The glomerulonephritides

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Abstract

The glomerulonephritides are a group of disorders characterized by intraglomerular inflammation. The clinical presentation is variable, ranging from asymptomatic microscopic haematuria to sudden onset frank haematuria with rapidly deteriorating renal function. Proteinuria, oedema, and hypertension are often associated. The most common underlying aetiology is acute post streptococcal glomerulonephritis (APSGN). Other aetiologies include Henoch–Schonlein purpura (HSP), IgA nephropathy, juvenile systemic lupus erythematous (JSLE) and membranoproliferative glomerulonephritis (MPGN). Focussed clinical evaluation and investigations are key to establishing a timely diagnosis. Management and prognosis is dependent upon the underlying cause. APSGN and HSP nephritis require mainly supportive treatment and having excellent outcomes. In contrast, it is crucial to recognise and promptly refer children with rapidly progressive crescentic nephritis in order to preserve renal function.

Keywords children; glomerulonephritis; haematuria; hypertension; proteinuria

Introduction

Glomerulonephritis (GN) refers to an acute inflammatory condition of the kidneys mainly affecting the glomeruli. It is usually caused by an immunological trigger leading to an inflammatory response, involving proliferation of the glomerular tissue and damage to the basement membrane, mesangium or capillary endothelium. The clinical presentation is variable, ranging from asymptomatic microscopic haematuria to sudden onset frank haematuria with acute kidney injury (AKI). Proteinuria, oedema, and hypertension are also usually seen. Certain forms of GN require limited medical input on an outpatient basis, while others necessitate urgent, sometimes life-saving therapeutic intervention (see Box 1). The ability to promptly diagnose this condition using clinical history, examination, and focussed radiological and laboratory based tests is of vital importance.

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Epidemiology – incidence, UK and worldwide

GN represents around 10–15% of all childhood glomerular disease. GN is quite rare in infancy. The vast majority of cases are due to acute post streptococcal GN (APSGN) and Henoch–Schonlein purpura (HSP) nephritis, both of which commonly affect children aged 3–10 years. The true incidence of GN is unknown as, due to the subclinical nature of the APSGN in over half those affected, it is likely to be under-reported. The incidence of APSGN has fallen in the developed world; however it remains one of the main causes of acute kidney injury in the developing world and is associated with significant morbidity and mortality. North American data suggests GN accounts for around 13% of end-stage renal disease (ESRD) in children whereas in the UK, GN accounts for less than 5% of the childhood ESRD population.

Pathogenesis

The pathogenesis of glomerular injury, although not fully understood, involves both cellular and humoral immunity. In the humoral immune response antigens may bind to the antibodies locally in the glomerulus as happens in anti-glomerular basement membrane disease (anti-GBM). Alternatively, antigens become trapped within the glomerulus, such as streptococcal antigens in APSGN. Circulating immune complexes may also become trapped within the glomeruli. Cellular immunity involves activation of T cell lymphocytes and macrophages, leading to an inflammatory cascade involving the complement system, coagulation system and leucocyte recruitment.

The complement system can be activated by either the classical, lectin or alternative pathway. The route of activation can guide the clinician to the underlying diagnosis, e.g., alternative pathway activation leads to low serum C3 levels, but normal C4 and is typically seen in APSGN.

Initial assessment

Detailed history-taking, examination and focussed use of laboratory and radiological tests are the cornerstones of obtaining a quick and accurate diagnosis in cases of GN (see Box 2). In many cases, long-term prognosis is associated with initial clinical presentation, and certain signs/symptoms would necessitate early paediatric nephrology involvement (see Box 3).

History

Most children will present with either oedema or macroscopic haematuria. Oedema is usually mild and periorbital, but ankle and genital swelling can occur. Any recent changes in weight or urine output would be important to note. A preceding pharyngitis or pyoderma is suggestive of APSGN. Medications such as non-steroidal anti-inflammatory agents can cause AKI and therefore a detailed drug history is important to exclude alternative pathology. A family history of renal disease and deafness supports a diagnosis of Alport syndrome. Dysuria or loin tenderness suggests pyelonephritis or nephrolithiasis rather than GN. Resolved or current rashes could suggest either APSGN or systemic vasculitis. Any joint pain or neurological symptoms may point to the latter.

Etiology of glomerulonephritis

Primary causes of GN

- Acute post infectious GN (usually PSGN) — may follow Staphylococcal, Mycoplasma, *E. coli*, EBV, CMV, HSV, Hepatitis B and C as well as fungal or parasitic infection
- IgA nephropathy
- Membranoproliferative GN
- Focal segmental glomerulosclerosis
- Anti-glomerular basement membrane nephropathy
- Drug induced (e.g., ciclosporin, non-steroidal anti-inflammatory medication)

Systemic causes of GN

- Henoch–Schonlein purpura (IgA vasculitis)
- Systemic lupus erythematous
- Granulomatosis with polyangiitis
- Microscopic polyangiitis
- Alport syndrome
- Shunt nephritis
- Haemolytic uraemic syndrome

Box 1

Investigations of glomerulonephritis

Urinalysis

- Dipstick urine
- Urine microscopy and culture (to confirm haematuria and detect casts)
- First morning UPCR (indicate level of proteinuria)

Haematology

- Full blood count
- Peripheral blood film (if haemolytic uraemic syndrome suspected)

Renal function

- Serum urea, creatinine and electrolytes
- Serum albumin, bicarbonate, calcium and phosphate

Bacteriology

- Throat swab
- ASOT and DNase B titres

Immunology

- C3 and C4
- Immunoglobulins
- ANCA, ANA, dsDNA and anti GBM antibodies

Box 2

Examination

It is important to assess the degree of fluid overload by recording weight changes, examining the extent of the oedema, checking for a raised jugular venous pulse, hepatomegaly, cardiomegaly, bi-basal lung crepitations, and measuring blood pressure (BP). A full neurological examination may be warranted if suggested from the history or if hypertension is present.

Indications for referral to tertiary nephrology

Features necessitating paediatric nephrologist input ± renal biopsy

- Rapidly progressive glomerulonephritis
- Significant proteinuria
- Family history of glomerular disease
- Microscopic haematuria for more than 2 years
- Macroscopic haematuria for more than 3 months
- Persistent proteinuria (UPCR of more than 50 mg/mmol) for more than 6 months
- Oligo anuria/Impaired renal function
- Hypertension
- Low C3 for more than 3 months
- Positive ANA or ANCA
- Recurrent nephritis

Box 3

A patient presenting for the first time with symptoms of GN can be classed in one of the following four groups:

1. Acute GN

Sudden onset haematuria (macro or microscopic) with proteinuria ± oedema. There is normal or impaired renal function with or without the presence of hypertension. The most common cause is APSGN, but any cause of GN can present in this way.

2. Rapidly progressive GN (RPGN)

RPGN comprises acute nephritis accompanied by rapidly declining renal function over a period of days. The primary culprits are HSP nephritis, IgA nephropathy (IgAN), pauci-immune GN and anti GBM disease. Prompt diagnosis and urgent treatment is required to preserve renal function.

3. Recurrent episodes of macroscopic haematuria

Macroscopic haematuria is suggestive of an underlying diagnosis of IgAN or Alport's syndrome which is a basement membrane disease. In IgAN haematuria often presents a few days after an upper respiratory tract infection unlike PSGN where the history of respiratory infection is usually 1–2 weeks prior clinical presentation.

4. Chronic GN

Presentation is usually insidious with minimal symptoms. Microscopic haematuria and proteinuria are often discovered on routine urinalysis in asymptomatic patients. Due to the lack of symptoms in early stage disease there is often already renal impairment, biochemical disturbance and hypertension at presentation. This picture may be seen in membranoproliferative GN (MPGN), IgAN and juvenile systemic lupus erythematosus (JSLE).

Investigations (Box 2)

Urine should undergo dipstick testing for blood and protein. Urine microscopy is mandatory to confirm haematuria and leukocyturia. The presence of red cell casts strongly supports a diagnosis of GN. Renal function should be checked by measuring plasma urea, creatinine and electrolytes. As some patients will