Post-Infectious Glomerulonephritis

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1. Introduction

This chapter will provide a comprehensive review of post-infectious glomerulonephritis focusing in particular on the changing epidemiology and long term outcome.

The immunological response of the kidney to an insult results in glomerulonephritis. The insult can result from a large number of conditions, both infectious and non-infectious. Regardless of the initial insult, the outcome is similar in terms of pathology and clinical symptoms. The most common and most-studied cause is post streptococcal Glomerulonephritis (PSGN). A list of causes is presented in Table 1.

INFECTIOUS
Bacterial: *Streptococcal (PSGN)*, methicillin-resistant *Staphylococcus aureus* (MRSA), pneumococcal pneumonia, typhoid, secondary syphilis, meningococcemia, infective endocarditis, shunt nephritis, sepsis
Viral: Hepatitis B, infectious mononucleosis, mumps, measles, varicella, vaccinia, echovirus, parvovirus, and coxsackievirus
Parasitic: Malaria, toxoplasmosis
Fungal: cryptococccus imitis

NON INFECTIOUS
Primary glomerular diseases: Membranoproliferative GN (MPGN), IgA nephropathy, mesangial proliferative GN
Multisystem systemic diseases: Systemic lupus erythematosus, vasculitis, Henoch-Schönlein purpura, Goodpasture syndrome, Wegener granulomatosis
Miscellaneous: Gullian-barre syndrome, pertussis-tetanus vaccine, serum sickness

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Table 1. Causes of post-Infectious Glomerulonephritis

2. Burden of disease and changing epidemiology

Of all the bacterial pathogens, group A streptococcus (GAS) causes the widest range of illness in humans. These illnesses range from local infections of the skin and throat (impetigo and pharyngitis respectively) to invasive infections as well as the significant post-infectious immunological sequelae such as the well documented acute rheumatic fever and acute post-streptococcal glomerulonephritis and the lesser known PANDAS (Paediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcus) [1].

While global estimates of the burden of disease due to GAS infections are difficult to get, some estimates have been reported which are based on published population studies. The estimate of 500 000 deaths per year due to GAS makes it a major human Pathogen [2]. This minimal estimate places GAS infections as less common than HIV, *Mycobacterium tuberculosis*, *Plasmodium falciparum* and *Streptococcus pneumonia* but as common as rotavirus, measles, *Haemophilus influenzae* type b and hepatitis B as a cause of global mortality [2]. In addition there is the long-term morbidity associated with GAS infections.

The global burden of severe group A streptococcal disease is concentrated largely in developing countries and within disadvantaged populations living in developed countries such as Aboriginal Australians. The review of population based studies estimated the prevalence of severe GAS disease at a minimum of 18·1 million cases, with 1·78 million new cases each year [2]. The greatest burden was due to rheumatic heart disease, with a prevalence of at least 15·6 million cases, with 282 000 new cases and 233 000 deaths each year. The burden of invasive GAS diseases was found to be unexpectedly high, with at least 663 000 new cases and 163 000 deaths each year. In addition, there were more than 111 million prevalent cases of GAS pyoderma, and over 616 million incident cases per year of GAS pharyngitis [2]. The review estimated that over 470 000 cases of acute post-streptococcal glomerulonephritis occur annually, with approximately 5000 deaths (1% of total cases), 97% of which were in less developed countries [2].

The global incidence of acute PSGN was estimated at 472,000 cases per year, of which 456,000 (96.6%) occurred in less developed countries [3, 4]. A similar distribution of higher incident cases in less developed countries is also reported in a review of population based studies [2]. A review of 11 population-based studies documenting the incidence of acute PSGN in children from less developed countries or those that included substantial minority populations in more developed countries, estimated 24·3 cases per 100,000 person as the median PSGN incident rate [2]. The same review estimated an incidence in adults of 2 cases per 100,000 person-years for developing countries and 0.3 per 100,000 person-years in developed countries [2]. Due to the paucity of data in adults with PSGN, the estimate for developing countries was based on data from Kuwait and for developed countries on data from Italian Biopsy Registry and the most conservative estimates were reported [2]. Another recent study described a slightly higher incidence of 9.5-28.5 cases per 100,000 person-years in developing countries [5]. These rates represent only the clinical cases. When asymptomatic cases are screened for in household contacts and family members, asymptomatic disease is reported to be 4-19 times greater [5-7].

PSGN can occur sporadically or epidemically. The changing pattern of PSGN over the last few decades has been described in studies from Florida [8] and Singapore [9]. The overall incidence of PSGN has decreased over the last few decades [10]. The reasons for this decline have not been clearly delineated but possible reasons are the widespread use of antibiotics, changes in etiological pathogens, altered susceptibility of the host, better health care delivery and improved socioeconomic and nutritional conditions [8-10]. Nevertheless, epidemics and clusters of cases continue to appear in several regions of the world and sporadic cases of PSGN account for 21% (4.6–51.6%) of children admitted to the hospital with acute renal failure in developing countries [5]. Although epidemic PSGN has decreased dramatically and is almost unknown in the developed world, epidemics of PSGN continue to occur in the developing world, mainly in Africa, West Indies and the Middle East, as well as in Indigenous people living in the developed world [11]. Epidemics are described mainly in "closed" communities, clusters of densely populated

dwellings or areas with poor hygienic conditions, both urban and rural. These conditions are especially prevalent in Aboriginal peoples of Australia living in remote communities, in settings with a high burden of infectious disease and overcrowding [11, 12]. Sporadic cases of PSGN occur in the Northern Territory of Australia each year with outbreaks every 5-7 years [13]. PSGN in New Zealand occurs mostly in children of Pacific Island and Maori heritage (>85% of cases) [14]. Sporadic cases of PSGN also continue to be reported from all over the world.

The rates are higher in children than in adults, and PANDAS is described solely in the paediatric age group. PSGN primarily affects children, aged 2-12 years, with clinically detectable cases estimated to be 10% of children with pharyngitis and up to 25% of children with impetigo during epidemics [15, 16]. Children account for 50-90% of epidemic cases, with 5-10% occurring in people > 40 years and 10% in those below 2 years of age [5]. PSGN is uncommon below 3 years of age and rarely seen below 2 years [17]. This low incidence of PSGN is likely to be due to the decreased immunogenicity of children below 2 years of age, for although GAS pharyngitis is uncommon in children of this age, GAS skin infections are common. Decreased immunogenicity likely results in less robust immune complex formation thus leading to less PSGN [18].

Males have more symptomatic disease, but this difference is no longer present when symptomatic and asymptomatic cases are considered together [19]. Spontaneous recovery occurs in almost all patients, including those who develop renal insufficiency during the acute phase [16], with 1% of all paediatric patients developing renal insufficiency.

There are no large scale published studies of bacterial infections associated with GN other than streptococcal infection. These are limited to small cases series and individual cases reports. The most common of these are related to staphylococcal infections, both methicillin sensitive [20] and methicillin resistant [21, 22]. A case series of 10 cases, age range 21-65 years, of MRSA-associated glomerulonephritis reported polyclonal increases of IgA and IgG and massive T cell activation and suggested the role of the enterotoxin as a bacterial super-antigen initiating the immunological response leading to the glomerulonephritis [22]. The histopathologic findings on immunofluorescence in the patients with MRSA infection with nephritis resemble those seen in IgA nephropathy [22]. Nephritis associated with endocarditis and ventricular shunts is associated with staphylococcal infection [22]. A number of infections can cause nephritis as listed in table 1. Most have been reported as case reports, such as a report of nephritis following malaria due to *falciparum vivax* infection in a 7 year old girl [23], and a report of nephritis following pneumococcal pneumonia in an adult male [24].

Hepatitis-B-associated glomerulonephritis (HBGN) is a distinct entity occurring frequently in hepatitis-B-prevalent areas of the world. The disease affects both adults and children who are chronic hepatitis-B-virus (HBV) carriers with or without a history of overt liver disease. The diagnosis is established by serologic evidence of HBV antigens/antibodies, presence of an immune complex glomerulonephritis, immunohistochemical localization of 1 or more HBV antigens and pertinent clinical history [25]. With the high incidence of hepatitis B in Asia, this entity assumes a greater public health importance. A study from China reported 205 cases from a single hospital from September 1995 to November 2008 [26]. In this series, the peak incidence of HBV-GN was between 20 -40 years of age, with a 3:1 predominance of males. The most common clinic manifestation was nephrotic syndrome and the most common pathology was membranous nephropathy. Decreased renal function was present in 10% of cases. The degree of albuminuria correlated with the viral load [26].

Renal disease is not uncommon in those infected with HIV. The most common manifestation of HIV in the kidney is HIV-associated nephropathy (HIVAN). Immunotactoid glomerulonephritis is a rare disorder found in 0.06% of renal biopsies characterized by organized tubular immune complex deposits. This is seen more commonly Caucasians and tends to occur in an older age group. There are 6 reported cases of HIV associated immunotactoid glomerulonephritis [27].

3. Pathogenesis

The kidney has a limited number of ways of responding to injury. Similar pathological signs may be the end result of different processes, produced by different initiating mechanisms and different molecular pathways may perpetuate the injury process. The initiation and development of the inflammatory response of the kidney to infection are still poorly understood.

The pathognomonic feature of PSGN is the deposition of immune complexes in the glomerular basement membrane. A proposed sequence of events is that a nephritogenic antigen(s) leads to the activation of the complement pathway and/or activates plasmin or production of the circulating immune-complexes. These then lead to increased permeability of the glomerular basement membrane, which allows deposition of the immune complexes, and leakage of the protein and red blood cells. The nephritogenic antigen is responsible for the C3 deposition, the recruitment of immune cells, tissue destruction and IgG deposition which further aggravates tissue injury. Complement activation leads to the release of cytokines, such as C5a, which attracts phagocytes, and proliferation of intrinsic cells and formation of a membrane attack complex which also aggravate the process. The definitive nephritogenic antigen has not yet been defined, although a large number of streptococcal factors (M proteins) have been proposed as the triggering factor. M proteins are present on the pili of the organism and more than 100 have been identified so far. Nephritogenic M proteins are types 1, 2, 4, 3, 25, 49, and 12 following skin infections and types 47, 49, 55, 2, 60, and 57 following throat infections [28]. Infections with nephritogenic streptococci have considerable variability in their ability to cause nephritis. The reason for this variability is not known.

Pathology shows typical glomerular changes which include proliferation of mesangial, endothelial and epithelial cells, inflammatory exudate and deposition of C3 early in the disease process followed by deposition of IgG. This immune deposition has been classified into 3 patterns [29]. The "starry sky" pattern represents an irregular and finely granular deposit of C3 and IgG along the glomerular capillary walls and in the mesangium. This occurs early in the course of the disease and is also seen in subclinical cases [28, 29]. The "mesangial pattern" has mainly C3 and some IgG in the mesangium. The "garland pattern" shows dense deposits along the capillary walls, is commonly associated with severe proteinuria and a poor prognosis [28, 29].

The immunological response of the kidney to an insult results in glomerulonephritis. The causal factors that underlie acute GN can be broadly divided into infectious and noninfectious groups. The most common infectious cause of acute GN is infection by *Streptococcus* species (ie, group A, beta-hemolytic). Nonstreptococcal postinfectious GN may also result from infection by other bacteria, viruses, parasites, or fungi. Bacteria besides group A streptococci that can cause acute GN include diplococci, other streptococci, staphylococci, and mycobacteria. *Salmonella typhosa*, *Brucella suis*, *Treponema pallidum*, *Corynebacterium bovis*, and actinobacilli have also been identified.

In the absence of evidence of a recent group A beta-hemolytic streptococcal infection, infections with Cytomegalovirus (CMV), coxsackievirus, Epstein-Barr virus (EBV), hepatitis B virus (HBV) [30], rubella, rickettsiae (as in scrub typhus), and mumps virus may be accepted as causal organisms. Similarly, attributing glomerulonephritis to a parasitic or fungal etiology requires the exclusion of a streptococcal infection. Possible organisms are *Coccidioides immiti, Plasmodium malariae, Plasmodium falciparum*, *Schistosoma mansoni*, *Toxoplasma gondii*, filariasis, trichinosis, and trypanosomes. While hepatitis B infection has been well documented as a cause of renal involvement and glomerulonephritis [25, 26], acute GN is as a rare complication of hepatitis A [31].

Noninfectious causes of acute GN may be divided into primary renal diseases, systemic diseases, and miscellaneous conditions or agents. The primary renal diseases are membranoproliferative glomerulonephritis (MPGN), IgA nephropathy and mesangial proliferative glomerulonephritis. Multisystem systemic diseases that can cause acute GN are vasculitis such as Wegener granulomatosis, polyarteritis nodosa and hypersensitivity vasculitis, collagen-vascular diseases like systemic lupus erythematosus (SLE) which causes glomerulonephritis through renal deposition of immune complexes, Henoch-Schönlein purpura and Goodpasture syndrome. Miscellaneous noninfectious causes are Guillain-Barré syndrome, Diphtheria-pertussis-tetanus (DPT) vaccine and serum sickness. These are summarised in table 1.

It is important to identify the exact aetiology of the glomerulonephritis as the prognosis differs widely depending on the underlying cause. There are a number of clinical and laboratory features that may help to differentiate between or even point to a particular cause of glomerulonephritis. The latent period between infection and nephritis is helpful in differentiating PSGN from IgA nephropathy. In contrast to the latent period of 2-3 weeks seen in PSGN, the nephritis of IGA nephropathy may occur either at the same time or just 1-2 days after an upper respiratory infection. Similarly, patients with nephritis of chronic infection have an active infection at the time nephritis becomes evident. Despite the chronic nature of the underlying infection, the associated nephritis can present acutely. Circulating immune complexes play an important role in the pathogenesis of acute GN in these diseases.

The failure of the C3 levels to return to normal should prompt consideration of the possibility of MPGN or SLE as the underlying cause. MPGN is a chronic disease which can manifest with an acute nephritic picture. Gross haematuria is unusual in lupus nephritis. Other associated systemic findings may identify the underlying systemic disease, for example, vasculitic lesions of the lower extremities point to an underlying vasculitis as the cause of glomerulonephritis.

4. Clinical presentation

The typical presentation is the abrupt onset of acute nephritis occurring 1-3 weeks after a streptococcal throat infection and 3-6 weeks after skin infection [28]. The nephritis is characterised by the triad of oedema, gross haematuria, and hypertension. The classical presenting feature is the presence of "coca-cola" coloured urine which is characteristic of homogenous gross haematuria [32]. Other common features are facial puffiness and hypertension secondary to fluid overload and urinary abnormalities such as albuminuria and the presence of red cell casts. General features like malaise, weakness, and anorexia may occur in about half the patients and a minority complain of nausea and vomiting. Within a

week or so from onset of symptoms, most patients with PSGN begin to experience spontaneous resolution of fluid retention and hypertension and the urine abnormalities begin to subside. The low C3 levels begin to rise and normalise by 8 weeks. Normal urine findings are found by 12 weeks.

Microscopic haematuria is universally present. Of the triad of features, oedema is seen in 85% of cases and is often the presenting symptom, gross haematuria in 40% of cases (range 30-50%) and hypertension in 50-95% of hospitalised cases. Approximately 95% of clinical cases have at least 2 manifestations, and 40% have the full-blown acute nephritic syndrome. The puffiness of the face or eyelids is sudden, usually prominent upon awakening and tends to subside at the end of the day if the patient is active. The oedema is a result of a defect in renal excretion of salt and water leading to fluid overload. The severity of edema does not correlate well with the degree of renal impairment.

In most cases, urinary abnormalities clear by 12 weeks, although proteinuria may persist for 6 months to 3 years and microscopic haematuria from 1 year to 4 years after the onset of nephritis [33]. In some cases, generalized edema and other features of circulatory congestion, such as dyspnea, may be present.

Accompanying this clinical picture is laboratory evidence of streptococcal infection, typically increasing antistreptolysin-O titers (ASOT) or streptozyme titres following throat infections and anti-DNase B titers following skin infections. Complement levels are decreased; low C3 levels are found in almost all patients with acute PSGN and C4 levels may be slightly low. These low levels of C3 usually normalize within 8 weeks after the first sign of PSGN [34], although up to 12 weeks has been reported [33]. The typical accompanying histopathology is one of diffuse cellular proliferation in the glomerulus, an exudate containing neutrophils and monocytes and variable degrees of complement and immunoglobulin deposition. In most cases, hypertension subsides, renal function returns to normal and all urinary abnormalities eventually disappear [33].

There is, however, a wide variation in the clinical presentation as well in the histopathology associated with PSGN. At the severe end of the spectrum is a rapidly rising azotemia with a rapidly progressive nephritic picture associated with severe cell proliferation, massive exudates and crescent formation in biopsy specimens. This is seen in <5% of PSGN cases [19]. The severity of renal failure tends to be directly related to the degree of proliferation and crescent formation, and about 50% of these patients recover renal function [35]. This type of presentation is more common in the elderly. The mild end of the spectrum, represented by subclinical or asymptomatic glomerulonephritis, is more common. Diligent examination of people with acute, trivial or self-limited infections caused by a range of organisms including various bacteria, parasites or viruses reveal subclinical infection in the form of microscopic hematuria, proteinuria and pyuria. Histopathology reveals mesangial proliferation with mesangial deposits of C3 and IgG deposits [19]. Asymptomatic household contacts of PSGN cases show sub-clinical disease 4-5 times more commonly than the acute classical presentation [6, 36]. An older study puts the ratio of asymptomatic cases as high as 19:1 [7].

5. Typical findings on investigations

Urinalysis reveals haematuria in all patients and proteinuria (from trace to 2+ on dipstick testing) is usually present. Proteinuria may be in the nephrotic range and is usually

associated with more severe disease. Red blood cell casts are pathognomonic of acute glomerulonephritis. Occasionally other cellular casts and pyuria are present.

Serological evidence of an antecedent streptococcal infection is present in the form of raised ASOT (> 200 IU/ml) and increased anti-DNAse B (which is a better serological marker of preceding streptococcal skin infection). Bacteriological evidence of streptococcal disease may be present in throat or skin swabs.

Complement levels especially C3 are low at the onset of symptoms. C4 is usually within normal limits in post-streptococcal GN. Causes of nephritis with low complement besides PSGN are MPGN, SLE, cryoglobulinemia, Diabetes Mellitus and Hepatitis C Virus. These diseases should be screened for in case of either an atypical presentation or atypical clinical course of the glomerulonephritis.

Renal function tests, blood urea, sodium, potassium and serum creatinine may be elevated in the acute phase and reflect the decrease in the glomerular filtration rate that occurs at this time. These elevations are usually transient. Failure of renal function tests to normalize within several weeks or months suggests that the patient may not have PSGN and indicates the need to seek an alternative diagnosis by further investigation. The full blood count may show anaemia which is usually dilutional and will return to normal once the fluid overload resolves.

Renal ultrasound is not required to make a diagnosis of glomerulonephririts. Renal ultrasound images usually reveal normal-sized kidneys bilaterally. Renal imaging is often done to confirm that there are two kidneys and that they are structurally normal. It may be done as a prelude to a renal biopsy. PSGN is a clinical diagnosis and requires the detection of glomerulonephritis and evidence of preceding streptococcal infection. A renal biopsy is indicated in cases with an atypical presentation, an atypical course, persistence of clinical features, or a persisting low level of complement (C3) or abnormal renal function tests. Features that suggest a diagnosis other than PSGN in the early stages may also indicate a need for a biopsy. These include the absence of the latent period between streptococcal infection and acute glomerulonephritis, anuria, rapidly deteriorating renal function, normal serum complement levels, lack of rise in antistreptococcal antibodies, general symptoms of systemic disease and either persistent hypertension or lack of improvement in glomerular filtration rate for more than 2 weeks. In the recovery phase, persistent low C3 beyond 8 and definitely beyond 12 weeks from the onset of illness would indicate a need to look for alternate causes and for a renal biospsy.

6. Treatment

Treatment of PSGN remains largely supportive. Complete recovery occurs in over 90% of children, but only 60% of adults fully recover. The rest develop hypertension or renal impairment.

Treatment is directed towards monitoring the signs and symptoms, in particular facial puffiness and hypertension, the main cause of which is fluid overload. Treatment when it is required, is mainly directed towards managing the fluid overload, which is responsive to diuresis and sodium restriction. Effective diuresis reduces cardiac congestion and controls hypertension and in most cases no further treatment is required. Strict input-output monitoring is recommended during the acute phase.

As the hypertension is caused by fluid overload, loop diuretics are the first line treatment and may be adequate for control of hypertension. Furosemide in a dose of 40 mg either

orally or intravenously is given 12 hourly. Usually treatment is required for less than 48 hours. Sometimes other anti-hypertensive agents may be needed, especially when the blood pressure is very high and it is unsafe to wait for the effect of diuretic therapy. Nifedipine is then given every 4-6 hours in doses of 5-10 mg. Rarely parenteral hydralazine may be required. Captopril has shown to be effective [37, 38] but should be used in caution in the presence of renal failure and hyperkalemia. Occasionally acute renal failure requires dialysis. Pulmonary oedema may be complication of severe fluid overload and needs urgent treatment.

It is important to check serum complement levels 6-8 weeks after initial testing to make sure they have returned to normal. Blood pressure should be monitored every month for 6 months and then 6 monthly. Renal function tests and serum creatinine levels repeated every 3 months after the acute phase for 1 year and then yearly after that. Urine should be checked for hematuria and proteinuria every 3-6 months.

Aggressive therapy using pulse methyprednisolone has been used in adults with poor prognostic factors such as nephritic range proteinuria, cellular crescents on biopsy and renal insufficiency [39]. Plasmapharesis and pulse methyprednisolone was successfully used in a 6 year old girl with garland pattern PSGN [40]. Whether this would benefit all patients with poor prognosis has not been studied.

Penicillin treatment is given to treat any persisting streptococcal infection [41]. Methicillin resistant staphylococcus should be treated with appropriate antibiotics. Specific infections require treatment with specific antibiotics or antiviral agents. Treatment of the underlying infection may resolve the glomerulonephritis as well. A review of six trials (a total of 159 patients) of which five were specified as hepatitis B virus-associated membranous glomerulonephritis (HBV-MN) showed that antiviral therapy for hepatitis B infections including IFN and lamivudine is effective in leading to remission of proteinuria, HBeAg clearance, and HBV-DNA reduction in both children and adults [42].

7. Preventing spread

A case of PSGN has 2 or more of the following clinical manifestations: oedema, macroscopic hematuria or dipstick hematuria of ≥ 2, or diastolic blood pressure of >80mmHg if ≤ 13 years of age and >90 mmHg if >13 years of age, in the presence of a reduced complement level (C3) and evidence of streptococcal infection by either elevated ASO or anti-DNAse B titres or positive cultures of GAS from skin, if sores are present, or from the throat in the absence of skin sores.

There is evidence that outbreaks can be halted by treating all children with any evidence of skin sores with intra-muscular (IM) benzathine penicillin to stop the transmission of the bacteria in the community [43]. In experimental PSGN, the nephritic process is prevented if penicillin is given within 3 days of the streptococcal infection [41]. Prevention of epidemics requires the control of spread of skin sores and infected scabies [44]. Following the identification of a case(s), family and household members are screened for the presence of skin sores and scabies and tested for urinary abnormalities. Those with skin manifestations are treated with penicillin. Those with urinary abnormalities undergo complete investigation for PSGN including urea, electrolytes, C3, ASO, anti-DNAse B and cultures for streptococcal infection.

Prevention of epidemics of PSGN requires a community level control of skin sores and infected scabies. Promotion of regular washing, especially of children, will prevent spread.

Improvement in housing, especially reduction in overcrowding, will hinder spread of infectious disease. The significant decline in PSGN in Singapore children is attributed to an improvement in the socioeconomic status, the health care system and urbanization of the country [9].

Although research into the development of a vaccine is advanced and 3 GAS vaccines have been approved for phase 1 human trials [45], it is unlikely to be available in the near future.

8. Prognosis

In keeping with the clinico-pathological picture, the prognosis of PSGN is also extremely variable, and largely influenced by clinical presentation and histopathology. An episode of PSGN may result in complete recovery, progression of symptoms or progression to renal failure. Persistence of symptoms may represent either a slow recovery, limited injury without further progression or progression to renal failure.

The immediate prognosis is generally good. In general, children are believed to have an excellent prognosis with the majority showing complete recovery [5]. Fewer than 1% of children have elevated serum creatinine values after 10-15 years of follow-up. Adults have a poorer prognosis overall. Early mortality can be as high as 25% in the elderly who have congestive cardiac failure or azotemia in the early phase. In adults approximately 25% will progress to chronic renal failure. These are usually those with massive proteinuria which suggests a worse prognosis and often signifies the garland pattern of immune deposits on pathology.

It is difficult to predict the prognosis in an individual case particularly early in the disease. While a typical presentation and clinical course indicates a good prognosis and an atypical presentation, severe persistent hypertension and abnormal renal function tests, massive proteinuria and older age group suggest a poor prognosis, there is a lack of a clinical or biochemical marker that might differentiate those with a good prognosis from those with a poorer outcome. Neutrophil gelatinase-associated lipocalin (NGAL), is emerging as a promising biomarker of acute kidney injury [46, 47], but has not yet been evaluated in PSGN.

However, some studies have reported persistent urinary abnormalities [8, 11, 19, 48, 49] and subtle abnormalities in renal function, as defined by reduction in renal functional reserve, in patients who had recovered from PSGN without apparent sequelae [50]

Epidemic cases have a better prognosis than sporadic cases [14, 51, 52], but not always. An outbreak of PSGN in Brazil following an epidemic of *Streptococcus equi zooepidemicus* resulted in a high prevalence of renal abnormalities at a mean follow-up of 5.4 years [53, 54]. These were, however, mainly adult patients. A study of Iranian children has shown that even mild PSGN may result in impaired renal function and that a rising diastolic blood pressure may be an early sign of worsening renal function [55].

Elderly people have poorer outcomes as do those with co-morbidities, including diabetes, cardiovascular and liver diseases [5, 28]. In an Aboriginal population with high rates of ESRD, follow-up of children 6-18 years (mean 14.6 years) after epidemic PSGN showed that risk of overt proteinuria was 6 times (95% CI 2.2-16.9) greater than in healthy controls after adjustment of age, sex and birth weight [11, 56]. The Australian Aboriginal population is at considerably higher risk than the general Australian population of developing chronic diseases such as diabetes mellitus, cardiovascular and renal diseases. There is also a greater burden of infectious disease and adverse early life factors such as low birth and infant weights. It is proposed that in this high risk population with multiple adverse renal

influences, childhood PSGN might be a more important risk factor for ESRD than it would be in lower risk populations [11, 44, 57].

9. References

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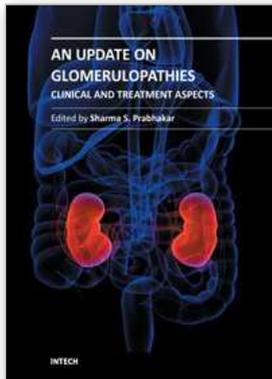
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