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ORIGINAL ARTICLE

Clinical features and outcomes of anti-neutrophil cytoplasmic autoantibody-associated vasculitis in Chinese childhood-onset patients

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Abstract

Data on anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV) are limited in children. This study is to determine the clinical features and outcomes of childhood-onset AAV. A retrospective study was performed on patients who were diagnosed with AAV before 18 years old in Xiangya Hospital. Their medical records were analyzed by retrospective review. Sixteen patients were diagnosed with AAV before 18 years old in the past 9 years, with an average age of 13.3 ± 3.3 years and 13 of them were female. There were 15 patients with microscopic polyangiitis (MPA) and 1 with Wegener's granulomatosis. The interval between onset of disease and diagnosis of AAV was 2 (1.5–3) months. Most patients (15/16, 93.8%) had multi-organ involvement, and all patients had renal involvement with 7 (43.8%) patients requiring dialysis at presentation. Eleven patients underwent a renal biopsy, of which mixed class and sclerotic class were the most two common histological types. All patients received immunosuppressive therapy for induction therapy including intravenous administrations of methylprednisolone (MP) pulse therapy for 8 patients. 8 patients (50%) achieved remission after induction therapy. After a median follow-up of 46.3 ± 36.1 months, nine (56.3%) patients progressed to end-stage renal disease (ESRD) and 5 (31.3%) patients died. Childhood-onset AAV showed similar clinical and pathological features compared to those of adults, except that it usually occurs in girls. The most commonly involved organ was the kidney, and it had a high risk of progression to ESRD. Early diagnosis and initiation of appropriate immunomodulatory therapy would be important to improve outcomes.

Keywords Anti-neutrophil cytoplasmic antibody-associated vasculitis · Clinical features · Renal involvement · Outcomes · Childhood-onset

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Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a group of disorders characterized by necrotizing inflammation of small- to medium-sized vessels and includes microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA). AAV involves multiple organs, particularly the lungs and kidneys, which might lead to rapidly progressive glomerulonephritis and even progress to end-stage renal disease (ESRD) or death [1]. AAV mainly occurs in adults with the peak age of onset between fifty and seventy years old but can present at any age [2]. Compared with adults, the incidence of AAV in children is lower, and there are few studies on childhood-onset AAV [3, 4]. Most of the clinical information and treatment strategies applied to pediatric patients are inferred from adult evidence [5]. Therefore, it is necessary to give more attention and perform further studies on this population.

This retrospective study aimed to summarize the clinical features and outcomes of AAV in children in a single Chinese cohort, in order to provide some suggestions for childhood-onset AAV.

Materials and methods

Patients

All patients newly diagnosed with AAV between January 1, 2012, and December 31, 2020, were recruited from the Departments of Pediatrics, Nephrology, Rheumatology and Immunology, Xiangya Hospital, a mixed tertiary hospital. Patients aged less than 18 years old and who fulfilled the 2012 Chapel Hill Consensus Conference nomenclature for AAV were included [6]. Their clinical and pathological data were retrospectively collected from the medical records and analyzed. Moreover, we contacted each patient's family via phone to determine their status by June 30, 2021.

Definitions

Birmingham Vasculitis Activity Score (BVAS) was used to measure disease activity [7]. The Pediatric Vasculitis Activity Score (PVAS) was used instead of BVAS [8]. Organ system involvement was considered only if the manifestations were due to AAV [7]. Hematuria was defined as ≥ 5 red blood cells per high-power field in centrifuged urinary sediments. Complete remission was defined as the absence of disease activity attributable to active disease qualified by the need for ongoing stable maintenance immunosuppressive therapy for more than 1 month [9]. Partial remission was defined as at least 50% reduction of disease activity score and absence of new manifestations [9]. Treatment resistance was defined as unchanged or increased disease activity in patients with acute AAV after 4 weeks of treatment with standard induction therapy or a reduction of 50% in PVAS after 6 weeks of treatment. Chronic persistent disease defined as the presence of at least 1 major or 3 minor items on the PVSA list after 12 weeks of therapy [9]. It did not apply to any of the treatment response definitions if the patient died within 1 month.

Detection of ANCA

Cytoplasmic ANCA (*c*-ANCA) and perinuclear ANCA (*p*-ANCA) were detected by indirect immunofluorescence (IIF) (Euroimmun, Lübeck, Germany). ANCA against proteinase 3 (PR3-ANCA) and myeloperoxidase (MPO-ANCA) were tested using antigen-specific ELISA (Inova Diagnostics, San Diego, USA). Standard protocols were performed according to the manufacturer's instructions.

Renal pathology

Direct immunofluorescence, light microscopy, and electron microscopy were all performed on each renal specimen. Then two renal pathologists examined specimens independently. Glomerular and tubulointerstitial lesions were evaluated according to the classification system of ANCA-associated glomerulonephritis proposed by Berden et al. [10] and Chen et al. [11], respectively. In brief, all biopsies were classified as focal class (≥ 50% normal glomeruli), crescentic class (≥ 50% glomeruli with cellular crescents), sclerotic class (≥ 50% globally sclerotic glomeruli), and mixed class (the left). The percentage of interstitial fibrosis and tubular atrophy was used for scored interstitial and tubular lesions semi-quantitatively that was score 0 for absent, 1 for 1–20%, 2 for 21–50%, and 3 for > 50%.

Ethics statement

This research was approved by the Ethics Committee of Xiangya Hospital. Informed consent was obtained from all of the patients' parents or guardians included in the study.

Statistical analysis

All data were analyzed using the statistical software Graphpad Prism, version 7. Normally distributed characteristics are presented as means and standard deviations (SDs). Non-normal distribution was expressed as median with interquartile range (IQR). Kaplan–Meier curves and

log-rank tests were used to analyze patient overall survival and renal survival.

Results

Cohort characteristics and clinical features

A total of 16 patients ≤ 18 years were diagnosed with AAV in our center in the past 9 years. The average age of the patients was 13.3 ± 3.3 (5–18) years. A summary of all the childhood-onset AAV patients is shown in Table 1. Among the 16 patients, 13 were female (81.3%) and 3 were male (18.7%). There were 15 patients with MPA and 1 patient with GPA. The interval between onset of disease and the diagnosis of AAV was 2 (interquartile range (IQR), 1.5–3) months.

As shown in Table 2, kidney was the most frequently involved organ (16/16, 100%), and the most common manifestation was hematuria (100%). Fourteen (87.5%) patients presented with proteinuria. Eleven (68.8%) patients exhibited a rise in creatinine or fall in creatinine clearance and 7 (43.8%) of them required dialysis at presentation. The respiratory system was the second most involved organ with 11 (68.8%) patients exhibiting pulmonary involvement and followed by general condition (62.5%). Most patients (15/16, 93.8%) had multi-organ involvement. The PVAS was 18.7 ± 6.2.

Laboratory data

Laboratory data are listed in Table 3. Anemia was found in thirteen (81.3%) patients, and the mean hemoglobin was 91.3 ± 22.6 g/L. Only 4 and 2 patients had elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), respectively. Anti-MPO/p-ANCA positivity was seen in 14 (87.5%) and anti-PR3/c-ANCA positivity in 2 (12.5%) patients.

Renal Histopathology

Renal biopsies were performed in 11 patients (68.8%). The detailed histopathological characteristics are presented in Table 1. Among these 11 patients, there were 4 cases of sclerotic class, 1 case of focal class, 1 case of crescentic, and 5 cases of mixed class according to Berden et al. classification system of ANCA-associated glomerulonephritis. Tubulointerstitial injury scores of the cases ranged from 1 to 3 were 5, 3, and 3, respectively, according to Chen et al.

Treatment

All patients received corticosteroids for induction therapy (Table 1). Pulse methylprednisolone (MP) pulse therapy was performed in 8 patients. Nine patients received a combination of corticosteroid and intravenous cyclophosphamide. Other immunosuppressants for induction therapies included mycophenolate mofetil (MMF) for 4 cases and tacrolimus for 2 cases. Three patients received plasma exchange (PE), and three patients received intravenous immunoglobulins (IVIG).

Outcome

All patients were followed up until death or the final follow-up date (June 30, 2021). The time from diagnosis of AAV to the last follow-up was 46.3 ± 36.1 months (range 0.5–111 months). Eight (50%) patients achieved remission after induction therapy. At the end of follow-up, five patients maintained their clinical remission, nine patients were dialysis-dependent including 7 patients who required dialysis at the time of onset and 2 patients including one GPA relapsed and progressed to ESRD during the follow-up. None of the 7 patients receiving dialysis at presentation recovered their renal function. Among the 9 patients requiring dialysis, 4 cases died, 2 cases underwent renal transplantation, and 3 cases continued to receive dialysis until the last follow-up. The renal survival of the patients is shown in Table 1 and Fig. 1a.

Of the 16 patients, 5 (31.3%) patients died and 4 of them, who received pulse MP, died during induction therapy. The causes of death were infection for 4 cases and cardiac arrest for 1 case. The patient survival of the patients is shown in Table 1 and Fig. 1b.

Discussion

Up to now, reports of childhood-onset AAV are rare, and the management mainly depends on clinical trials conducted in adults [5, 12]. In this retrospective study, we described the clinical characteristics and prognosis of AAV in children.

In our study, the male-to-female ratio was 1:4.3. In line with the other studies in childhood-onset AAV [13–15], girls seem more likely to be stricken with this disease. Although previous studies suggested that men and women were equally affected by AAV [16, 17]. The reason for this gender difference between children and adults is unclear. In addition, we found that pediatric AAV patients had similar clinical features compared with adults. In accordance with the composition of AAV in Chinese adults [16, 17], and

Table 1 Outline of 16 childhood-onset AAV patients

Patient	Gender	Age	Int (d)	Diagnosis	PVAS	Glomerular lesions	Tubulointerstitial injury score	Treatment	Treatment response	Follow-up time (month)	Dialysis-dependent	Outcome
1	*M*	9	20	MPA	15	Sclerotic	2	MP, OP, MMF	CR	22	No	Alive
2	*F*	13	36	MPA	21	Sclerotic	2	MP, OP, CYC	TR	78	Yes	Alive
3	*F*	14	60	MPA	25	NB	NB	OP, MMF	CR	58	No	Alive
4	*F*	14	44	MPA	18	Sclerotic	2	MP, OP, IVIG	TR	111	Yes	Alive
5	*F*	14	30	MPA	9	NB	NB	OP, CYC, PE	PR	31	No	Alive
6	*F*	14	100	MPA	20	Mixed	3	OP	TR	65	Yes	Alive
7	*F*	15	54	MPA	19	NB	NB	MP, OP, CYC, IVIG	TR	1	Yes	Died
8	*F*	16	50	MPA	26	Sclerotic	3	OP, CYC, PE	TR	20	Yes	Died
9	*F*	16	76	MPA	10	Mixed	1	OP, FK506	CR	66	No	Alive
10	*F*	18	50	MPA	6	Mixed	3	OP, CYC	CR	72	No	Alive
11	*F*	11	36	MPA	16	NB	NB	MP, OP, MMF, PE	NA	0.5	Yes	Died
12	*F*	10	39	MPA	26	Crescentic	1	MP, OP, CYC, IVIG	TR	2	Yes	Died
13	*F*	5	385	MPA	18	Mixed	1	MP, OP, CYC	TR	1	No	Died
14	*M*	15	240	MPA	22	Mixed	1	OP, FK506	PR	42	Yes	Alive
15	*F*	12	87	MPA	23	Focal	1	OP, MMF	CR	80	No	Alive
16	*M*	17	153	GPA	25	NB	NB	MP, OP, CYC	PR	91	Yes	Alive

Int (d) interval between onset of disease and the diagnosis (days); *PVAS* pediatric vasculitis activity score; *ESRD* end-stage renal disease; *M* male; *F* female; *MPA* microscopic polyangiitis; *GPA* granulomatosis with polyangiitis; *NB* no biopsy; *MP* methylprednisolone pulse; *OP* oral prednisone; *CYC* cyclophosphamide; *MMF*, mycophenolate mofetil; *IVIG* intravenous immunogloblin; *PE* plasma exchange; *FK506* tacrolimus; *CR* complete remission; *PR* partial remission; *TR* treatment resistance; *NA* not applicable

Table 2 Organ involvement of 16 childhood-onset patients

Organ involvement	Number (%)
General	10 (62.5)
ENT involvement	2 (12.5)
Mucous membrane/ocular involvement	2 (12.5)
Pulmonary involvement	11 (68.8)
Cardiovascular	2 (12.5)
Abdominal	3 (18.8)
Renal involvement	16 (100)
Hematuria	16 (100)
Proteinuria	14 (87.5)
Rise in creatinine	11 (68.8)
Renal failure requiring dialysis at present	7 (43.8)
Recent-onset HBP	9 (56.3)
Neurological	2 (12.5)
Multi-organ involvement	15 (93.8)

ANCA anti-neutrophil cytoplasmic autoantibody; *MPO* myeloperoxidase; *p-ANCA* perinuclear ANCA; *PR3* proteinase 3; *c-ANCA* cytoplasmic ANCA; *ENT* ear, nose, and throat; *HBP* high blood pressure

Table 3 Laboratory data of 16 childhood-onset patients

Laboratory data	
White blood cells(10^9/L)	6.9 (5.9–10.8)
Hemoglobin (g/L)	91.3 ± 22.6
Platelet (10^9/L)	202.1 ± 107.1
Serum albumin (g/L)	39.1 ± 7.3
Serum globulin (g/L)	24.8 ± 4.6
Proteinuria (g/24 h)	1.36 ± 1.06
Serum creatinine (μmol/L)	403.6 (66.2–677.2)
eGFR (mL/min/1.73 m^2)	13.81 (7.27–113.2)
ESR (mm/h)	17.93 ± 17.67
CRP (mg/L)	4.76 (1.66–13.85)
C3 (mg/L)	734.5 ± 135.4
C4 (mg/L)	152 (123–194)
IgA (mg/L)	1590 ± 768
IgG (g/L)	10.56 ± 3.18
IgM (mg/L)	1135 (966–1398)
ANCA positive	
Anti-MPO/p-ANCA (*n*, %)	14 (87.5)
Anti-PR3/c-ANCA (*n*, %)	2 (12.5)

eGFR estimated glomerular filtration rate; *ESR* erythrocyte sedimentation rate; *CRP* C-reactive protein; *C3* complement 3; *C4* complement 4; *IgA* immunoglobulin A; *IgG* immunoglobulin G; *IgM* immunoglobulin M

unlike the United Kingdom and northern Europe [18], MPA was strikingly predominant in children in our study. It could be explained by genetic background differences [19].

Most patients had multi-organ involvement, and the most frequently involved organ was the kidney, present in all cases, including nearly half of patients requiring dialysis at presentation. Furthermore, 56.3% of patients were dialysis-dependent during follow-up, which was similar to the results of Wu et al. [20]. Yu et al. [15] and Sun et al. [21] also reported that the rate of renal insufficiency at diagnosis was high and dialysis dependence appeared to be more common in pediatric patients than in adults. However, none of these patients requiring dialysis at presentation stopped dialysis after therapy in our study. The renal survival appeared to be worse in pediatric patients than in adults, as more than 20% of MPO-AAV adult patients who were dialysis-dependent had achieved renal recovery by 12 months in our previous study [22]. On the other hand, the eGFR at presentation was also lower in those pediatric patients [23]. Previous studies demonstrated that patients with decreased eGFR had poor renal survival [24, 25], and lower baseline eGFR is an independent risk factor for ESRD progression in AAV children [20]. In addition, the PVAS in children was higher compared to adults. It was suggested that patients with a higher BVAS have less chance of recovering renal function. Another explanation might be due to the delay of diagnosis. In all, renal involvement in children showed severe manifestations at onset and the prognosis was poor, which suggested that we need to pay more attention to annual physical checks include urine screening [13].

Of the 11 patients who received renal biopsies, mixed class (45.5%) was the most common type, followed by sclerotic class (36.4%). The renal histopathology types were similar to those of adults [16]. Chang et al. reported that the probability of progressing to ESRD increased in mixed, crescentic, and sclerotic classes [26]. The focal class might have the best renal outcome. The poorer renal biopsy classes might also be attributable to worse renal outcome.

In our study, the majority of patients treated with steroids combined CYC for induction therapy. All patients received corticosteroids and half of them performed pulse MP. As far as we know, there are no specific guidelines for therapeutic management in pediatric AAV patients. The recommended regimens were inferred from adult experiences and studies. It has been recommended that using pulse methylprednisolone (MP) before starting high dose oral steroids by Kidney Disease: Improving Global Outcomes (KDIGO) guidelines (2012) [27]. However, our previous work suggested that pulse MP to standard immunosuppressive induction therapy appeared to be of no benefit in terms of improving patient outcomes [22]. The benefits and risks of pulse MP need further research.

After a median follow-up of 46.3 months, 5 of the 16 (31.3%) patients died and 4 deaths were at the dialysis-dependent stage. Furthermore, 4 patients who received pulse MP died during induction therapy. The main cause of death was infection. The relatively high mortality rate might be explained by a high PVAS at presentation as BVAS was

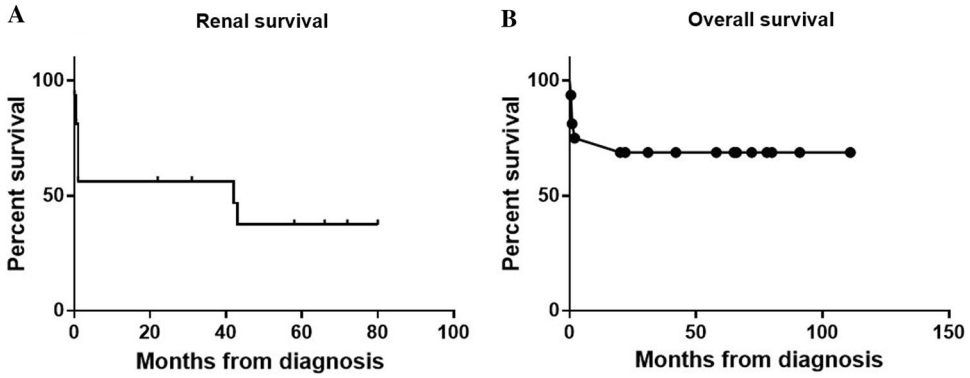

Fig. 1 Renal survival (**a**) and overall survival (**b**) of patients according to the age of patients. Time (months) refers to the time since the start of diagnosis

demonstrated to be an independent predictor for all-cause death [28]. What's more, both BVAS and eGFR at onset were shown to be an independent predictor for therapy-related death [29].

There are also some limitations in our study. First, this was a retrospective study that we could not obtain precise information prior to case presentation. Second, this study was performed in a single center and the sample size was small, and as such our results may not be generalizable to other populations. Further observation of more patients in multiple centers is needed.

In conclusion, childhood-onset AAV is a complex disease that can lead to serious consequences or even death and any organ of the body can be involved. Early diagnosis and initiation of appropriate immunomodulatory therapy would be important to improve outcomes.

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Declarations

Conflict of interest The authors report no conflict of interest.

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