Internal Medicine: Open Access

Xia et. al, Intern Med 2015, 5:4
DOI: 10.4172/2165-8048.1000196

Research Article Open Access

# Clinical Characteristics and Etiologic Analysis of Scabies-Associated Glomerulonephritis

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**Received date:** June 19, 2015, **Accepted date:** July 08, 2015, **Published date:** July 16, 2015



## Abstract

**Objective:** Scabies-associated glomerulonephritis (SGN) is often seen in certain populations, but little is known about its incidence, clinical characteristics, prognosis and pathogenesis.

**Methodology:** 376 patients with scabies were enrolled and divided into scabies-alone group (group A) and SGN group (group B) based on the presence or absence of glomerulonephritis. Clinical indicators and various biomarkers, including serum C-reactive protein, complement components C3 and C4, immunoglobulin, TNF-α, IL-6, IL-1β, and IL-18 in the early stage of the disease, were determined before and after treatment. All patients were follow-up in the clinic.

**Results:** 16 scabies patients developed SGN in this study. The clinical manifestations included glomerular hematuria and/or mild-moderate proteinuria. The manifestations associated with kidney injury in most of these patients completely resolved 2-6 months after scabies was cured. Compared to the patients in group A, the levels of serum CRP, IgG, TNF-α, IL-6, and IL-18 increased significantly and the serum C3 level decreased significantly in the patients in group B. Twelve patients with SGN achieved a clinical cure. Compared to the early stage of the disease, the levels of serum IgG, hs-CRP, TNF-α, IL-6, and IL-18 in these patients decreased significantly after being cured, and the serum C3 level increased significantly.

**Conclusions:** SGN is generally mild and has a good prognosis. The mechanisms may involve the generation of specific antibodies stimulated by itch mites, triggering of excessive immune and inflammatory responses.

**Keywords:** Scabies; Acute glomerulonephritis; Prognosis; Pathogenesis; Cytokines

## Introduction

Scabies is a contagious skin disease caused by itch mites. The symptoms of scabies include pruritus, papulae, papulovesicles, and secondary cutaneous infections. Substantial evidence indicates that scabies is a risk factor for developing acute glomerulonephritis: the distribution areas of high prevalence of scabies overlap that of high incidence of acute glomerulonephritis [1]; a rising prevalence of scabies over time was paralleled by an increasing incidence of acute glomerulonephritis [1-3]; seasonal variation in the occurrence of scabies was followed by similar patterns in patients newly diagnosed with acute glomerulonephritis [3,4].

Furthermore, the induction of glomerulonephritis by scabies is not uncommon, especially in certain populations, such as some students and migrant workers in rural and remote cities.Scabies is strongly associated with poverty and overcrowding [5,6]. Our study aimed at profiling the incidence, clinical characteristics, outcomes, and pathogenesis of Scabies-associated glomerulonephritis (SGN) to provide scientific guidelines for the prevention and therapy of this disease.

## Patients and Methods

### Patients

Three hundred seventy-six scabies patients (321 males and 55 females) who were diagnosed and treated in our hospital between June 2012 and September 2014 were included in this study. The average age of the patients was 23.4 ± 4.5 years. All patients were diagnosed by mites testing. The patients had no history of kidney diseases or injuries before the onset of scabies and the potential diseases which likely lead to acute kidney injuries were also excluded. The patients signed informed consent documents at the time of enrollment in the study and were divided into scabies-alone (group A) and SGN groups (group B) according to the routine urinalyses and renal function test results. The patients received long-term treatment and follow-up in the clinic. This study was approved and monitored by the Ethics Committee of our hospital.

### Collection of the general clinical information

The following information was collected and recorded: age; gender; time of onset of scabies; blood pressure; and a history of fever, pharyngalgia, cough, and other prodromal symptoms of infection within 4 weeks of the initial evaluation.

### Treatment and follow-up

The patients were administered 10% sulfur ointment for treating scabies after the diagnosis was established. Antibiotics were administered to the patients who developed local infections or had an abnormal increase in the WBC count. Other treatments, including diuresis, ACEIs or ARBs for controlling blood pressure or proteinuria, and anticoagulation, were offered based on the specific needs of the patients. All patients received regular outpatient follow-up. The endpoints of follow-up in group A included complete recovery of the skin damage caused by scabies and inexistence of previous symptoms (e.g., pruritus) in three serial follow-up visits. For patients in group B, clinical cure of scabies and glomerulonephritis was achieved, which was confirmed by three serial follow-up visits. The manifestations of kidney damage, such as hematuria, proteinuria, and edema, disappeared completely. Kidney function returned to normal after treatment.

### Laboratory tests

The laboratory indices of the patients in the early stage of disease were measured and recorded. These indices included the following: routine blood testing, routine urinalysis, serum creatinine (Scr), blood urea nitrogen (BUN) and high-sensitivity C-reactive protein (hs-CRP) levels, autoantibody titers, and serum complement components C3 and C4, serum IgA, IgG, and IgM levels. All patients were given an anti-streptolysin O test. Serum was isolated from peripheral blood and serum TNF-α, IL-6, IL-1β, and IL-18 levels were determined using ELISA kits (R&D Systems, Shanghai, China). For the patients in group B, when they achieved the endpoint of follow-up, the above indices were re-tested.

### Statistical analysis

Numerical data are presented as the ± SD, and count data are presented as a frequency or percentage. A t-test was used for comparing numerical data of the two groups and a chi-square test was used for comparing count data. Statistical significance was defined as a $P<0.05$. SPSS17.0 was used for statistical analysis.

## Results

### Comparison of the general clinical indicators between the two groups

Most of the patients were boarding students and migrant workers. Sixteen patients had kidney damage diagnosed by clinical examination and laboratory testing. The clinical manifestations mainly included glomerular hematuria and/or proteinuria. The proteinuria was generally mild to moderate and only one patient met the criteria for nephrotic syndrome. Other symptoms included hypertension (n=1), facial edema (n=4), lower limbs edema (n=1), generalized edema (n=1), and mild lumbago and discomfort (n=5). Seven patients had no apparent symptoms.

There were no patients with renal functional decrease. A comparison of general patient information between the two groups showed a younger average age for group B than group A, and the difference was statistically significant. There were no significant differences in the gender ratios, time of onset of scabies, blood pressure, and incidence of prodromic infections between the two groups. The results are shown in Table 1.

| | A group | B group |
|---|---|---|
| Age (y) | 33 ± 11.2 | 18.4 ± 5.3* |
| Gender ratio (M/F) | 307/53 | 14/2 |
| Duration (d) | 23.9 ± 2.5 | 25.4 ± 15.8 |
| Systolic BP (mmHg) | 121 ± 11.6 | 118 ± 21.4 |
| Diastolic BP (mmHg) | 75 ± 4.2 | 76 ± 16.3 |
| Prodromic infection (%) | 6.7 | 8.6 |
| Notes: *Compared with group A, $P<0.05$. | | |

**Table 1:** Comparison of the general clinical information between the two groups.

### Comparison of laboratory indices between the two groups

The levels of serum hs-CRP, IgG, TNF-α, IL-6, and IL-18 in the group B patients were significantly higher than group A, while the level of serum C3 was significantly lower than group A; the differences were statistically significant. There is no difference in hemoglobin, serum creatinine, blood urea nitrogen, serum albumin, serum IgA, IgG, IgM and anti-streptolysin O test between the two groups (Table 2).

| | **A group** | **B group** |
|---|---|---|
| Hbg/L | 128 ± 20.3 | 132 ± 18.2 |
| Scr (μmol/L) | 66.2 ± 16.1 | 59.6 ± 16.4 |
| BUN (mmol/L) | 6.51 ± 3.21 | 5.90 ± 2.12 |
| hs-CRPmg/L | 5.29 ± 0.51 | 29.37 ± 14.95** |
| Anti-O test (+) (%) | 0.56 | 6.25 |
| C3(g/L) | 1.01 ± 0.51 | 0.37 ± 0.21* |
| C4(g/LI) | 0.32 ± 0.14 | 0.33 ± 0.17 |
| IgG(g/L) | 9.55 ± 2.49 | 16.25 ± 3.67* |
| IgM(g/L) | 1.47 ± 0.25 | 1.62 ± 0.72 |
| IgA(g/L) | 3.18 ± 0.37 | 2.71 ± 1.09 |
| TNF-α(pg/ml) | 37.33 ± 0.51 | 49.88 ± 7.24* |
| IL-6(pg/ml) | 10.24 ± 5.14 | 36.15 ± 4.87* |
| IL-1(pg/ml) | 28.63 ± 1.19 | 34.83 ± 11.15 |
| IL-18(pg/ml) | 13.72 ± 2.48 | 98.76 ± 36.92* |
| Notes: *Compared with group A, $P<0.05$**Compared with group A, $P<0.01$. Hb, hemoglobin; Scr, serum creatinine; BUN, blood urea nitrogen; hs-CRP, high-sensitivity C-reactive protein; C3, serum complement components C3; C4, serum complement components C4. | | |

**Table 2:** Comparison of laboratory indices between the two groups.

### Patient outcomes

Three hundred fifty-one of 360 patients in group A were cured; five patients were not cured due to repeated infections and four patients

were lost to follow-up. Scabies resolved completely in 16 group B patients after active treatment; 12 patients terminated follow-up 2–6 months after scabies was cured and they met the standard for a clinical cure of kidney damage. Four patients had persistent hematuria and/or proteinuria, declined renal biopsies, and continued to receive ACEIs or ARBs treatment in the clinic. The condition of one patient who had met the criteria for nephrotic syndrome was significantly relieved after treatment with prednisolone 1 mg/(kg·d) in combination with valsartan and clopidogrel. The proteinuria decreased from 3.8g/24h to 1.4g/24 h after eight weeks' treatment.

### Comparison of laboratory indices before and after SGN was cured

The levels of serum IgG, hs-CRP, TNF-α, IL-6, and IL-18 in 12 group B patients who had completed their follow-up decreased significantly after the glomerulonephritis was clinically cured, while the serum C3 level increased significantly. Compared with the values in the early stage of the disease, the differences achieved statistical significance as indicated in Table 3.

| | Onset | After Clinical Cure |
|---|---|---|
| Hbg/L | 133 ± 17.6 | 140 ± 28.6 |
| Scr (μmol/L) | 59.4 ± 15.83 | 60.6 ± 14.3 |
| BUN (mmol/L) | 6.2 ± 2.44 | 5.4 ± 2.58 |
| hs-CRPmg/L | 27.48 ± 14.62 | 7.32 ± 2.83* |
| C3 (g/L) | 0.36 ± 0.21 | 1.37 ± 0.14* |
| C4 (g/LI) | 0.64 ± 0.16 | 0.70 ± 0.29 |
| IgG (g/L) | 15.71 ± 3.58 | 9.20 ± 2.51* |
| IgM (g/L) | 1.71 ± 0.74 | 1.56 ± 0.19 |
| IgA (g/L) | 2.71 ± 1.12 | 2.53 ± 0.59 |
| TNF-α (pg/ml) | 47.86 ± 7.05 | 25.48 ± 5.23* |
| IL-6 (pg/ml) | 36.47 ± 5.81 | 11.10 ± 3.82** |
| IL-1 (pg/ml) | 35.13 ± 5.26 | 30.85 ± 6.81 |
| IL-18 (pg/ml) | 89.48 ± 33.72 | 42.95 ± 16.74* |

Notes: *Compared with onset of the disease, P<0.05; **Compared with onset of the disease. P<0.01. Hb, hemoglobin; Scr, serum creatinine; BUN, blood urea nitrogen; hs-CRP, high-sensitivity C-reactive protein; C3, serum complement components C3; C4, serum complement components C4.

**Table 3:** Comparison of laboratory indices in the early stage of disease and after clinical cure.

## Discussion

Scabies, presenting as herpes and papulovesicles, is a contagious skin disease caused by an infestation of the itch mite, Sarcoptes scabiei. The characteristic manifestations of scabies are the tunnels formed in the cuticle and prickle cell layer of the epidermis. The disease is common in rural and remote districts and has a relatively high incidence in students and migrant workers in cities. SGN exhibits the clinical manifestations of scabies and acute glomerulonephritis. The diagnostic standards of SGN include the following: a history of infection by itch mites, and clinical manifestations of acute glomerulonephritis after the infection by itch mites and other factors which likely cause kidney injuries have been ruled out.

The clinical characteristics and pathogenesis of SGN are not fully understood. In our study, among 376 patients with scabies, 16 developed SGN (4.26%). These 16 patients mainly presented with glomerular hematuria and/or proteinuria, and the proteinuria was generally mild to moderate. Only one patient met the diagnostic criteria for nephrotic syndrome. The presentation of kidney lesions in 12 patients completely resolved and satisfied the clinical cure standards 2-6 months after scabies was cured. The remaining four patients have continued to receive outpatient treatment, but no patient undergo renal biopsies.

The kidney damage induced by scabies are probably mediated by the following two pathways: (1) The immune and inflammatory responses induced by a variety of antigens sourcing from *S. scabiei*. (2) Post-infectious glomerulonephritis induced by secondary topical infections of excoriated skin because scabies generally leads to serious pruritus. Indeed, the former pathway may be the major one leading to SGN. The mites hosting under the cuticle can produce soluble antigens via saliva, feces, and other secretions. In addition, various antigens can be released by dead and disintegrated mites. These antigens are probably more important and have greater pathogenic effects in inducing immune and inflammatory responses of the human body than live mites. The antigens can spread to the dermis through subcutaneous intercellular fluid and stimulate immune and inflammatory responses [7]. There is evidence which indicates that extracts of dead or live mites can influence the number of inflammatory cells in local tissues and blood circulation during immune or inflammatory responses of the host [8-10]. Some soluble antigens can migrate and localize in the glomerulus via the circulation to form in situ antigens. These antigens can also form immune complexes by interacting with specific antibodies of the human body and accumulate in the glomerulus to induce kidney lesions.

There are still controversial opinions regarding the effects of scabies infections on the immune response in humans. Some studies have shown that the levels of IgG and IgM in scabies patients before and after treatment are higher than healthy control subjects [11-15]; however, some studies have suggested that there are no significant differences in serum IgG and IgM levels between healthy subjects and scabies patients [16,17]. Therefore, some researchers believe that the increase in the levels of serum antibodies in scabies patients should be associated with secondary infections induced by other pathogens. A retrospective study in Australia which involved 78 scabies patients showed that the level of serum IgG in scabies patients was two times higher than healthy control subjects [18]. Another study reported that the levels of IgG and IgE in scabies patients were increased and CD8+ T cells were the primary infiltrating cells. This finding suggested that scabies infections not only activate the humoral immune response, but also triggers the cellular immune response [19]. During the development of post-infectious glomerulonephritis, binding of specific IgG to the corresponding IgG Fc binding protein can activate the complement system and initiate harmful effects on the kidney. The kidney lesions in animal models with a deficiency of the IgG Fc binding protein induced by streptococcal infection were significantly reduced [20].

In our study the overall level of IgG in scabies patients remained in normal range, however, SGN patients showed a significantly higher IgG level and lower complement C3 level when compared with

patients without glomerulonephritis. The levels of serum CRP, TNF-α, IL-6, and IL-18 were also increased in these patients. Compared to the scabies patients without glomerulonephritis, the differences were statistically significant. Our study also showed that the levels of IgG, CRP, TNF-α, IL-6, and IL-18 decreased significantly when the patients were clinically cured and the decreased level of C3 reverted to a normal level. We speculate that the pathogenesis of SGN involves the binding of *S. scabiei*-specific IgG to the Fc binding protein in the host kidney through its Fc fragment and subsequent deposition of the IgG complex in kidney tissues. This complex can activate the complement system and inflammatory cells and promote the release of a variety of inflammatory cytokines to cause kidney injuries, thus serving as the primary mechanism underlying the pathogenesis of the disease.

Similar to post-streptococcal glomerulonephritis, the serum C3 level of SGN patients displayed a dynamic change. Some studies have suggested that *S. scabiei* infections lead to the local deposition of C3 in the skin, which induces a strong inflammatory response [18,19,21]. This deposition of C3 in the skin probably explains, in part, the decreased C3 level in the early stage of the disease. Some study reported that infestation with Sarcoptes Scabiei is associated with group-A streptococcal pyoderma which in turn predisposes to acute glomerulonephritis [22]. But in our study, we didn't find significant difference in the anti-streptolysin O test between scabies-alone patients and SGN patients.

Infestation with *S. scabiei* stimulates dermal microvascular endothelial cells to produce various inflammatory mediators, such as IL-1, IL-6, IL-8, IL-10, and TNF-α, these mediators participate in the regulation of inflammatory and immune responses [8]. Although there is big difference in the structure of IL-1 and TNF-α, the functions of IL-1 and TNF-α overlap. Both IL-1 and TNF-α can induce and activate T cells, neutrophils, and macrophages, and promote the expression of various inflammatory cytokines and mediators. In animal experiments, there is a significant positive correlation between the concentration of intravenously injected TNF-α and the degree of kidney injury. TNF-α can induce chemotaxis and aggregation of leucocytes and injure vascular endothelial cells. The harmful effects of TNF-α on the kidney are similar to the untoward effects of endotoxin [23,24]. In the early stage of SGN, we showed that the serum level of TNF-α increased significantly and gradually returned to normal after clinical cure; however, the serum IL-1 level did not undergo an obvious change.

IL-6 and IL-18 are two pro-inflammatory cytokines which are closely related to kidney damage. It has been reported that in patients with post-streptococcal glomerulonephritis the level of circulating IL-6 is increased significantly and the high level is important for the development and progression of glomerulonephritis [25]. Knock-out of the IL-18 receptor remarkably reduces kidney injury in C57BL/6 mice induced by bovine serum albumin [26]. The IL-18 receptor deficiency also inhibits the production of IFN-γ and the activity of NK cells, thus decreasing the inflammatory response in the kidney [27,28].

The pathogenesis of SGN is complex. The clinical characteristics and prognosis continue to gain the attention of researchers. Based on our limited data, patients with SGN exhibit mild clinical symptoms and signs and have a good prognosis. Twelve of 16 patients (75%) achieved a clinical cure after active treatment of scabies; however, given the limited sample size, our results warrant further studies with larger samples for confirmation.

## Acknowledgements

This study was supported by the Medical Science Project Fund of the Health Bureau of Chongqing City (No. 2012-2-3932).

## Author Contributions

Zhenglan Gao initiated the study and collected the data. Hongfei Zhao, Hua Gan, Zheng Xiang and Yunfeng Xia participated in the study design and data analysis. Yunfeng Xia wrote the paper. All investigators approved the final version.

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