ANCA Associated Vasculitides in Children: Recent Advances

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Childhood onset anti-neutrophilic cytoplasmic antibody (cANCA) associated vasculitis (AAV) is a rare group of primary systemic vasculitides affecting medium and small blood vessels characterized by pauci-immune necrotizing inflammation in association with autoantibodies against the cytoplasmic region of the neutrophil (ANCAs against proteinase 3 (PR3-ANCA) or myeloperoxidase (MPO-ANCA)). This group of vasculitides includes granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis (EGPA), and renal limited ANCA vasculitis. These disorders are associated with severe and sometimes organ/life threatening clinical manifestations characterised by multisystem involvement, frequent relapses and a high cumulative morbidity (1). In a recent series with 28 children, at presentation 14 (50%), 5 (18%), and 4 (14%) children required intensive care unit care, ventilator support, and dialysis, respectively. At a median follow-up of 3.3 years, 10 (37%) children had chronic kidney disease (CKD) (stage 3 and greater) (2). In another pediatric series, after a median follow-up of 5.8 years, 55% of the patients had CKD stages 1-3 (55%) and 32% of patients progressed to end-stage kidney disease (ESRD) (3). Based on a systematic review and metaanalysis, cGPA and cMPA occurred predominantly in female adolescents. For cGPA, the most frequent initial presentations are ear-nose-throat (ENT) disease (82%), constitutional symptoms (73%), renal (65%) and lung (61%) manifestations (4). Relapses occurred more frequently in GPA (67-100 %) than in MPA (25-50 %). The leading causes of death were the disease itself, and infections (4).
In a recent French registry, cAAV and matched adult-onset controls (aAAV) were compared in terms of initial presentation and late outcome results. Data based on 35 cAAV (25 GPA, 4 MPA, 6 EGPA) and 151 aAAV (106 GPA, 17 MPA, 28 EGPA) demonstrated that cAAV was a severe disease, characterized by a higher relapse rate, more accrued damage particularly in ERT and longer maintenance therapy than for aAAVs. Renal involvement and death rate were not significantly d ifferent between the two series (5).

In diagnosis, granulomatous inflammation in histopatologic examination is a very important finding (6) Immunologically, ANCAs were detected in >90 % of children with GPA or MPA) (5), however, they are overall poor biomarkers of disease activity. They may be useful for the prediction of flares of renal and/or pulmonary vasculitis. Moreover, patients with proteinase 3 (PR3)-AAV may respond better to rituximab than cyclophosphamide (7). There are several promising biomarkers are pipeline. Newer understanding of neutrophil extracellular traps and complement activation have provided better insights into disease pathogenesis (1).

No specific pediatric treatment recommendations exist due to rare nature of the illness in pediatric population. (8). Traditionally more severe disease has been managed with the 'gold standard' treatment of glucocorticoids and cyclophosphamide (9). A recent pediatric systematic review showed that combined corticosteroids and cyclophosphamide was used first remission-inducing treatment in 76% and 62% of GPA and MPA cases, respectively (5). Other agents employed in remission induction include anti-tumor necrosis factor-alpha therapy and mycophenolate mofetil. Recently, however, increasing consideration is being given to rituximab (RTX) as a therapy for children in severe or relapsing disease, particularly for those at risk for glucocorticoid or cyclophosphamide toxicity (9). Recruitment of paediatric patients to recent vasculitis trials may be helpful for generationg pediatric specific data rather than simply extrapolation from adult studies. (8,9). Two pivotal randomized controlled trials, RITUXVAS and rituximab in ANCA-associated vasculitis (RAVE), provide high-quality evidence demonstrating rituximab (RTX) is efficacious in inducing remission in adult ANCA-associated vasculitis (AAV) patients compared with cyclophosphamide (CYC). RAVE also demonstrated superiority of RTX to oral CYC for induction of remission in relapsing disease Disappointingly, the RTX regimen was not associated with reduction in early serious adverse events (8). In particular, the 6-month interim results of the PEPRS trial provide encouraging data specific to children. In the current practice, RTX has been reserved in severe/renal or life threatening disease/refractory disease (9). However, due to special concerns related to side effects of seroids and cyclophosphamide including growth, preservation of fertility, and potential for high cumulative medication doses, children with AAV may be considered as candidates for RTX even as a first-line remission induction therapy (8).

Most recently, there is a particular emphasis on the role of the alternative pathway of complement in the treatment of AVV. Targeting the activation of neutrophils by the anaphylatoxin C5a may serve as an additional therapeutic strategy, however the results of clinical studies are awaited (10).

In conclusion, cAAVs are a rare group of severe vasculitides, pathogenesis remains not fully understandable, high quality studies on treatment alternatives are lacking. There is a significant need for developing pediatric-specific consensus treatment guidelines for cAAV (11).

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Arteriovenous Fistulas in Children

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Vascular access is key to adequate dialysis and overall quality of care. Starting with a well functioning arteriovenous fistula (AVF) in children requiring chronic haemodialysis (HD) is the optimal strategy for minimising access problems. There are several advantages ofAVFs over CVCs including better quality dialysis, fewer infections, fewer access changes and less hospitalization (1). However, data from the International Paediatric Haemodialysis Network registry showed that AVFs are used in only 25% of children on HD (2). Similarly, a survey across European pediatric nephrology centers reported that AVFs were used in 38% of the children, who are predominantly adolescents (3). Central venous catheters (CVCs) remain the predominant choice of vascular access in children, despite problems of malfunction and infection and need for access replacement (2,3). Cuffed CVCs should be reserved for very small children depending on vessel size and surgical expertise, those requiring urgent or unplanned HD and where a short period on HD is anticipated before transplantation (1).

For adults on HD, the principle of “Fistula First” has been key to changing the attitude to vascular access for HD. However, in children, technical difficulties in forming AVFs, dialysis nursing expertise, patient concerns regarding puncture pain and a paucity of experience in managing complications has resulted in reluctance in considering an AVF for children with ESKD (1). On the other hand, well structured vascular access teams can provide satisfactory AVF patency rates. A dedicated pediatric vascular access clinic that is run jointly by a transplant surgeon, paediatric nephrologist, dialysis nurse and a clinical vascular scientist specialised in vascular sonography for the assessment and surveillance of AVFs represented a very good primary maturation rate of 83% (10/12). Assisted maturation was 100%, with two patients requiring a single angioplasty (4). Another pediatric study showed that the primary and secondary patency rates at 1, 2, 3 years were: 60%, 49%, 42%, and 82%, 72%, 54%, respectively. The median (range) maturation time was 4.53 months (5).

Creating an AVF in the non-dominant arm at least 3 months before its anticipated use is suggested. Pre-operational duplex ultrasound of upper limb arteries and veins is adviced. In children in whom central venous stenosis is suspected, such as those with previous CVCs, performing appropriate imaging of central veins by venography, computed tomography-angiography or non-contrast magnetic resonance imaging is recommended. AVF creation in the ipsilateral arm of a central venous stenosis should be avoided (1).

Maturation can be assessed 4 to 6 weeks after AVF formation by clinical examination and duplex ultrasound imaging and first cannulation should be performed when AVF has matured adequately by using either rope ladder or button hole technique (1,6).

Anti-platelet agents such as aspirin, ticlopidine or clopidogrel, given in the first few months after AVF creation, reduces AVF thrombosis (7). Anticoagulation may be particularly relevant in the youngest children or those with a pro-coagulant state, such as children with nephrotic syndrome. In the absence of evidence in children, the use of aspirin can be suggested as a pragmatic approach, at least for the first few months, after AVF formation. In addition, expert opinion suggests that maintaining adequate intravascular volume by reducing the ultrafiltration for a few HD sessions after AVF creation, and allowing permissive hypertension by adjusting antihypertensive medications may prevent early AVF thrombosis (1).

For long-term AVF patency, AVF surveillance is very important. Early diagnosis and prevention of access dysfunction are aimed. Proactive monitoring of vascular access can decrease frequency of thrombosis and hospitalization, as well as the need to revert to CVCs for dialysis access (8).

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Vascular access in children on hemodialysis

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A well functioning vascular access is key to adequate dialysis and overall dialysis quality. There are three forms of vascular access for the treatment of children with end stage kidney disease (ESKD) by hemodialysis: tunnelled central venous catheters (CVCs), arteriovenous fistulas (AVF), and arteriovenous grafts (AVG) made by prosthetic or biological material.

As it is well stated in adults' "Fistula first" initiative, current pediatric guidelines advocate use of AVF over CVC for children (1). However, data from ESPN/ERA-EDTA registry showed that 393 (55.1%) of 713 children started HD with a CVC (2). In an earlier study from Europe, CVC were used in 67 of 111 (60%) patients, 42 patients (38%) had an AVF and two patients (2%) an AVG (3).

While AVFs may not be suitable in the very young or those with an anticipated short dialysis course before transplantation, many pediatric studies have shown that AVFs are superior to CVCs in terms of event free access survival (1). Therefore, wherever possible, AVF should be considered at the first order. On the other hand, 14% of newborn and small infants have been undergoing HD and CVCs are the only access for HD in those individuals (4).
Data from multiple observational studies and the International Pediatric Haemodialysis Network registry suggest that CVLs are associated with a significantly higher rate of infections and access dysfunction, and need for access replacement (1). CVC related bloodstream infections and thrombotic events should be prevented by using catheter lock solutions including antibiotics, heparin, taurolidine, citrate, tissue plasminogen activator (t-PA), etc. Among them t-PA is the most effective one in preventing and treating catheter thrombosis (1).

Microsurgical AVF creation at the wrist can be performed with satisfactory results and should be the preferred technique in the pediatric population (5). A dedicated team consisting of vascular surgeon, pediatric nephrologist, dialysis nurse and vascular sonographist is of particular importance for primary and secondary AVF maturation (6). Radiologists experienced in pediatric vascular interventions can also provide good catheter outcomes. Therefore, it is important to provide the right vascular access for the right patient at the right time, with an emphasis on venous preservation at all times.

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