Clinical characteristics and outcomes of childhood-onset ANCA-associated vasculitis: a French nationwide study

Anne-Sylvia Sacri1,*, Tristan Chambaraud2,*, Bruno Ranchin3, Benoît Florkin4, Hélène Sée5, Stéphane Decramer6, Hugues Flodrops7, Tim Ulinski8, Emma Allain-Launay9, Olivia Boyer10, Olivier Dunand11, Michel Fischbach12, Eric Hachulla13, Christine Pietrement14, Patrick Le Pogamp15, Jean-Louis Stephan16, Alexandre Belot3, Hubert Nivet17, François Nobili18, Loïc Guillemin19, Pierre Quartier4, Georges Deschênes5, Rémi Salomon10, Marie Essig2 and Jérôme Harambat1


Correspondence and offprint requests to: Jérôme Harambat; E-mail: jerome.harambat@chu-bordeaux.fr

*These authors contributed equally to this work.

ABSTRACT

Background. Data on anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis are scarce in children. The current study is aimed at describing the clinical features and outcomes of childhood-onset ANCA-associated vasculitis (AAV).

Methods. We conducted a retrospective French multicentre study involving patients in whom AAV was diagnosed before the age of 18 years. Inclusion criteria were (i) granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA) according to classification criteria of the European League

Against Rheumatism/Paediatric Rheumatology European Society, and (ii) ANCA positivity. Patient and renal survival were analysed.

Results. Among 66 children included, 80% were female, 42% had GPA and 58% MPA including renal-limited vasculitis, 67% were pANCA+ and 33% cANCA+. The mean incidence of reported cases increased to 0.45 per million children/year in the period 2006–10. Median age at diagnosis was 11.5 years, and median time to diagnosis was 1 month. Initial symptoms included fever and fatigue (79%), skin lesions (41%), arthritis (42%), pulmonary (45%) and renal involvement (88%). Clinical features were similar between GPA and MPA with the
exception of upper airway impairment (28%) specific of GPA. Ninety percent of the patients achieved remission after induction treatment. After a median follow-up of 5.2 years, 4 patients (6%) died, corresponding to a mortality rate of 1.2 per 100 person-years, and 22 patients (34%) developed end-stage renal disease (ESRD). Renal survival was 74, 70 and 59% at 1, 5 and 10 years, respectively. In a multivariable Cox regression model, baseline glomerular filtration rate, ethnic origin, histopathological classification and era of treatment were associated with the occurrence of ESRD. Relapse-free survival was 57% at 5 years and 34% at 10 years of follow-up. Patient and renal outcome did not significantly differ between GPA and MPA.

Conclusion. Childhood-onset AAV is a rare disease characterized by female predominance, delayed diagnosis, frequent renal impairment and a high remission rate. Baseline GFR and new histopathological classification system are strong predictors of ESRD. Renal survival in childhood AAV has improved over time.

Keywords: ANCA-associated vasculitis, children, ESRD, outcome, relapse

INTRODUCTION

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are systemic diseases involving mostly the respiratory tract and the kidneys [1–9]. The group of AAV comprises granulomatosis with polyangiitis (Wegener’s) (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) (EGPA). Since the discovery of ANCAs, significant improvements have been achieved regarding physiopathology, management and outcome of AAV. The physiopathology involves adaptive immunity through anti-myeloperoxidase (MPO), and anti-proteinase 3 (PR3), but also T CD8+ memory cells and innate immunity via IL-17 [10–17]. Genetic factors and environment are evenly implicated. The treatment of AAV involves the use of steroids in combination with immunosuppressive cytotoxic agents such as cyclophosphamide, or biologics like rituximab to induce disease remission [18–22]. Maintenance therapy usually combines lower doses of steroids and other immunosuppressive agents, most commonly azathioprine or methotrexate [18, 23–25]. The use of cyclophosphamide has dramatically changed the prognosis of AVV [18].

ANCA-associated vasculitis has been mainly reported in adults with an estimated annual incidence of approximately 10–20 per million and a peak age of onset in patients aged 65–74 years [26]. In contrast, data in children are scarce. Most of the paediatric reports are limited to single-centre case series data of which are often difficult to generalize [27–30]. The largest study so far is a cross sectional report from a voluntary-based registry in North America including 65 paediatric GPA [31]. However, the incidence of the disease, the frequency and determinants of relapse and end-stage renal disease (ESRD) and the impact of treatment in paediatric patients with AAV remain poorly understood. This study aimed to describe the clinical features, management and outcome of childhood-onset AAV. A secondary objective was to investigate factors associated with the occurrence of ESRD.

METHODS

Study design and population

The current study is a nationwide retrospective study including patients with paediatric-onset AAV. All French paediatric nephrology and rheumatology units, adult nephrology and internal medicine departments were contacted through the society members’ mailing list. Referral units were directly contacted by one of the authors. All centres were asked for patients who were being currently followed at the time of the study or had been previously followed in their unit.

Patients included had to fulfil the following criteria: age at diagnosis <18 years old, diagnosis of AAV, positivity of ANCA as detected by immunofluorescence (IF) or enzyme-linked immunosorbent assay (ELISA) at diagnosis or during follow-up. Patients with EGPA and those with ANCA-negative pauci-immune crescentic glomerulonephritis were excluded from the analysis.

Classification criteria

Classification of AAV was based on the EULAR/PReS classification criteria for vasculitis in children endorsed in 2008 [32]. We therefore retrospectively defined GPA as the association of ANCA positivity (MPO-ANCA, PR3-ANCA or no specificity) and the presence of at least 2 of the 5 following criteria: (i) histopathology (granulomatous inflammation on biopsy), (ii) upper airway involvement (chronic purulent or bloody nasal discharge or recurrent epistaxis, crusts, granuloma, nasal septum perforation or saddle nose deformity, chronic or recurrent sinus inflammation), (iii) laryngotracheo-bronchial involvement (subglottic, tracheal or bronchial stenoses), (iv) pulmonary involvement (alveolar haemorrhage, presence of nodules, cavities or fixed infiltrates on chest radiograph or CT scan) and (v) renal involvement (proteinaemia, haematuria or necrotizing pauci-immune glomerulonephritis).

Since there is no consensus regarding the classification of MPA, we used the algorithm developed by Watts et al. [33] as usually proposed in the literature. Patients with the association of ANCA and either (i) a clinical presentation compatible with AAV without fulfilling the EULAR/PReS criteria for GPA, or (ii) renal-limited vasculitis, were classified as MPA.

Data collection and clinical definitions

Data were recorded from medical charts using a standardized data collection form including information about sex, ethnicity, age at initial symptoms, age at diagnosis, clinical and laboratory characteristics at disease onset, treatments and main events (first relapse, disease extension to another organ, ESRD and death).

Haematuria, defined as ≥2+ on dipstick, was classified as negative, microscopic or gross. Proteinuria was categorized as positive if >0.15 g/day or 20 mg/mmol of urine protein/creatinine ratio, elevated if >0.5 g/day or 60 mg/mmol or heavy if
≥3 g/day or 300 mg/mmol. Glomerular filtration rate (GFR) was calculated by the updated Schwartz formula before the age of 18 and by MDRD formula for patients having reached adulthood [34, 35]. Acute kidney injury (AKI) was defined as a GFR decrease >50% or doubling of creatinine. Initial renal biopsy findings were retrospectively grouped into four categories (labelled as focal, crescentic, sclerotic and mixed) according to the new histopathological classification system [36].

Outcome measures like remission, response and refractory disease were defined using EULAR criteria recommended for clinical trials [37]. A remission was defined as the absence of disease activity according to validated disease activity scores in adults (BVAS and BVAS/WG) [38, 39] and a minimal immunosuppressive therapy determined by a maintenance dose of prednisone ≤7.5 mg/day during at least 3 months. Patients presenting with ESRD and showing no sign of disease activity were considered as being in remission with ESRD [38, 39]. Response was defined as a ≥50% reduction in the disease activity score in the absence of new organ involvement. A refractory disease was defined as either (i) unchanged or increased disease activity after 4 weeks of treatment, (ii) lack of response after 6 weeks of treatment or (iii) chronic persistent disease i.e. presence of one major item or three minor items in the disease activity score despite 8 weeks of treatment.

Statistical analysis

The characteristics of the patients at disease onset and at diagnosis were expressed as number and percentage for categorical variables and median with interquartile range (IQR) or mean with standard deviation (SD) for quantitative variables. Kaplan–Meier estimates were used to assess time to ESRD and time to first relapse. Potential determinants of ESRD were investigated using Cox regression models. Variables with P-values <0.10 in univariable analyses as well as possible confounding factors were entered in the full multivariable analysis. The subsequent multivariable modelling procedure was based on a stepwise backward selection. Variables with P-values >0.05 were removed from the models unless they had a confounding effect. Results are reported as hazard ratio (HR) with 95% confidence intervals (CI). All analyses were carried out using SAS software, version 9.2 (SAS Institute, Cary, NC, USA).

RESULTS

Population demographics

A total of 66 patients with a diagnosis of AAV during childhood between 1986 and 2011 have been included (28 GPA, 23 MPA and 15 renal-limited AAV). MPA and renal-limited AAV had similar features and were grouped together for this study (n = 38). The average annual incidence of reported cases over the 25-year period was 0.22 (95% CI 0.04, 0.62) per million children, increasing from 0.10 in 1986–90 to 0.45 per million children in 2006–10. Median age at diagnosis was 11.5 years (IQR 9.6–13.1). There was a predominance of girls (75% in GPA and 89% in MPA) and patients were mostly Caucasians (Table 1). The median follow-up time was 5.2 years (IQR 1.4–9.0).

Initial presentation

The median interval from symptom onset to diagnosis was 1.0 months (IQR 0.6–7.9). Fever and general symptoms (fatigue/malaise) were present in more than half of the cases. Renal impairment was frequent (n = 58, 88%). Two-thirds of patients (n = 44) presented with AKI with a need for dialysis in nine cases (14%). Among these nine dialysis dependant patients, three did not recover renal function and ESRD was present at diagnosis. The most frequent extra-renal presenting manifestations were pulmonary (45%), mucocutaneous (42%) and articular (41%). Upper airway manifestations were seen in 75% of children with GPA. Serology tests by IF showed positivity for pANCA in 43 children (65%), for cANCA in 22 (33%) and for both pANCA and cANCA in one patient. Using ELISA, anti-MPO positivity was reported in 39 patients and anti-PR3 positivity in 22. The clinical and laboratory characteristics at diagnosis are detailed in Tables 1 and 2.

Histopathology

Renal biopsies results were available in 44 children with AKI. Detailed renal histology data are provided in Table 3. According to the new pathologic classification [36], the distribution of renal biopsy findings was categorized as follows: 6 (14%) focal, 13 (30%) crescentic, 17 (39%) sclerotic and 8 (18%) mixed lesions. Among the 13 patients with GPA who had a biopsy performed in an other organ than the kidney (nasal septum, upper airways, lungs or skin), a granuloma was found in nine (70%) cases.

Treatment

All children received an induction therapy with corticosteroids, either intravenously (n = 57, 86%) or orally (n = 9, 14%). Forty-four patients (67%) were treated with a combination of corticosteroid and cyclophosphamide (IV in 31 patients). Other induction therapies included plasma exchanges (n = 11), rituximab (n = 9) and mycophenolate mofetil (n = 3). Plasma exchanges and rituximab have been increasingly used over time (Figure 1). In the last 3 years of the study period, rituximab was used as induction therapy in 9 out of 13 patients. Maintenance therapy consisted of oral corticosteroids alone in 19 (29%) patients or in combination with azathioprine, mycophenolate mofetil or methotrexate in 42 (65%) patients. One patient received azathioprine alone and four patients were not given maintenance therapy.

Treatment response and remission

Overall, the response rate (decrease in disease activity score by 50% from baseline) was 100% after a median time of 26 days (IQR 17–41). Data about remission were available in 63 patients. After induction therapy, a remission was obtained in 46 patients (73%), 16 patients (25%) had a refractory disease, a majority of whom received corticosteroids alone and one patient died (Figure 2). Among the 16 children with refractory disease, 13 experienced lack of response after 6 weeks of treatment, two had similar or increased disease activity score after 4 weeks and one still had an active disease despite 8 weeks of treatment. A secondary remission was reached by 15 of these
16 patients with the need of an adjuvant therapy, mainly cyclophosphamide (Figure 2). Overall, 61 patients achieved complete remission after a median time of 6.7 months (IQR 4.9–10.1).

Relapse
Twenty-seven patients (41%) experienced a least one relapse after a median time from diagnosis of 29 months (IQR 14–89). Patients with GPA tended to relapse more frequently \( (n = 14, 50\%) \) than those with MPA \( (n = 13, 34\%) \). The most common sites for first relapse were kidneys \( (n = 12) \), lungs \( (n = 5) \) and upper airways \( (n = 5) \). Relapse-free survival was 87% (CI: 81–98) at 1 year, 57% (CI: 44–73) at 5 years and 34% (CI: 16–51) at 10 years of follow-up. The median time to first relapse was 7.4 years (Figure 3A). Twenty (30%) patients (36% of GPA and 26% of MPA) had an extent of involvement to another organ system during follow-up including kidneys \( (n = 9) \), skin \( (n = 7) \), lungs \( (n = 6) \) and joints \( (n = 5) \). At last follow-up, 57 patients (89%) were in remission including 21 GPA (75%) and 36 MPA (95%). Almost half \( (n = 29) \) were ANCA positive, 25 of whom (86%) remained in remission.

Renal outcome
During follow-up, 22 patients (34%) reached ESRD and 15 additional ones (23%) developed chronic kidney disease. ESRD occurred in 7 out of 28 (25%) patients with GPA and in 15 out of 38 (39%) patients with MPA. Among ESRD patients, 17 were transplanted and 5 were on dialysis at last follow-up. Renal survival was 74 (CI: 65–87), 70 (CI: 60–83) and 59% (CI: 45–77) at 1 year, 5 years and 10 years after diagnosis, respectively (Figure 3B). The median time to ESRD was 12.9 years (lower CI: 6.7 years). In multivariable analysis, an increase in 1 mL/min/1.73 m² in baseline estimated GFR was associated with a 5% decrease risk of ESRD (HR 0.95; CI 0.92–0.98; \( P < 0.001 \)), a non-Caucasian ethnicity was associated with a 3-fold higher risk of ESRD of borderline significance (HR 2.94; CI 0.98–9.04; \( P = 0.05 \)) and a more recent era of treatment (2005–11 versus 1986–04) was associated with 2.5-fold lower risk of ESRD (HR 0.38; CI 0.12–0.97; \( P = 0.04 \)).
variables sex, age at diagnosis, diagnosis delay, type of AAV and ANCA specificity were not associated with the risk of progression to ESRD. Among patients with a renal biopsy at the time of diagnosis, those with sclerotic or mixed lesions had a 3-fold increased risk of ESRD compared to those with focal or crescentic patterns.

**Mortality**

Four patients (6%) died (2 GPA, 2 MPA) during the follow-up period leading to a mortality rate of 1.7 per 100 person-years. The causes of death were septic shock 3 months after the start of treatment in a 4 years old child, cerebral vasculitis 16 months after diagnosis in a 14 years old patient with uncontrolled disease, respiratory failure in a 13 years old patient on dialysis with chronic respiratory insufficiency after the start of treatment in a 4 years old child, and cardiac arrest while on dialysis after a first renal transplant failure 7 years after diagnosis in an 18 years old patient.

**DISCUSSION**

This French nationwide study describes the clinical manifestations and outcomes of 66 patients with paediatric-onset AAV. Given the rarity of AAV in children, this is the largest cohort in Europe to date. The other large-sized cohort of paediatric AAV published by a North American network did not provide yet follow-up data [31].

Reliable epidemiological data on childhood AAV are scarce. Overall, we found a low incidence of paediatric AAV in France approaching 0.5 per million children per year. This is in line with the estimated incidence reported in young Swedish aged 18–30 years [40] but far below the average incidence of 2.75/million/year reported in Southern Alberta [7]. However, the latter study was based on 15 patients in a 15-year period and the incidence during the first 10 years remained <1/million/year. We found around 60% of MPA and 40% of GPA. This is in contrast with the paediatric literature where MPA appears to be less common than GPA [6, 27–31, 40–46]. However, there are regional differences with a greater proportion of MPA in reports from Asia [6, 44] and Eastern Europe [46].

As in other paediatric reports, we found a median age at diagnosis of around 13 years for GPA and 11 years for MPA and a predominance of girls. Time to diagnosis was short and similar to recent reports [29, 31]. However, the diagnosis was delayed by 6 months or more in one-third of the patients, especially those with mild renal or pulmonary impairment.

Almost 90% of our patients had renal impairment and we identified only one case of limited GPA [47]. In paediatric studies, renal impairment ranges from 50 to 100% of children with GPA [27–29, 31, 40, 45] whereas it is less frequent in adults: 10–20% at diagnosis and 60–80% during the evolution [48]. Lung involvement is more frequent in children with GPA (70–100%) who mainly present with interstitial syndrome, nodules and pleurisy [49–51] than in those with MPA (30–

---

**Table 2. Laboratory features at presentation**

<table>
<thead>
<tr>
<th>ANCA testing</th>
<th>GPA (n = 28)</th>
<th>MPA (n = 38)</th>
<th>Total (n = 66)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IF for pANCA positive</td>
<td>43 (65%)</td>
<td>39 (55%)</td>
<td>82 (61%)</td>
</tr>
<tr>
<td>Anti-MPO positive on ELISA</td>
<td>6 (21%)</td>
<td>33 (86%)</td>
<td>40 (61%)</td>
</tr>
<tr>
<td>Anti-PR3 positive on ELISA</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Negative on ELISA</td>
<td>1 (4%)</td>
<td>4 (11%)</td>
<td>5 (7%)</td>
</tr>
<tr>
<td>IF for cANCA positive</td>
<td>22 (33%)</td>
<td>39 (100%)</td>
<td>61 (92%)</td>
</tr>
<tr>
<td>Anti-MPO positive on ELISA</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Anti-PR3 positive on ELISA</td>
<td>18 (64%)</td>
<td>4 (11%)</td>
<td>22 (33%)</td>
</tr>
<tr>
<td>Negative on ELISA</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>IF for pANCA and cANCA positive</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Anti-MPO positive on ELISA</td>
<td>0 (0%)</td>
<td>1 (3%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Anti-PR3 positive on ELISA</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Haematological tests</th>
<th>GPA (n = 28)</th>
<th>MPA (n = 38)</th>
<th>Total (n = 66)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaemia</td>
<td>42 (64%)</td>
<td>49 (25%)</td>
<td>91 (57%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2 (3%)</td>
<td>2 (3%)</td>
<td>4 (6%)</td>
</tr>
<tr>
<td>Leucocytopenia</td>
<td>2 (3%)</td>
<td>5 (13%)</td>
<td>7 (11%)</td>
</tr>
<tr>
<td>Elevated sedimentation rate</td>
<td>49 (94%)</td>
<td>14 (36%)</td>
<td>63 (95%)</td>
</tr>
<tr>
<td>Antinuclear antibodies positivity</td>
<td>8 (13%)</td>
<td>2 (5%)</td>
<td>10 (15%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Complement system tests (n = 55)</th>
<th>GPA (n = 28)</th>
<th>MPA (n = 38)</th>
<th>Total (n = 66)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low serum C3</td>
<td>1 (2%)</td>
<td>4 (11%)</td>
<td>5 (8%)</td>
</tr>
<tr>
<td>Low serum C4</td>
<td>4 (7%)</td>
<td>1 (3%)</td>
<td>5 (8%)</td>
</tr>
</tbody>
</table>

**Table 3. Renal pathology at diagnosis (n = 44)**

<table>
<thead>
<tr>
<th>Pathological features</th>
<th>GPA (n = 28)</th>
<th>MPA (n = 38)</th>
<th>Total (n = 66)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of glomeruli, median (IQR)</td>
<td>14 (10–20)</td>
<td>30 (13–45)</td>
<td>40 (19)</td>
</tr>
<tr>
<td>Proportion of glomeruli with fibrinoid necrosis, median (IQR)</td>
<td>30 (13–45)</td>
<td>44 (24–66)</td>
<td>74 (38)</td>
</tr>
<tr>
<td>Proportion of glomeruli with cellular crescents, median (IQR)</td>
<td>50 (25–65)</td>
<td>43 (24–66)</td>
<td>93 (51)</td>
</tr>
<tr>
<td>Presence of endocapillary proliferation, n (%)</td>
<td>10 (23)</td>
<td>44 (12–66)</td>
<td>54 (32)</td>
</tr>
<tr>
<td>Proportion of glomerular sclerosis, median (IQR)</td>
<td>33 (16–61)</td>
<td>32 (13–66)</td>
<td>65 (38)</td>
</tr>
<tr>
<td>Proportion of glomeruli with fibrous crescents, median (IQR)</td>
<td>40 (30–65)</td>
<td>25 (13–66)</td>
<td>65 (38)</td>
</tr>
<tr>
<td>Presence of tubular atrophy, n (%)</td>
<td>22 (52)</td>
<td>42 (12–66)</td>
<td>64 (38)</td>
</tr>
<tr>
<td>Presence of interstitial fibrosis, n (%)</td>
<td>25 (60)</td>
<td>42 (12–66)</td>
<td>67 (40)</td>
</tr>
<tr>
<td>Presence of granuloma, n (%)</td>
<td>1 (2)</td>
<td>44 (12–66)</td>
<td>45 (27)</td>
</tr>
</tbody>
</table>
50%) who usually show alveolar haemorrhage [6, 41–44]. There was no patient with cavity in our cohort, two cases being described in the paediatric literature [45, 52] while it seems more common among adults [49]. We found that 75% of our patients with GPA had upper respiratory impairment which is consistent with the 60–90% proportion in the paediatric literature, mainly sinusitis and recurrent epistaxis [27, 29, 40, 48]. Almost half of this cohort had cutaneous impairment. In paediatric studies, 30–50% of children have cutaneous manifestations [6, 27, 28, 31, 40, 41, 43–45], mainly purpura in both vasculitis while mouth ulcers and nodules are more frequent in GPA [6, 27–29, 40, 45, 48]. Joint impairment can concern up to 80% of children with GPA who usually present polyarthralgia [27, 28, 40, 41, 45, 48], arthritis remaining scarce [29].

We found that patients with MPA were predominantly pANCA/anti-MPO+ (almost 90%) whereas GPA were cANCA/anti-PR3+ in two-third of cases. Given the retrospective design, we only included ANCA-positive children to ensure a reliable diagnosis in case of clinical symptoms compatible with paediatric AAV. This choice may have resulted in an underestimation of AAV incidence, ANCA-negative forms representing 10% of patients with AAV at presentation [13, 28, 31]. Nevertheless, our results are in accordance with the paediatric literature where GPA is associated with PR3-ANCA in 70–90% [27, 40, 49] and MPA is associated with MPO-ANCA in 60–80% of cases [6, 53].

All patients from this study received corticosteroids, two-third of them in combination with cyclophosphamide as induction therapy. There are currently no clinical trials being performed in paediatric AAV, and treatment is based on lessons from the adult literature. Our study design and the heterogenous therapeutic strategies used did not allow for assessing the respective treatment effects in our study. However, children who received steroid treatment alone for induction frequently needed adjuvant therapy to reach complete remission. Severe infection is one of the most common treatment-related side effects in AAV. One child died of bacterial infection in our study. Fewer treatment-related adverse events have

FIGURE 2: Disease course in childhood-onset ANCA-associated vasculitis. CYP, cyclophosphamide; PE, plasma exchanges; IVIG, intravenous immunoglobulin; RTX, rituximab; ESRD, end stage renal disease.
been reported in children than in adult studies [27, 40, 42, 48]. However, a recent report with a long follow-up from 11 to 30 years highlighted severe complications due to immunosuppressive treatments such as infertility and cancer [54]. In the recent years, we have observed a decrease in the use of oral cyclophosphamide and a more frequent use of rituximab. Two trials conducted in adult patients provided evidence for non-inferiority of rituximab as compared with cyclophosphamide to induce remission [55, 56].

The absence of disease activity was assessed by a standardized score for adults adapted with children norms. No paediatric score is used in current practice for children, a Paediatric Vasculitis Activity Score (PVAS) is being validated [57]. The outcome after treatment was characterized by a response for all children and a remission for almost all. In paediatric studies, the rate of remission reported is usually high ranging from 80% to 90% [27, 29, 31, 43, 48]. Forty percent of the children in remission experienced a first relapse which is lower than in other paediatric studies (60–80%) [28, 40, 43] except in one study including MPA [6]. Long-term prognosis appears to be favourable with ~90% of children in remission after a median follow-up of 5 years. There was no association between the remission status and the presence of ANCA, which was positive for almost half the children in clinical remission at last follow-up. ANCA titre does not justify an intensification in treatment [18, 43, 53] but an increase in titre should make search for clinical signs of relapse. The mortality is lower in paediatric patients with AAV (6% in our study, 0–12% in other studies) compared to adult patients (25% in Walsh et al. [58]).

Renal survival was 70% at 1 year and remained stable thereafter (60% at 10 years). The occurrence of ESRD in paediatric AAV studies ranges from 10 to 50% [27, 29, 41, 46]. There are limited data on predictors of renal outcome among children with AAV. A Japanese study of 31 children with ANCA-associated glomerulonephritis found that serum creatinine >2.5 mg/dL and chronic glomerular lesions at diagnosis lead to a poorer renal survival [6]. Our study is the first to provide a multivariable analysis of the determinants of ESRD in paediatric AAV. A decrease in baseline GFR and, in the subgroup of patients with kidney injury, an initial renal biopsy classified as sclerotic were associated with a higher risk of subsequent ESRD suggesting that chronicity is the main determinant of poor renal prognosis. We also found that non-Caucasian patients are at higher risk of ESRD than Caucasians, as shown in lupus nephritis. We hypothesized that they were more likely to present with late diagnosis but the association between ethnicity and renal survival remained even after controlling for baseline GFR and diagnosis delay. Finally, we observed a significantly improved renal prognosis in the most recent period. Since we did not observe a decrease in diagnosis delay during the study period we can speculate that a better management of paediatric AAV may be responsible for this effect.

This study has several limitations. This is a retrospective, multicentric study with data collected over a long period. There is lack of homogeneity regarding the availability and accuracy of medical records. The dramatic change in incidence over time suggests underreporting of patients in the early period of the study. Moreover, our main source of patients was paediatric nephrology centres which may have resulted in an over-representation of kidney impairment. To minimize these drawbacks and allow for reliable comparisons, we used standardized classifications for AAV and definitions recommended by EULAR for histological criteria and outcome. To our knowledge this study is the largest so far to address the questions of incidence and short- and long-term outcomes in children with AAV.

In conclusion, childhood-onset AAV is characterized by female predominance, frequently delayed diagnosis, high remission rate and improvement over time in renal outcome. Paediatricians should be aware of the early diagnosis and treatment of this disease.

**CONFLICT OF INTEREST STATEMENT**

None declared.

**REFERENCES**


52. Haliloglu M, Karcaaltincaba M, Toru M et al. CT presentation of Wegener's granulomatosis in a child: rapidly progressive changes of pulmonary nodules to cavities. Eur J Radiol 2000; 35: 12–14

Received for publication: 30.6.2014; Accepted in revised form: 6.1.2015