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Review

The emerging concept of ANCA-associated vasculitis related to inborn errors of immunity

Clément Triaille [a,b,*], Benjamin Terrier [c,d], Alice Hadchouel [e,f], Elie Haddad [g], Augusto Vaglio [h,i,1], Marie-Louise Frémond [j,k,1]

[a] Pôle de Pathologies Rhumatismales Systémiques et Inflammatoires (RUMA), Institut de Recherche Expérimentale et Clinique (IREC), Université catholique de Louvain, Brussels, Belgium
[b] Department of Pediatrics, CHU Sainte-Justine, Université de Montréal, Montreal, Quebec, Canada
[c] Department of Internal Medicine, Hospital Cochin, AP-HP, Paris, France
[d] Université Paris Cité, Paris, France
[e] AP-HP, Hôpital Universitaire Necker-Enfants Malades, Service de Pneumologie Pédiatrique, Centre de Référence pour les Maladies Respiratoires Rares de l'Enfant, Paris, France
[f] INSERM U1151, Institut Necker Enfants Malades, Université Paris Cité, Paris, France
[g] Department of Pediatrics, Department of Microbiology, Immunology and Infectious Diseases, CHU Sainte-Justine Azrieli Research Center, Université de Montréal, Montreal, Quebec, Canada
[h] Nephrology and Dialysis Unit, Meyer Children's Hospital IRCCS, Firenze, Italy
[i] Department of Biomedical, Experimental and Clinical Sciences "Mario Serio", University of Firenze, Firenze, Italy
[j] Laboratory of Neurogenetics and Neuroinflammation, Imagine Institute, INSERM UMR1163, Paris, France
[k] Paediatric Immunology-Hematology and Rheumatology Unit, Necker Hospital, APHP Centre, Université Paris-Cité, Paris, France

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ABSTRACT

ANCA-associated vasculitis (AAV) is a group of rare small vessels vasculitis that preferentially affect the kidneys, lungs and upper airways. Although the detailed pathophysiology remains unclear, genetic background has been shown to play a role in sporadic forms of AAV. The discovery of these susceptibility genes (and associated biological pathways) involved in AAV have shaped the current understanding of AAV pathophysiology. In addition to common genetic polymorphisms, specific rare inborn errors of immunity (IEI) have been described with a high frequency of ANCA (antineutrophil cytoplasmic antibodies) positivity and vasculitis features in young individuals (in addition to other manifestations). A systematic literature search revealed that patients with pathogenic variants in *COPA, STING1, DNASE1L3,* and *PIK3CD* are at increased risk of developing ANCA and AAV features, including alveolar hemorrhage, interstitial lung disease, pauciimmune glomerulonephritis, and upper airways involvement (septum perforation, saddle-nose deformity, chronic nasal/sinuses ulceration). Some of these IEI may also present with a mixed phenotype and/or auto-antibodies profile associating features of AAV and other autoimmune diseases (in particular systemic lupus erythematosus). Notably, a proportion of reports and series lack serological (ANCA specificity and titers) and/or histopathological data, making challenging to assess the likelihood for ANCA pathogenicity in some patients with IEI (as opposed to unspecific signs of biologic autoimmunity). This point is nonetheless essential to make appropriate therapeutic decisions. In addition, since most of the genes mentioned above are involved in the type 1 interferon signaling, the role of this pathway in AAV etiopathogenesis deserves further investigation.

In this review, we will describe these IEI, their overlap with sporadic AAV, and their evocative features. Next, we will discuss how these monogenic conditions might inform our general understanding of AAV pathophysiology. We also propose some directions for future research in order to better define the link between ANCA and IEI. Finally, we will consider how making the diagnosis of an IEI in a patient with AAV features might impact individual management.

* Corresponding author at: Department of Pediatrics, CHU Sainte-Justine, 3175 Chem. de la Côte-Sainte-Catherine, Montreal, Quebec, Canada.
E-mail address: clement.triaille@uclouvain.be (C. Triaille).

[1] Augusto Vaglio and Maire-Louise Frémond contributed equally.

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1. Introduction

Anti-neutrophil cytoplasmic antibodies (ANCA) are auto-antibodies directed against proteins in neutrophil cytoplasmic granules: proteinase 3 (PR3) or myeloperoxidase (MPO). ANCA are strongly associated with small-vessel vasculitis in humans and mice (ANCA-associated vasculitis, AAV) [1]. Although present at low titers in a small fraction of healthy adults (unknown in healthy children), ANCA detected in patients with AAV are considered to be high-affinity, class-switched antibodies, with particular epitope specificity [2–5]. Besides their diagnostic and prognostic relevance, ANCA also play a direct pathogenic role in AAV.

The role of genetic susceptibility in sporadic AAV has been highlighted through genome-wide association studies. For instance, polymorphism at multiple genetic loci have been associated with a (slightly) increased risk of having AAV [6–8]. These data refined our current understanding of the pathophysiology of AAV. More recently, evidence has accrued that some specific rare monogenic inborn errors of immunity (IEI) present with a high frequency of ANCA positivity, and features reminiscent of AAV. The potential utility of these monogenic disorders to provide new insights into AAV pathogenesis has been largely underappreciated thus far.

In this review, we will: (i) summarize the current understanding of the mechanisms underlying sporadic forms of AAV; (ii) describe the IEI associated with increased risk of AAV; (iii) discuss how these rare conditions might inform about AAV pathophysiology; and (iv) briefly review current challenges in the management of IEI patients with (suspected) AAV.

2. Sear strategy and selection criteria

A literature search was performed to identify inborn errors of immunity reported in association with ANCA. The following terms were searched on PubMed in November 2024: (ANCA) AND ((MONOGENIC) OR (PRIMARY IMMUNE DEFICIENCY) OR (INBORN ERROR OF IMMUNITY) OR (INTERFERONOPATHY)). The results of this literature search (Supplementary Fig. 1) were combined with the authors' knowledge and experience on the topics discussed in this narrative review.

3. Clinical presentation and treatment of sporadic AAV

AAV are a group of systemic small-vessel vasculitis that may present with variable clinical features [9,10]. The majority of AAV occur in patients in their 4th to 7th decades, occasionally in adolescents/young adults, and exceptionally in younger children [10,11]. Frequently involved organs include lungs (alveolar hemorrhage, interstitial lung disease), kidneys (crescentic pauci-immune glomerulonephritis leading to chronic renal insufficiency), and upper respiratory tract (chronic rhinitis/sinusitis, airway stenosis, cartilage destruction). Other organs such as joints, skin, eyes and peripheral nervous system may also be affected. Systemic features (fatigue, weight loss, fever) are also commonly observed. The diagnosis of AAV is based on suggestive clinical, radiological and histological features (e.g. pauci-immune glomerulonephritis, granulomatous inflammation), and autoimmune serology [9]. Thus, the identification of ANCA is strongly supportive but not sufficient for the diagnosis of AAV. ANCA titers and MPO/PR3 specificity also need to be taken into account [9].

The clinical features of AAV in the pediatric populations appear broadly similar than in adults [12], but their respective frequency may differ. Kidney appears to be the most commonly targeted organ, with a significant risk of kidney failure [13–15]. Crescentic glomerulonephritis seems more common than in adults [12,16]. Systemic features, ENT and lung involvement are also frequent [14].

Traditionally, AAV have been classified into "granulomatosis with polyangiitis – GPA", "microscopic polyangiitis – MPA" and "eosinophilic granulomatosis with polyangiitis – EGPA", depending on organ involvement, histological and biological features. Yet, recent data on prognosis, treatment response and genetic associations suggest that classifying patients based on ANCA subtypes (PR3 or MPO) might be more relevant, making the boundary between GPA and MPA thinner [17]. EGPA probably represents a separate entity and will not be covered in this review, as this phenotype has not, to our knowledge, been reported in association with IEI.

The current standard-of-care treatment for AAV is based on disease severity and ANCA subtypes, and comprises remission-induction and remission-maintenance phases [9,18,19]. High-dose steroids and cyclophosphamide or rituximab are used as induction therapy for severe cases. More recently, avocapan (C5a receptor 1 antagonist) has been introduced in the induction phase [20]. Remission maintenance therapy usually consists in azathioprine or rituximab and the lowest possible steroid dose, for a minimum of two to four years.

4. Environmental and polygenic risk factors in sporadic AAV

The genetic background modulates the risk of developing AAV, as shown by multiple genome-wide association studies and candidate gene associations studies. For in-depth description of sporadic AAV genetics, we refer the reader to a recent thorough review on this topic [17]. Polymorphisms at multiple loci have been associated with AAV diagnosis, and differ between PR3 and MPO ANCA: i.e. the *HLA* region, *PRTN3*, *SERPINA1, PTPN22, CTLA4, BACH2, TLR9* (Table 1). Identification of these genetic associations has uniquely informed and shaped our current understanding of AAV etiology.

In addition to the genetic background, other factors play a role in the development of AAV. Surprisingly, males and females seem to be similarly affected in adults, which is an infrequent observation in autoimmune conditions. In contrast, a female susceptibility is reported in pediatric cohorts [15,16]. Environmental risk factors also likely contribute to the development of AAV such as silica exposure, inhaled pollutants and infectious triggers. How these toxic and infectious triggers contribute to AAV development is unclear, yet interaction with DNA-sensing pathway through STING (Stimulator of Interferon Genes) in the lungs is suspected (i.e. for silica) [21].

Some drugs can also induce MPO or PR3 ANCA and vasculitis features, usually reversible after exposure cessation [18].

5. Summary of sporadic AAV pathophysiology

The sequence of immunological events leading from loss of tolerance to neutrophil antigens, to vascular inflammation is still poorly defined [17]. Yet, once they are present at high titer/affinity, ANCA are considered key pathogenic players as they are able to activate neutrophils. ANCA are directed against specific proteins located in the

Table 1
Genes associated with AAV susceptibility in sporadic forms of AAV (both MPO and PR3 positive, and monogenic IEI.

Selected susceptibility genes in sporadic AAV	IEI genes with high frequency of ANCA and AAV-like symptoms
HLA locus	*COPA*
PTPN22	*STING1*[*]
LEPR	*DNASE1L3*
FCGR3B	*PIK3CD*
CTLA4	
TLR9	
GHSR	
PRTN3	
SERPINA1	

Susceptibility genes in bold in the first column represent the loci most consistently associated with AAV.
[*] Previously named *TMEM173*.

Table 2
Features overlapping between IEI with AAV and sporadic AAV.

	COPA	SAVI	DNASE1L3	APDS1
ANCA positivity	~60 %	~70 %	~55–85 %	Unknown (few reports)
Lung involvement				
DAH	+++			
ILD, Fibrosis, nodules		+++	+	+
Renal involvement				
Pauci-immune crescentic GN	+	+	+	+
Other types of GN or nephropathy	+++			
Upper airways (nasal septum perforation, saddle nose)		++	+	+

Abbreviations: ANCA: Anti-neutrophil cytoplasmic antibodies; APDS1: Activated phosphoinositide 3-kinase delta syndrome type 1; COPA: Coatomer protein complex subunit α; DAH: diffuse alveolar hemorrhages; DNASE1L3: Deoxyribonuclease 1 L3; GN: glomerulonephritis; ILD: interstitial lung disease; PIK3CD: Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Delta; SAVI: STING-associated vasculopathy with onset in infancy.

neutrophil cytoplasmic granules, namely myeloperoxidase (MPO) and proteinase 3 (PR3). Priming of neutrophils by specific triggers leads to exposition of MPO and PR3 to the membrane, making them available for recognition by ANCA. ANCA bind their antigens (through the antigen-binding fraction) but also FcR on the membrane (through the Fc fraction), leading to neutrophil activation. Activated neutrophils adhere to vascular walls in small vessels through expression of adhesion molecules, degranulate, and initiate further inflammatory processes (including involvement of neutrophil extracellular traps and alternative complement pathway activation). Ultimately, such inflammation of small vessels induces organ dysfunction and damage.

6. Inborn errors of immunity associated with increased risk of AAV

Over the last decade, several monogenic IEI syndromes with high frequency of ANCA positivity and phenotypes reminiscent of AAV have been described (genes involved are listed in Table 1). Here, we will only focus on IEI with high frequency of ANCA and clinical, radiological, and histological features consistent with systemic small vessels vasculitis. Table 2 summarizes the clinical and serological overlap between these IEI-related AAV and sporadic AAV. Notably, these IEI might present as true AAV mimic, or a more mixed phenotype associating AAV features

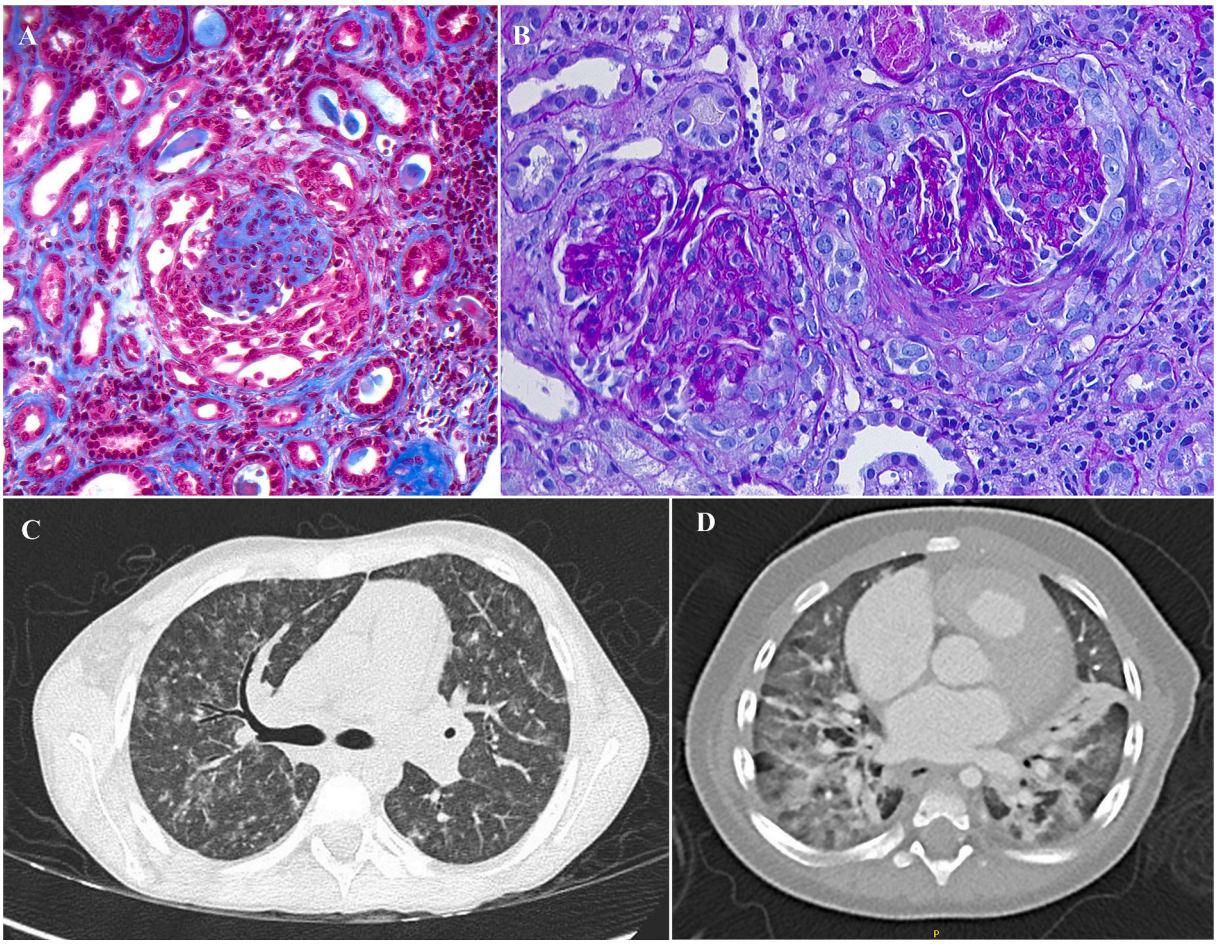

Fig. 1. A. Renal biopsy from 4.5-years-old child with COPA syndrome and strongly positive MPO-ANCA, showing crescentic glomerulonephritis and sclerosis. Immunofluorescence revealed a pauciimmune pathology. B. Renal biopsy in a 7-years-old patient with DNASE1L3 deficiency, positive MPO-ANCA and ANA showing extracapillary hypercellularity with cellular crescents and endocapillary hypercellularity surrounded by interstitial inflammation (reproduced from [23] with authorization from Elsevier). C. High resolution chest CT scan of a patient with DNASE1L3 deficiency and strongly positive MPO-ANCA, showing diffuse ground glass opacities. D. Chest CT scan of a 2-years-old patient with T21 showing severe patchy interstitial lung disease with grounded glass and fibrosis. Patients was tested positive for ANA (1/320), positive for ENA (for SSB/La, U1 RNP, RNP 70, Jo 1, Ro60, and Ro52), strongly positive for c-ANCA and p-ANCA and positive for MPO. Bronchoalveolar lavage showed increased hemosiderin-loaded macrophages. The patient responded well to steroids and rituximab therapy. Elevated expression of ISG were found in patients shown in A-B, but not in C-D.

with other autoimmune diseases, mainly those of systemic lupus erythematosus (SLE) [22,23].

These conditions are rare: although their exact prevalence is unknown, less than 100 patients have been reported for each (over a 10–15 years period since their discovery). They induce a profound immune dysregulation, with early development of biological and/or clinical autoimmunity and autoinflammation. Detailed review of genotypes, immunological dysregulations or (putative) pathogenic mechanisms of these disorders is outside the scope of this review. Intriguingly, a critical role of type 1 interferon (IFN) has been demonstrated (or suspected) in most of these disorders, leading to their classification in the family of "type 1 monogenic interferonopathies". In the following paragraphs we will mainly summarize the phenotypic presentations of these IEI, with a focus on similarities with AAV.

A preliminary remark should be considered upfront: in most of these rare diseases, the causative relationship between the presence of ANCA and clinical presentation is not always strongly documented. For instance, multiple patients with a given IEI may have positive ANCA and alveolar hemorrhage or glomerulonephritis, but it is not always clear if these features are directly caused by ANCA (genuine AAV), or are driven by alternative mechanisms, in the presence of ANCA as epiphenomenon of a broad susceptibility to autoimmunity. Furthermore, the description of ANCA titers and/or specificity (MPO/PR3, or absence thereof) is lacking in many case reports and series. In contrast, in some reports, a diagnosis of AAV is well supported by ANCA specificity and typical histological findings. With these caveats in mind, we will describe the IEI that may present with ANCA and/or genuine AAV phenotype, typically at a much younger age than sporadic forms of AAV.

6.1. *COPA syndrome*

Germline monoallelic mutations in coatomer protein complex subunit α (*COPA*) cause COPA syndrome [24–26]. COPA syndrome is essentially transmitted in an autosomal dominant manner, with a variable penetrance (~25 % of individuals carrying pathogenic variants are clinically asymptomatic). Mutations have a dominant negative effect on the complex retrograde trafficking of proteins between Golgi and endoplasmic reticulum, ultimately leading to STING constitutional activation at the Golgi, increased Nf-κB and IRF3 signaling, and excessive type 1 IFN response. Although most cases have onset in infancy, there is a wide phenotypic variability (even within families), and some individuals are diagnosed during adulthood. The majority of COPA patients have multiple auto-antibodies (ANA, RF), and up to 60 % have positive ANCA [27,28]. Clinical hallmarks of COPA syndrome include pulmonary involvement (alveolar hemorrhage, interstitial lung disease (ILD), fibrosis), seropositive arthritis and "immune-mediated" nephropathy [27]. While chest-CT and lung biopsies are usually suggestive of small vessel vasculitis (capillaritis, alveolitis, increased siderophages in the broncho-alveolar lavage) [27,29], the histology of nephritis is reportedly variable and more reminiscent of lupus nephritis than of AAV [29,30], but pauci-immune glomerulonephritis can also be seen [22] (Fig. 1A). Severe complications include end-stage organ failure (lungs, kidneys) associated with high mortality. All reported cases have an overexpression of IFN-stimulated genes (ISG) in peripheral blood (so called *interferon signature*), while asymptomatic carriers display normal or mildly elevated IFN score.

6.2. *SAVI*

STING-associated vasculopathy with onset in infancy (SAVI) is caused by gain-of-function mutations in *STING1* (previously called *TMEM173*) [31,32]. Most mutations are monoallelic, and inherited with a dominant pattern or occurring de novo, and a few cases of biallelic mutations have been reported. All of these mutations induce a gain-of-function and constitutional activation of STING, leading to uncontrolled type 1 IFN secretion and Nf-κB related inflammation. They are highly penetrant, and most individuals are symptomatic before 2 years of age. As for COPA syndrome, most patients have biological signs of autoimmunity (ANA, RF), and > 70 % have positive ANCA [33]. SAVI also manifests with a pulmonary phenotype (predominantly pro-fibrotic ILD), and skin vasculopathy is much more frequent than in COPA syndrome. This acral vasculopathy can sometimes be very severe with cases of autoamputation/loss of tissue and osteolysis. Upper airway involvement reminiscent of AAV has also been reported in up to a quarter of patients (nasal septum perforation, saddle nose deformity) [31,34–37]. Yet, it is not clear from the literature if this occurred preferentially in ANCA-positive patients or not. Pauci-immune glomerulonephritis has also been reported in a few ANCA-positive patients [33,38]. Severe complications include end-stage organ damage (lungs, kidneys), extensive skin/soft tissue or fingers/toes necrosis, and high mortality. In addition, IFN signature is positive in virtually all individuals.

6.3. *DNASE1L3 deficiency*

Biallelic deleterious variants in *DNASE1L3* (Deoxyribonuclease 1 L3) lead to accumulation of extracellular nucleic acid debris from apoptotic cells. This material is sensed by immune cells (danger-associated molecular pattern) through the TLR/MYD88 pathway, ultimately triggering excessive type 1 IFN response [39]. DNASE1L3 deficiency is highly penetrant and usually presents in infancy (median age of onset ~6 years) with autoimmunity predominantly involving kidney and skin [40,41]. The clinical phenotype is reportedly reminiscent of early onset SLE-like syndrome or urticarial vasculitis [40,42]. Yet ~55–85 % of patients are also ANCA-positive, and pulmonary involvement (including lung vasculitis and alveolar hemorrhage) occurs in 1/5–6 patients [23,41,42]. Furthermore, some patients have been shown with pauci-immune glomerulonephritis [23] (Fig. 1B-C). By contrast with previous conditions, increased ISG expression can be transient in DNASE1L3 deficiency, and reportedly correlates with clinical flares [42].

6.4. *APDS 1*

Activated phosphoinositide 3-kinase delta syndrome type 1 (APDS 1) is an IEI caused by monoallelic gain-of-function mutations in the *PIK3CD* gene (Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Delta). *PIK3CD* has multiple complex roles in immune system homeostasis [43,44]. Contrary to previous disorders, there is no specific link to type 1 IFN responses unless in infectious conditions. APDS1 phenotype is dominated by lymphoproliferation and immunodeficiency, with increased susceptibility in particular to recurrent respiratory infections with lung damage [45]. Yet, some patients also suffer from autoimmunity (thyroiditis, colitis, SLE phenotype), and multiple children have been recently described with positive ANCA and phenotype closely resembling AAV: upper airway involvement (chronic sinusitis, nasal perforation, saddle nose deformity), pulmonary nodules and ILD and glomerulonephritis characterized by mesangial proliferation without immune deposits [46–49].

6.5. *Other conditions*

AAV-like manifestations and positive ANCA has also been reported less consistently in other conditions. For instance, a rare complication of trisomy 21 (T21) is pulmonary hemosiderosis, as a consequence of diffuse alveolar hemorrhage [50] (Fig. 1D). Although the condition is likely multifactorial, it is intriguing to note that 28–40 % of these patients tested positive for ANCA, in addition to other autoantibodies [50,51]. Several reports have also described crescentic pauciimune glomerulonephritis in T21 patients with positive MPO or PR3 ANCA [52–54]. Noteworthy, accumulating evidence suggest that T21 is associated with a dysregulation of type 1 IFN, potentially explaining the increased susceptibility of these patients for autoimmunity [55–57]. Prolidase deficiency, an inborn error of metabolism leading to immune

Box 1
Next steps to further explore the role of ANCA in IEI.

Next steps to further explore the role of AAV associated with IEI
Better reporting of ANCA specificity (MPO/PR3) and titers in IEI patients
Investigation of ANCA epitope specificity in patients with IEI
Analysis of potential association between ANCA presence/specificity/titers and specific organ involvement in larger cohorts of IEI
Report of ANCA and PR3/MPO titers kinetics during treatment and flares
Systematic comparison of radiological and histological features in sporadic AAV patients and IEI with positive ANCA

Abbreviations: AAV: ANCA-associated vasculitis; ANCA: Anti-neutrophil cytoplasmic antibodies; IEI: inborn error of immunity; MPO: myeloperoxidase; PR3: proteinase 3.

dysregulation (possibly through type 1 IFN pathway) can also manifest as diffuse alveolar hemorrhage with positive ANCA [58]. Other rare cases of IEI with vasculitis and positive ANCA include 22q11 microdeletion syndrome (unpublished observation), common variable immunodeficiency (CVID) and VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome [59–61].

Finally, other IEI may present with infectious susceptibility and features suggestive of AAV (e.g. TAP deficiency, hypomorphic RAG1 mutations [62,63]), stressing the need to perform broad genetic testing when searching for IEI. These patients usually have granulomatous disorders but negative MPO/PR3 specificity.

7. Potential lessons to be learned from IEI concerning AAV pathophysiology

It is universally accepted that rare monogenic diseases can provide unique insights into pathogenic process involved in more common, multifactorial diseases. In fact, every immunologist has at least once heard the quote from Archibald Garrod, a pioneer of medical genetics, who stated: "*The study of nature's experiments is of special value; and many lessons which rare maladies can teach could hardly be learned in other ways*."

This approach has indeed been extremely useful in some complex immunological diseases by deciphering genes and pathways that play key roles in their monogenic phenocopies. SLE is a prototypic example of this paradigm: discovery of genetic defects causing early-onset SLE has been pivotal to identify the role of type 1 IFN, or complement pathway in sporadic SLE. By contrast, the potential lessons to be learned from monogenic disorders has been largely underappreciated in AAV. Our review illustrates that specific IEI included in the group of type 1 interferonopathies provide indeed a high risk for SLE-like syndromes, but also for ANCA development, AAV-like phenotypes, and SLE-AAV mixed syndromes. This somewhat challenges the current view that SLE is the immune disorder specifically associated with monogenic interferonopathies [64].

This observation raises several questions. First, does the presence of ANCA in patients with specific IEI represent genuine AAV or a non-specific sign of autoimmunity? Unfortunately, few data are available to address this question. Box 1 summarizes some approaches that might help address this issue (i.e. investigation of ANCA epitope specificity [5]). If these monogenic defects indeed cause genuine AAV, is this a direct consequence of uncontrolled IFN signaling?

Second, might type 1 IFN play a (currently underrecognized) role in the pathogenesis of *sporadic* AAV? Interestingly, some literature provides indirect evidence supporting this hypothesis: for instance, susceptibility genes for sporadic AAV include *TLR9* (Toll-like receptor 9), an important inducer of type 1 interferons [65]. Another study found increased MxA expression in kidney biopsies, and increased IFNα in the serum of patients with active AAV [66]. Furthermore, a novel mice model of pulmonary AAV has highlighted the role of the STING/IRF3/IFN-I axis in pulmonary hemorrhages and inflammation [67]. The mice phenotype severity was improved by pharmacological inhibition of STING, IFNAR-1, or JAK1/2 inhibitor (baricitinib). Finally, several studies investigating peripheral blood transcriptomic (using bulk or

Box 2
Features prompting consideration of underlying IEI in a patient with ANCA and AAV-like phenotype.

Onset at pediatric age
Familial history of AAV, IAH, ILD, lung fibrosis, SLE, other rare autoimmune conditions …
Presence of multiple autoantibodies in addition to ANCA (ANA, ENA, dsDNA, RF, anti-CCP …)
Mixed phenotype: AAV-SLE, AAV-seropositive JIA
Multiple autoimmune conditions (outside typical manifestations of AAV): thyroiditis, NMO, …
Severe skin vasculopathy (including tissue loss, amputation)
Lymphoproliferation, infection susceptibility (including before immune suppressive therapies)
Elevated interferon signature?

Abbreviations: AAV: ANCA-associated vasculitis; ANA: antinuclear antibodies; ANCA: Anti-neutrophil cytoplasmic antibodies; CCP: anti-cyclic citrullinated peptides; dsDNA: double-stranded DNA; IAH: intra-alveolar hemorrhage; ILD: interstitial lung disease; JIA: juvenile idiopathic arthritis; NMO: neuromyelitis optica; RF: rheumatoid factor; SLE: systemic lupus erythematosus.

Box 3
Examples of key questions faced by physicians when caring for a patient with (confirmed or suspected) IEI and positive ANCA.

Are ANCA playing a pathogenic role in the manifestations of my patient? Should the patient received validated treatment regimen for AAV (if not yet the case)?
Could the patient beneficiate from therapy used for monogenic IFNpathies (if not yet the case)?
Does the IEI diagnosis impact the recurrence risk upon treatment tapering/cessation?
Should HSCT be discussed?
Is there a specific treatment option in development for this patient (DNASE1L3, APDS1)?
Is my patient at increased infectious/malignancy risk? Should infectious prophylaxis and/or specific monitoring be discussed?

single cell assays) in human AAV have evidenced an enrichment of IFN-related genes in a subset of AAV patients [67–70], while this signal was not found in other comparable works [71–75]. The reasons for the discrepant findings between studies remain unclear.

In conclusion, further studies are required to better evaluate if (i) elevated frequency of ANCA positivity in specific IEI with AAV-like phenotype represent true autoimmune systemic vasculitis or an unspecific sign of auto-immunity, without direct pathogenic role; (ii) type 1 IFN might participate in sporadic forms of AAV. Notably, the observed association between IFNpathies and AAV does not presage which can cause the other, for instance, interferonopathies may primarily lead to small vessels inflammation, which in turn would induce neutrophils damage, exposition of intra-neutrophilic proteins, and secondary auto-antibodies against neutrophils components.

8. Personalized management of IEI with ANCA and AAV-like features

Our review informs clinicians on rare IEI that may mimic sporadic AAV. As one can expect, most cases of IEI will present in early childhood, but onset/diagnosis at adolescent or adult age have also been reported [38,76,77]. Such IEI are associated with profound defects in immune homeostasis, consequently affected individuals will frequently present multiple auto-antibodies in addition to ANCA, or mixed phenotypes e.g. AAV-SLE overlap. Box 2 summarizes clinical clues that should prompt genetic investigations looking for IEI when a patient presents with a phenotype resembling AAV.

A likely useful and increasingly accessible screening tool to perform is the expression analysis of a set of ISG (IFN signature) using qPCR or Nanostring technology [78]. Although not a diagnostic tool, it may provide relevant information within a couple of weeks, when critical therapeutic decisions need to be made. Indeed, most of IEI associated with AAV have been associated with persistent elevated IFN signature, contrary to sporadic AAV [71]. DNASE1L3 deficiency represents an exception, as the elevated IFN signature may be transient, and only present during flares [42]. Importantly, the positive and negative predictive values of such an assay for detection of monogenic type 1 interferonopathies have never been systematically assessed. In addition, the activation of the type 1 IFN pathway may also be searched for in the affected tissues (e.g. on kidney biopsies) through staining for type 1 interferon-induced proteins such as MXA (Myxovirus Protein Resistance 1) [79]. In APDS1, there is no chronic IFN pathway activation, but rather specific T and B cell defects (lymphopenia, normal to elevated serum immunoglobulin M (IgM) levels, and reduced levels of IgG with impaired ability to produce antibodies against vaccines). Confirmatory genetic diagnosis of an IEI rely on standard molecular testing, depending on the technique and available resources (gene panel, (trio) whole exome/genome sequencing, etc.).

Diagnosis of IEI in a patient with positive ANCA and AAV phenotype will have several implications. The first one will be the screening and genetic counselling of the family. This should be systematic given the variable penetrance and/or phenotypic expression of many IEI. Making an IEI diagnosis will also raise relevant issues regarding the management (Box 3). As of now, many of these interrogations remain unanswered. The conviction that ANCA are pathogenic in a given patient with IEI will be based on clinical, radiological, and histological features, along with ANCA specificity and titer. These questions (and corrolary therapeutic decisions) are best addressed on an individual basis, by expert multidisciplinary teams. Finally, some of these IEI might benefit from specific treatment approaches in the future, such as enzyme replacement therapy in DNASE1L3 deficiency, or leniolisib in APDS1 [80,81].

9. Conclusion

In the last decade, several IEI have been reported with a high frequency of ANCA seropositivity, and features reminiscent of AAV: pulmonary, renal and upper airways involvement. In this review, we identify and describe these IEI, with a focus on AAV-like features. Most of these conditions have been classified in the family of type 1 interferonopathy, and can present with a mixed phenotype of SLE / AAV. To date, it is unclear if these rare monogenic diseases can provide useful insights into the pathophysiology of sporadic forms of AAV. Progress needs to be accomplished to evaluate why ANCA specifically develop in these IEI, and if they are playing a pathogenic role, as in sporadic AAV. Clarifying this question will be challenging but might have significant impact on the clinical management of these patients and be relevant for more common conditions.

Declaration of competing interest

The authors have no conflict of interest to disclose in relationship with the present manuscript.

Fig. 1B was reprinted with permission from Elsevier from: Volpi S, Angelotti ML, Palazzini G, Antonelli G, Ravaglia F, Garibotto F, et al. Lupus Nephritis Patterns and Response to Type I Interferon in Patients With DNASE1L3 Variants: Report of Three Cases. Am J Kidney Dis. 2024 Dec;84 [6]:791–797.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.autrev.2025.103824.

Data availability

No new data were generated for this manuscript.

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