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Clinical significance of anti-phospholipid antibodies in Henoch Schönlein purpura

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ABSTRACT

Background: Henoch Schönlein purpura also known as IgA vasculitis is described histologically by IgA deposition in the blood vessel walls and presents with kidney involvement, palpable purpura, arthralgia, and abdominal pain. Our study aims to evaluate the association between anti-phospholipid antibody, anti-cardiolipin antibody, anti-beta(2) glycoprotein 1 antibody and Anti-phosphatidylserine/prothrombin antibodies and IgA vasculitis. Treatment response with intravenous steroids and cyclophosphamide was also studied based on resolution of antibody titer.

Methods: We conducted an observational study in three Rheumatology clinics at Ahmedabad, India. Data was collected for a period of 6 months. Diagnosis of IgA vasculitis was determined based on the International Chapel hill consensus conference 2012. Disease activity was assessed based on antibody titer, histological grading and through a pre-determined clinical form to assess objective clinical symptoms. P value of less than 0.05 was considered significant

Results: Study evaluated antibody titer of 178 patients. Sixty one percent of the patient's had positive antiphospholipid antibody titer with predominant antibody subtype as IgG. Inflammatory markers were significantly higher in patient having anti-phospholipid antibody titer. Anti-phospholipid antibody was present in 100 percent patients who had vascular thrombosis. IgG subtype of anti-cardiolipin antibody were found in 60 percent of the patients with renal complication.

Conclusions: Anti-phospholipid antibody have a close association with IgA vasculitis. Anti-phospholipid antibody has a significant role in mounting inflammatory response and vascular thrombosis. Combination treatment of intravenous steroids and cyclophosphamide found to be more effective in resolution of titer

Keywords: Vasculitis, antibodies, anti-phospholipid, Henoch Schönlein purpura

INTRODUCTION

Henoch Schönlein purpura also known as IgA vasculitis is described histologically by IgA deposition in the blood vessel walls and presents with kidney involvement, palpable purpura, arthralgia, and abdominal pain. We have restricted insight of Henoch Schönlein purpura in adults as it is unusual. Further research was stimulated because of recent discovery of new organ systems involved with this disease. Anti-phospholipid antibodies

is an antibody directed against membrane phospholipids which are the characteristic finding in patients with antiphospholipid syndrome.³ Anti-phospholipid antibodies have multitude of functions which include but are not limited to inflammatory response, thrombotic response, and altering platelet function. They all indicate association amongst blood vessel thrombosis and inflammation.⁴ Thrombosis is fairly common in vasculitis and anti-phospholipid syndrome.⁵ There are very few studies which describe an association among antiphospholipid antibodies and Henoch Schönlein purpura in

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adults. Few studies have reported association between Henoch Schönlein purpura in adults and Antiphosphatidylserine/prothrombin antibodies, IgA anticardiolipin antibodies and anti-beta (2) glycoprotein 1 antibodies. ^{6-11,13,14} Purpose of this study is to evaluate the relationship between anti-phospholipid antibodies and Henoch Schönlein purpura in adults.

METHODS

An observational study in three rheumatology clinics was conducted at Ahmedabad, India. Data was collected for a period of 6 months from January 2020 to June 2020. The three Rheumatology clinics combined provide medical care for approximately 150000 patients per year. The study included all adults who were diagnosed with IgA vasculitis and presented to the clinic at that time. Diagnosis of IgA vasculitis was determined based on the International Chapel Hill consensus conference 2012. Patient who underwent lab testing and histological workup were added to the study. Disease activity was assessed based on antibody titer, histological grading and through a pre-determined clinical form to assess objective clinical symptoms. Anti-phospholipid antibody titer was measured in each patient three times during the period of 6 months. Antibodies against anti-cardiolipin, anti-beta glycoprotein 1 and Anti-phosphatidylserine/ prothrombin were also measured. Microsoft 2010 excel sheet was used for data analysis. P value of less than 0.05 was considered significant.

RESULTS

The study was performed for 6 months during which antibody titers for anti-phospholipid antibodies and Antiphosphatidylserine/prothrombin antibodies were obtained in 178 patients, Antibody titer for anti-beta (2) glycoprotein 1 was obtained in 114 of 178 patients and antibody titer for lupus anticoagulant was obtained in 130 of 178 patients. There were 68 percent males and 32 percent females. Median age of the study population was 52 (45.6-69.4) year. The median symptom duration was 19 (15-38) days before presentation to the clinic. Sixty one percent of the patient's had positive anti-phospholipid antibody titer. Anti-phospholipid antibody subtypes were IgG 60 percent, IgM 28 percent and IgA 12 percent. Positive antibody titer for anti-cardiolipin antibody was seen in 13 percent patients with subtype IgA being 80 percent, IgM 12 percent, IgG 8 percent. Titers for antibeta (2) glycoprotein 1 antibody were positive in 14 percent patient followed by Anti-phosphatidylserine/ prothrombin antibodies at 7 percent. Lupus anticoagulant titer was positive in 16 percent patients. Inflammatory markers(ferritin, LDH and CRP) were significantly higher in patient having anti-phospholipid antibody titer as compared to the other antibodies; RR 4.1 (95% CI 3.2-5.5, p<0.02). We found that 24 hour protein excretion was higher in patients with anti-phospholipid antibody titer as compared to those with other antibodies by 20 percent; RR 3.1 (95% CI 2.1-4.5, p<0.01). Patients who had renal

complications had significantly more anti-cardiolipin antibody titer as compared to the study group; RR 2.2 (95% CI 1.5-3.6, p<0.01). IgG subtype of anti-cardiolipin antibody were found in 60 percent of the patients with renal complication followed by 31 percent IgM, and 9 percent IgA. In patients with renal complications, antiphospholipid antibodies were found to be positive only in those who had positive IgG subtype of anti-cardiolipin antibody. Cardiac complications were also seen more commonly in patients who had anti-cardiolipin antibody; RR 1.4 (95% CI 1.1-1.7, p<0.01). Eight percent of the study population had complications of vascular thrombosis. All of them had antibody titer positive for anti-phospholipid antibody. Among anti phospholipid antibody subtype, 60 percent were IgM, 37 percent were IgG, 3 percent were IgA. Of the patients who suffered vascular thrombosis, 90 percent had superficial vein thrombosis, 3 percent had deep vein thrombosis and remaining 7 people had mesenteric or splenic with thrombosis.

Intravenous steroids were used in treatment of 78% patients. Post-treatment there was 93 percent for Antiphosphatidylserine/prothrombin antibodies, 80 percent resolution of antibody titer for anti-phospholipid antibody, 63 percent for anti-cardiolipin antibody, and 38 percent for anti-beta (2) glycoprotein 1. Immunosuppressive medications like cyclophosphamide were used in 38 percent of the study population. Seventeen percent of them were in combination with intravenous steroids. Of the patients who were treated only with cyclophosphamide, resolution of antibody titer of Antiphosphatidylserine/prothrombin antibodies was noted in 60% patients followed by 48 percent in anti-cardiolipin antibody, 42 percent in anti-beta (2) glycoprotein 1 and 12 percent in anti-phospholipid. Combination treatment of intravenous steroids and cyclophosphamide found to be more effective in resolution of titer of Antiphosphatidylserine/prothrombin antibodies in 98 percent patients, 96 percentinanti-phospholipid antibody patients, 79 percent in anti-cardiolipinantibody, and 79 percent inanti-beta (2) glycoprotein 1. Other treatment options that were used were monoclonal antibodies in 3 percent patient population which showed 13 percent in anticardiolipin antibody titer, 12 percent resolution of antiphospholipid antibody titer, and 12 percent in anti-beta (2) glycoprotein 1 titer.

Patients who had only positive anti-phospholipid antibody titer had significant resolution with intravenous steroids as compared to other antibody titers; RR 3.2 (95% CI 2.1-3.8, p<0.01). Patient on cyclophosphamide and intravenous steroid had significantly better resolution of anti-phospholipid antibody titer as compared to intravenous steroids alone; RR 2.8 (95% CI 1.9-3.2, p<0.03). IgG subtype of anti-phospholipid antibody were more responsive to intravenous steroid as compared to intravenous steroids and cyclophosphamide combined; RR 1.6 (95% CI 1.1-2.7, p<0.01). Proteinuria resolved in 60 percent of the patient post treatment with

cyclophosphamide and intravenous steroids combined as compared to 34 percent patient's post treatment with steroid alone; RR 4.2 (95% CI 3.1-5.5, p<0.02).

DISCUSSION

Our study aimed at evaluating the association between anti-phospholipid antibody and IgA vasculitis. We also aimed to evaluate the association between anti-cardiolipin antibody, anti-beta (2) glycoprotein 1 antibody and Antiphosphatidylserine/prothrombin antibodies with IgA vasculitis. Treatment response with intravenous steroids and cyclophosphamide was also studied based on resolution of antibody titer. Sixty percent of patients were found to have anti-phospholipid antibody titer positive which is close to some studies. 4,8,9,11 Most common antibody subtype of anti-phospholipid antibody was IgG at 60 percent followed by IgM at 28 percent. Inflammatory markers were found to be elevated in patients with positive anti-phospholipid antibody titer. This finding further confirmed a known fact that antiphospholipid antibody are associated with increased inflammatory response. 12-14 More males were found to have positive anti-phospholipid antibody titer as compared to females but statistical significance could not be determined due to small sample size. Few studies report that males have increased titers for this antibody similar to our study. 9,11 Females were found to have more anti-cardiolipin antibody as compared to males which was confirmed by few studies.¹⁴

Intravenous steroids were found to be very effective in reducing the titer of anti-phosphatidylserine/prothrombin antibodies followed by anti-phospholipid antibody and then anti-cardiolipin antibody. Similar results were found in few studies. 15-17 Cyclophosphamide combined with intravenous steroids was found to be more effective than steroids alone with resolution of titer of Anti-phosphatidylserine/prothrombin antibodies up to 98 percent followed by anti-phospholipid antibodies. Some benefit of monoclonal antibodies was also seen but were far exceeded by steroids and cyclophosphamide. 17

Anti-phospholipid antibodies have been proven to have pro-thrombotic effect which was confirmed by our study which showed 100 percent of the patients who had thrombosis having positive anti-phospholipid antibody titer. IgM subtype of anti-phospholipid antibody was most commonly seen with thrombosis. Some studies had shown to have similar outcomes. 16 One study attributed increased thrombotic risk due to anti-phospholipid antibody secondary to neutrophil extracellular traps. 12 Some studies have also shown an association of thrombosis with anti-beta (2) glycoprotein 1 antibodies as well.18 We found statistically significant association between renal complication and anti-cardiolipin antibody. Our study also noted that increased protein excretion was more commonly seen in anti-phospholipid antibody as compared to anti-cardiolipin antibody. This is in agreement with few studies.^{7,10,12} Few studies have also shown association between kidney involvements with anti-cardiolipin antibody. ¹⁶ An association between anticardiolipin antibodies and cardiac complication was noted in our study. This is in agreement with few studies that report anti-cardiolipin antibody to accelerate atherosclerosis leading to cardiovascular disease with increased cardiovascular mortality. ¹⁹

Limitations

Current study was limited by short-term follow-up of the patient to see complete resolution of these antibodies after treatment with intravenous steroid or cyclophosphamide. Further studies are required to see the long-term benefit in resolution of these antibodies with these treatments. Further studies are also needed to evaluate association between anti-phospholipid antibodies and the thrombotic effect on spleen and mesenteric vein.

CONCLUSION

Current study was able to evaluate previous studies which reported statistically significant association between antiphospholipid antibodies with IgA vasculitis. Current study also confirmed that anti-phospholipid antibodies play a significant role in thrombosis and inflammation. Further studies are needed for the evaluating the effect of steroids IN patient with IgA vasculitis with specific IgG subtype of anti-phospholipid antibodies.

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Ethical approval: The study was approved by the

Institutional Ethics Committee

REFERENCES

- 1. Lally L, Sammaritano LR. Vasculitis in antiphospholipid syndrome. Rheum Dis Clin North Am. 2015;41(1):109-23.
- 2. Hočevar A, Rotar Ž, Žigon P, Čučnik S, Ostrovršnik J, Tomšič M. Antiphospholipid antibodies in adult IgA vasculitis: observational study. Clin Rheumatol. 2019;38(2):347-51.
- 3. Norden DK, Ostrov BE, Shafritz AB, Von-Feldt JM. Vasculitis associated with anti-phospholipid syndrome. In: Seminars in arthritis and rheumatism. USA: WB Saunders; 1995:24(4);273-81.
- 4. Kawakami T, Yamazaki M, Mizoguchi M, Soma Y. High titer of serum antiphospholipid antibody levels in adult Henoch-Schönlein purpura and cutaneous leukocytoclastic angiitis. Arthritis Rheum. 2008;59(4):561-7.
- 5. Chen KR, Carlson JA. Clinical approach to cutaneous vasculitis. Am J Clin Dermatol. 2008;9(2):71-92.
- 6. Tajima C, Suzuki Y, Mizushima Y, Ichikawa Y. Clinical significance of immunoglobulin A antiphospholipid antibodies: possible association

- with skin manifestations and small vessel vasculitis. J Rheumatol. 1998;25(9):1730-6.
- Bueno Filho R, Cordeiro AP, Almeida FT, Shaletich C, Costa RS, Roselino AM. Rare association of cutaneous vasculitis, IgA nephropathy and antiphospholipid antibody syndrome with tuberculous lymphadenitis. Clinics (Sao Paulo). 2012;67(12): 1497-500.
- 8. Burden AD, Tillman DM, Foley P, Holme E. IgA class anticardiolipin antibodies in cutaneous leukocytoclastic vasculitis. J Am Acad Dermatol. 1996;35(3 Pt 1):411-5.
- 9. Lockshin MD, Sammaritano LR, Schwartzman S. Validation of the Sapporo criteria for antiphospholipid syndrome. Arthritis Rheum. 2000;43(2):440-3.
- Filho R, Cordeiro AP, Almeida FT, Shaletich C, Costa RS, Roselino AM. Rare association of cutaneous vasculitis, IgA nephropathy and antiphospholipid antibody syndrome with tuberculous lymphadenitis. Clinics (Sao Paulo). 2012;67(12):1497-500.
- 11. Heineke MH, Ballering AV, Jamin A, Ben Mkaddem S, Monteiro RC, Van Egmond M. New insights in the pathogenesis of immunoglobulin A vasculitis (Henoch-Schönlein purpura). Autoimmun Rev. 2017; 16(12):1246-53.
- 12. Banday AZ, Jindal AK, Kaur A, Saka R, Parwaiz A, Sachdeva MUS, et al. Cutaneous IgA vasculitis-presenting manifestation of a novel mutation in the IKZF1 gene. Rheumatology (Oxford). 2021;60(3): e101-3.
- 13. Fujiwara K, Shimizu J, Tsukahara H, Shimada A. Lupus anticoagulant-hypoprothrombinemia syndrome and immunoglobulin-A vasculitis: a

- report of Japanese sibling cases and review of the literature. Rheumatol Int. 2019;39(10):1811-9.
- Yachoui R, Sehgal R, Amlani B, Goldberg JW. Anti-phospholipid antibodies-associated diffuse alveolar hemorrhage. In: Seminars in arthritis and rheumatism. USA: WB Saunders; 2015:44(6);652-7.
- Audemard-Verger A, Pillebout E, Guillevin L, Thervet E, Terrier B. IgA vasculitis (Henoch-Shönlein purpura) in adults: Diagnostic and therapeutic aspects. Autoimmun Rev. 2015;14(7):579-85.
- Selewski DT, Ambruzs JM, Appel GB, Bomback AS, Matar RB, Cai Y, et al. Clinical Characteristics and Treatment Patterns of Children and Adults With IgA Nephropathy or IgA Vasculitis: Findings From the CureGN Study. Kidney Int Rep. 2018;3(6):1373-84.
- 17. González-Gay MA, López-Mejías R, Pina T, Blanco R, Castañeda S. IgA Vasculitis: Genetics and Clinical and Therapeutic Management. Curr Rheumatol Rep. 2018;20(5):24.
- 18. Kimball AS, Obi AT, Diaz JA, Henke PK. The Emerging Role of NETs in Venous Thrombosis and Immunothrombosis. Front Immunol. 2016;7:236.
- 19. Du L, Wang P, Liu C, Li S, Yue S, Yang Y. Multisystemic manifestations of IgA vasculitis. Clin Rheumatol. 2021;40(1):43-52.

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