IgA Vasculitis in Henoch-Schönlein Purpura

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Introduction
Henoch-Schönlein purpura (HSP), also termed IgA vasculitis (IgAV), is a systemic vasculitis with an outstanding cutaneous involvement. HSP is a small-vessel vasculitis formed by palpable purpura on the lower extremities (mainly on distal parts) and IgA-dominant immune complex deposition within the wall and lumen of dermal vessels in the lesions. This problem is associated with joint, gastrointestinal and renal involvement, although the level and severity of involvement may be variable. HSP also termed IgA vasculitis (IgAV), is a systemic vasculitis with an outstanding cutaneous involvement. Most patients receive only supportive therapy with hydration and rest and symptomatic relief of pain with analgesics. The vast majority of patients with HSP recover spontaneously. The course of renal diseases, diagnosis and the management are discussed in this review.

Keywords: Henoch-Schönlein purpura; IgA vasculitis; Child.

Review
http://journals.sbmu.ac.ir/jpn
DOI: http://dx.doi.org/10.20286/jpn-04018


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Introduction
Henoch-Schönlein purpura (HSP), also termed IgA vasculitis (IgAV), is a systemic vasculitis with an outstanding cutaneous involvement. HSP is a small-vessel vasculitis formed by palpable purpura on the lower extremities (mainly on distal parts) and IgA-dominant immune complex deposition within the wall and lumen of dermal vessels in the lesions. This problem is associated with joint, gastrointestinal and renal involvement, although the level and severity of involvement may be variable. The histologic findings in the kidney are identical in patients with IgA-nephropathy. Additionally, high circulating levels of galactose-deficient IgA1 could be found in patients with both IgA-nephropathy and HSP (IgAV). Both of these two findings support that these disorders may have a common pathogenesis [3]. Although the prominent deposition is the result of IgA in both HSP (IgAV) and IgA nephropathy, the renal injury may be mediated at least in part by IgG autoantibodies directed against mesangial cell antigens [4,5]. The course of the renal disease and circulating antibodytiters are almost parallel, and these autoantibodies have not been proven to be present in patients with HSP (IgAV) with not involved kidney [5]. HSP (IgAV) is more common in children, but adult patients are more prone to renal involvement and if occurs, it would be more severe, and needs forceful therapy in older children and adults [6-10]. IgA nephropathy is the most common cause for primary glomerulonephritis in most developed countries of the world [1-8]. Patients with IgA nephropathy may occur at any age, but the incidence peak is in the second and third decades of life. There is nearly a 2:1 male to female ratio in North America and Western European population, although this difference is not among populations in the Pacific Rim. IgA nephropathy occurs with greatest frequency in Asians and Caucasians, and rare in black population [4,6,9]. The reported incidence of mesangial IgA deposition in apparently healthy individuals ranges from 3 to 16 percent [10,11]. These cases had no clinical features of nephritis but their renal biopsy was consistent with IgA nephropathy. Multiple studies have showed that IgA deposition

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may be found in other forms of glomerulonephritis. These particularly include thin basement membrane nephropathy, lupus nephritis, minimal change disease, and diabetic nephropathy. These findings are most probably due to chance associations since IgA deposition is common in the general population. Variations in disease prevalence may be the result of regional differences in screening for kidney disease and kidney biopsy practices [5,6]. Many patients with IgA nephropathy are detected on routine urine screening since their sole clinical manifestation is asymptomatic hematuria and/or proteinuria. The transmission pattern among the affected families is autosomal dominant.

Renal manifestations

The classic tetrad of Henoch-Schönlein purpura (HSP), is rash, arthralgias, abdominal pain, and renal disease, which can occur at any time and in any order over a period of several days to several weeks [7,8,11,12]. Renal involvement is typically noted within a few days to one month following the onset of systemic symptoms, but has no correlation with the severity of extra renal involvement. The urinalysis in patients with HSP (IgA V) nephritis reveals active sediment characterized by microscopic or macroscopic hematuria with or without RBC and other cellular casts or proteinuria. There is a strong correlation between the severity of the renal presentations and the findings on renal biopsy [13-19]. For instance, patients with only asymptomatic hematuria usually reveal only focal mesangial proliferation, whereas patients with proteinuria have more marked cellular proliferation and, if in nephrotic range, may have crescent formation [15,19]. Patients with recurrent attacks of purpura or macroscopic hematuria often have exacerbation of renal symptoms and biopsy-confirmed worsening of glomerular lesions.

Patients with IgA nephropathy usually present in one of three ways; the relative frequency depends on most parts upon screening practices (which will lead to increased diagnosis of asymptomatic cases) and the particular population being evaluated [4,5]:

- Approximately 40-50% present with one or recurrent episodes of visible hematuria, usually consecutive to an upper respiratory infection. This has sometimes been termed "synpharyngitic hematuria". These episodes can be produced by bacterial tonsillitis or by viral upper respiratory infections. They may even occur in individuals who have already undergone tonsillectomy. The first episode may probably represent the onset of the disease. One of the complaints of the patients is flank pain during acute episodes, which usually reflects stretching of the renal capsules. The patients may also show low-grade fever. These features can mimic urinary tract infection or urolithiasis. Most patients have only episodic visible hematuria and episodes usually relapse for a few years.
- Another 30-40% have microscopic hematuria and usually mild proteinuria, and are incidentally detectable on a routine examination [21, 22]. In these patients, the duration of disease is unknown. Gross hematuria will eventually occur-25% of these patients.
- Less than 10% present with either nephrotic syndrome or acute rapidly progressive glomerulonephritis picture characterized by edema, hypertension, and renal insufficiency accompanied hematuria. In rare cases, IgA nephropathy may present with malignant hypertension. It is usually assumed that these patients have presumably had a long standing disease, which was not detected earlier because the patient did not have visible hematuria or undergo routine urinalysis. Rarely, patients develop acute kidney injury with or without oliguria. This may be the result of crescentic IgA nephropathy, or to heavy glomerular hematuria inducing tubular occlusion and/or damage by red cells. The latter is usually a reversible circumstance, although incomplete recovery of renal function may occur [23].

If there is crescentic IgA nephropathy, there should be an increase in the absolute number of dysmorphic red cells excreted in the urine, which is typically seen at least 50% of all red cells, and always an absolute increase in the number of other dysmorphic cells. Beside the severity of HSP (IgAV) nephritis, there are multiple factors that could have contributed to the high rate of adverse renal outcomes:

- Baseline values prior to the onset of HSP (IgAV) nephritis probably were never assessed, so older patients might have an underlying chronic kidney disease such as nephrosclerosis. The findings on renal biopsy are consistent with this consideration. Adverse renal predictors on multivariate analysis included a serum creatinine above 120 µmol/L (1.35 mg/dL), proteinuria greater than 1 g/day, and on renal biopsy, glomeruli with fibrinoid necrosis (a sign of active disease) or signs of chronic disease such as interstitial fibrosis involving more than 10% of the interstitium, and glomerulosclerosis in more than 20% of glomeruli. But, most of the patients who had a creatinine clearance below 50 mL/min within four months of presentation were over 60–years-old. Thus, the high rate of adverse renal outcomes in this study may not accurately describe the prognosis of HSP (IgAV) nephritis in young adults.
- Other factors that may contribute to the high rate of adverse renal outcomes are the long period of follow-up in comparison to other studies, as well as possible.
selection bias since all patients had renal disease severe enough to warrant renal biopsy.

**Diagnosis**

The suspicion of a diagnosis of IgA nephropathy is generally based upon the clinical history and laboratory data. The diagnosis can be confirmed only by kidney biopsy with immunofluorescence or immunoperoxidase studies for IgA deposits.

Indications for renal biopsy: According to the generally benign course of patients with IgA nephropathy who have isolated hematuria, a renal biopsy is usually performed only if there are signs suggestive of more severe or progressive disease such as persistent protein excretion above 1000 mg/day (which may increase over time) or an elevated serum creatinine concentration [37]. New onset hypertension or a significant elevation in blood pressure above a previous stable baseline that does not exceed 140/90 mmHg (e.g., from 100/60 to 130/80 mmHg) is also associated with a greater likelihood of progressive disease but is mainly seen in those patients who also have one or both of the other adverse predictors.

**Differential diagnosis**

Hereditary nephritis and thin basement membrane nephropathy are the two other major glomerulopathies that present with persistent isolated hematuria [21,22]. The diagnosis of any of these disorders can only be made by renal biopsy, or by assumption in hereditary nephritis if there is a family history of renal failure with or without deafness, or in thin basement membrane disease if approximately one-half of first-degree relatives have hematuria.

Membranoproliferative glomerulonephritis (MPGN) may also present with episodic visible hematuria in children and young adults, and therefore should be considered in the differential diagnosis. Again, the definitive diagnosis of this disorder is made by renal biopsy.

**Treatment**

Most patients receive only supportive therapy with hydration and rest and symptomatic relief of pain with analgesics. The vast majority of patients with HSP recover spontaneously. There is indicative evidence that glucocorticoids amplify the rate of disappearance of the arthritis and abdominal pain; however they do not appear to prevent recurrent disease [12].

Renal disease: Specific treatment of HSP (IgAV) nephritis should be considered only in patients with marked proteinuria and/or impaired renal function during the acute episode [36]. We strongly recommend acquiring a renal biopsy in this setting since the severity of the histologic lesions (particularly the degree of crescent formation) appears to be the best indicator of prognosis. Patients with limited evidence of renal involvement such as microscopic hematuria, macroscopic hematuria of short duration, or mild proteinuria, generally do not need the renal biopsy and are not given specific therapy for renal disease but should be followed up closely for worsening of proteinuria or impairment of renal function [30].

No controlled trials could prove that therapy with conventional doses of glucocorticoids has a beneficial effect in patients with renal involvement [7,11,13,31,32]. By comparison, high dose methylprednisolone may be beneficial in patients with advanced disease, which is usually termed crescentic nephritis. In this setting, a regimen consisting of pulse intravenous methylprednisolone (250 to 1000 mg/day for three days) followed by oral prednisone (1 mg/kg/day for three months) may be beneficial [17,33]. This regimen is primarily aimed at reversing the inflammatory process (such as macrophage infiltration), instead of the IgA deposition itself. One prospective, but uncontrolled, study used this regimen in 38 children presenting with the nephrotic syndrome and/or crescents affecting more than 50% of glomeruli [17]. Only four (10%) progressed to end-stage renal disease, three of which had been treated late in the course of their disease. Thus, early therapy may be important to prevent or postpone irreversible glomerular injury.

Cyclophosphamide alone or with glucocorticoids does not appear to reduce protein excretion or improve or preserve renal function [21,22]. Limited data suggest that cyclosporine may be beneficial in patients with HSP (IgAV) and severe proteinuria [34,35]. As an example, in one observational study, of 29 children who had persistent nephrotic range proteinuria despite oral glucocorticoids, 26 patients (90%) achieved complete remission with combined treatment with cyclosporine (5mg/kg/day with target serum levels of 50-150 mg/ml) and ACE inhibitors. Oral glucocorticoids were withdrawn shortly after cyclosporine was initiated and intravenous pulse methylprednisolone was not used. Two patients had partial remission but continual hematuria and/or proteinuria. It is not possible to determine from this study whether the reduction in proteinuria was due to the cyclosporine or ACE inhibitor.

Other combined regimens that have been evaluated in children with crescentic nephritis include glucocorticoids and azathioprine (in an uncontrolled study, renal function was improved in 19 of 21 children) [36] and multidrug regimens such as glucocorticoids, cyclophosphamide, and dipyridamole, or glucocorticoids, cyclophosphamide,
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Recurrent glomerular disease, often seen in association with active extra renal involvement, can lead to loss of the graft [33,34,36]. Although one study suggested that this was more likely in patients with aggressive initial disease and relatively rapid progression to end-stage renal disease [37-38], the association between recurrence and severity of the original disease was not confirmed in a later report. Some authors recommended that renal transplantation could be delayed for at least 12-24 months after the disappearance of purpura. However, this approach does not prevent recurrent disease in any patients [38].

Some observations suggest that the risk of recurrent disease may be higher in living related donors, a finding similar to that seen in IgA nephropathy. However, this observation was not confirmed in the retrospective series of 339 patients that is cited above, in which the rate of recurrence was the same for those who received kidneys from deceased donors versus living related donor (13 vs. 14.3, respectively) [40].

Prognosis
The short- and long-term outcomes of children with Henoch-Schönleinpurpura (HSP), also called immunoglobulin A vasculitis (IgAV), are generally excellent. In the absence of significant renal disease, the initial episode of HSP (IgAV) typically resolves within one month. In two-thirds of children, there are no recurrent episodes [5,10]. In the remaining one-third of patients, HSP (IgAV) recurs at least once, typically within four months of the initial presentation [4,16,22]. Each subsequent episode has similar clinical findings, but its duration is generally milder and/or shorter than the preceding one. Relapses are more common in patients with nephritis, in those with evidence of acute inflammation (e.g., elevated erythrocyte sedimentation rate [ESR]), and in patients who received glucocorticoids treatment [16]. These findings suggest that patients who have more severe course of HSP (IgAV) are at risk of recurrence.

One retrospective review reported a longer mean interval time of 13.5 months between the first and second episode of HSP (IgAV) than was reported previously [28]. In addition, there was no difference in clinical and laboratory findings between patients with recurrent disease and those without recurrence. The reasons for these differences between study results are not clear.

Morbidity rate in the initial phase of HSP (IgAV) is primarily a result of gastrointestinal complications, including intussusception and, less commonly, bowel ischemia, bowel perforation, or pancreatitis. The long-term morbidity in patients with HSP (IgAV) is

heparin/warfarin, and dipyridamole [21,27-29]. However, since spontaneous recovery is often observed in patients with crescent formation, it is still unknown whether these regimens are preferable to no or less aggressive therapy.

Plasmapheresis has also been used in a few patients with severe, usually crescentic, disease and rapidly progressive renal failure [33,30,31]. Its efficacy is uncertain (due in part to concurrent administration of glucocorticoids) and there are some potential side effects. Nonetheless, limited data suggest that plasmapheresis alone may be curative in some patients. As an example, among nine children with crescentic nephritis, plasmapheresis was the only therapy for renal involvement, with glucocorticoids only being used for severe abdominal pain [31]. At follow-up at nearly 10 years, four children had complete recovery and two had only microscopic hematuria. The rest three children had recurrent proteinuria, with progression to end-stage renal failure.

Intravenous immune globulin has been used in a few patients with IgA-nephropathy or HSP (IgAV) nephritis with heavy proteinuria and a progressive reduction in glomerular filtration rate [22]. More data are required to confirm its efficacy.

Renal transplantation can be performed in these patients who progress to end-stage renal disease, although recurrent disease could occur [33-37]. Deposition of IgA in the graft is common, but many cases are subclinical. An early study suggested that clinically evident recurrence occurs in approximately 35% of patients at five-years-old with a rate of graft loss due to recurrent disease of 11% [13]. Other reviews suggest a lower rate of recurrence (2.5 and 11.5% at 5 and 10 years-old in one small series) but still show a relatively high risk of graft loss due to patients with HSP (IgAV) compared to other renal allograft recipients with recurrent disease[26,28]. As an example, a retrospective review demonstrated that 13.5% graft loss due to recurrent HSP (IgAV) in 330 patients [28]. It seems that the overall graft survival be the same for patients.

The diagnosis of recurrent renal disease is based not only upon the demonstration of mesangial IgA deposits but also clinical features of the disease, since isolated deposits can be seen without any clinical features of HSP (IgAV). It is even possible that asymptomatic IgA deposits may have been present in the donor kidney prior to transplantation. This phenomenon has been proved in several reports, but the IgA deposits disappeared within weeks after transplantation due presumably to the lack of circulating IgA-containing immune complexes in the recipient [29,20]. Thus, persistent deposits may presumably reflect recurrent disease.

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the result of renal disease. The risk of chronic renal disease is increased in adults [28]. The severity of renal involvement correlates with the severity of the initial renal presentation and histologic changes could be seen via renal biopsy. Risk factors for a worse renal prognosis include nephrotic range proteinuria, elevated serum creatinine, hypertension, and certain histologic findings.

**Follow-up**

Ninety percent of children who develop renal involvement do so within two months of onset, and 97 percent within six months [23]. Accordingly, all patients with Henoch-Schönlein purpura (HSP), also called immunoglobulin A vasculitis (IgAV), should be monitored for the blood pressure and urinalysis tests weekly or biweekly for the first and second month after presentation. One study suggested that home urine dipstick testing was adequate for detecting development of nephritis [10]. Once the disease appears to be subsiding, additional follow-up for urine and blood pressure monitoring should be scheduled monthly for one year after the initial presentation. To identify patients, who may develop late renal disease, continued screening (e.g., urinalysis and blood pressure measurements) should be performed by the primary care clinician during the subsequent well-child visits. A serum creatinine should be obtained to assess renal function in those patients with significant or continuous urinary abnormalities or elevated blood pressure. Patients with persistent proteinuria, hypertension, or renal insufficiency should be referred to a pediatric nephrologist for further evaluation and treatment. In addition, pregnant women with a history of HSP (IgAV) should be monitored closely, as they have a higher risk of hypertension [23].

**Conflict of Interest**

None declared

**Financial Support**

None declared

**References**

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2006;21:54.