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Renal involvement in IgA vasculitis; possible correlation with positive antiphospholipid antibodies

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ABSTRACT

IgA vasculitis is a hypersensitivity vasculitis, which is usually self-limiting. Renal involvement is the most damaging long-term complication of IgA vasculitis, happening in 20% - 100% of cases. Some factors have been reported to be associated with renal involvement in IgA vasculitis; however, no biomarker has been proved as a risk factor for renal involvement and its severity yet. We followed 48 patients with a confirmed diagnosis of IgA vasculitis for six months. We checked these patients for renal involvement by microscopic urine examination. We checked aPL antibodies in all patients on admission and 12 weeks later. Urinalysis showed renal involvement in 14 of 48 patients with IgA vasculitis (29.16%). Antiphospholipid antibodies were positive in 9 patients with IgA vasculitis and renal involvement (9 out of 14, 64.28%), while they were positive in only six patients with IgA vasculitis without renal involvement (6 out of 34, 17.64%), showing a moderate correlation between positive aLP and renal involvement in patients with IgA vasculitis, with a kappa index of 0.457. Serum aPL antibodies, as a tool to predict renal involvement in IgA vasculitis, show a sensitivity of 64.3%, a specificity of 82.4%, PPV of 60.0% and NPV of 84.8%, demonstrating that a positive serum aPL antibody can be used to positively predict the renal involvement, while a negative result is not strong enough to rule out future renal involvement.

Keywords: IgA vasculitis, antiphospholipid antibodies, lupus anticoagulant, anticardiolipin antibodies, and anti-b2 glycoprotein antibodies

Introduction

IgA vasculitis is a hypersensitivity vasculitis characterized by the deposition of IgA-containing immune complexes within the blood vessels throughout the body. The dominant clinical features include nonthrombocytic purpura (with lower limb dominance), abdominal pain, arthritis/ arthralgia, and renal involvement (1).

Renal involvement is the most damaging long-term complication of IgA vasculitis. 20% - 100% of children with IgA vasculitis will have renal involvement (2), 80% of them present with isolated hematuria and/or proteinuria, whereas only 20% have acute nephritis or nephrotic syndrome at presentation. Renal involvement usually develops by four weeks (3). Most patients with renal involvement have a favorable prognosis. However, around 20% of these patients develop end-stage renal disease (2,4). IgA vasculitis nephritis is the only disease manifestation that may be associated with long-lasting morbidity; hence, the long-term prognosis of IgA vasculitis is mainly determined by the progression of renal involvement (4,5).

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Some factors have been reported to be associated with renal involvement in IgA vasculitis, such as age at onset (older than ten years at onset), gender (male gender is a risk factor), digestive tract symptoms, persistence (for more than one month) or recurrence of purpura, WBC >15X10^9/L and platelet count >500X10^9/L and, upper respiratory tract infection, especially streptococcal infection with elevated ASO, and decreased C3 level (4,6). Onset at an older age (>6 years), longer interval between IgA vasculitis symptom onset and IgA vasculitis diagnosis (>8 days), presence of angioedema, recurrence of purpura, and CNS involvement are factors associated with increased risk of severe kidney disease (1). However, no biomarker has been proved as a risk factor for renal involvement and its severity yet (7).

Association between IgA vasculitis and antiphospholipid (aPL) antibodies has been first reported in 2000 (8). Since then, the presence of aPL antibodies in patients with IgA vasculitis has been reported to be associated with disease activity (9,10), and central nervous system involvement (11). However, the association between aPL antibodies and renal involvement and prognosis in IgA vasculitis remains unrevealed.

In the present study, to confirm the correlation between renal involvement in IgA vasculitis and aLP antibodies, we report the 6-month follow-up of 48 patients with IgA vasculitis.

Method

Ethics approval

The ethics committee of Shahid Beheshti Medical University (SBMU) approved this study, in accordance with ethical standards of the local committee of the SBMU's ethics board and the Declaration of Helsinki. The ethical approval number is **IR.SBMU.RETECH.REC.1397.595.** We obtained informed consent from the parents of all patients.

Clinical investigation

According to 2008 criteria of EULAR-PRES for diagnosing IgA vasculitis (palpable purpura (mandatory criterion) in the presence of at least one of the following four features: diffuse abdominal pain, any biopsy showing predominant IgA deposition, arthritis or arthralgia, and renal involvement [any hematuria and/or proteinuria]) (12), 48 pediatric patients were diagnosed with and admitted IgA vasculitis at Mofid Children Hospital (SBMU, Tehran, Iran) from September 2015 to June 2017.

We considered the following criteria for diagnosing renal involvement in IgA vasculitis: (1) hematuria in urine analysis (both microscopic and gross hematuria); (2) proteinuria in urine analysis; and (3) both proteinuria and hematuria (12). We followed all patients for six months since children with no urinary pathology during the first six months after the onset of IgA vasculitis will not develop renal impairment during the long term follow-up (13).

Detection of antiphospholipid antibodies

We obtained two serum samples from all patients with IgA vasculitis to detect for aPL antibodies, the first sample on patient admission, and the second one, 12 weeks later, to make sure that the aPL antibodies are still elevated. All samples were preserved at -80°C, no more than four weeks before the detection of antiphospholipid antibodies. Laboratory assessment of antiphospholipid antibodies was based on the latest update of the classification criteria for definite antiphospholipid antibody syndrome (14). Lupus anticoagulant was detected with the Kaolin conglutination time method, whereas anticardiolipin antibodies and anti-b2 glycoprotein I antibodies were detected by enzyme-linked immunosorbent assays. Detection of positive titers of even one of these antiphospholipid antibodies was recognized as a positive result.

Statistical methods

Statistical analyses were performed using SPSS version 22.0 (IBM, New York, NY, USA). A chi-square test was used to compare the rate of positive aPL in patients with IgA vasculitis, with and without renal involvement. P-value of less than 0.05 was regarded as statistically significant.

Results

We included 48 patients with a confirmed diagnosis of IgA vasculitis based on clinical criteria and skin biopsy of the cutaneous lesions. Skin biopsy showed

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neutrophilic infiltrate in the wall of small vessels, perivascular neutrophilic infiltration in the dermis, endothelial swelling, perivascular edema with RBC extravasation, and leukocytoclastic vasculitis and nuclear derbies.

Among these 48 patients, we had 31 boys and 17 girls (the ratio of boys to girls was 1.82:1), with the mean age of 6.2 ± 2.3 (5 - 9 years).

Renal involvement

At the time of diagnosis, the renal involvement was discovered in only 1 of the cases as microscopic hematuria. During the six-month course of follow-up, urinalysis showed renal involvement in 14 of 48 patients with IgA vasculitis (29.16%), including the first case. They included ten boys and four girls (the ratio of boys to girls was 2.5:1). All renal complications appeared within six months during the course of IgA vasculitis and included hematuria and proteinuria. All 14 patients with renal involvement showed microscopic hematuria, and just 2 cases had gross hematuria, 5 of them presented with proteinuria, and just one patient showed nephrotic-range syndrome.

Antiphospholipid antibodies in IgA vasculitis children

At the time of the patient admission, the aLP antibody was positive in 15 patients and negative in 33 patients. The second test was performed in all patients 12 weeks after the first test, and the result of the aPL tests was again positive in the 15 positive patients and negative in the 33 negative patients. Antiphospholipid antibodies were positive in 9 patients with IgA vasculitis who showed renal involvement (9 out of 14, 64.28%) during the follow-up, while they were positive in only six patients with IgA vasculitis without renal involvement (6 out of 34, 17.64%). Hence, the positive percentages of lupus anticoagulant, anticardiolipin antibodies, and anti-b2 glycoprotein antibodies (antiphospholipid antibodies) in serum were much higher in children with IgA vasculitis with renal involvement ($P < 0.01$, Table 1) and there is a moderate correlation between positive aLP and renal involvement in patients with IgA vasculitis, with a kappa index of 0.457.

Table 1: Serum aPL antibodies result in IgA vasculitis patients

	With Renal Involvement	Without Renal Involvement	Total
Positive aPL	9	6	15
Negative aPL	5	28	33
Total	14	34	

Based on these findings, if we use aLP for predicting renal involvement in patients with IgA vasculitis, the sensitivity is 64.3%, the specificity is 82.4%, PPV 60.0%, and NPV 84.8%.

Discussion

Although IgA vasculitis is a self-limiting disease in the majority of cases, the long-term prognosis of IgA vasculitis is primarily dependent on the severity of renal involvement, which may manifest as persistent hematuria or proteinuria, nephrotic or nephritic syndrome or even end-stage renal disease (15). There are some interventions, like leukocytapheresis or cyproheptadine, that can prevent or at least decrease the occurrence of renal involvement in patients with IgA vasculitis. To be effective, this prevention or delay of this renal disease needs early suspicion of renal involvement in IgA vasculitis (6).

Early diagnosis is partly relying on knowing the risk factors for renal involvement. Wang et al. in a retrospective review on Chinese children, reported several risk factors for renal involvement in IgA vasculitis patients, including onset at an older age, colder season, longer interval between symptom onset of IgA vasculitis and its diagnosis, rural residency, skin lesion recurrence, angioedema and CNS involvement (1). Several of these reported risk factors have just a statistical relationship, not a cause-effect relationship.

Chan et al. in a meta-analysis reported some factors associated with renal involvement in IgA vasculitis, such as age at onset (older than ten years at onset), gender (male gender is a risk factor), digestive tract symptoms, persistence (for more than one month) or recurrence of purpura, WBC $>15\times10^9$/L and platelet count $>500\times10^9$/L and, upper respiratory

tract infection, especially streptococcal infection with elevated ASO, and decreased C3 level [6].

De Almeida et al., in a retrospective study, analyzed the initial prognostic factors for renal involvement in IgA vasculitis and could find the severe abdominal pain among several risk factors as the only independent variable associated with nephritis, not other forms of renal involvement (16).

Kaku et al., in a prospective study, assess risk factors associated with renal involvement in IgA vasculitis patients. This is the first study to report this relationship. They found that higher age at onset (>7 years), persistent purpura, and a decreased F XIII activity were associated with increased risk of renal involvement. They also found that corticosteroid treatment for IgA vasculitis decreased the risk of involvement in IgA vasculitis patients (4). There are controversies on this latter finding in more recent studies. Chartapisak et al., in a review, analyzed the available articles and found that corticosteroids do not prevent or alter the course of renal involvement in IgA vasculitis (3). In 2014, Davin et al. reported that prompt institution of aggressive immunosuppressive treatment could blunt the risk of renal disease progression (17). This finding, although not strongly proved yet, has an important implication that if the patient with IgA vasculitis is treated early and correctly, the risk of renal involvement will be decreased, underscoring the importance of identifying the risk factors.

Among the studies reporting these risk factors, we could not find any humoral marker associated with an increased risk of renal involvement. There are several reports of association of antiphospholipid antibodies with IgA vasculitis disease and different manifestations of this disease. Basaran Kaya et al. and Yang et al. reported IgA antiphospholipid antibodies to be associated with IgA vasculitis disease activity. They proposed that aPL antibodies may play a role in IgA vasculitis onset (9,18).

Kawakami et al. reported the association between high titer serum aPL and cutaneous leukocytoclastic angiitis in IgA vasculitis patients (19). Sokol et al. reported the association of serum and CSF aPL titers with neurologic involvement in IgA vasculitis patients (20).

Whether IgA vasculitis has a coincidental association with aPL antibodies is still poorly understood; however, it seems to be more than a coincidence. IgA vasculitis-related antibodies cause vasculitis, which exposes the endothelial phospholipids, otherwise nonexposed, allowing aPL antibodies to interact with them (21).

Our results show a moderate correlation between serum aPL antibodies and renal involvement. This correlation can not only show the positive serum aPL antibodies as a risk factor for renal involvement in IgA vasculitis patients but can also show a cause-effect relationship. In other words, this correlation may propose the aPL antibodies as a causative factor for renal involvement in IgA vasculitis.

This may have important diagnostic and treatment implications. Literature shows an earlier diagnosis of renal involvement leads to more rapid treatment establishment, which clearly improves the prognosis. If positive aPL antibodies can predict renal involvement in IgA vasculitis, it can help the earliest treatment, hence improving the prognosis more.

If we consider positive serum aPL antibody as a tool to predict renal involvement in IgA vasculitis, our study shows a sensitivity of 64.3%, a specificity of 82.4%, PPV of 60.0% and NPV of 84.8%, showing that a positive serum aPL antibody can be used to positively predict the renal involvement, while a negative result is not strong enough to rule out future renal involvement.

This study can only open a new vision into the correlation of aPL antibodies and renal involvement in IgA vasculitis patients. The main limitation of this study is the limited number of patients and lack of renal biopsy as a diagnostic and follow-up tool for renal involvement since renal biopsy was not part of our management protocol for renal complications in IgA vasculitis. Hence, we need multicenter, more extensive cohort studies to reach a better and more accurate conclusion on the relationship between serum aPL antibodies and renal involvement in IgA vasculitis patients.

Conclusion

Positive aPL antibodies in a patient with IgA vasculitis can be considered as an alarm for probable renal involvement during the course of IgA vasculitis, necessitating closer screening and follow-up for renal involvement in these patients, to diagnose and treat the nephritis earlier.

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