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Association of Childhood IgA Vasculitis With Allergic Rhinitis and Chronic Rhinosinusitis

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Introduction: Immunoglobulin A vasculitis (IgAV) is related to chronic inflammation; however, little is known about the associations between IgAV and allergic rhinitis (AR) or chronic rhinosinusitis (CRS). We evaluated the relationships among IgAV, AR, and CRS in children.

Methods: The clinical data of children with IgAV who were hospitalized from January to December 2019 were analyzed retrospectively. Four groups were created, the simple AR, simple CRS, AR + CRS, and non-AR or non-CRS groups, to explore the relationships among IgAV, AR, and CRS.

Results: We included 504 children with IgAV; and 357 (70.8%) were combined with AR or CRS, including 51 with simple AR, 70 with simple CRS, and 236 with AR + CRS. The incidences of renal involvement and recurrent rash were significantly higher in the simple AR group than in the non-AR or non-CRS group ($P < 0.001$). The incidences of renal involvement and recurrent rash were significantly higher in the AR + CRS group than in the non-AR or non-CRS group ($P < 0.001$). The incidences of renal involvement between the simple CRS group and non-AR or non-CRS group did not differ significantly, but that of recurrent rash was significantly higher than that in the other groups ($P < 0.001$). Age, abdominal pain, recurrent rash, simple AR, and AR combined with CRS were risk factors for renal involvement (all odds ratio [OR] > 1, $P < 0.05$).

Conclusion: Chronic rhinitis may be related to the pathogenesis of IgAV, and AR or CRS may be the triggering factors of IgAV. AR may be a risk factor for renal involvement and recurrent rash in patients with IgAV.

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IgAV, formerly known as Henoch-Schonlein purpura, is the most common vasculitis in children, mainly involving the skin, gastrointestinal tract, joints, and kidneys.[1] Invasion of the central nervous system, scrotum, and lungs has been reported in a few cases.[2-4] Development of IgAV nephritis (IgAVN) from IgAV occurs in approximately 20% to 80% of cases[5] and is the most serious complication of IgAV and the main factor affecting the long-term prognosis.[6]

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The incidence of IgAV is 3 to 27 of 100,000 children worldwide.[7] The annual incidence of IgAV is significantly lower in Black children than in White or Asian children.[8] The incidence of IgAV is highest in children aged 4 to 7 years old, the average onset age is 6 years, and the male-to-female ratio is 1.2:1.[8] IgAV mainly occurs in late autumn, winter, and spring but rarely in summer.[9] The main IgAV-triggering factor is mucosal infection, especially respiratory and intestinal mucosal infections.[10]

In previous cases, we found that in patients with IgAV, it is often accompanied with AR and/or CRS, suggesting that AR and/or CRS may be the triggers of IgAV. In addition, faced with the treatment of IgAV, clinicians often ignore potential long-term triggers. CRS and AR are chronic diseases that cause nasal inflammation.[11] AR is mainly mediated by IgE and is a

chronic allergic inflammation of nasal mucosa characterized by paroxysmal sneezing, runny nose, and stuffy nose.[12] CRS is a chronic infectious inflammation of the paranasal sinus mucosa.[13] The link between allergies and recurrent infection is well-known, and allergies are often associated with chronic infection and tonsillitis.[14] Chronic tonsillitis may be related to the pathogenesis of IgAV and is one of the important factors leading to recurrent rash and IgAVN in IgAV.[15] AR is a possible risk factor for recurrent IgAV.[16] The sources of ear, nose, throat, and oral cavity infections in children with IgAV have been evaluated, and the prevalence of sinusitis was significantly increased.[17] Active treatment of oral and otorhinolaryngological diseases may reduce the risk of recurrent IgAV or nephritis.[18]

The correlation between AR, CRS, and IgAV has not been reported in detail, especially because there is little or no related research outside Asia. The study aim was to conduct a retrospective analysis of pediatric IgAV cases in our hospital to explore the relationships among IgAV, AR, and CRS; so that clinicians may pay attention to the treatment of IgAV triggers in its treatment in order to achieve the purpose of effective control of IgAV.

METHODS

Subjects

The study subjects were children with IgAV who were hospitalized in our hospital from January to December 2019. These are based on the EULAR/PRINTO/PRES IgAV classification criteria;[19,20] purpura or petechiae (mandatory) with lower limb predominance and at least any of the following: (i) Abdominal pain: diffuse abdominal colicky pain with acute onset assessed by history and physical examination. May include intussusception and gastrointestinal bleeding. (ii) Histopathology: typically leukocytoclastic vasculitis with predominant IgA deposit or proliferative glomerulonephritis with predominant IgA deposit. (iii) Arthritis or arthralgia: arthritis of acute onset defined as joint swelling or joint pain with limitation on motion. Arthralgia of acute onset is defined as joint pain without joint swelling or limitation on motion. (iv) Renal involvement is characterized by proteinuria (24-hour urinary protein $>$ 0.3 g or morning urine albumin-to-creatinine $>$ 30 mg/mmol) or hematuria (urine erythrocyte $>$ 5/high power field) or erythrocyte tube type. The CRS diagnostic criteria were as follows[21]: $\geq$ 2 symptoms of suppurative rhinorrhea, nasal congestion, facial pressure or pain or cough for $\geq$ 3 months, and evidence of endoscopic mucosal edema, purulent drainage or nasal polyps, and/or computed tomography scan showing ostiomeatal complex or sinus edema. The following AR diagnostic criteria were used[22]: when patients present with a history and physical exam consistent with an allergic cause and 1 or more of the following symptoms: nasal congestion, runny nose, itchy nose, or sneezing. Findings of AR consistent with an allergic cause include, but are not limited to, clear rhinorrhea, nasal congestion, pale discoloration of the nasal mucosa, and red and watery eyes. For patients who were clinically diagnosed as AR but for whom empirical treatment was ineffective or when the diagnosis was not clear, IgE (skin or blood) tests were performed. AR includes intermittent ($<$ 4 d/wk or $<$ 4 wk/yr) and persistent ($>$ 4 d/wk and $>$ 4 wk/yr). For patients with AR or CRS who cannot be diagnosed, we ask senior rhinologists to help with the diagnosis. Recurrent rash was defined as IgAV with new rash more than 3 times a month, or asymptomatic patients with new lesions or other systemic symptoms at least 2 weeks after treatment.[23] The follow-up period is 6 months, which is based on the fact that 97% of cases have renal involvement within 6 months after the onset of the first symptom.[24] The diagnosis of AR and CRS in all patients was earlier than or at the same time as IgAV.

Data Collection

The clinical data of the inpatients with IgAV, such as gender, age, main clinical manifestations, recurrent rash, and chronic rhinitis, were collected. The children with IgAV were divided into 4 groups: the simple AR group, simple CRS group, AR + CRS group, and non-AR or non-CRS group. The clinical data from the groups were compared and statistically analyzed.

Statistical Analysis

SPSS ver. 26.0 software (IBM SPSS Statistics for Windows, IBM Corp., Armonk, NY) was used to perform statistical analysis, and the normally distributed measurement data were analyzed by the independent sample t test. Nonnormally distributed data were described by the median (P25–P75), and the rank sum test was used for comparisons between groups. The counting data were described by the constituent ratio or as a percentage. The Chi-square test was performed to evaluate significant differences between the subject groups. Bivariate analysis was conducted to examine the predictor variables on the renal involvement. Only those variables with $P < 0.25$ during bivariate analyses were chosen for subsequent analyses. Only noncollinear covariates were included in binary logistic regression to assess the possible association between each independent and dependent variable. $P < 0.05$ was statistically significant.

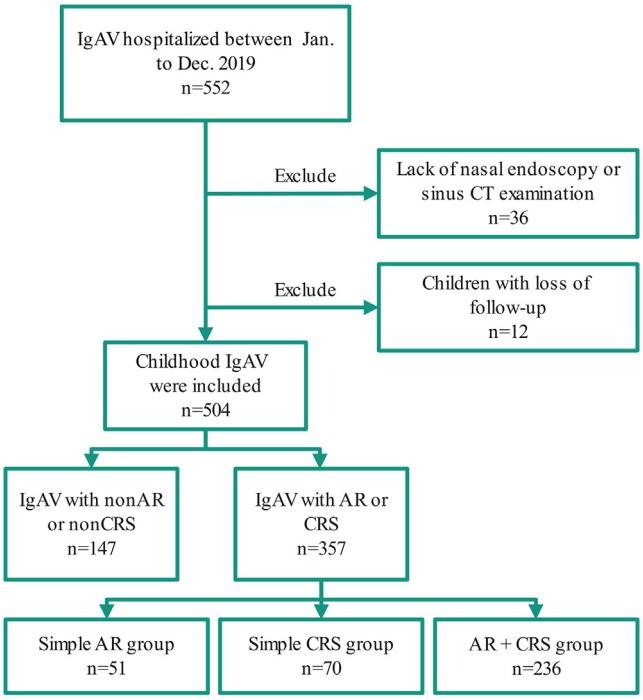

Figure 1. Flow chart of patient screening. AR, allergic rhinitis; CRS, chronic rhinosinusitis; IgAV, IgA vasculitis.

RESULTS

Characteristics of the Children With IgAV

A total of 552 children with IgAV were treated in our pediatrics department from January to December 2019; of those, 36 children repeatedly had ≥2 symptoms of suppurative rhinorrhea, nasal congestion, facial pressure or pain or cough, but lacked nasal endoscopy or sinus computed tomography examination, so they were excluded. Twelve children were excluded because of the loss of follow-up. Finally, 504 children were analyzed, including 272 males (54.0%) and 232 females (46.0%), with an average age of 8.6 ± 3.5 years. IgAV was associated with abdominal pain in 231 cases (45.8%), arthritis or arthralgia in 310 cases (61.5%), renal involvement in 244 cases (48.4%, including 52 cases of isolated hematuria, 73 cases of isolated albuminuria and 119 cases of proteinuria plus hematuria), and recurrent rash in 187 cases (37.1%). There were 357 cases of IgAV combined with AR or CRS, including 51 cases with simple AR, 70 with simple CRS, and 236 with AR + CRS. There were 147 children with non-AR or non-CRS (Figure 1 and Table 1).

Comparisons of IgAV Between the Simple AR Group and the Non-AR or Non-CRS Group

There were no significant differences in gender and age between the AR group and non-AR or non-CRS groups ($P > 0.05$). There were no significant differences in the incidences of abdominal pain and arthralgia between the 2 groups; however, the incidences of renal involvement and recurrent rash were significantly higher in the simple AR group than in the non-AR or non-CRS group ($P < 0.05$) (Table 2).

Table 1. Clinical manifestations of of 504 children with IgAV

Patient characteristics	Number of cases (%)
Abdominal pain	231 (45.8%)
Arthritis or arthralgia	310 (61.5%)
Renal involvement	244 (48.4%)
Isolated hematuria	52 (21.3%)
Isolated proteinuria	73 (29.9%)
Hematuria and proteinuria	119 (48.8%)
Recurrent rash	187 (37.1%)
AR or CRS	357 (70.8%)
Simple AR group	51 (14.3%)
Simple CRS group	70 (19.6%)
AR and CRS group	236 (66.1%)

AR, allergic rhinitis; CRS, chronic rhinosinusitis; IgAV, IgA vasculitis.

Comparisons Between IgAV With Simple CRS Group and the Non-AR or Non-CRS Group

There were no significant differences in gender and age between the simple CRS group and non-AR or non-CRS group ($P > 0.05$). There were no significant differences in the incidences of abdominal pain, arthralgia, and renal involvement between the 2 groups; however, the incidence of recurrent rash was significantly higher in the CRS group than in the control group ($P < 0.001$) (Table 3).

Comparisons Among the AR + CRS Group and the Non-AR or Non-CRS Group

There were no significant differences in gender and age between the AR + CRS group and non-AR or non-CRS group ($P > 0.05$). There were no significant differences in the incidences of abdominal pain and arthralgia between the 2 groups; however, the incidence of renal involvement and recurrent rash were significantly increased in AR + CRS group ($P < 0.001$) (Table 4).

Factors Related to Renal Involvement

In order to explore the influencing factors of renal involvement, the data of this study were taken as samples, with renal involvement as dependent

Table 2. Comparisons of IgAV between the simple AR group and the non-AR or non-CRS group

Patient characteristics	Simple AR	Non-AR or Non-CRS	t or $\chi 2$	*P*-value
Cases	51	147		
Male-to-female ratio	32:19	84:63	0.490	0.484
Age (yr)	8.9 ± 3.2	8.1 ± 4.0	1.351	0.180
Abdominal pain	28 (54.9%)	70 (47.6%)	0.803	0.370
Arthritis or arthralgia	32 (62.7%)	85 (57.8%)	0.379	0.538
Renal involvement	28 (54.9%)	51 (34.7%)	6.448	0.011
Recurrent rash	25 (49.0%)	17 (11.6%)	31.783	0.000

AR, allergic rhinitis; CRS, chronic rhinosinusitis; IgAV, IgA vasculitis.

Table 3. Comparisons of IgAV between the simple CRS group and the non-AR or non-CRS group

Patient characteristics	Simple CRS	.Non-AR or non-CRS	*t* or $\chi 2$	*P*-value
Cases	70	147		
Male-to-female ratio	35:35	84:63	0.977	0.323
Age (yr)	8.5 ± 3.2	8.1 ± 4.0	0.830	0.408
Abdominal pain	24 (34.3%)	70 (47.6%)	3.433	0.064
Arthritis or arthralgia	45 (64.3%)	85 (57.8%)	0.825	0.364
Renal involvement	19 (27.1%)	51 (34.7%)	1.237	0.266
Recurrent rash	23 (32.9%)	17 (11.6%)	14.299	<0.001

AR, allergic rhinitis; CRS, chronic rhinosinusitis; IgAV, IgA vasculitis.

Table 5. Predictors of renal involvement: bivariate analysis

Variables	Correlation coefficient	*P*-value
Gender	−0.026	0.554
Age	0.196	<0.001
Abdominal pain	0.105	0.018
Arthritis or arthralgia	−0.041	0.353
Recurrent rash	0.209	<0.001
Simple AR	0.162	<0.001
Simple CRS	−0.010	0.819
AR and CRS	0.288	<0.001

AR, allergic rhinitis; CRS, chronic rhinosinusitis.

variables; and gender, age (≤6 years, 6–12 years, and 13–18 years old), abdominal pain, arthritis or arthralgia, recurrent rash, simple AR, simple CRS, and AR combined with CRS as independent variables. First, bivariate analysis was performed, and the results showed that age, abdominal pain, recurrent rash, simple AR, and AR combined with CRS were significantly correlated with renal involvement (Table 5). Multicollinearity analysis was performed before incorporating these factors that were significantly associated with renal involvement into the binary Logistic regression model. The results showed no multicollinearity and retrospective analysis could be performed. Age (OR = 1.823, 95% confidence interval [CI] = 1.367–2.431), abdominal pain (OR = 1.690, 95% CI = 1.136–2.513), recurrent rash (OR = 1.616, 95% CI = 1.067–2.448), simple AR (OR = 7.046, 95% CI = 3.470–14.308), AR combined with CRS (OR = 4.380, 95% CI = 2.861–6.707) were risk factors for renal involvement (Table 6).

DISCUSSION

There are few detailed reports on the relationship between chronic rhinitis and IgAV. In this study, patients with IgAV combined with AR or CRS accounted for 70.8% of the subjects, among whom IgAV combined with AR accounted for 56.9% and IgAV combined with CRS accounted for 60.7%. The incidence of AR in Chinese children is approximately 22%,[25] and the incidence rate of CRS in children is 2.1% to 15.0%,[26] both of which are significantly lower than those in children with IgAV combined with AR and CRS; suggesting that AR, CRS, and IgAV may be correlated. AR or CRS may be the trigger of IgAV. The incidence of renal involvement and recurrent rash was significantly increased in patients with IgAV with AR, and the possibility of recurrent rash was significantly increased in patients with IgAV with CRS. These data suggest that AR or CRS may be one of the increased risk factors for renal involvement and recurrence in patients with IgAV.

The International Chapel Hill Consensus Conference in 2012 renamed Henoch-Schonlein purpura to IgAV. This consensus is based on the pathophysiological characteristics of the disease, that is, abnormal IgA deposits in the blood vessel wall.[27] This study suggests that AR may be the trigger of IgAV, which may not be due to "allergic" factors, but may be related to mucosal immune response and increased susceptibility to viruses and bacteria after the destruction of respiratory epithelial barrier in patients with AR.

It is reported that 90% of patients with IgAV develop symptoms of upper respiratory tract infection within 3 weeks before onset.[28] It is suggested that infection or contact with mucosal antigen may trigger the pathogenesis of IgAV. This can also explain the regional and seasonal distribution of IgAV.[29] Studies have found that AR is closely related to virus infection.[30] During allergic inflammation, the expression of ICAM-1,[31,] the main receptor of rhinovirus, is

Table 4. Comparisons of IgAV between the AR + CRS group and the non-AR or non-CRS group

Patient characteristics	AR + CRS	non-AR or non-CRS	*t* or $\chi 2$	*P*-value
Cases	236	147		
Male-to-female ratio	121:115	84:63	1.255	0.263
Age (yr)	8.9 ± 3.4	8.1 ± 4.0	1.700	0.090
Abdominal pain	109 (46.2%)	70 (47.6%)	0.075	0.785
Arthritis or arthralgia	148 (62.7%)	85 (57.8%)	0.909	0.340
Renal involvement	146 (61.9%)	51 (34.7%)	26.770	<0.001
Recurrent rash	25 (49.0%)	17 (11.6%)	63.091	<0.001

AR, allergic rhinitis; CRS, chronic rhinosinusitis; IgAV, IgA vasculitis.

Table 6. Binary Logistic regression analysis of renal involvement related factors

Variables	*P*-value	OR (95% CI)	VIF
Age	<0.001	1.823 (1.367–2.431)	1.022
Abdominal pain	0.010	1.690 (1.136–2.513)	1.013
Recurrent rash	0.023	1.616 (1.067–2.448)	1.101
Simple AR	<0.001	7.046 (3.470–14.308)	1.130
AR and CRS	<0.001	4.380 (2.861–6.707)	1.219

AR, allergic rhinitis; CRS, chronic rhinosinusitis; CI, confidence interval; OR, odds ratio; VIF (variance inflation factor), an indicator of measuring multicollinearity; VIF >1 0 indicates high correlation and VIF around 1 indicates no such correlation and regression can be conducted.

upregulated. This phenomenon increases the tissue's susceptibility to rhinovirus infection. IL-13 is also released during allergic airway inflammation. IL-13 affects the ciliary beat frequency, thereby promoting viral invasion of nasal mucosa.[32] Nasal irrigation can be used alone or in combination with other treatments for a variety of diseases, including CRS and AR, and for the treatment and prevention of upper respiratory tract infections, especially in children.[33]

The relationship between AR and CRS is controversial, is commonly thought to be an inciting factor in the development of CRS or a comorbidity or associated factor for the propagation of the CRS disease state. The basic principle is that mucosal inflammation caused by allergy may lead to obstruction of the orifice of the paranasal sinus, leading to secondary infection.[34] CRS is usually divided into 2 subtypes, namely chronic sinusitis with nasal polyps and CRS without nasal polyps. Studies have shown that there is no correlation between allergies and disease severity in patients with chronic sinusitis with nasal polyps. There may be a link between allergy and CRS without nasal polyps, especially 2 subtypes of allergic fungal rhinosinusitis and central compartment atopic disease.[34]

In addition, the oral and intestinal microflora of children with IgAV changed significantly.[35,36] The changes in mucosal microbiota in the respiratory and digestive tracts may be an important triggering factor of IgAV. A flora imbalance in both patients with AR and those with CRS have previously been reported.[37,38] In the absence of acute infection, the destruction of stable microflora may lead to the deterioration of chronic inflammatory diseases.[39]

This study showed that recurrent skin purpura is more likely to develop in the simple AR group, simple CRS group, and AR with CRS group than in the non-AR or non-CRS group; and patients with AR and CRS are more likely to have renal involvement. We speculate that there are 2 reasons why patients with IgAV with AR and CRS have recurrent rashes and an increased risk of renal involvement. First, the nasal-associated lymphoid tissue located in the lamina propria and submucosa of the nasal cavity is the main site for the induction of abnormal glycosylated IgA1. When nasal-associated lymphoid tissue encounters mucosal antigens or exogenous antigens, antigen-presenting cells activate immature B cells to convert into IgA antibody-secreting cells through T-cell dependent and T-cell independent pathways. T-cell independence is induced by cytokines derived from activated protein C, activated by TLR ligands, such as IL-6, B cell–activating factor, and a proliferation-inducing ligand. Sustained and overactivation of TLR affects B cell–activating factor or a proliferation-inducing ligand and promotes the production of glycosylated IgA1.[40] Second, patients with AR may have recurrent tonsillitis.[14] The germinal center of the tonsil contains cells that produce A proliferation-inducing ligand. B lymphocyte in the germinal center of the tonsil may be involved in the pathogenesis of IgAVN by producing A proliferation-inducing ligand. Many studies in Japan have proven that tonsillectomy can effectively treat IgAVN.[41-43] There was no significant difference in renal involvement between IgAV with simple CRS group and non-AR or CRS group, and it could not be ruled out that the renal involvement was related to different types of CRS, especially CRS related to infection. There is no clear classification of CRS in this study. In addition, prevalence of CRS does appear to be age-related. It is most common among 2- to 6-year-olds with gradually decreasing prevalence with increasing age.[44] Renal involvement increases with age.[45] This may be an important reason why there is no significant difference between the 2 groups.

The analytical data shows that age, abdominal pain, and recurrent rash are the risk factors of renal injury, which is basically consistent with the conclusions of previous studies.[46-48] There are many studies on the factors influencing renal involvement in IgAV. Retrospective analysis shows that age and abdominal pain are independent risk factors for renal involvement in patients with IgAV.[49] A retrospective analysis of 2731 children with IgAV showed that age of onset $>$ 6 years, cold season, interval between symptom onset and diagnosis $>$ 8 days, living in rural areas, recurrence, angioedema, and central nervous system involvement were important risk factors for renal involvement.[45] In these studies, the most common risk factors for renal involvement are age, digestive tract reaction, and recurrent rash. In turn, renal involvement increases the risk of recurrence of purpura.[16] The incidence of renal involvement increases with age, which may be related to the content of IgA. The average saliva IgA level increased with age, and the average saliva IgA level was significantly higher for the subjects aged 11 to 20 years than for the subjects aged 1 to 10 years.[50] Another possibility is the number of memory B cells. The study found that there is high expression of memory B cells in the tonsil and peripheral blood of patients with IgA nephropathy.[51] The number of memory B cells is higher in adult peripheral blood than in children.[52] Abdominal pain can be used as a risk factor for renal involvement, which may be the injury of intestinal mucosa and further aggravate the immune response. Studies have shown that a variety of renal diseases are closely related to mucosal over immune response and proposed the concept of a mucosal-renal axis.[53]

In a Japanese study, 74.0% of children with IgAV had sinusitis, tonsillitis, and other infectious diseases, of which the prevalence of sinusitis was the highest, accounting for 53.7%. In this study, through active intervention of infected foci, that is, patients with focal infection were treated with antibiotics, sinus irrigation, tooth extraction, and so forth, the incidence of glomerulonephritis decreased from 17% to 54% previously reported to 13%.[17] Periodontitis, tonsillitis, and sinusitis are closely related to IgAV. Through the treatment of local lesions, the recurrence rate of IgAVN is significantly reduced.[41,54] Active treatment of AR or CRS may reduce kidney involvement and recurrent rash. Unfortunately, we have not done a comparative trial, which is the deficiency of this study.

To summarize, chronic rhinitis may be related to the pathogenesis of IgAV, and AR or CRS may be the triggering factors of IgAV. AR may be a risk factor for renal involvement and recurrent rash in patients with IgAV.

DISCLOSURE

All the authors declared no competing interests.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request, conditional on institutional review board approval.

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