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EDITORIAL

Course of paediatric ANCA-associated glomerulonephritis: advocating for an age-inclusive approach

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Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a group of diseases characterised by systemic involvement of small-to-medium vessels with necrotising inflammation that, by virtue, can affect all organs. Even though the underlying pathophysiology is still not fully understood, a central role is devoted to autoantibodies against two major neutrophil proteins, either proteinase 3 (PR3-ANCA) or myeloperoxidase (MPO-ANCA), in granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). These autoantibodies are able to prime and activate neutrophils that, together with other inflammatory cells such as macrophages, monocytes and the complement system, lead to the observed endothelial injury. Both diseases, GPA and MPA, have a predilection for pulmonary and kidney involvement, with 58.6% and 82.2%[1] of adults with AAV presenting with ANCA-glomerulonephritis (GN). The incidence of PR3-ANCA is highest in countries with higher latitudes, and PR3-ANCA vasculitis rarely occurs in Japan and China.[2] A significant proportion of patients with ANCA-GN remain negative for ANCA but show signs of kidney disease, which is characterised by the absence or only a faint staining for immunoglobulins or complement. In children, the disease is ultra-rare, meaning precise estimates related to epidemiology are missing; however, the underlying disease pathophysiology is believed to be sufficiently similar to that of adults, with subtle differences reported in the frequency of organ involvement. For example, ANCA-GN in GPA seems to be more common in children than in adults, while a comparable frequency is reported in MPA (figure 1). The largest cohort studies reported from Northern America (40 centres), Europe (three centres) and Asia (two centres) revealed that GPA is almost four times as common as MPA.[3] In children enrolled on the A Registry for Children with Vasculitis (ARChiVE) registry from 2004 to 2015, initial treatment among 231 children consisted of corticosteroids (96.5%), cyclophosphamide (75.8%), rituximab (12.1%) and plasma exchange (21.2%).[4] The limited information derived from published cohort data related to key outcomes in childhood-onset ANCA-GN suggests an increased chance of disease reversibility with more kidney function recovery following treatment initiation. The literature also reports the impact of the ANCA serotype (PR3-ANCA vs MPO-ANCA) on kidney function outcomes, disease relapse risk and damage accrual during shorter-term follow-up.

In this issue, the ARChiVE/Pediatric Vasculitis Initiative (PedVas) registry reports on 406 children with AAV collected over 15+ years, with the primary aim of investigating the predictive value of the ANCA serotype on kidney disease course and prognosis. In total, 68% of the cohort were female and 310 (76.4%) children with AAV had kidney disease. More patients with MPO-ANCA+ had kidney disease (n=111, 88.1%) in comparison to those presenting with PR3-ANCA+ (n=179, 77.2%) or ANCA-negativity (n=20, 50.0%) (figure 1). Those with MPO-ANCA+ vasculitis more commonly presented with severely and moderately impaired kidney function at baseline, defined as estimated glomerular filtration rate (eGFR) <15 mL/min/1.73 m^2 (15.9% vs 6.0%) and eGFR between 15 and 49 mL/min/1.73 m^2 (19.8% vs 8.2%).[5] In other words, 35.7% and 14.2% presented with an eGFR below 50 mL/min/1.73 m^2, and thus kidney function in children is less severely impacted at the time of diagnosis. In the UK National Registry of Rare Kidney Diseases (RaDaR), the median age at diagnosis was >60 years for females and males with AAV, and the

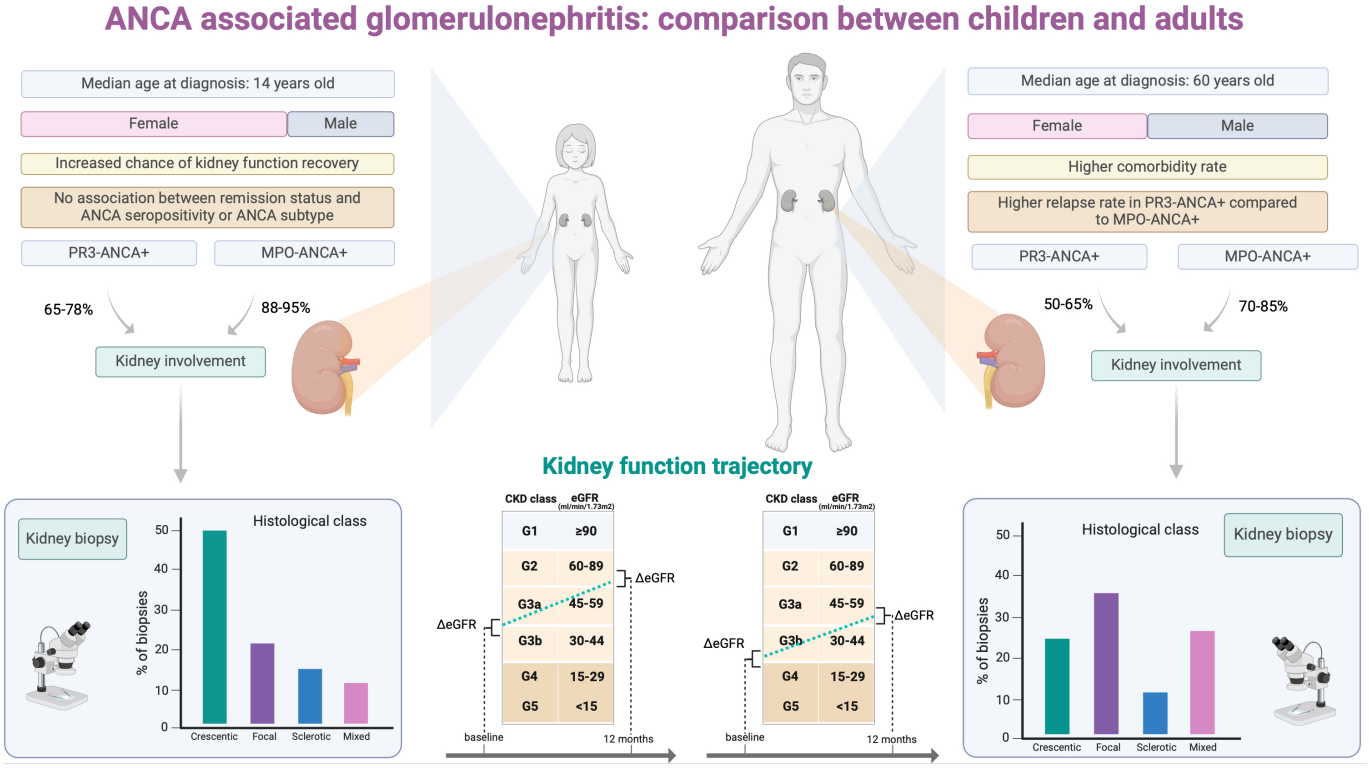

Figure 1 ANCA-associated glomerulonephritis is rare in children. Differences reported in this study and others include a skewed distribution towards more frequent AAV in females in comparison to males. Kidney disease is encountered more frequently in children with PR3-ANCA vasculitis in comparison to adults. More children present with a crescentic class according to the Berden histopathological classification,[7] which is also associated with a greater kidney function recovery potential. In the short-term follow-up, the risk of relapse seems to be balanced in children with PR3-ANCA+ and MPO-ANCA+, which is in contrast to adults, where a higher relapse rate is reported in patients with PR3-ANCA+. This figure was created with the help of BioRender.com. ANCA, antineutrophil cytoplasmic antibody; eGFR, estimated glomerular filtration rate; MPO, myeloperoxidase; PR3, proteinase 3.

average eGFR at the time of initial presentation was 29.5 and 31.4 mL/min/1.73 m^2,[6] indicating that presentation between children and adults differs. The 10-year kidney survival in RaDaR was approximately 80%, and given the median age at presentation, most patients did not progress to kidney failure.[6] The median age in the paediatric population reported from the ARChiVE/PedVas registry was 14 years,[5] thus, children with ANCA-GN are likely to progress through the stages of chronic kidney disease (CKD) over their life course. Preserving kidney function is therefore important in this population.

The goal of therapeutic studies related to ANCA-GN is to achieve maximum kidney function recovery. An international study including one centre from Canada and multiple Italian sites reported on 85 children with ANCA-GN, of whom the majority were histologically sub-classified as crescentic (50.6%), followed by focal (21.2%), sclerotic (15.3%) and mixed (12.9%) according to the Berden classification (figure 1).[7] The eGFR at baseline differed significantly across the different histological classes; the crescentic and sclerotic classes had a baseline eGFR of 23 and 21 mL/min/1.73 m^2 and those in the focal and mixed classes presented with an eGFR of 80 and 53 mL/min/1.73 m^2, respectively.[8] Contrasting findings have been reported in adults, where the majority presents with a focal class (35.9%) and a crescentic class is found in 25.5% of patients with ANCA-GN. Interestingly, the eGFR at the time of diagnosis of adults with ANCA-GN and either a crescentic or sclerotic class is consistent with the findings in children (eGFR 18 and 19 mL/min/1.73 m^2). In line with paediatric ANCA-GN, those with a mixed and focal class had less significant kidney dysfunction at baseline, with reported average eGFR values of 27 and 50 mL/min/1.73 m^2, respectively.[9] Of relevance, the kidney function trajectory of children with ANCA-GN differs from that of adults. At the time of the last follow-up, in children not requiring kidney replacement therapy, the eGFR increased by 23 mL/min/1.73 m^2 in the focal, by 39 mL/min/1.73 m^2 in the mixed and by 49 mL/min/1.73 m^2 in the crescentic class, while a decline to 10 mL/min/1.73 m^2 was found in the sclerotic class.[8] This places those children in the sclerotic class at greater risk of kidney failure, while the other classes may permit longer-term kidney failure-free survival. This is in contrast to adults, who only experience a modest increase in eGFR of 8 mL/min/1.73 m^2 and 10 mL/min/1.73 m^2 in the focal and mixed classes, a greater increase of 19 mL/min/1.73 m^2 in the crescentic class and a decline of −1 mL/min/1.73 m^2 in the sclerotic class over a 5-year observational period.[9] In the paper

by Mann *et al*,[5] 14 children with PR3-ANCA and 20 with MPO-ANCA vasculitis presented with an eGFR <15 mL/min/1.73 m^2 at baseline. The eGFR in the PR3-ANCA+ patients increased from 11.8 at baseline to 20.5 mL/min/1.73 m^2 (+8.7 mL/min/1.73 m^2) at 12 months, while there was an increase from 13 to 44.6 mL/min/1.73 m^2 (+31.6 mL/min/1.73 m^2) in the MPO-ANCA+ patients. This is an unexpected finding, although based on a small cohort size, as kidney disease in PR3-ANCA vasculitis is more acute in adults and this subset of patients exhibits a higher recovery potential. In adult patients with an eGFR ≤30 mL/min/1.73 m^2, a single-centre study reported an eGFR increase of 12.5 mL/min/1.73 m^2 in PR3-ANCA+ vs 8.5 mL/min/1.73 m^2 in MPO-ANCA+ individuals. This also translated into a higher likelihood of kidney failure-free survival.[10] Taken together, the findings in children with ANCA-GN support the notion of greater plasticity, even in severe inflammatory disease states, translating into better outcomes compared with disease onset in adulthood. The reasons for this remain speculative. First, children are likely to have normal kidney function prior to disease onset, as they rarely have additional comorbidities and lack naturally occurring age-related organ damage. Second, experimental studies suggest a greater potential for mice treated with a clone-directed therapy to attenuate crescentic lesions and promote differentiation into podocytes.[11] The proportion of children presenting with a crescentic class exceeds the numbers observed in adults, and this might be one particular explanation for greater kidney function recovery. Other potential factors influencing the eGFR recovery seen in children may be related to a different response to immune stimuli across different age groups, as has been exemplified by CD8+T cell responses towards viral infections,[12] highlighting that restoration of immune competence or fast achievement of therapeutic response is pivotal in predicting the trajectory of kidney function.

Many scientific questions remain unanswered in the childhood population. One of the major limitations of the large investigation by Mann *et al*[5] is that the role of currently used histopathological classification or prediction tools has not been investigated. Additionally, potential differences in treatment regimens have not been reported. Moreover, specific therapies such as the recently approved oral C5aR1 inhibitor avacopan are not approved for the management of childhood AAV, perhaps because there are major challenges in conducting clinical trials in this vulnerable population with ultra-rare diseases, leading to a lack of evidence generation and representing an age-related inequality in terms of therapeutic options. In adults with an eGFR <20 mL/min/1.73 m^2, therapy with avacopan in the Avacopan for the Treatment of ANCA-Associated Vasculitis (ADVOCATE) trial led to an increase in eGFR of 16.1 mL/min/1.73 m^2 at week 52, which was 8.4 mL/min/1.73 m^2 greater than in the comparator group.[13] In children with disease-related damage, further inequities are witnessed in the management of kidney function preservation, with therapies such as the sodium-glucose cotransporter-2 inhibitors remaining untested in a robust way. Moreover, even in the adult population, ANCA-GN was a common direct or indirect (lack of allowance of intravenous therapies or higher doses of glucocorticoids) exclusion criterion in the landmark trials performed for these agents.[14] The current analysis by Mann *et al*[5] is limited by the relatively short-term follow-up and therefore the effects of the ANCA serotype, for instance, on the risk of disease relapse might have been missed. Other common complications, such as cardiovascular disease or side effects of higher cumulative glucocorticoid exposure, are seen during an observational period that expands beyond what has been reported in the current study. Notably, in the context of CKD, blood pressure and cholesterol management changes and more rigorous control of traditional cardiovascular risk factors are required once CKD is established.[15] Despite the limitations, large cohort studies, such as this one, provide an important contribution to understanding the natural history of this disease in children, thus better enabling inclusion in future clinical trials. Improving the outcomes for this disease in all patients is important. An age-inclusive approach to evidence generation in AAV would not only represent fairness, but the inclusion of children in clinical trials would also provide an important contribution to achieving efficacy endpoints due to their larger gain in kidney function recovery.

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