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Effect of TCM Combined with Western Medicine on CD19+ B Lymphocytes in Children with IgA Vasculitis with Nephritis

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Abstract: Introduction: Children with IgA vasculitis with nephritis (IgAVN) usually accepted TCM combined with western medicine therapy, but its effect on immune function is not clear, here is to analyze the change of peripheral blood CD19+ B lymphocytes in children with IgAVN after treatment of TCM combined with AECI or/and immunosuppressive agents. Methods: 46 children with IgAVN diagnosed from April 2016 to April 2017 were included and followed up in out-patient department till Dec 2021. All children with IgAVN were treated with TCM combined with ACEI or/and glucocorticoid steroids, with/without glucocorticoid-sparing agents. During treatment, urinary erythrocytes / urinary protein, peripheral blood CD (cluster of differentiation) of lymphocytes and serum immunoglobulins were tested before and after treatment. Results: All children with IgAVN except one were complete remission and no child progressed to CKD after 5-6 years follow-up. The counts of CD19+ B lymphocytes and CD19+ % in children with complete remission were significantly reduced after TCM combined with ACEI or/and glucocorticoid steroids with/without glucocorticoid-sparing agent ($P < 0.01$), the levels of serum IgA in children with complete remission and partial remission after 6 month combined therapy were significantly decreased ($P < 0.01$, $P < 0.05$), and IgM in partial remission children after 6 month combined therapy was significantly lower ($P < 0.05$). Conclusion: Peripheral blood CD19+ B lymphocytes in children with IgAVN decreased when it gained remission with treatment of TCM combined with ACEI or/and glucocorticoid steroids with/without glucocorticoid-sparing agent, suggesting that change of peripheral blood CD19+ B lymphocytes could be used to evaluate effect of therapy.

Keywords: IgA Vasculitis with Nephritis, Traditional Chinese Medicine (TCM), CD19+ B Lymphocytes

1. Introduction

Immunoglobulin A vasculitis (IgAV), formerly known as Henoch-Schönlein purpura (HSP), is the most common form of systemic, immune complex-mediated, small-vessel leukocytoclastic vasculitis in children [1], which is characterized by immunoglobulin A1 (IgA1)-dominant immune deposits affecting small vessels, and often involves skin, gastrointestinal tract, joints, and kidney [2]. Aberrantly glycosylated IgA1, deficient in galactose residues (Gd-IgA1), initiates the production of autoantibodies IgG or IgA directed against Gd-IgA1, resulting in circulating immune complexes (IgA-CIC), deposited in the renal mesangium leading to the release of cytokines and chemokines, development of inflammation, causing glomerular damage [3]. In children, IgAV has a median estimated incidence of 14 cases/100,000 children/year [4, 5]. The peak age is 6 years [6]. Renal involvement is the key factor for long-term prognosis, with a median 30% of cases progressing to renal failure. Children with early renal biopsy at diagnosis seem to have a better renal outcome at 5 years compared to those without an early biopsy at diagnosis or biopsied later [7]. Ongoing kidney

disease was the most common persistent organ manifestation, skin disease was the most common feature in relapsing patients, followed by nephritis. 7% patients developed nephritis after diagnosis, within the first 6 months of follow-up. At final follow-up, 15% patients had chronic kidney disease Stage G3a, and no clear choice of ACEI or/and glucocorticoid steroids with/without glucocorticoid-sparing agent including mycophenolic acid, cyclophosphamide, rituximab, calcineurin inhibitors, and complement inhibitors could be particularly effective [8, 9]. Though treated with ACEI or/and glucocorticoid steroids with/without glucocorticoid-sparing agent, some children still relapse with recurrent urinary red blood cells and urinary protein. In our hospital, Children with HSPN often accepted combined therapy with traditional Chinese medicine and ACEI or/and glucocorticoid steroids with/without glucocorticoid-sparing agent. The purpose of this study is to retrospectively analyze the changes of immune function of children with IgAVN treated with combined traditional Chinese and ACEI or/and glucocorticoid steroids with/without glucocorticoid-sparing agent in Children's Hospital of Fudan University.

2. Methods

2.1. Desgin and Patients

This study was approved by Medical Ethics Committee of Children's Hospital of Fudan University and performed at single clinical center. Children with IgAVN diagnosed from April 2016 to April 2017 in the inpatient department of Children's Hospital of Fudan University and voluntarily accepted TCM combined Western medicine were recruited and followed up in out-patient department till Dec 2021.

2.2. Diagnostic Criteria

Diagnosis criteria for IgAV with nephritis in children is defined as IgAV with isolated microscopic (and/or macroscopic) hematuria with or without proteinuria, nephritic and/or nephrotic syndrome [10].

2.3. Inclusion Criteria

Children satisfied with the diagnostic criteria of IgAVN and signed the informed consent by parents were included.

2.4. Exclusion Criteria

Children with abnormal renal function, or secondary IgAVN, or accompanied with other diseases, or blood pressure higher than the 95th percentile of blood pressure of children of the same age and sex, or difficult to oral traditional Chinese medicine were excluded.

2.5. Treatment

According to the KIDGO guideline and European consensus [10, 11], ACEI or glucocorticoid steroids with/without glucocorticoid-sparing agent was administered to children with IgAVN, added with oral granules of TCM. The clinical efficacy of the combined treatment was evaluated after 6 months and at the monment of complete remission. The granule is composed of Rehmannia glutinosa, red peony, Poria cocos, Cornus, yam, peony bark, Golden Cherry, Euryale ferox, Eclipta, licorice. During the treatment, urinary erythrocytes / urinary protein, peripheral blood CD (cluster of differentiation) of lymphocytes and serum immunoglobulins were tested before and after treatment. After treatment, complete remission was defined as both urinary RBC and protein are negative, partial remission as urinary protein or RBC negative but the other still positive, and no remission as urinary RBC or/and protein still positive as that before treatment.

2.6. Statistical Methods

Used Graphpad prism 9.3.1 soft to perform t-test for the changes of immune function of children before and after treatment.

3. Results

3.1. Efficacy of Treatment

There were 46 children included, of which 30 boys, 16 girls, and ages at diagnosed time varied from the minimum age of 4 years old to the maximum age of 14 years old, 3 cases aged 4-5 years old, 3 cases aged 6-7 years old, 10 cases aged 8 years old, 10 cases aged 9 years old, 5 cases aged 10 years old, 7 cases aged 11 years old, 4 cases aged 12 years old, 3 cases aged 13 years old and 1 case aged 14-15 years old. There were 4 children with isolated proteinuria, 5 children with isolated hematuria, 37 children with hematuria and proteinuria. According to renal pathology, there were 4 cases of Lee IIA, 4 cases of Lee IIIA, 4 cases of Lee IIIB, 2 cases of Lee IVA and 2 cases of Lee IVB. 46 children with IgAVN were treated with traditional Chinese medicine combined with ACEI or/and glucocorticoid steroids, with/without glucocorticoid-sparing agents.

Of the children with IgAVN after 6 months of combined therapy, 25 children (54.3%) were with complete remission, 8 children (17.4%) were with partial remission and 13 children (28.3%) were without remission. After 6 months therapy, 3 children were lost to follow-up, and one child still accepts treatment over 7 years due to hematuria relapses. All other children with IgAVN were complete remission and no child progressed to CKD after 5-6 years follow-up.

3.2. Impact of Combined Therapy on Children's Immune Function

After combined therapy for 6 months, absolute count of blood CD19+ B lymphocytes and the percentage of blood CD19+ B lymphocytes decreased significantly in children with complete remission ($p<0.01$), while absolute count of blood CD19+ B lymphocytes and the percentage of blood CD19+ B lymphocytes did not decrease significantly in children with partial remission or without remission ($p>0.05$).

Complete remission after followed-up from 6 to 72 months, absolute count of blood CD19+ B lymphocytes and the percentage of blood CD19+ B lymphocytes decreased significantly in children with complete remission ($p<0.01$) (Table 1). Serum IgA level in children with complete remission and with partial remission significantly decreased than that before treatment ($P<0.01$, $P<0.05$); the serum IgM level in children with partial remission significantly decreased than that before treatment ($P<0.05$) (Table 2).

Table 1. *Blood CD19+ B lymphocyte.*

		C-remission	P-remission	Non-remission	F-remission
CD19+ Count	Pre-T	672±106.4	553.3±104.3	772.3±268.5	728.6±98.36
	Post-T	310.9±40.2**	345±76.48	407.7±55.95	341.7±42.94**
CD19+%	Pre-T	22.68±2.09	18.36±1.91	21.17±4.3	23.68±2.078
	Post-T	13.47±1.09**	16.36±2.74	14.07±1.48	14.68±1.48**

C-: complete, P-: Partial, F-: Final, -T: treatment, **p<0.01.

Table 2. *Serum immunoglobins.*

		C-remission	P-remission	Non-remission
IgA	Pre-T	2.75±0.19	2.86±0.24	1.87±0.37
	Post-T	1.99±0.22**	2.05±0.31*	1.48±0.25
IgG	Pre-T	12.29±1.76	11.95±2.29	8.76±1.14
	Post-T	8.68±0.77	9.38±0.68	8.7±0.66
IgM	Pre-T	1.35±0.1	1.57±0.13	1.66±0.19
	Post-T	1.24±0.09	1.01±0.1*	1.14±0.08
IgE	Pre-T	44.38±12.67	57.48±5.08	199.7±102
	Post-T	25.55±5.55	53.82±13.88	179.8±75.93

C-: complete, P-: Partial, F-: Final, -T: treatment, * p<0.05.

4. Discussion

Henoch-Schönlein purpura, now called immunoglobulin A (IgA) vasculitis, is a systemic, immune complex-mediated, small-vessel leukocytoclastic vasculitis characterized by nonthrombocytopenic palpable purpura, arthritis, and abdominal pain. IgA vasculitis spontaneously resolves in 94% of children and 89% of adults. Long-term prognosis is dependent on the extent of renal involvement. Six months of follow-up is prudent to assess for disease relapse or remission [11]. 30-50% of children are shown nephrological symptoms during the course of the disease, and in up to 91% of cases within 6 weeks of the onset of the first symptoms. Nephritis may lead to chronic kidney disease (CKD) and end-stage renal disease (ESRD) [12]. Factors associated with long-term end-stage renal disease (ESRD) include baseline renal function impairment and baseline proteinuria >1 or 1.5 g/day, and on renal biopsy degree of interstitial fibrosis, sclerotic glomeruli and fibrinoid necrosis. Treatment of severe involvement, including severe gastrointestinal complications or proliferative glomerulonephritis, remains controversial, with no evidence that corticosteroids or immunosuppressive agents improved long-term outcome [13]. In this study, 46 children were included, 4 children were with isolated proteinuria, 5 children with isolated hematuria, 37 children with hematuria and proteinuria. Proteinuria in children ranged from 1+ to 3+ according to urine tape test. There were 4 cases of Lee IIA, 4 cases of Lee IIIA, 4 cases of Lee IIIB, 2 cases of Lee IVA and 2 cases of Lee IVB according to renal biopsy analysis. After 6 months of combined therapy, 25 children (54.3%) were with complete remission, 8 children (17.4%) were with partial remission and 13 children (28.3%) were without remission. Over 6 months therapy, 3 children were lost to follow-up, and one child accepts treatment for over 7 years due to hematuria relapses. All other children with IgAVN were complete remission and no child progressed to CKD after 5-6-year follow-up. It was shown 30% children with IgVAN present a persistent renal disease at the end of a 3-year follow-up [14]. In our study, except one child still accepts therapy due to hematuria relapses and 3 children were lost to follow-up, all other children were complete remission, and the renal function was normal.

Consensus management guidelines suggest using oral corticosteroids for milder disease, oral, or intravenous corticosteroids plus azathioprine or mycophenolate mofetil or intravenous cyclophosphamide for moderate disease and intravenous corticosteroids with cyclophosphamide for severe disease [15]. In HSP children who have severe nephritis or renal involvement with proteinuria of greater than 3 months, an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker should be considered in addition to corticosteroids to prevent and/or limit secondary glomerular injury [16]. The only randomised study performed in adults with IgAV and renal involvement showed that immunosuppressive therapy with cyclophosphamide did not improve renal outcome nor did it affect patient survival. rituximab could be an effective therapeutic option for adult-onset IgAV [17]. Children with IgAVN in Children's Hospital of Fudan University usually accepted treatment of traditional Chinese medicine on the basis of immunosuppressives, and it was found that most children with HSPN are mainly Yin deficiency, with blood stasis and dampness in accordance to TCM theory. The decoction originated from Liuwei Dihuang pill, Erzhi Pill and Shuilu erxiandan was used for children with IgAVN and displayed good effect on IgAVN. The decoction is composed of Radix rehmanniae, Paeonia obovata, Wolfiporia cocos, Cornus officinalis, Rhizoma dioscoreae, Paeonia suffruticosa, Rosa laevigata, Semen euryales, Herba ecliptae prostratae, Glycyrrhiza uralensis. Radix rehmanniae is sweet, bitter and slightly cold, which is moisten, and can nourish yin and clear away heat. It is good at entering the blood and can dredge the meridians and disperse blood stasis. Radix rehmanniae is matched with the bitterness and slight cold of Paeonia obovata,

which has the function of heat-clearing and blood-cooling, invigorating blood circulation and hemostasis. It is combined with Herba ecliptae prostratae to nourish the Yin of the liver and kidney by its sweet, sour and cool nature. Paeonia suffruticosa is cooling and pungent. It is good at clearing blood-heat accompanying yin-deficiency. Cornus officinalis is warm and nourishing, tonifying liver and kidney, benefiting essence and blood, defense against essence leakage and solidifying yuan. Rhizoma dioscoreae is sweet, flat and nourishing, so as to benefit kidney yin and consolidate essence, The combination of the two herbs is to consolidate essence and Qi, benefit kidney essence; Semen euryales is sweet and astringent, tonifying but not greasy, benefiting kidney and consolidating essence, Rosa laevigata tastes sour and astringent, good at entering kidney meridians, specialized in consolidating essence, and is compatible with Semen euryales. It is used for kidney deficiency and weakness, Wolfiporia cocos is sweet and light, exudes benefits, dispels water dampness but does not hurt health, and Glycyrrhiza uralensis is used to reconcile various herbs. In this study, 14 children accepted glucosteroid combined with herbs, 11 children were treated with mycophenolate mofetil, glucosteroid and herbs, 8 children were treated with cyclophosphamide and glucosteroid initially, followed with mycophenolate mofetil, glucosteroid and herbs, 19 children treated with herbs only. In 6 months, 25 children gained remission, one of which relapsed after 18 months and treated with mycophenolate mofetil, glucosteroid and herbs for 24 months, followed with mycophenolate mofetil and herbs for another 6 months, till now with only herbs treatment due to recurrent hematuria relapse. Within 12 months, another 4 children gained remission; till 18 months, another 3 remissions, till 36 months another 4 remission, till 72 months another 6 remission.

IgAN and IgAVN have a shared feature regarding galactose-deficient IgA1-oriented pathogenesis. Glomerular galactose-deficient IgA1 was specifically detected in IgAN and IgAVN but not in the other renal diseases. Galactose-deficient IgA1 was localized predominantly in the mesangial region as IgA deposition [18]. CD3+, CD4+, CD8+ and NK cell levels of peripheral blood mononuclear cells in the HSPN group and the NHSPN group significantly decreased, and the CD19+ level significantly elevated; whereas the HSPN group had a more significant change than the NHSPN group. Serum IgA and IgG of the HSPN group and the NHSPN group significantly increased, and IgM, C3, and C4 significantly decreased; while the HSPN group had a more significant change than the NHSPN group [19]. All patients with IgA nephropathy were significantly more likely to have CD19(+)CD5(+) B cells in the peripheral blood, peritoneal fluid, and kidney biopsies. Patients who had IgA nephropathy and responded to treatment demonstrated a significant decrease in CD19(+)CD5(+) B cells in the peripheral blood, peritoneal fluid, and kidney. Patients who had IgA nephropathy and did not respond to treatment, the frequency of CD19(+)CD5(+) B cells did not change. CD19(+)CD5(+) B cells isolated from patients with untreated IgA nephropathy expressed higher levels of IgA, produced more IFN-gamma, and were more resistant to CD95L-induced apoptosis than cells isolated from control subjects and patients with lupus [20]. After 6-month therapy with this decoction combined with immunosuppressive agents, serum IgA decreased significantly in children with complete or partial remission, serum IgM decreased in children with partial remission. CD19+ B lymphocyte in children with complete remission decreased significantly after combined therapy.

5. Conclusion

Treatment of ACEI or/and glucocorticoid steroids with/without glucocorticoid-sparing agent combined with TCM could reduce peripheral blood CD19+ B lymphocytes in children with IgAVN when the disease gained remission, suggesting that change of peripheral blood CD19+ B lymphocytes could be used to estimate therapy effect, and further study should be focused on the mechanism of herbs effect on peripheral blood CD19+ B lymphocytes in children with IgAVN.

Author Contributions

Liu Jun-chao and Yu Jian arranged TCM treatment for children with IgVAN in Children's Hospital of Fudan University. Xu Hong, Shen Qian, Sun Li, Liu Hai-mei, Li Guo-min arranged Western medicine treatment for children with IgAVN in Children's Hospital of Fudan University. Data was collected by Liu Junchao, and Liu Junchao also analyzed the data for statistics.

Conflict of Interest

All the authors do not have any possible conflicts of interest.

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References

[1] M. Piram, A. Mahr, Epidemiology of immunoglobulin A vasculitis (Henoch-Schonlein): current state of knowledge, Curr Opin Rheumatol. 25 (2013) 171-8, doi: 10.1097/BOR.0b013e32835d8e2a.

[2] J C Jennette, R J Falk, P A Bacon, et al., 2012 revised international chapel hill consensus conference nomenclature of vasculitides, Arthritis Rheum. 65 (2013) 1-11, doi: 10.1002/art.37715.

[3] Licia Peruzzi, Rosanna Coppo, IgA vasculitis nephritis in children and adults: one or different entities?, Pediatr Nephrol. 36 (2021) 2615-2625, doi: 10.1007/s00467-020-04818-7.

[4] S Hu, A Birg, M Hovaida, M W Gavin, D McCarthy, Avoiding "Rash" Conclusions: Challenge of IgA Vasculitis in Adults, Dig Dis Sci. 62 (2017) 874-878, doi: 10.1007/s10620-017-4505-2.

[5] Janet M M Gardner-Medwin, Pavla Dolezalova, Carole Cummins, Taunton R Southwood, Incidence of Henoch-Schönlein purpura, Kawasaki disease, and rare vasculitides in children of different ethnic origins, Lancet. 360 (2002) 1197-202, doi: 10.1016/S0140-6736(02)11279-7.

[6] Pillebout E, Verine J, Henoch-Schonlein purpura in the adult, Rev Med Interne. 35 (2014) 372-81, doi: 10.1016/j.revmed.2013.12.004.

[7] Yang J, Okpe A, Pathak A, In Every Man, There Is a Child: Henoch-Schonlein Purpura in an Adult With Liver Cirrhosis, Cureus. 13 (2021) e18270, doi: 10.7759/cureus.18270.

[8] Delbet JD, Parmentier C, Herbez Rea C, et al., Management of IgA Vasculitis with Nephritis, Paediatr Drugs. 23 (2021): 425-435, doi: 10.1007/s40272-021-00464-0.

[9] Marina Avramescu, Annie Lahoche, Julien Hogan, et al., To biopsy or not to biopsy: Henoch-Schönlein nephritis in children, a 5-year follow-up study, Pediatr Nephrol. 37 (2022): 147-152, doi: 10.1007/s00467-021-05086-9.

[10] Ozen S, Marks SD, Brogan P, et al., European consensus-based recommendations for diagnosis and treatment of immunoglobulin A vasculitis-the SHARE initiative, Rheumatology (Oxford). 58 (2019): 1607-1616, doi: 10.1093.

[11] Reamy BV, Servey JT, Williams PM, Henoch-Schonlein Purpura (IgA Vasculitis): Rapid Evidence Review, Am Fam Physician. 102 (2020) 229-233.

[12] Dyga K, Szczepańska M, IgA vasculitis with nephritis in children, Adv Clin Exp Med. 29 (2020): 513-519, doi: 10.17219.

[13] Audemard-Verger A, Pillebout E, Guillevin L, et al., IgA vasculitis (Henoch-Shonlein purpura) in adults: Diagnostic and therapeutic aspects, Autoimmun Rev. 14 (2015): 579-85, doi: 10.1016/j.autrev.2015.02.003.

[14] Delbet JD, Geslain G, Auger M, et al., Histological prognostic factors in children with Henoch-Schonlein purpura nephritis, Pediatr Nephrol. 35 (2020): 313-320, doi: 10.1007/s00467-019-04363-y.

[15] Oni L, Sampath S, Childhood IgA Vasculitis (Henoch Schonlein Purpura)-Advances and Knowledge Gaps, Front Pediatr. 7 (2019) 257, doi: 10.3389 / fped. 2019. 00257.

[16] Leung AKC, Barankin B, Leong KF, Henoch-Schönlein Purpura in Children: An Updated Review, Curr Pediatr 16 (2020) 265-276, doi: 10.2174 / 1573396316666200508104708.

[17] Maritati F, Canzian A, Fenaroli P, Vaglio A, Adult-onset IgA vasculitis (Henoch-Schonlein): Update on therapy, Presse Med. 49 (2020) 104035, doi: 10.1016/j.lpm.2020.104035.

[18] Suzuki H, Yasutake J, Makita Y, et al., IgA nephropathy and IgA vasculitis with nephritis have a shared feature involving galactose-deficient IgA1-oriented pathogenesis, Kidney Int. 93 (2018) 700-705, doi: 10.1016/j.kint.2017.10.019.

[19] Su Q, Jiang L, Chai J, et al., Changes of Peripheral Blood Lymphocyte Subsets and Immune Function in Children with Henoch-Schonlein Purpura Nephritis, Iran J Immunol. 18 (2021): 221-225, doi: 10.22034/iji.2021.89742.1964.

[20] Yuling H, Ruijing X, Xiang J, et al., CD19+CD5+ B cells in primary IgA nephropathy, J Am Soc Nephrol. 19 (2008) 2130-9, doi: 10.1681/ASN.2007121303.