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Comparison of the clinicopathological characteristics of children with anti-neutrophil cytoplasmic antibody-associated vasculitis with/without infection at diagnosis

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Abstract

Background Infectious episodes contribute to morbidity and mortality in patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). Renal involvement, also known as ANCA-associated glomerulonephritis (AGN), is frequently observed in AAV. Little is known about whether co-infection at initial diagnosis is associated with renal outcome and prognosis in children with AGN.

Methods Clinical and prognostic data for children admitted to our center with AAV from January 2001 to August 2023 were analyzed retrospectively. We compared the incidence of end-stage renal disease (ESRD) and mortality according to infection status at initial diagnosis.

Results A total of 33 children with AGN were included in this study, 22 had an infection at the time of AGN diagnosis. A trend toward higher levels of proteinuria in the infected group than in the non-infected group was observed ($p=0.42$). Patients in the infected group had higher creatinine and lower eGFR values than those in the non-infected group ($p=0.09$). A significant decrease in HGB was observed in the infected group ($p<0.05$). There were no significant differences in the baseline values of ALB and complement c3 between the two groups. A similar proportion of patients in both groups required dialysis at the time of diagnosis (27.3% vs. 31.8%). Patients with infection presented with significantly greater ESR and CRP levels ($p<0.05$), and the most commonly infected site was the lung. After 6 months of treatment, compared with those in the non-infected group, the median levels of creatinine and proteinuria were higher in the infected group. Besides, lower levels of eGFR and ALB were also observed in the infected group. 5 (45.5%) and 13 (59.1%) patients died or progressed to ESRD, respectively, in the non-infected group and infected group at the last follow-up.

Conclusions Infection at initial diagnosis does not affect the outcomes of children with AGN, although it could lead to a reduction in kidney function.

Keywords Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, Infection, End-stage renal disease

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Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a systemic autoimmune disorder that is characterized by small- and medium-sized vascular inflammation, with an estimated incidence of 200–400 cases per million people [1–4]. According to the patterns of clinical involvement, AAV consists of four distinct disease phenotypes: granulomatosis with polyangiitis (GPA, formerly Wegener's granulomatosis), microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis (EGPA), and renal-limited vasculitis (RLVs). AAV has been reported mainly in adults and rarely in children because of the rare incidence of vasculitis in children and because most reports are based on a single center [5].

AAV involves many organs, such as the kidneys, lungs, skin, and brain. Renal involvement, also known as ANCA-associated glomerulonephritis (AGN), is frequently observed in ANCA patients, especially GPA and MPA patients, and is associated with substantial morbidity and mortality [6–8]. AGN occurs in more than 50% of patients and then progresses to renal failure or even death within 5 years; in some cases, dialysis is necessary at the time of initial diagnosis [9, 10]. Although AAV is rare in childhood, kidney involvement is very common and severe in children with AAV, with an incidence of 60-90%, and the rate of ESRD ranges from 10 to 40% [5, 11]. Hence, identifying potential prognostic clinical indicators of renal outcome in children with AGN is important.

Chronic nasal transport of *Staphylococcus aureus* increases the risk of developing AAV [12]. Moreover, infections may occur both in the early stages of the onset of AAV and as a complication in individuals receiving treatments. Mechanistically, infection leads to a more disturbed and inflammatory response in patients, as indicated by increased disease activity at the onset of AAV in patients. In addition, the infection rate in patients with AGN was higher than that in patients with other kidney diseases [13]. However, there is still a lack of research on the impact of co-infection in patients with early AGN on poor kidney prognosis.

Thus, we retrospectively analyzed the diagnostic clinical and histological parameters of 33 children with AGN to investigate the occurrence of infection at the onset of AGN and whether infection was associated with renal outcome and prognosis in children with AGN.

Materials and methods

Patients

This was a single-center retrospective study. All patients newly diagnosed with AAV at Guangzhou Women and Children's Medical Center from January 2001 to August 2023 were screened. Patients were divided into the infected group and non-infected group according to whether there was infection at the time of AGN diagnosis. The study was approved by the Guangzhou Women and Children's Medical Center Institutional Review Board. Informed consent was waived by the committee because of the retrospective nature of the study.

The inclusion criteria were as follows: (1) fulfilled the Chapel Hill Consensus Conference nomenclature; (2) had ANCAs detected in the serum; (3) had kidney damage confirmed by renal biopsy or clinical manifestations of hematuria, proteinuria, and/or renal insufficiency without evidence of cocurrent kidney injury from other causes.

The exclusion criteria were as follows: (1) secondary vasculitis; (2) other co-existing autoimmune diseases; (3) patients with ≤3 months of follow-up who did not reach the endpoint.

Data

Demographic data (age and sex), clinical manifestations, baseline laboratory characteristics (including creatinine, evaluated glomerular filter ratio (eGFR), hemoglobin, platelet count, leukocyte count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum albumin, complement C3, ANCA serology, infection sites and pathological characteristics at onset), treatment, and prognosis were analyzed. Renal pathological characteristics at initial diagnosis were divided into four patterns: sclerotic, focal, crescentic, and mixed. There were two endpoints in our study: chronic kidney disease (CKD) and end-stage renal disease (ESRD). ESRD was defined as an eGFR < 15 ml/min/1.73 m^2 or ongoing dialysis or kidney transplantation. CKD was defined as a confirmed estimated glomerular filtration rate < 60 ml/minute/1.73 m^2. ANCA serology was classified into 4 patterns: cytoplasmic ANCA (cANCA), perinuclear ANCA (pANCA), proteinase 3-ANCA (PR3-ANCA), or myeloperoxidase-ANCA (MPO-ANCA). The infection parameters included the site and severity of infection, including the CRP level, leukocyte count, and ESR. Treatment of children with AGN included corticosteroids, cyclophosphamide (CTX), rituximab (RTX), and plasma exchange.

Statistical analysis

Continuous and normally distributed data are expressed as the mean ± standard deviation (SD), and Student's *t* test was used for comparisons between groups. Nonnormally distributed data are expressed as medians (interquartile ranges, IQRs) and were evaluated via the Mann–Whitney U test or Wilcoxon rank-sum test. Pearson's chi-square test or Fisher's exact test was used for comparisons of categorical variables. $P < 0.05$ was considered statistically significant. Data analysis was performed with SPSS version 2024.

Table 1 Demographic data of our study patients at first admission

Parameters: s: median (IQR) or mean ± SD		Non-infected group (*n* = 11)	Infected group (*n* = 22)	*p*-value
Basic information	Male	1	1	1
	Female	10	21	
	Age	9.27 ± 3.8	9.18 ± 3.0	0.94
	Time from symptom onset to diagnosis (days)	61 (45, 91)	38 (27.7, 90.2)	0.79
Kidney findings	Proteinuria (mg/kg.d)	51.9 ± 47.9	68.6 ± 51.4	0.42
	Hematuria	7 (63.6%)	13 (59.1%)	0.38
	Nephrotic range proteinuria	6 (54.5%)	14 (63.6%)	0.71
Basic laboratory examination	Serum ALB (g/L)	35.3 ± 5.6	32.8 ± 6.2	0.27
	Creatinine (μmol/L)	67.2 (29.0, 333.0)	203.0 (95, 509.3)	0.09
	Complement c3 (g/L)	1.0 (0.7, 1.2)	0.94 (0.71, 1.1)	0.78
	HGB (g/L)	95.2 ± 20.2	73.5 ± 18.3	0.00
	eGFR (ml/min/1.73 m^2)	68.1 (15.7, 157.2)	25.2 (9.0, 44.4)	0.09
Dialysis is required		3 (27.3%)	7 (31.8%)	

Results

Demographic and clinical characteristics

Table 1 shows the baseline patient characteristics at disease onset. A total of 33 children with AGN met the inclusion criteria, 22 of whom had an infection at the time of AGN diagnosis. In our study, significantly more girls presented with AGN than boys did in both the infected group and the non-infected group. There was no significant difference in the age at diagnosis ($p=0.94$) or the time from symptom onset to diagnosis ($p=0.79$) between the infected group and the non-infected group. We observed a trend toward higher levels of proteinuria in the infected group than in the non-infected group (68.6±51.4 mg/kg.d vs. 51.9±47.9 mg/kg.d, $p=0.42$). Hematuria was present in 13 (59.1%) patients and 7 (63.6%) patients in the infected group and the non-infected group, respectively. Moreover, 14 (63.6%) patients in the infected group presented with nephrotic-range proteinuria, whereas 6 (54.5%) patients in the non-infected group presented with nephrotic-range proteinuria. Patients in the infected group had higher creatinine values and lower eGFR than those in the non-infected group, although the difference was not significant ($p=0.09$). In addition, a significant decrease in HGB was observed in the infected group ($p=0.00$), which suggested that infection may cause anemia in children with AGN. There were no significant differences in the baseline values of ALB and C3 between the two groups. Although the infected group had higher creatinine levels and lower HGB, a similar proportion of patients in both groups required dialysis at the time of diagnosis (3 (27.3%) vs. 7 (31.8%)). Our medical center started universal testing for PR3- and MPO ANCA as late as 2007 and a total of 7 patients (4 in the infected group and 3 in the non-infected group) were diagnosed with AAV earlier than 2007, with 3 were positive for pANCA, 1 was negative for ANCA in the infected group, while 3 were positive for pANCA in the non-infected group. After 2007, of the 18 children in the infected group, 12 were positive for pANCA and MPO-ANCA (66.7%), 1 was positive for pANCA (5.6%), 1 was positive for cANCA and PR3-ANCA (5.6%), 1 was positive for cANCA and MPO-ANCA (5.6%), 2 was positive for pANCA and cANCA combined with MPO-ANCA (11.1%), and 1 were negative for ANCA (5.6%). Of the 8 patients in the non-infected group after 2007, 5 were positive for pANCA and MPO-ANCA (62.5%%), 1 was positive for pANCA (12.5%), and 2 were positive for MPO-ANCA (25.0%).

Table 2 The infection characteristics of our study at first admission

mean ± SD or median (IQR)	Non-infected group (*n* = 11)	Infected group (*n* = 22)	*p*-value
Infection indicator			
ESR (mm/hr)	31.4 ± 16.0	54.3 ± 37.9	0.03
CRP (mg/L)	0.6 (0.4, 1.2)	10.3 (0.6, 23.4)	0.03
WBC (×10^9/L)	8.8 (5.9, 10.4)	8.4 (7.0, 13.4)	0.55
PLT (×10^9/L)	377.8 ± 178.7	346.1 ± 198.2	0.66
IgA	1.8 ± 0.7	1.6 ± 0.8	0.50
IgM	1.8 ± 0.7	1.75 ± 1.3	0.94
IgG	10.0 ± 3.5	11.7 ± 4.7	0.30

Infection characteristics of our study

Table 2 displays baseline characteristics stratified by inflammatory markers, including WBC counts and ESR and CRP levels. Compared with patients in the non-infected group, patients in the infection group presented significantly greater ESR ($p=0.03$) and CRP ($p=0.03$) values, whereas WBC counts did not significantly differ between the two groups ($p=0.55$). ANCA generic markers of inflammation (ESR and CRP) are generally associated with the prediction of disease activity, and our results further illustrate that ESR and CRP are possibly sensitive biomarkers of infection in patients with AAV. There was no significant difference in the deposition of IgM, IgG, or IgA between the two groups. As Table 3 showed, 19 patients in the infected group had infections at the time of diagnosis (before induction treatment), and only 3 children got infections approximately 5 to 12 days after receiving induction therapy. There were 16 (72.7%) lung infections, 3 (13.6%) tonsil infection, 1 (4.5%) intestinal infection, and 2 (9.1%) mixed lung and intestinal infections. Viruses or bacteria were isolated from each

Table 3 Cases of the patients in the infected group

No	Gender	Time of infection		Infection site	Pathogen detection methods	Type of infection	Time of anti-infective treatment (days)	Require ICU stay
		Diagnosis	Induction therapy					
1	F	√		Lung	Sputum	B	20	√
2	F	√		Tonsil	Throat swabs	B	7	
3	F	√		Lung	Throat swabs	MP, V	10	
4	F		√	Lung	BALF	F	16	
5	F	√		Lung	Sputum	B	10	
6	F	√		Lung	Sputum	B	14	
7	F	√		Lung	Throat swabs	MP	7	
8	F	√		Lung and intestine	Throat swabs/stool	MP, B	8	
9	F	√		Lung	Sputum	B	10	
10	F	√		Lung	Sputum	B, V	7	
11	F	√		Tonsil	Throat swabs	B	10	
12	F	√		Lung	Throat swabs	MP	5	
13	F	√		Lung	Sputum	B	15	√
14	F	√		Tonsil	Throat swabs	B	7	
15	F	√		Lung	Sputum	B	24	
16	M	√		Lung	Throat swabs	B	9	
17	F	√		Lung	Sputum	B	11	
18	F		√	Lung and intestine	Sputum/stool	B	14	
19	F	√		Lung	Sputum	B	9	
20	F	√		Lung	BALF	B, F, V	26	√
21	F		√	Intestine	Stool	B	14	
22	F	√		Lung	Throat swabs	V	7	

BALF: broncho-alveolar lavage fluid; B: bacteria; V: virus; F: fungus; MP: mycoplasma

Table 4 Comparison of treatment between the infected group and the non-infected group

Therapy		Non-infected group ($n=11$)	Infected group ($n=22$)	*p*-value
Glucocorticoids	yes	9 (81.8%)	20 (90.9%)	0.59
	no	2	2	
CTX	yes	9 (81.8%)	15 (68.2%)	0.68
	no	2	7	
Plasma exchange	yes	1	4	0.64
	no	10	18	
RTX	yes	0	1	1.00
	no	9	19	

CTX: cyclophosphamide; RTX: rituximab

Table 5 Comparison of renal pathology between the infected group and non-infected group

Parameters: s: *n* (%) or median (IQR)	Non-infected group ($n=11$)	Infected group ($n=22$)	*p*-value
Berden histological class			
Focal	3 (27.3%)	4 (18.2%)	0.28
Crescentic/mixed	5 (45.5%)	16 (72.7%)	
Sclerotic	3 (27.3%)	2 (9.1%)	
Renal biopsy			
Glomerular sclerosis (%)	38.2 (3.21, 80.7)	12.1 (0.0, 50.6)	0.26
Global sclerosis (%)	11.7 (0.0, 44.8)	6.6 (0.00, 31.1)	0.78
Segmental sclerosis (%)	1.3 (0.0, 53.1)	0 (0.0, 10.8)	0.61
Crescents (%)	22.4 (8.1, 63.6)	34.9 (8.1, 62.0)	0.76

patient. Antibiotics, antiviral treatment, or immune support treatment were given based on the pathogen and site of the infection. Besides, the duration of anti-infective treatment ranged from 5 to 26 days in light of the severity of the patient's infection. 3 patients were hospitalized in the ICU for treatment because renal function deteriorated rapidly, hypoxemia or metabolic acidosis at the time of initial diagnosis, all of them underwent hemodialysis and plasma exchange, and two of them required mechanical ventilation. After infection control, they started induction therapy.

Comparison of treatments between the infected group and non-infected group

Treatment for AAV in our study is shown in Table 4. Most people in both groups had received treatment with corticosteroids and cyclophosphamide after the diagnosis of AAV, with 9 (81.8%) and 20 (90.9%) patients in the non-infected and infected groups, respectively. 9 (81.8%) and 15 (68.2%) were treated with CTX in the non-infected and infected groups, respectively. Only a few patients were treated with plasma exchange and RTX.

The pattern of renal pathology

All patients enrolled in this study underwent renal biopsy (Table 5). There were 4 focal cases (18.2%), 16 crescentic/mixed cases (72.7%), and 2 sclerotic cases (9.1%) in the infected group. The distribution of pathological types in the non-infected group was similar, with 3 cases of focal (27.3%), 5 cases of crescentic/mixed (45.5%), and 3 cases of sclerotic (27.3%) ($p=0.28$). The focal phenotype was associated with the best prognosis, whereas the prognosis of crescentic and sclerotic phenotypes was poor [14, 15]. In our study, crescentic/mixed classes were dominant in the infected group, suggesting that infection could predict the Berden classification and indicate a poorer prognosis in children with AAV.

Kidney outcome of the study cohort

A total of 30 patients, of which 21 were in the infected group and 9 were in the non-infected group, had the first 6 months of follow-up data, and the clinical manifestations of follow-up patients were analyzed. After 6 months of treatment, compared with those in the non-infected group, the median levels of creatinine and proteinuria were higher in the infected group. Besides, lower levels of eGFR and ALB were also observed in the infected group. At the end of follow-up, 1 patient in the non-infected group was lost, and 5 (45.5%) and 13 (59.1%) patients died or progressed to ESRD, respectively, in the non-infected group and infected group (See Table 6).

Table 6 Comparison of laboratory test indicators and clinical outcomes between the infected group and non-infected group at the last follow-up

Parameters: s: *n* (%) or median (IQR)	Non-infected group	Infected group	*p* value
The first 6 months of follow-up	$n=9$	$n=21$	
Creatinine (μmol/L)	39.1 (28.5, 452.5)	275.0 (85.5, 510.0)	0.19
eGFR (ml/min/1.73m^2)	113.2 (12.26, 172.1)	18.0 (10.5, 52.9)	0.19
Proteinuria (mg/kg.d)	8.9 (4.1, 80.5)	62.5 (10.7, 103.5)	0.20
Serum ALB (g/L)	36.5 ± 8.2	35.1 ± 7.1	0.52
Last follow-up outcome	$n=10$	$n=22$	
ESRD or dead	5 (45.5%)	13 (59.1%)	0.71
Not ESRD	5	9	

Discussion

AAV is a chronic disease that often relapses and can be organ- or life-threatening. Although increasingly recognized, AAV is still rare in childhood, and clinical data concerning pediatric AAV are scarce because most pediatric reports are based on single-center and national retrospective cohort studies [16]. The kidney is one of the most common clinical manifestations of AAV. In addition, infectious episodes contribute significantly to morbidity and mortality in patients with AAV and may trigger relapses of AAV in adults [17–19]. However, it is unclear whether co-infection at the time of diagnosis can affect the outcomes of children with AGN.

In this study, we retrospectively analyzed the clinical characteristics and outcomes of children with AGN with and without co-infections at the time of initial diagnosis. A total of 22 children (66.7%) had infections when diagnosed with AGN, indicating that prior infection may be positively associated with the morbidity of children with AGN. Girls were mostly affected in both the infected and non-infected groups, which was consistent with the findings of previous studies. The results indicated that infection may affect the Berden classification of patients with AGN, as crescentic/mixed classes were dominant in the infected group. Additionally, infection at initial diagnosis did not affect the outcomes of patients with AGN, although it could lead to a reduction in kidney function.

Infections can directly or indirectly lead to kidney damage. The proportion of patients in the infected group with proteinuria or hematuria was greater, whereas the values of ALB and eGFR were lower in the non-infected group, indicating that the infected group had severe kidney involvement (Table 1). The 33 children enrolled were predominantly pANCA and MPO-ANCA positive, concurred with previous studies reporting that MPO-ANCA vasculitis occurred more commonly in China, suggesting that the pattern of disease onset in children may be the same as in adults [20, 21]. Anemia is a common complication for patients with AGN, and its severity is significantly associated with the degree of renal dysfunction and life prognosis. In our study, at the time of diagnosis of AGN, all patients presented anemia, but the HGB level was significantly lower in the infected group than in the non-infected group. The cause and pathogenesis of anemia in the infected group and whether anemia affects the prognosis of children with AGN should be further investigated [22].

Chronic inflammation is an important pathogenic feature of AAV. Multiple different indicators of inflammation, including CRP and ESR, have been used to evaluate the inflammatory status of patients with AAV [23]. The values of ESR and CRP in the infected group were significantly greater ($p<0.05$), suggesting that infection may aggravate the inflammatory response and promote disease progression. In addition, in the infected group, most patients had lung infections (72.7%), which further suggests that upper respiratory disease is associated with pANCA vasculitis [24]. Furthermore, previous studies have shown that the Berden classification is correlated with prognosis, as the prognosis of the focal class is the best, whereas the prognosis of the sclerotic class is the worst. In our study, crescents/mixes were dominant in the infected groups, suggesting that infection could predict the Berden classification in children with AAV. This result also demonstrates the rationale for the lack of a significant difference in prognosis between the two groups. This finding also provides potential guidance and suggestions for treatment strategies.

The present study has several limitations. First, we began collecting ANCA clinical cases a long time ago and followed them up as long and regularly as possible. However, some patients subsequently went to other hospitals for treatment or changed their contact information, and did not return to our medical center for follow-up examinations on time, resulting in incomplete follow-up data. Moreover, some patients outcome was ascertained through phone calls. Second, this was a single-retrospective study with a small sample size. More sample data could be obtained through multicenter cooperation in the future to clarify the implications of infection at initial diagnosis for the prognosis of children with AGN. In addition, clinical manifestations from many patients could not be obtained at the last follow-up and we could only use the 6-month follow-up data for analysis. Therefore, a large cohort of patients is needed to validate the present results in future studies.

In conclusion, co-infection at initial diagnosis may be positively associated with the morbidity of children with AGN but not with the outcomes of children with AGN.

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Author contributions

Study concept and design: L.L.L., H.D., and M.T. Acquisition, analysis, or interpretation of data: H.Y.D., X.Q.L, and M.Z. Drafting of the manuscript: L.L.L. Critical revision of the manuscript for important intellectual content: X.G. and L.L.L. Statistical analysis: H.T. Resources: X.G. Study supervision: X.G. All authors reviewed the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Review Committee of Guangzhou Women and Children's Medical Center (ID:284B00). It is affirmed that the collected data were solely utilized for clinical research, and the provided information will remain confidential, exclusively serving this research.

Participants were assured of data privacy, and the confidentiality of the data for research purposes was emphasized.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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