritis.^[8] It is estimated that 5% of children with APSGN develop acute renal failure requiring dialysis, and that another 5% of cases develop irreversible rapidly progressive renal failure or go on to develop chronic renal failure.
- The current literature advises indefinite follow-up of all children after APSGN, as it appears that more patients develop ongoing chronic kidney disease than formerly believed.^[5,6,9]

Nephrotic syndrome (NS)

NS is a clinical syndrome consisting of oedema, 3+ proteinuria on urine dipstick test, hypoalbuminaemia <25 g/l, with or without accompanying hyperlipidaemia.

The classic prototype of NS is minimal-change nephrotic syndrome (MCNS), in which case there is no identifiable cause. The incidences of different histological lesions associated with NS vary amongst different population groups and are influenced by genetic and environmental factors.^[10] MCNS is the most common form of NS in white and Indian children in SA, but in black children and those of mixed race, other types of NS occur more commonly.^[11]

Clinical features

Classic MCNS typically presents between the ages of 2 - 6 years, with a slight male predominance. In some patients oedema develops insidiously starting with peri-orbital oedema only (Fig. 3), whereas in others rapid fluid accumulation leads to the development of anasarca (generalised oedema, ascites and pleural effusions). In most cases there is no history of a preceding infection. Blood pressure is usually normal but may be elevated in those with fluid



Fig. 3. Peri-orbital oedema in a child with nephrotic syndrome.

overload. Microscopic haematuria may be present in up to one-third of cases. Renal function is normal.

Special investigations

Special investigations should be done to confirm the diagnosis and to rule out infections or underlying immune-mediated forms of glomerular disease causing secondary NS.

- Urine protein: creatinine on a spot urine sample >0.2 g/mmol confirms nephrotic range proteinuria (normal value <0.02 g/mmol).
- S-urea, creatinine and electrolytes are usually normal.
- S-albumin is <25 g/l and total cholesterol are elevated.
- Serum complement C3 and C4 levels are usually normal.
- Serological tests should be done to exclude infections like syphilis, hepatitis B and C, HIV and cytomegalovirus or EBV infection.
- Auto-antibodies including anti-nuclear factor and anti-dsDNA to exclude SLE or other auto-immune diseases which may present with NS.
- Kidney sonar is done to exclude morphological abnormalities of the kidney.
- Kidney biopsy is done to make a specific histological diagnosis. Light microscopy is normal in children with MCNS. Electron microscopy shows fusion of podocyte foot processes (Figs 4 and 5).

Indications for kidney biopsy in children with NS:

- Children with a positive family history of kidney disease

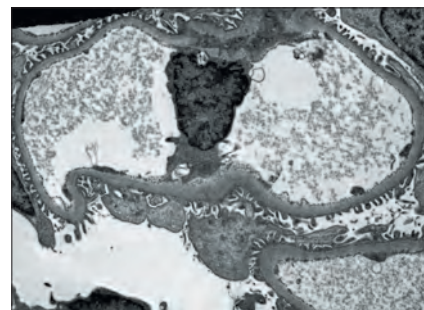


Fig. 4. Electron microscopy photo of a normal glomerulus with epithelial cells with normal loose foot processes.

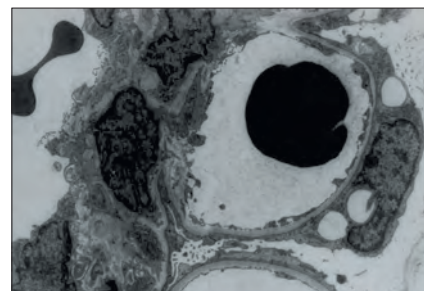


Fig. 5. Electron microscopy photo of a glomerulus in MCNS showing diffuse effacement of epithelial foot processes.

- Children younger than 2 years or older than 6 years
- Children who in addition to the classic features of MCNS also have macroscopic haematuria and hypertension (nephritic-nephrotic picture)

- Persistent hypertension
- Arthritis, vasculitis or other skin lesions associated with immune-mediated disease
- Anaemia or other haematological changes
- Associated hepatosplenomegaly
- Associated systemic disease.

Differential diagnosis

- Congenital NS and inherited forms of NS
- Immune-mediated kidney disease like SLE, HSP, IgA glomerulonephritis
- Secondary NS due to infections like HIV infection or hepatitis B or C
- Alport syndrome
- Reflux nephropathy.

Treatment

- Bed rest for management of anasarca.
- Diet: oral fluid and protein intake is not restricted, salt intake is restricted.
- Where a treatable underlying cause exists this should be treated, e.g. HIV infection.
- Pneumovac vaccine is given once.
- Lasix 1 - 2 mg/kg per dose is given orally for those with fluid overload. Beware of over-treatment, because dehydration is associated with an increased risk of thrombo-embolic complications.
- Corticosteroid treatment: steroid responsiveness is the most important factor in determining the prognosis.

Most children with MCNS respond to corticosteroid treatment. For this reason paediatricians in First-World countries with a predominant Caucasian population have implemented a policy of empiric corticosteroid treatment for children with classic clinical features of MCNS without doing a kidney biopsy first.^[12]

However, this guideline is not applicable in children with nephrotic syndrome with atypical features, as is the common experience in Third-World countries, including South Africa. There is a much higher incidence of other types of NS in the non-Caucasian population groups in SA, in which case treatment should primarily be guided by the renal histopathology report.^[11]

Relapses are common in children with MCNS and are the commonest indication for second-line immunosuppressive treatment. For a more detailed description of treatment of NS see reference 13.

Haemolytic uraemic syndrome (HUS)

The diagnosis of HUS is based on three criteria:

- microangiopathic haemolytic anaemia with fragmented erythrocytes
- thrombocytopenia
- acute renal failure (ARF).

There are 3 broad categories of HUS:

- typical, usually diarrhoea positive (D+) HUS
- atypical, usually diarrhoea negative (D-) HUS
- secondary HUS, secondary to drugs, malignancy, etc.

This discussion will be limited to typical (D+) HUS, which represents 90% of HUS in children and which is the most common cause of ARF in children. The incidence of (D+) HUS is the greatest in children between 6 months and 5 years of age. It is an acute disease characterised by prodromal diarrhoea followed by acute renal failure.

The most common cause of (D+) HUS is enterohaemorrhagic *Escherichia coli* (EHEC), serotype 0157:H7. EHEC produces a toxin, called Shiga toxin (Stx) because of its similarity to the Stx of *Shigella dysenteriae* type 1. The toxin, which is absorbed from the intestines, damages the endothelium of

small vessels, in particular in the kidneys, mesenterium and brain, resulting in microangiopathic haemolytic anaemia, platelet aggregation and local intravascular coagulation.

Clinical features of (D+) HUS

After an incubation period of 3 - 8 days patients develop abdominal cramps, nausea and vomiting followed by watery diarrhoea, which becomes bloody-mucoid. Acute renal failure often develops rapidly and coincides with the onset of anaemia. Anaemia is progressive, and urine output falls precipitously, resulting in extracellular fluid overload and oedema. Hypertension develops in 30 - 50%. Central nervous system involvement is common and frequently presents with irritability, seizures and paresis. Although the kidneys, gastrointestinal tract and the brain are the organs mostly affected, widespread involvement of other organs is possible, including the pancreas, myocardium and musculoskeletal system.

Treatment

At present there is no proven active treatment for EHEC infection or HUS.¹⁴ The role of antibiotics during the diarrhoeal phase of the disease is controversial.¹⁵ Some antibiotics cause a burst of toxin from the affected bacteria and therefore there is risk associated with its use. Given that EHEC are not enteroinvasive and the infection is self-limiting, there is no indication for their use.¹⁴

- Supportive care, including attention to fluid and electrolyte balance, metabolic balance, optimal nutrition and blood pressure remains the mainstay of treatment.
- Intravascular volume status should be monitored carefully. Early intravascular volume expansion with isotonic saline may reduce the incidence of oligo-anuric renal failure. Twice-daily weight measurements are a valuable tool in the assessment of the fluid status in a small child.
- Hypertension should be treated aggressively.
- Packed cell transfusion is given when the haemoglobin is less than 6 g/dl.
- Platelet transfusions are generally contraindicated as (D+) HUS is not associated with a bleeding tendency.
- Early institution of peritoneal dialysis (PD) is an important factor affecting immediate survival. The most common indication for dialysis is to allow

optimal feeding in an anuric patient. Other common indications for dialysis include volume overload, hypertension, hyperkalaemia and encephalopathy.

Prognosis

Mortality from (D+) HUS is about 2%. However, it should be kept in mind that although the glomerular filtration rate returns to normal in most patients, there may be permanent nephron loss which may later result in the development of chronic renal failure.^[14]

References

- Manalich R, Reyes L, Herrera M, et al. Relationship between weight at birth and the number and size of renal glomeruli in humans: a histomorphometric study. *Kidney Int* 2000;58:770-773. [http://dx.doi.org/10.1046/j.1523-1755.2000.00225.x]
- Vikse BE, Irgens LM, Leivestad T, et al. Low birth weight increases the risk of end-stage renal disease. *Am J Soc Nephrol* 2008; 9:151-157. [http://dx.doi.org/10.1681/ASN.2007020252]
- White S, Percovic V, Cass A, et al. Is low birth weight an antecedent of CKD later in life? A systematic review of observational studies. *Am J Kidney Dis* 2009;54:248-264.
- Stollerman GH. Rheumatogenic and nephritogenic streptococci. *Circulation* 1971;43:915-921.
- Eison MT, Ault BH, Jones DP, et al. Post-streptococcal acute glomerulonephritis in children: clinical features and pathogenesis. *Pediatr Nephrol* 2011;26:165-180.
- Singh GR. Managing the risks of chronic renal disease. *Pediatr Clin N Am* 2009;56:1363-1382.
- Strife CF, Mc Adams AJ, McEnery PT, et al. Hypocomplementemic and normocomplementemic acute nephritis in children: a comparison with respect to etiology, clinical manifestations, and glomerular morphology. *J Pediatr* 1974;84:29-38. [http://dx.doi.org/10.1016/S0022-3476(74)80549-4]
- Yoshizawa N. Acute glomerulonephritis. *Intern Med* 2000;39(9):687-694.
- Schacht RG, Gallo GR, Gluck MC, et al. Irreversible disease following acute post streptococcal glomerulonephritis. *J Chronic Dis* 1979;32:515-524. [http://dx.doi.org/10.1016/0021-9681(79)90113-9]
- Ingulli E, Tejani A. Racial differences in the incidence and renal outcome of idiopathic focal segmental glomerulosclerosis in children. *Pediatr Nephrol* 2001;5:393-397. [http://dx.doi.org/10.1007/BF01453661]
- Bhimma R, Coovadia HM, Adhikari M. Nephrotic syndrome in South African children: changing perspectives over 20 years. *Pediatr Nephrol* 1997;11:429-434. [http://dx.doi.org/10.1007/s004670050310]
- International Study of Kidney Disease in Children. Nephrotic syndrome in children: Prediction of histopathology from clinical and laboratory characteristics at the time of diagnosis. A report of the International Study of Kidney Disease in Children. *Kidney Int* 1978;13:159-165. [http://dx.doi.org/10.1038/ki.1978.23]
- Report of a workshop by the British Association for Paediatric Nephrology and Research Unit, Royal College of Physicians. *Arch Dis Child* 1994;70:151-157. [http://dx.doi.org/10.1136/adc.70.2.151]
- Johnson S, Taylor CM. What's new in haemolytic uraemic syndrome? *Eur J Pediatr* 2008;167:965-971. [http://dx.doi.org/10.1007/s00431-008-0745-7]
- Safdar N, Said A, Gangnon RE, et al. Risk of haemolytic uremic syndrome after antibiotic treatment of *Escherichia coli* O157:H7 enteritis: a meta-analysis. *JAMA* 2002;288:996-1001. [http://dx.doi.org/10.1001/jama.288.8.996]

IN A NUTSHELL

- The most commonly acquired kidney diseases in children are post-infectious glomerulonephritis, nephrotic syndrome and diarrhoea-associated haemolytic uraemic syndrome.
- In all of the above cases examination of the urine is of critical importance.
- Acute post-streptococcal glomerulonephritis (APSGN) is a non-suppurative, immunologically mediated complication of group A beta-haemolytic streptococcal infections.
- APSGN usually develops 10 - 14 days after a skin or throat infection with a nephritogenic strain of group A streptococcus.
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- The classic prototype of NS is minimal-change nephrotic syndrome (MCNS), in which case there is no identifiable cause.
- MCNS is the most common form of NS in white and Indian children in SA, but in black children and those of mixed race, other types of NS occur more commonly.
- Because most children with MCNS respond to corticosteroid treatment, empiric treatment for children with classic clinical features of MCNS is often given without doing a kidney biopsy first.
- There is a much higher incidence of other types of NS in the non-Caucasian population groups in SA, in which case treatment should primarily be guided by the renal histopathology report.
- The diagnosis of haemolytic uraemic syndrome (HUS) is based on three criteria:
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