Glomerulonephritis: is it worth worrying about?

Peter W Mathieson

ABSTRACT – Glomerulonephritis (GN) is a group of conditions characterised by inflammation in the filtering units of the kidney which may be 'primary'; secondary to drugs, infections or tumours; or the presenting feature of systemic disease. GN is treatable, causes significant morbidity and mortality, and is a potentially preventable cause of renal failure and cardiovascular risk. It can only be precisely identified and characterised by renal biopsy which is usually undertaken in specialist nephrology centres. The role of the non-specialist is to know when and how urgently a patient should be referred to such a centre. This review aims to provide guidance on when to suspect GN, how to investigate this possibility and when to refer for further investigation. Clinically urgent situations are highlighted. The importance of urinary abnormalities, particularly proteinuria (even if aysmptomatic and only detected on routine screening) is emphasised. Earlier recognition of GN will improve patient outcomes.

KEY WORDS: cardiovascular risk, glomerulonephritis, haematuria, nephrotic syndrome, proteinuria, renal failure

This article is based on a lecture given at the RCP Update in Medicine Meeting in Birmingham on 8 December 2004 by **Peter W Mathieson** FRCP, Professor of Renal Medicine, University of Bristol, Southmead Hospital, Bristol

Clin Med 2005;**5**:264–6

The term glomerulonephritis (GN) describes a group of conditions in which there is injury to the glomeruli, the filtering units of the kidney. My choice of title for this review was based on two aspects of my own personal experience. First, I remember when I was a medical student revising for my pathology examinations, I was daunted by the complex terminology associated with GN and decided that the subject was too esoteric to be a likely examination question. Therefore I felt it was 'not worth worrying about' and I omitted that section of my notes from my revision plans. Unfortunately for me, the final examination included an essay question on GN! Second, a friend of mine who is a general practitioner told me recently that she and her primary care colleagues are very concerned about GN as they realise that this is sometimes an urgent and important diagnosis to make. They routinely test urine samples in their surgeries and need guidance on when to suspect GN and how to react to the possibility that a patient has this condition. My aim here is to demystify GN, provide guidelines about when to suspect it, and give some general principles governing how to react to this diagnostic possibility. My answer to the question posed in the title is inevitably that YES, GN *is* worth worrying about, and I aim to provide guidance on when and how to turn the worrying to the patient's advantage.

Terminology

The obtuse terminology describing the various histological subtypes of GN is at least partly responsible for the perception that this is a complicated group of conditions, only understood by nephrologists in their ivory towers. However, the non-nephrologist should not be concerned about the detailed classification of GN. The different subtypes can only be identified accurately by renal biopsy: since this is only undertaken in specialist centres, the role of the generalist is to identify when and how urgently a given patient should be referred to such a specialist service.

One classification that *is* useful in clinical practice is illustrated in Table 1 and based on the fact that GN can occur as a primary entity or secondary to drugs, infections or tumours. Examples of drugs that can induce GN include non-steroidal anti-inflammatories and anti-rheumatic agents such as gold and penicillamine. In such cases, if the offending drug is stopped, the GN will resolve. Infections which are major causes of GN worldwide include hepatitis B and C and malaria. Here, the management should be directed to the underlying infection and if it can be eradicated the GN can be expected to improve. GN has been described as a complication of many different tumours but is most commonly associated with epithelial malignancies: again, if the underlying cause can be successfully treated the GN should

Table 1. Classification of GN.

Primary	
	– isolated GN, eg IgA nephropathy
	– as part of systemic disease, eg lupus
Secondary	
	– drugs, eg non-steroidal anti-inflammatories, gold, penicillamine
	– infections, eg hepatitis B, hepatitis C, malaria
	– tumours, eg bronchial carcinoma

resolve. In situations where there is no identifiable underlying cause, the GN is considered 'primary'. This can be an isolated condition, ie tissue injury is confined to the kidney, of which the most common type is IgA nephropathy (Berger's disease), or it can be part of a systemic inflammatory disease such as systemic lupus erythematosus or systemic vasculitis.

WHY is GN worth worrying about?

GN is a treatable cause of morbidity and mortality; an important cause of renal failure; a treatable cause of hypertension, hyperlipidaemia and increased cardiovascular risk; and also may be the presenting feature of serious systemic disease. Early diagnosis, including referral to a specialist centre, is key to preventing irreversible damage.

Nephrotic syndrome is the clinical syndrome associated with heavy proteinuria: its morbidity and mortality are due to tissue oedema, increased susceptibility to infection, a thrombotic tendency and hyperlipidaemia which may be severe and treatment-resistant.[1]

The UK currently has around 40,000 patients on renal replacement therapy, over 650 per million population, costing over £700 million per year, so that 2% of the NHS budget is spent on 0.1% of the population (figures from the UK Renal Registry). Most registries estimate that at least 10% of end-stage renal failure is due to GN. Hypertension and hyperlipidaemia are recognised cardiovascular risk factors: in adults, often no underlying cause will be found but these may be features of GN and attention to the underlying condition may be required before the cardiovascular risk can be improved.

GN may be the presenting feature of important systemic illnesses such as systemic vasculitis and systemic lupus erythematosus.

If GN is diagnosed, treatment[2] can be aimed at:

- reducing symptoms and signs, eg using diuretics and salt restriction for troublesome oedema, antihypertensives, lipid-lowering agents, possibly anticoagulants
- preventing/retarding progressive loss of excretory renal function
- targeting the underlying GN itself, often using corticosteroids, antimetabolites (eg azathioprine) or cytotoxic agents (eg cyclophosphamide).

WHEN is GN worth worrying about?

When proteinuria, with or without associated haematuria, is found it is important to consider GN. Quantification of proteinuria is important in assessing its significance (see below). Wider use of health screening, including dipstick urine testing for blood and protein, increases the likelihood of identifying GN at an asymptomatic stage. Patients with peripheral oedema should always have their urine tested, as should patients with 'premature' hypertension. Unexplained impairment of excretory renal function is an absolute indication for urine testing. Features such as an unexplained rash (especially if clinically or on biopsy it is vasculitic), inflammatory arthritis, troublesome nosebleeds, persistent upper airway/sinus inflammation or haemoptysis should all lead to urine testing, because if there is renal involvement in a systemic inflammatory condition this influences management.

Key Points

The terminology surrounding subtypes of glomerulonephritis (GN) is daunting but should not concern the non-nephrologist

The role of the generalist is to know when to suspect GN, how to further assess this diagnostic possibility, how to decide on referral to a renal unit, and how to assess clinical urgency

GN is a treatable cause of renal failure and of increased cardiovascular risk

Proteinuria on dipstick testing should always be quantified, ideally by urinary albumin:creatinine ratio

Proteinuria of ++ strongly suggests GN and is unlikely to be explained by urinary infection: simply sending a mid-stream urine sample is not adequate

If there is proteinuria, this should be quantified. Urinary dipsticks are semi-quantitative: a trace or even 1+ of proteinuria may be normal, especially in upright posture, with fever or after exercise; 2+ or more of proteinuria is pathological. A positive reaction for protein on a urinary dipstick should be followed by quantification, ideally by albumin/creatinine ratio. This can be performed on a random untimed urine sample: expression as the ratio corrects for urinary concentration. We now rarely ask patients to perform timed urine collections since these are notoriously inaccurately performed. An albumin/creatinine ratio of greater than 10 is abnormal; if it is greater than 100 the patient has heavy albuminuria and is likely to have GN until proven otherwise. A dipstick test showing proteinuria of 2+ or greater implies glomerular disease and is very unlikely to be explained by infection: sending off a mid-stream urine sample to check for urinary infection is not an adequate response to the finding of heavy proteinuria.

Macroscopic haematuria is more likely to have a urological cause than a nephrological one: the exception is so-called synpharyngitic haematuria when the patient develops macroscopic haematuria at the time of a throat infection (or indeed any other acute infection): this is virtually diagnostic of one of the more common forms of GN, IgA nephropathy.[3] Simple urine microscopy can reveal casts, tubular-shaped structures comprised of cell debris and/or intact cells, a sign of cell damage in the kidney and therefore suggestive of a renal cause for haematuria. If proteinuria is associated with haematuria, a renal cause is likely and initial investigation should be nephrological.

Excretory renal function can be assessed by measuring plasma or serum creatinine. Creatinine is released from turnover of muscle cells and excreted by the kidney. Creatinine production varies with muscle mass, so ideally the measurement of creatinine should be corrected for age, gender and body mass and

expressed as a calculated creatinine clearance. No urinary measurements are required. Several formulae are available for correction of plasma creatinine, and many laboratories will now report a calculated creatinine clearance if they are given details of body weight, age and gender. The 'gold-standard' test of excretory renal function is an isotope clearance study, usually with chromium-labelled ethylenediaminetetraacetic acid (EDTA), but these are expensive and cumbersome so they are rarely used in routine clinical practice.

Serial measurements of plasma/serum creatinine and/or calculated creatinine clearance are most useful: changes within the normal range are significant and can indicate important loss of renal function.

WHAT should you do when GN is suspected?

You should decide, using history, examination and simple investigations, whether there is evidence to support your suspicion of GN. The aim is to decide whether to refer the patient for a specialist opinion, and if so, how urgently.

From the history: have there been urinary abnormalities such as frothiness (indicating the presence of protein), dark urine or visible blood, or markedly reduced urinary volume? Have there been any systemic symptoms such as fever, rash, joint pain or swelling, red eyes, nasal/sinus or other respiratory symptoms? How long have any symptoms been present?

From clinical examination: blood pressure, oedema, systemic features.

From simple investigations: dipstick test of urine for blood and protein, urine microscopy for casts. Quantify proteinuria if present by sending random urine sample for albumin/creatinine ratio. Assess excretory renal function by plasma creatinine and if possible calculated creatinine clearance; compare with any previous readings.

Further laboratory tests which are useful to exclude systemic diseases include ANCA (anti-neutrophil cytoplasm autoantibody, typically positive in systemic vasculitis);[4] serological tests for systemic lupus erythematosus (serum complement C3 and C4, antinuclear and/or anti-double stranded DNA antibodies); screening tests for myeloma (serum immunoglobulin electrophoresis, urinary Bence-Jones protein).

The information obtained should be used to decide on the need for specialist referral and the degree of urgency: if there is evidence of progressive loss of excretory renal function then referral to a renal unit is urgent. *If in doubt, refer!* Most renal physicians will be happy to discuss patients over the telephone or by email. Helpful information to convey to the nephrologist includes measurements of excretory renal function, ideally including previous values; quantification of proteinuria, information on urine microscopy; and simple kidney imaging, eg by ultrasound, to assess renal size/symmetry and to exclude obstruction as a cause of renal impairment.

Conclusions

GN is important because it is treatable, causes significant morbidity and mortality, and is a preventable cause of renal failure and cardiovascular risk. GN should be suspected in any patient with oedema and/or hypertension and/or impairment of excretory renal function; also in any patient with proteinuria with or without haematuria.

Clinical suspicion of GN should lead to simple investigations of urine and blood to support the possibility and decide on urgency of referral.

References

1 Bernard D. Extra-renal complications of the nephrotic syndrome. *Kidney Int* 1988;**33**:1184–202.

2 Mathieson PW. Treatment of glomerulonephritis. In Weber J (ed), *Horizons in medicine,* Vol 15. London: Royal College of Physicians, 2003:13–21.

3 Nolin L, Courteau M. Management of IgA nephropathy: evidence-based recommendations. *Kidney Int Suppl* 1999;**70**:S56–62.

4 Kamesh L, Harper L, Savage CO. ANCA-positive vasculitis. *J Am Soc Nephrol* 2002;**13**:1953–60.