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ORIGINAL ARTICLE

Pediatric ANCA vasculitis: clinical presentation, treatment, and outcomes in a French retrospective study

Sarah-louisa Mahi[1] · Siamak Bahram[2] · Jérôme Harambat[3] · Lise Allard[3] · Etienne Merlin[4] · Alexandre Belot[5] · Bruno Ranchin[5] · Julie Tenenbaum[6] · Marie Magnavacca[7] · Lucile Haumesser[8] · Emma Allain-Launay[9] · Christine Pietrement[10] · Hugues Flodrops[11] · Mahe Ruin[11] · Claire Dossier[12] · Stéphane Decramer[13] · Claire Ballot-Schmitt[14] · Olivia Gillion Boyer[15] · Laure Seugé[15] · Tim Ulinski[16] · Ariane Zaloszyc[1,2]

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Abstract

Background PediatricANCA vasculitis is a rare group of diseases with a scarcity of data in children. Annual incidence appeared to increase in the last several years, placing higher interest in the clinical and therapeutical outcomes of the disorder. Also, the growing use of rituximab questions the latest outcomes in these diseases. We therefore conducted a retrospective study to better understand the current characteristics, management, and the latest outcomes of the disorder.

Methods We conducted a 9-year retrospective study of 46 children in 14 different centers across France to describe their clinical and laboratory presentations, therapeutic regimens, and kidney outcome.

Results P-ANCA appeared to be a potential marker for higher relapse risk. Compared to adults, we found that ear-nose-throat presentations were frequent (45.7%) and more severe. Despite an evolution in the treatment management, kidney outcome remained poor with a substantial proportion of chronic kidney disease (54.8% at 1 year). Mortality stays low with 3 patients (6.5%) deceased at the end of our study.

Conclusion Clinical presentation was as previously described and time to diagnosis remains long. P-ANCA is a statistically significant marker for increased relapse risk. We observed a modification in the treatment regimens over the past several years with a growing use of rituximab and a decreasing use of cyclophosphamide. Despite these changes, kidney outcome remains poor and prospective studies should be conducted to assess the most appropriate therapeutic modality for each patient.

Keywords ANCA-associated vasculitis · Pediatric · Relapse · Kidney outcome

✉ Ariane Zaloszyc
ariane.zaloszyc@chru-strasbourg.fr

1 Service de Pédiatrie 1, CHU University Hospital Hautepierre, 1, Avenue Molière, 67098 Strasbourg, France

2 Laboratoire d'Immunologie (HUS), ImmunoRhumatologie Moléculaire (INSERM UMR_S1109), CHU Strasbourg, Strasbourg, France

3 Service de Néphrologie Pédiatrique, Centre de Référence Maladies Rénales Rares du Sud-Ouest, CHU de Bordeux, Bordeaux, France

4 Service de Pédiatrie Générale Multidisciplinaire, CHU Clermont-Ferrand, Clermont-Ferrand, France

5 Service de Néphrologie-Rhumatologie-Dermatologie Pédiatriques, Hospices Civils de Lyon, Lyon, France

6 Service de Pédiatrie, CHU Arnaud de Villeneuve, Montpellier, France

7 Service de Pédiatrie, CHRU Nancy, Nancy, France

8 Departement Statistiques, CHU Strasbourg, Strasbourg, France

9 Service de Pédiatrie, CHU Nantes, Nantes, France

10 Servie de Pédiatrie Spécialisée Et Généralisée, CHU Reims, Reims, France

11 Service de Néphrologie Pédiatrique, CHU La Réunion, La Réunion, France

12 Service de Néphrologie Pédiatrique, CHU Robert Debré, Paris, France

13 Service de pédiatrie – néphrologie et médecine interne, CHU Toulouse, Toulouse, France

14 Service de Médecine Pédiatrique, CHU Besançon, Besançon, France

15 Service de Néphrologie Pédiatrique, Hôpital Necker Enfants Malades AP-HP, Paris, France

16 Service de Néphrologie Pédiatrique, CHU Trousseau, Paris, France

Introduction

Pediatric antineutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV) is a rare subtype of vasculitis with an annual incidence rate of 0.22 per million children in France between 1996 and 2011 [1]. A Canadian study suggests a much higher incidence at 6 per million population [2].

Pediatric systemic vasculitis is a group of diseases characterized by inflammation in the blood vessel wall and classified according to the vessel size [3, 4]. AAV preferentially involves medium to small vessel types and may lead to organ- or life-threatening manifestations and is frequently associated with ANCA (pANCA for perinuclear and cANCA for cytoplasmic) [5].

The most frequently involved organs are the kidneys and upper and lower respiratory tracts. AAV subtypes include granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis (EGPA), and pauci-immune glomerulonephritis.

The origin of the inflammation remains unknown and is probably multifactorial with a role of genetic factors (such as genes in major histocompatibility complex, MHC), epigenetic, environmental expositions and infectious triggers (S. aureus) [6, 7].

The treatment of AAV consists of two phases. Firstly the induction of the remission with corticosteroids and cyclophosphamide (CYC), and plasma exchanges for the most severe cases.

Since 2005 (and officially approved by the U.S. Food and Drug Administration, FDA, in 2019 for children over 2 years and above) [8], rituximab (RTX) has taken an important place in the treatment of AAV with a good medical response and fewer long-term risks, especially for children who might require several treatment courses. Indeed, treatments like CYC or other immunosuppressive drugs are significant and long-term side effects can be life-threatening, such as cancer or infectious complications [8, 9].

Secondly, during the maintenance phase corticosteroids are tapered slowly and other immunosuppressive drugs can be introduced such as azathioprine (AZA), methotrexate (MTX), mycophenolate mofetil (MMF), and lately RTX [8, 10, 11].

Most current clinical practices come directly from adult studies due to a lack of evidence in children [12]. The purpose of this study is to observe the latest outcomes of these disorders, especially with the changes in practices with the increasing use of RTX in the last few years. This report aims to describe the clinical and laboratory characteristics, treatment, and short-term outcomes in a French nationwide pediatric retrospective cohort of AAV.

Methods

Patients

Data for this descriptive study were retrospectively collected between October 2020 and April 2021. Pediatric nephrologists and rheumatologists from reference centers across France were contacted via mailing lists and asked to share their hospitalization reports and follow-up from patients who had been diagnosed with AAV before the age of 18, between 2011 and 2020. We collected data from the clinical reports at diagnosis, 6 months later, 12 months later, and from the last report. We also asked specialists to share their records in case of relapse. Lab data were collected from these reports. Median time for follow-up was 5.1 years ± 3.2 SD.

Data collection and definitions

AAV was diagnosed according to the EULAR/PReS consensus criteria for the classification of childhood vasculitis [4, 13–16]. As EGPA and pauci-immune constituted a small number ($N = 5$), these patients were considered as one subgroup "other vasculitis."

We collected clinical presentation at diagnosis and evaluated the disease activity according to the pediatric Birmingham Vasculitis Activity Modified Score (PVAS). ANCA status was known for each patient at diagnosis and was determined by indirect immunofluorescence. There were two possible antibody specificities: pANCA or cANCA. In the case of no specificity, it was defined as ANCA+. We tracked whether ANCA became negative after treatment or turned positive over disease course (defined as serological relapse).

Kidney impairment definitions

Estimated glomerular filtration rate (eGFR) was calculated initially and during follow-up using the Schwartz modified formula for children [17]. CKD stage was defined according to the National Kidney Foundation's classification from 2003 [18].

For kidney biopsy at diagnosis ($N = 31$), each result was classified as focal, crescentic, sclerotic, or mixed according to the histopathologic classification of ANCA-Associated Glomerulonephritis established in 2010 by Berden et al. [19]. Other organ biopsies were performed mainly to confirm the diagnosis of AAV and identify granulomatous lesions.

Therapeutic regimens

Treatment classification was separated into two categories: remission induction and maintenance [20–22]. Remission

assessment was established at the end of the induction period. The definition of remission was an inactive disease (PVAS = 0) with ≤ 0.2mg/kg/day corticosteroids (prednisone or prednisolone) according to EULAR recommendations adapted to children [23].

Relapse and kidney outcome

A relapse was also defined according to the EULAR recommendations as the recurrence or new flare caused by active inflammation attributable to the AAV. Finally, we measured the short-term kidney outcome at 6 and 12 months. Our initial kidney function reference was the highest creatinine value measured during the initial hospitalization. Follow-up in patients who had received a kidney transplant before 6 or 12 months were excluded from the kidney function follow-up.

Statistical analysis

To calculate the estimated annual incidence, we used the collected number of new cases per year. The denominator was the official census data of the same age provided by the French government (www.insee.fr). We then used the mean incidence between 2011 and 2020. Descriptive statistical analysis of qualitative data is presented by size, percentage and 95% confidence interval. The quantitative data are presented with the mean for the data having a normal distribution tested with the Shapiro-Wilk test, with the median or with the interquartile space. The regression models used were univariate and multivariate logistic regressions. The odds ratio and its 95% confidence interval as well as the p-value of the regression by variable were given. $P < 0.05$ was considered as statistically significant. The software used was R Studio version 4.0.1.

This study was approved by the local ethics committee on the 16th of April 2021 (CE-2021–46). All patients and families agreed to participate in this observational study.

Results

Epidemiological data

A total of 46 patients, 9 males (19.6%) and 37 females (80.4%) from 14 French centers were included. The annual incidence in our study was estimated to be 0.27 per million children. Between 2011 and 2015 the annual incidence was 0.18 per million children and between 2016 and 2020 it increased to 0.37 per million children. Mean age at diagnosis was 12.4 years (9.9, 14.5 years). Median follow-up was 38 months (3-124 months).

Clinical presentation at diagnosis

Thirty-eight patients (82.6%) were Caucasian; 18 patients (39.1%) had a family history of auto-immune disease and 7 (15.2%) had a family history of kidney diseases. Twenty-three patients (50%) were classified as GPA, 18 patients (39.2%) were classified as MPA, 3 patients (6.5%) were classified as EGPA, and 2 patients (5%) were classified as having pauci-immune glomerulonephritis. Patients with MPA were younger at diagnosis (9.8 vs. 13.5 years) as compared with other AAV subtypes. Clinical presentation is presented in Table 1. The median time between the onset of symptoms and diagnosis was 30 days (IQR 15–90).

Besides kidney impairment, the most frequently involved organs at diagnosis were lungs, ear-nose-throat (ENT), and joints. ENT damage was seen in 69.7% of GPA versus only 22.2% of MPA. Three patients (6.5%) presented with subglottic stenosis, and 2 (4.3%) with saddle nose deformation; all of them were GPA. While pulmonary impairment was equally distributed between the different subtypes, GPA tended to present with more severe symptoms. Nine patients (37.5%) required oxygen at diagnosis. Only one patient had a pericarditis at diagnosis and was classified as EGPA requiring an intensified treatment.

Immunofluorescence results

Among the 23 patients with GPA, 12 were positive for c-ANCA (52.2%), 10 were positive for p-ANCA (43.5%) and 1 ANCA without specificity (4.3%). All 18 MPA patients were p-ANCA positive (100%), 17 of them with MPO affinity and 1 without specificity. Four out of five patients with other vasculitis were ANCA positive, 3 with no specificity (60%) and 1 with p-ANCA (20%).

Kidney impairment at diagnosis and histopathology

Kidney impairment (78.3%) was the most common presentation at diagnosis. More than 70% presented at the time of diagnosis with hematuria and/or proteinuria, and among them 17 (37%) had nephrotic range proteinuria. Eleven patients had hypertension at diagnosis.

Thirty-four patients (73.9%) had decreased kidney function with an eGFR < 90mL/min/1.73m^2 at diagnosis. Nine patients (19.6%) required dialysis at presentation, 5 of them were MPA, 3 were GPA, and 1 of them was pauci-immune glomerulonephritis (Fig. 1).

Thirty-one patients had a kidney biopsy at diagnosis. Crescentic form was the most common lesion found in 24 patients (77.4%), 1 patient (3.2%) had focal lesions, 4 presented a mixed form (12.9%), and 2 presented a sclerotic

Table 1 Clinical symptoms at diagnosis

Initial presentation at diagnosis	MPA $N=18$ (%)	GPA $N=23$ (%)	Other vasculitis $N=5$ (%)	Total $N=46$ (%)
Mean age (years)	9.8 ± 3.7SD	13 ± 3.3SD	13.5 ± 2.5SD	11.9 ± 3.7SD
Female	16 (88.9)	17 (73.9)	4 (80)	37 (80.4)
Male	2 (11.1)	6 (26.1)	1 (20)	9 (19.6)
Fever > 38 °C	8 (44.4)	10 (43.5)	2 (40)	20 (43.5)
General symptoms	13 (72.2)	18 (78.3)	2 (40)	33 (71.7)
ENT impairment	4 (22.2)	15 (65.2)	2 (40)	21 (45.7)
Nose bleeding	*0*	*6*	*0*	*6*
Sinusitis	*1*	*8*	*1*	*10*
Chronic nose discharge	*2*	*3*	*0*	*5*
Nasal crusts	*0*	*7*	*0*	*7*
Nasal polyps	*0*	*1*	*1*	*2*
Subglottic stenosis	*0*	*3*	*0*	*3*
Gingivitis	*1*	*1*	*0*	*2*
Hearing loss	*0*	*2*	*0*	*2*
Saddle nose deformation	*0*	*2*	*0*	*2*
Lungs impairment	8 (44.4)	16 (69.6)	1 (20)	25 (54.3)
Pleural effusion	*1*	*0*	*0*	*1*
Abnormal chest imaging	*8*	*15*	*1*	*24*
Alveolar hemorrhage	*4*	*10*	*0*	*14*
Respiratory distress	*2*	*6*	*1*	*9*
Cutaneous impairment	6 (33.3)	7 (30.4)	1 (20)	14 (30.4)
Purpuric lesions	*4*	*6*	*0*	*10*
Cutaneous ulcerations	*0*	*2*	*0*	*2*
Cutaneous eruption	*2*	*0*	*0*	*2*
Acrosyndrome	*0*	*0*	*1*	*1*
Neurological impairment	0	4 (17.4)	0	4 (8.7)
Encephalitis	*0*	*1*	*0*	*1*
Facial paralysis	*0*	*1*	*0*	*1*
Mononeuritis	*0*	*1*	*0*	*1*
Multineuritis	*0*	*1*	*0*	*1*
Ophthalmologic impairment	2 (11.1)	7 (30.4)	1 (20)	10 (21.4)
Pseudo-tumor	*0*	*1*	*1*	*2*
Conjunctivitis	*2*	*4*	*0*	*6*
Scleritis	*0*	*2*	*0*	*1*
Joints impairment	8 (44.4)	14 (60.9)	0	22 (47.8)
Arthralgia	*7*	*13*	*0*	*20*
Tendinitis	*0*	*1*	*0*	*1*
Knee effusion	*1*	*0*	*0*	*1*
Digestive impairment	7 (38.9)	4 (17.4)	0	11 (23.9)
Abdominal pain	*4*	*2*	*0*	*6*
Colitis	*0*	*2*	*0*	*2*
Ileitis	*1*	*0*	*0*	*1*
Abdominal effusion	*1*	*0*	*0*	*1*
Cholecystitis	*1*	*0*	*0*	*1*
Pericarditis	0	0	1 (20)	1 (2.2)
Kidney impairment	17 (94.4)	17 (73.9)	2 (40)	36 (78.3)
Hematuria	*14*	*16*	*2*	*32*
Proteinuria	*15*	*13*	*2*	*30*
Hypertension	*6*	*4*	*1*	*11*
Anuria	*2*	*1*	*0*	*3*

MPA microscopic polyangiitis, *GPA* granulomatosis with polyangiitis, *ENT* ear-nose-throat

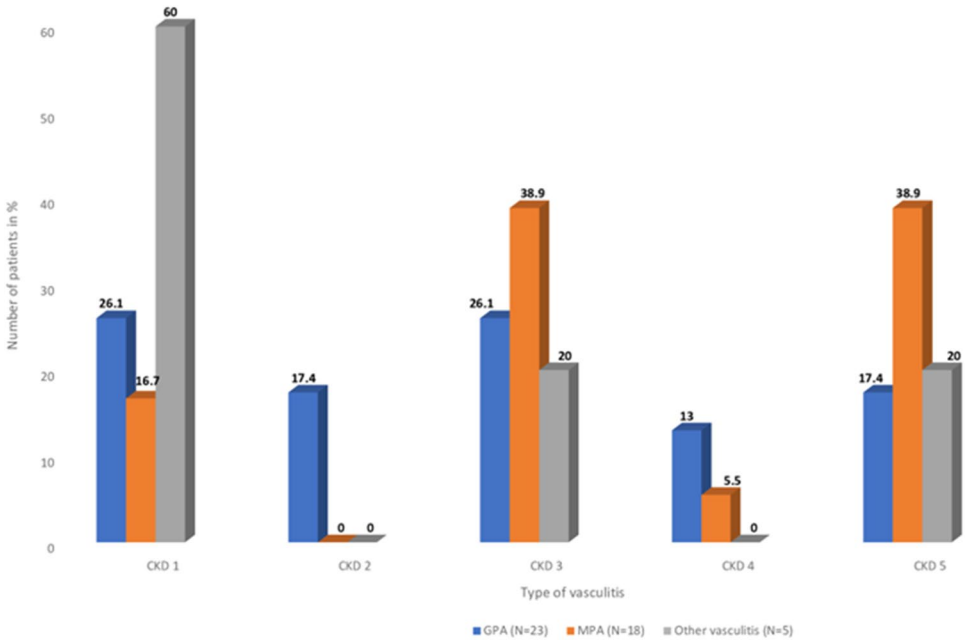


Fig. 1 Kidney function at diagnosis within each subgroup. This figure shows the kidney function of patients according to subgroup of disease. Normal function was eGFR > 90 mL/min/1.73 m^2, CKD2 was eGFR between 60 and 89 mL/min/1.73 m^2, CKD3 was between 30 and 59 mL/min/1.73 m^2, CKD4 was between 15 and 29 mL/min/1.73 m^2, and CKD 5D was < 15 mL/min/1.73 m^2. CKD, chronic kidney disease; MPA, microscopic polyangiitis; GPA, granulomatosis with polyangiitis

form (6.4%). Concerning the 11 patients (23.9%) that had another site biopsy at diagnosis, granulomatous lesions were found in 3, all of them within the ENT area.

Induction and maintenance therapies

Only one patient did not receive any treatment because of a non-severe form of EGPA. For induction therapy, 37 patients (80.4%) received intravenous (IV) corticosteroid pulses (methylprednisolone), with variable doses (from 500 to 1000 mg/m^2/day, with a maximum dose fixed at 1000 mg per day), followed by oral prednisone (78.3%) or prednisolone (15.2%). Five patients (10.9%) received only oral corticosteroids as induction treatment.

Sixteen patients (34.8%) received plasma exchanges at diagnosis: 8 were MPA among which one with CKD2, one with CKD3, three with CKD4 and three with CKD5; 8 were GPA with one CKD3 and seven CKD 5D. Eight patients (17.4%) received a combination of corticosteroids, CYC and RTX. Ten patients (21.7%) received corticosteroids and CYC and 17 patients (37%) received corticosteroids and RTX. Three patients (6.5%) received RTX alone with oral steroids (no pulses). To maintain remission, 7 patients (15.2%) received only oral steroids (1 to 2 mg/kg/day) without any immunosuppressive drugs. Twenty-one patients (45.6%) received oral steroids and RTX infusions. Five patients (32.6%) received oral steroids and MMF and 6 patients (13%) received oral steroids and AZA. Four patients (8.7%) received a combination of oral steroids, RTX and AZA. One patient received only AZA.

Thirty-seven patients (80.4%) achieved remission at the end of the induction period. Mean time to remission was 6.8 months ± 1.9 SD (Fig. 2). Among the 8 patients (17.4%) who did not reach remission with initial induction treatment, treatment was intensified. Three patients (6.5%) from the entire cohort died; one within 1 year after diagnosis, of an independent gastro-intestinal surgery complication, one from kidney failure and one 3 years after diagnosis in a traffic accident.

Clinical adverse events were observed for 25 patients (54.3%) and are listed in Table 2. Biological adverse events leading to treatment modifications were reported in 4 patients (8.7%). Two patients presented with severe neutropenia due to CYC injection requiring dose reduction in one and a switch to RTX for the other. Two patients on AZA required a treatment interruption, one for elevated liver enzyme and one due to anemia. For the 7 patients who presented an allergic reaction to RTX, only one needed a treatment discontinuation and RTX

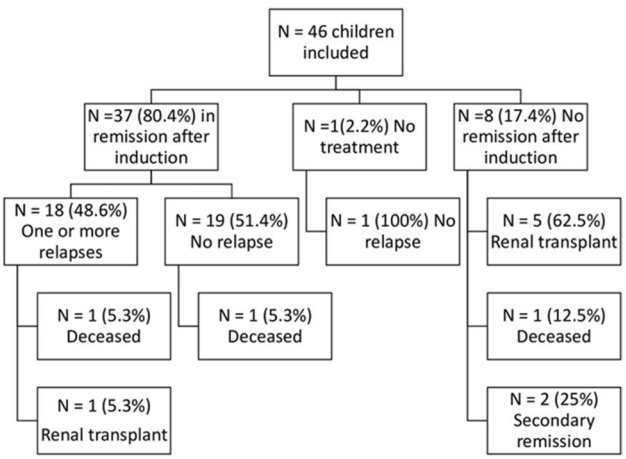


Fig. 2 Flow chart of disease course in childhood AAV

Table 2 Clinical treatment-related side effects

Related-treatment	Pathological features	Number of patients N = 25
Corticosteroids		
	Cushing's syndrome	8
	Early cataract	1
	Early osteopenia	1
	Intracranial hypertension (pulse)	1
Rituximab		
	Allergic reaction	7
	PRES syndrome	1
Plasma exchange		
	Allergic reaction	2
Cyclophosphamide		
	PRES syndrome	1
ACE inhibitors		
	Cough	2
	Hypotension	1

PRES posterior-reversible encephalopathy syndrome, *ACE inhibitors* angiotensin-converting enzyme inhibitors

could be reintroduced later. Others used premedication and slow perfusion for the next treatments.

Relapses

Twenty-one patients (45.6%) experienced at least one or more clinical relapses during follow-up. Median time to relapse was 12 months (10–42 months). Ten of the 21 relapsed while on therapy. We present relapse results in Fig. 3. Twelve (57.2%) of them were GPA, 7 (33.3%) were MPA, and 2 (9.5%) were other vasculitis (1 EGPA and 1 pauci-immune vasculitis). All relapsing patients had high ANCA titers, 8 of whom (38.1%) had a recent increase in ANCA titer. The most common organ relapses were kidney (42.8%), pulmonary (33.3%) and upper airways (23.8%).

We investigated variables associated with the risk of relapse (Table 3). We found a statistically significant difference for relapse risk according to ANCA status, initial serum creatinine, and kidney histopathology classification. Specifically, p-ANCA positivity, initial serum creatinine lower than 100 µmol/L, and mixed pathological findings were associated with a higher risk of relapse. We did not find any differences in relapse risk according to the time between symptoms onset and AAV diagnosis, the type of vasculitis and the patient's sex.

Kidney outcome at 6 and 12 months

Patients' CKD results during follow-up are presented in Fig. 4. At 6 months, 24 patients (52.2%) remained proteinuric despite angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) and 26 patients (56.5%) were receiving anti-proteinuric treatment. Eleven patients (23.9%) were still under antihypertensive drugs. Twenty-two patients (47.8%) had a decreased eGFR < 90mL/min/1. 73 m^2 (13 CKD2, 59.1%; 2 CKD3, 9.1%; 4 CKD4, 18.2%); and three of them (1 with MPA, 1 pauci-immune glomerulonephritis and 1 with GPA) had CKD 5D (13.6%). At 12 months, three patients were lost to follow-up.

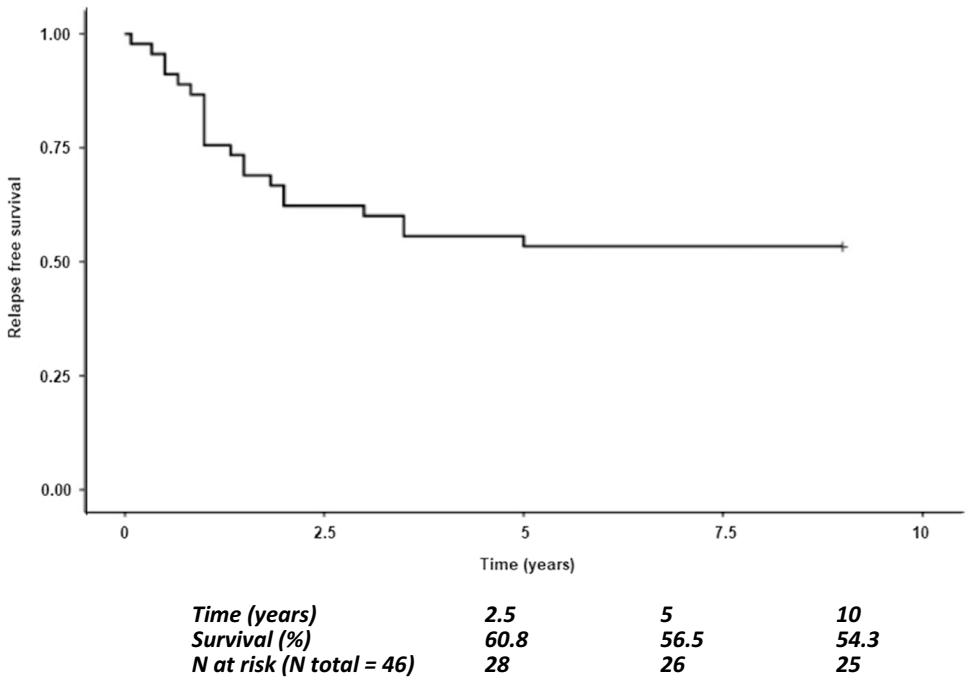


Fig. 3 Relapse-free survival in childhood-onset ANCA-associated vasculitis. Kaplan–Meier curve for relapse-free survival in time (years)

Table 3 Relapse outcome depending on some clinical, biological, histological, and treatment variables

		No relapse $N=25$ (%)	Relapse $N=21$ (%)	OR (univariable)	*p*-value
Age	Mean (SD)	11.8 ± 4.2	12.2 ± 2.9	0.95 (0.80–1.14)	$P=0.60$
Sex	Female	20 (80)	17 (81)	Reference	$P=0.88$
	Male	5 (20)	4 (19)	0.89 (0.19–3.92)	
Type of AAV					$P=0.75$
	MPA	11 (44)	7 (33.3)	Reference	
	GPA	11 (44)	12 (57.2)	1.56 (0.23–14.3)	
	Other	3 (12)	2 (9.5)	0.95 (0.10–7.31)	
ANCA status					**$P=0.046$**
	p-ANCA	12 (48)	17 (81)	Reference	
	c-ANCA	**9 (36)**	**3 (14.2)**	**0.22 (0.04–0.90)**	
	None	**4 (16)**	**1 (4.8)**	**0.16 (0.01–1.27)**	
Time between onset and diagnosis					$P=0.91$
	< 1 month	8 (32)	6 (28.6)	Reference	
	1–3 months	11 (44)	11 (52.4)	1.33 (0.35–5.31)	
	> 3 months	6 (24)	4 (19)	1.07 (0.19–5.88)	
Serum creatinine at diagnosis (µmol/l)					
	< 100	7 (28)	12 (57.2)	Reference	**$P=0.027$**
	> 100	**18 (72)**	**9 (42.8)**	**0.25 (0.07–0.86)**	
	< 400	17 (68)	15 (71.4)	Reference	$P=0.73$
	> 400	8 (32)	6 (28.6)	0.80 (0.22–2.85)	
Initial CRP (mg/l)	< 100	21 (84)	16 (76.2)	Reference	$P=0.55$
	> 100	4 (16)	5 (23.8)	1.56 (0.36–7.25)	
Transfusion at diagnosis	No	19 (76)	14 (66.7)	Reference	$P=0.34$
	Yes	6 (24)	7 (33.3)	1.90 (0.50–7.65)	
Initial histopathology					**$P=0.024$**
	Crescentic	17 (70.8)	8 (38.1)	Reference	
	Mixed	**2 (8.3)**	**2 (9.5)**	**2.13 (0.22–20.5)**	
	Sclerotic	2 (8.3)	0	1.4 (0–NA)	
	Focal	0	1 (4.8)	90.4 (0–NA)	

AAV ANCA-associated vasculitis, *ANCA* antineutrophil cytoplasmic antibody, *OR* odds ratio, *CRP* C-reactive protein. Statistically significant results are presented in bold entries

One patient had died. Among the remaining 42 patients, 7 (16.6%) were still on anti-hypertensive drugs. Twenty-one patients (52.4%) remained proteinuric despite treatment and 24 patients (57.1%) were receiving anti-proteinuric treatment. Twenty-three patients (54.8%) had a decreased eGFR < 90mL/min/1.73m^{2}at 12 months (14 CKD2, 60.9%; 3 CKD4, 13%); six of them (4 MPA, 1 pauci-immune glomerulonephritis and 1 GPA) had CKD 5D (26.1%). No statistically significant association was found for age, sex, type of AAV, ANCA status, time between onset and diagnosis, induction treatment and initial histopathology, and kidney function outcome at 6 and 12 months.

Among the 9 patients requiring dialysis at diagnosis, 8 were treated by kidney replacement therapy at last follow-up (6 received a kidney transplant and 2 were still on dialysis). In total, 6 patients (13.3%) had received a kidney transplant more than a year after diagnosis (from 15 to 44 months); three of them had MPA, 2 GPA and 1 pauci-immune glomerulonephritis.

Discussion

Childhood AAV is a rare and critical pediatric disease with only a few studies on the subject, and delay for diagnosis remains long with a median around 30 days [1, 24]. This can be explained by the lack of specificity of symptoms at onset which are present in other benign diseases.

The most common presentations are kidney (78.3%) and ENT (45.7%) disorders, and can be more severe than those reported in adults. Advances in the treatment of vasculitis have improved the disease outcomes in the last decades, with the use of CTC and CYC. More recently the use of RTX is increasing in pediatric AAV based on adult experience. Despite this change, kidney survival and relapse rates have stayed equivalent. The residual CKD is still about 20% at 5 years as compared to a previous French retrospective study [1]. Our study also highlighted a potential relapse marker with

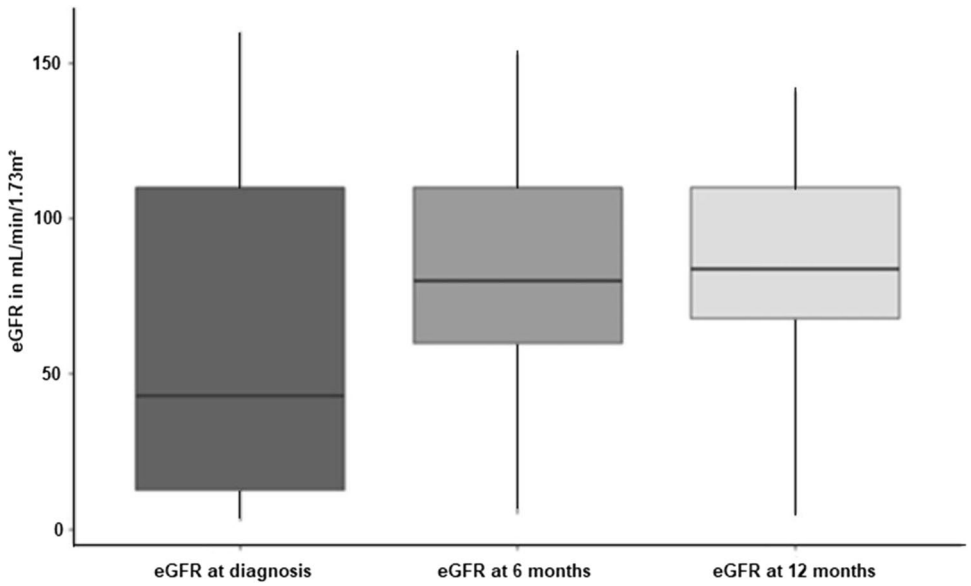


Fig. 4 Kidney function evolution over disease course. Evolution of kidney function at diagnosis, 6 and 12 months. Each box represents the median eGFR, the first and third quartiles, and the lowest and highest eGFR at each point

a statistical significance for p-ANCA. In the present study, the overall estimated incidence between 2011 and 2020 was 0.27 per million children per year which seemed to increase compared to the incidence observed by Sacri et al. between 1986 and 2011 [1]. However, between 2001 and 2011, the rate rose to 0.45, and then dropped to 0.18 between 2011 and 2016 in our study and increased again between 2016 and 2020 to 0.37. This high variability in case numbers may be explained by environmental or epidemic factors. In addition, we might not have collected all the new cases every year due to recall bias and the retrospective nature of the study. Therefore, we may have an underreported number of cases and an underestimation of the incidence. Regarding the clinical presentations our data were consistent with other studies. We observed a vast majority of Caucasian patients (82.6%) which is consistent with the major ethnic representation in France. Our cohort presented a strong female predominance [1, 24–27] in comparison to adult studies in which there is no difference between male and female or only a minimal male predominance [28]. We found a majority of GPA, followed by MPA, EGPA, and pauci-immune glomerulonephritis [1, 27, 29]. Furthermore, the MPA onset seemed to be at a younger age than GPA and other vasculitis [1, 26].

The clinical presentation was comparable to other studies: predominance of kidney, lung, upper airway, and joint damage associated in over 70% of cases, with poor overall condition.

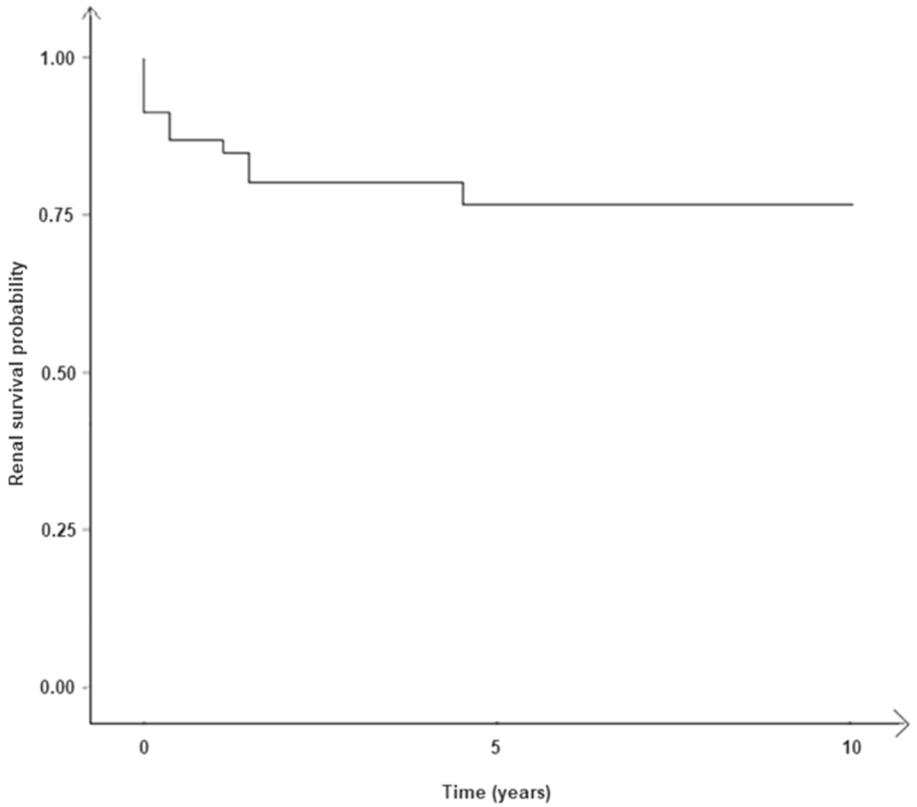
Aggressive forms were more frequent in pediatric patients who had subglottic stenosis and saddle nose deformations [30]. Lung and ENT impairment, mainly alveolar hemorrhage, was more frequent in GPA than in MPA.

Neurological involvement is rare in childhood AAV but occurred in our cohort in 4 patients (8.7%) at diagnosis, and all had MPA [27]. Eighty percent of our cohort had kidney impairment, which is consistent with other studies on pediatric AAV (50–100%) [1, 24–27, 31]. As for kidney histopathological findings in our study, the dominant form was crescentic, followed by mixed, focal lesions, and sclerotic. Mixed forms were associated with a higher relapse risk than crescent forms. This result might be due to a relatively small number of available biopsies. One might speculate that crescentic forms were treated more aggressively at disease onset.

P-ANCA was found as a significant risk factor for a higher relapse rate. That is in line with previous studies of kidney outcomes showing that presence of p-ANCA was associated with more severe disease and worse kidney function [25]. Surprisingly, we found that higher creatinine level (> 100 µmol/L) at diagnosis was a protective factor for relapse ($p < 0.05$). This might be explained by the fact that patients with more severe kidney impairment at diagnosis were treated more aggressively than the others. Interestingly, MPA patients seemed to present at diagnosis with more severe kidney injuries than other AAV subtypes, 38.9% having CKD 5D versus only 17.4% with GPA. Kidney outcome remained poor with about 20% of patients having CKD stage 3 to 5D at 6 and 12 months of disease onset.

In patients who received plasma exchange, we did not observe any change in eGFR at 6 and 12 months compared to others [32–34]. Interestingly, Marlais et al. found in their study on adverse kidney outcome in children with AAV that children who received plasma exchange at diagnosis were more likely to present kidney replacement therapy at last follow-up [35]. This result needs to be handled with caution as this treatment was reserved for patients who had more severe forms and who were more likely to have kidney failure at diagnosis. Also the plasma exchange group was very small in the study.

We found that the use of RTX has dramatically increased in the last 10 years: 61% in our study versus only 14% in the previous French survey by Sacri et al. However, therapeutical



Time (years)	1	5	10
Kidney survival (%)	82.6	78.3	78.3
N at risk (N total = 46)	38	36	36

Fig. 5 Kidney survival in childhood-onset ANCA-associated vasculitis. Kaplan–Meier curve for kidney survival (no dialysis, no kidney transplant) in time (years)

protocols remained comparable, except for the decreasing use of CYC which was partially replaced by RTX. We found comparable remission rate (78% in our study vs. 73%), relapse percentage (46% in our study vs. 41%), kidney survival at 5 years (78% in our study vs. 70%) and mortality rate (6.5% in our study vs. 6%) when comparing historical results before 2011 [1] with our study (Fig. 5). The influence of treatment on relapses and kidney outcomes must be interpreted with caution because our study was retrospective, and therapeutic regimens were heterogeneous despite some similarities.

The major limitation of our study was the retrospective design. Furthermore, most of the respondents were specialized pediatric nephrologists and it could have led to a selection bias in the severity of kidney involvement.

Conclusion

We observed severe kidney outcome, ENT and pulmonary clinical complications in pediatric ANCA vasculitis. Although the observational, retrospective design did not allow us to assess treatment efficacy, it seems that despite the increasing use of RTX in the last few years, AAV short-term prognosis remains unchanged.

Diagnostic delay remains a challenge and ANCA titers should be rapidly performed in a child who presents with symptoms compatible with AAV. Long-term prospective studies are warranted to identify the long-term treatment efficacy and tolerance.

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Declarations

Conflict of interest The authors declare no competing interests.

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