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REVIEW ARTICLE

NEPHROLOGY WILEY

Renal involvement in monogenic autoinflammatory diseases: A narrative review

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Abstract

Autoinflammatory diseases (AIDs) are mostly caused by dysfunctions in single genes encoding for proteins with a prominent role in the regulation of innate immunity, such as complement factors, inflammasome components, tumour necrosis factor (TNF)-α, and proteins belonging to type I-interferon (IFN) signalling pathways. Due to the deposition of amyloid A (AA) fibrils in the glomeruli, unprovoked inflammation in AIDs frequently affects renal health. In fact, secondary AA amyloidosis is the most common form of amyloidosis in children. It is caused by the extracellular deposition of fibrillar low-molecular weight protein subunits resulting from the degradation and accumulation of serum amyloid A (SAA) in numerous tissues and organs, primarily the kidneys. The molecular mechanisms underlying AA amyloidosis in AIDs are the elevated levels of SAA, produced by the liver in response to pro-inflammatory cytokines, and a genetic predisposition due to specific SAA isoforms. Despite the prevalence of amyloid kidney disease, non-amyloid kidney diseases may also be responsible for chronic renal damage in children with AIDs, albeit with distinct characteristics. Glomerular damage can result in various forms of glomerulonephritis with distinct histologic characteristics and a different underlying pathophysiology. This review aims to describe the potential renal implications in patients with inflammasomopathies, type-I interferonopathies, and other rare AIDs in an effort to improve the clinical course and quality of life in paediatric patients with renal involvement.

KEYWORDS
AA amyloidosis, AIDs, autoinflammatory diseases, FMF, non-amyloid kidney disease

Summary at a glance

The aim of this review is to describe the genetic background, clinical manifestations, and molecular mechanisms of renal involvement in autoinflammatory diseases. An up-to-date knowledge of the most common histopathologic features and correct treatment strategies is essential for a correct work-up and a good clinical prognosis for renal health.

1 | INTRODUCTION

Amyloidosis is a heterogeneous group of uncommon diseases caused by the extracellular deposition of fibrillar low-molecular weight protein subunits in different tissues and organs, which may result in severe organ dysfunction.[1] Many different proteins can cause extracellular deposition of amyloid, like serum amyloid A (SAA), monoclonal immunoglobulin (Ig) light chains, β2-microglobulin, and others. Under

polarized light, all amyloid fibrils form a β-pleated sheet structure that stains with Congo red and exhibits typical green birefringence.[2] These deposits may precipitate at the site of their synthesis, resulting in localized amyloidosis, or in distant organs, causing systemic amyloidosis.[3] Different kinds of hereditary and acquired amyloidosis have been identified. In the first group, various proteins, like transthyretin (TTR) and apolipoprotein A (apoA)-I, are genetically mutated, unstable, and prone to fibril formation.[4] In contrast, the main pathogenetic event in the second group is protein overproduction, resulting in secondary or reactive amyloidosis (AA amyloidosis), which is the most common form of amyloidosis in children, primarily due to chronic inflammatory diseases.[1,5] Autoinflammatory diseases (AIDs) are currently regarded as the most prevalent cause of secondary AA amyloidosis in children, due to the accumulation and deposition of SAA.[5] Differently, chronic infections like tuberculosis still represent an important cause of reactive amyloidosis in low-income countries.[6] AIDs are a large group of rare inherited diseases that are characterized by hyperactivation of the innate immunity, often impacting renal health due to the development of sterile inflammation and glomerular deposition of amyloid fibrils.[5,7] Although AIDs may be polygenic with epigenetic variables impacting their phenotype, the majority of them is caused by mutations in single genes, being referred to as "monogenic AIDs".[7,8] Unlike autoimmune disorders, AIDs are characterized by impaired function of the innate immunity, while it seems that circulating autoantibodies and the adaptive immune system do not have a pathogenic role.[7,9] Thus, AIDs can result from the disruption of a variety of molecular signalling pathways, and they include inflammasomopathies, disorders of tumour necrosis factor (TNF)/nuclear factor k-B (NF-kB) pathway, interferonopathies, and others (Table 1).[7,10] AIDs commonly present in childhood with a heterogeneous clinical phenotype, depending on the involved genes and their function. Recurrent high-grade fever is the most common manifestation, often presenting with a skin rash, organomegaly, and sterile serositis.[7] In AA amyloidosis, every single organ can be interested, but the kidneys are involved in 80%–90% of cases, while other tissues and organs are rarely involved.[7,11,12] SAA is an acute-phase protein mainly produced by hepatocytes under the stimulation of pro-inflammatory cytokines, such as interleukin (IL)-1, IL-6, and TNF-α.[1,11] In normal conditions, SAA is picked up by macrophages, transferred to the lysosomal compartment, and degraded entirely (Figure 1A).[1] Early-stage AA amyloidosis is characterized by low-grade proteinuria, which often progresses if the inflammatory stimulus persists, resulting in the development of nephrotic syndrome.[13] In untreated cases with persistent or recurrent inflammatory status, renal damage can progress, leading to end-stage kidney disease (ESKD).[14] Laboratory results may show microalbuminuria or proteinuria (>0.5 g/day), increased serum creatinine, and a reduced estimated glomerular filtration rate (eGFR). Diagnosis requires the demonstration of Congo-red staining of amyloid deposits in the renal biopsy, together with the typing of fibrils by immunohistochemistry or by proteomics-based techniques.[13] Despite the fact

TABLE 1 Autoinflammatory diseases (AIDs) with possible renal involvement.

Disease	Gene	Molecular pathway	Clinical features	Treatment
FMF	*MEFV*	Pyrin inflammasome and high IL-1β production	Recurrent fever, serositis, arthritis, ELE, AKD, NAKD	Colchicine, IL-1 inhibitors
MKD	*MVK*	Pyrin inflammasome and high IL-1β production	Recurrent fever, lymphadenitis, stomatitis, gastrointestinal symptoms, maculopapular rash, AKD	IL-1 inhibitors, TNF-α inhibitors, renal transplant
CAPS	*NLRP3*	NLRP3 inflammasome and high IL-1β production	Recurrent fever, urticarial rash, sensorineural hearing loss, skeletal abnormalities, AKD	IL-1 inhibitors
TRAPS	*TNFRSF1A*	TNF-α pathway overactivation	Recurrent fever, migratory rash, periorbital oedema, myalgias, stomatitis, AKD	IL-1 inhibitors
AGS	Various (mainly *TREX1*, *RNASEH2B*, *RNASEH2C*)	Type I IFN pathway	Encephalopathy, seizures, hepatitis, rash, cognitive impairment, glaucoma, growth delay, GN	CS, immunosuppressors, biologics, IVIg, JAKi
SAVI	*STING1/ TMEM173*	Type I IFN pathway	Small vessel vasculopathy, recurrent fever, failure to thrive, progressive interstitial lung disease, arthritis, GN	CS, immunosuppressors, biologics, IVIg, JAKi
COPA	*COPA*	Type I IFN pathway	Arthritis, interstitial lung disease with pulmonary haemorrhage, GN	CS, immunosuppressors, biologics, IVIg, JAKi
Monogenic SLE	Mainly *DNASE1L3*	Type I IFN pathway	SLE-like phenotype, small vessel vasculopathy, GN	CS, immunosuppressors, biologics, IVIg, JAKi

Abbreviations: AGS, Aicardi-Goutières syndrome; AKD, amyloid kidney disease; CAPS, cryopyrin-associated periodic syndromes; COPA, coatomer subunit-α syndrome; CS, corticosteroids; ELE, erysipelas-like erythema; FMF, Familial Mediterranean fever; GN, glomerulonephritis; IFN, interferon; IVIg, intravenous immunoglobulins; JAKi, Janus Kinase inhibitors; MKD, mevalonate kinase deficiency; NAKD, non-amyloid kidney diseases; SAVI, STING-associated vasculopathy of infancy; SLE, systemic lupus erythematous; TRAPS, TNF receptor-associated periodic fever syndrome.

TABLE 2 Renal findings in autoinflammatory diseases (AIDs).

Disease	AKD	NAKD
FMF	Yes	Focal segmental glomerulosclerosis, mesangial proliferative GN, IgA nephropathy, crescentic GN, diffuse proliferative GN, PAN-like presentation (renal vasculitis)
MKD	Yes	Not observed
CAPS	Yes	Not observed
TRAPS	Yes	Not observed
Interferonopathies	No	Lupus-like GN, podocytopathy-like lesions (minimal change lesions, focal segmental glomerulosclerosis), collapsing glomerulopathy, mesangial proliferative GN, membranous nephropathy, PAN-like presentation (renal vasculitis), thrombotic microangiopathy

Abbreviations: AKD, amyloid kidney disease; CAPS, cryopyrin-associated periodic syndromes; FMF, Familial Mediterranean fever; GN, glomerulonephritis; MKD, mevalonate kinase deficiency; NAKD, non-amyloid kidney diseases; TRAPS, TNF receptor-associated periodic fever syndrome.

that amyloid kidney disease (AKD) is the most common renal complication of AIDs, it has been known for more than 40 years that other renal diseases may be observed in such patients, named non-amyloid kidney diseases (NAKD). NAKD is characterized by a wide range of histopathologic patterns, including crescentic glomerulonephritis (GN), mesangial proliferative GN (MesPGN), focal glomerulosclerosis, and membranoproliferative GN (MPGN) (Table 2).[15,16] This review aims to evaluate the impact of AIDs on renal health by providing detailed information on the histopathologic findings and on their clinical implications, including the most recent evidence and future perspectives.

2 | INFLAMMASOMOPATHIES

One of the best-known innate immunity strategy against pathogens is represented by the activation of the inflammasome, which is a multiprotein complex that serves as a crucial platform for the host immunity.[17,18] Inflammasomes sense danger and cellular stress signals and induce inflammation by promoting the activation of pro-caspase-1 and mediating the release of pro-inflammatory cytokines, such as IL-1β and IL-18.[7,19] Inflammasomes are composed of three basic components: a changeable cytosolic sensor, an adaptor protein referred to as "apoptosis-associated speck-like protein containing CARD" (ASC), and the effector pro-caspase-1.[19,20] Once activated, inflammasomes are responsible for the cleavage and activation of pro-caspase in caspase, followed by the cleavage of pro-IL-1β in IL-1β.[19,20] Pathogenic mutations in genes encoding inflammasome sensor proteins can result in severe clinical phenotypes characterized by recurrent fever and systemic inflammation, often with renal implications. The most common inflammasomopathies with renal involvement are familial Mediterranean fever (FMF), mevalonate kinase deficiency (MKD), and cryopyrin-associated periodic syndromes (CAPS).

2.1 | Familial Mediterranean fever

FMF is an autosomal recessive inherited AID caused by mutations affecting the *MEFV* gene, located on chromosome 16p13.3. The product of this gene is the inflammasome sensor protein pyrin, which plays a key role in innate immunity.[21,22] Indeed, gain-of-function mutations of *MEFV* result in uncontrolled hyperactivation of the pyrin inflammasome, thus provoking systemic inflammation and increased expression of pro-inflammatory cytokines.[23] FMF is widespread among Eastern Mediterranean populations, especially in Turks, Armenians, and Arabs, although hundreds of cases have been documented in Europe, North America, and Japan.[24] High-grade fever lasting 12–72 h, arthritis, chest pain, and abdominal pain (due to sterile serositis) represent the classic presentation of FMF, while the presence of a pathogenic mutation or a variant of uncertain significance (VUS) of *MEFV*, according to the EuroFever registry (https://infevers.umai-montpellier.fr/web/search.php?n=1), is a mandatory criteria for the diagnosis.[25,26] The most feared complication in FMF is AA amyloidosis, resulting in chronic renal involvement and representing the first cause of morbidity and mortality in patients with FMF.[5,24,27,28] AKD is the most significant renal lesion, affecting up to 10% of FMF patients.[24,29] After a diagnosis of AKD, ESKD often occurs within 5 years, with a reported 5-year survival rate of 50%.[24,30] However, stunning progress has been made in early diagnosis and treatment, leading to better control of both systemic and renal inflammation. Although FMF is characterized by intermittent-recurrent inflammatory episodes, chronic inflammation may be observed in up to one-third of children during intercritical times, causing an elevated risk of renal AA amyloidosis over time.[21] Furthermore, SAA is elevated during FMF episodes, even in patients with subclinical inflammation. It is known that increased SAA levels correlate with an increased risk of AKD (Table 3). Indeed, after systemic inflammation, SAA (normal values less than 3 mg/L) can rapidly increase up to 1000-fold within 1 day.[14,31] The most relevant forms of human SAA are SAA1 and SAA2, encoded by the genes *SAA1* and *SAA2*, respectively.[32] Both SAA1 and SAA2 are serum precursors of amyloid A1 (AA1) and A2 (AA2) proteins, the leading protagonists of secondary amyloidosis. However, a specific genetic background is necessary for developing AKD, despite high levels of SAA.[32] Several polymorphisms affecting *SAA1* and *SAA2* have been largely studied, and accurate genotype–phenotype correlations have been provided.[32] The *SAA1α/α* genotype is associated with a 7-fold increased risk of AKD in FMF patients, compared to other *SAA1* genotypes, while the *SAA1γ/γ* genotype is associated with an increased risk of renal AA amyloidosis in Japanese individuals with rheumatoid arthritis (RA).[32,33] More recent studies have also confirmed the role of the *SAA1α* polymorphism in FMF-related AKD.[32] A greater macrophagic uptake of the isoform SAA 1α has been proposed, as shown in studies focusing

TABLE 3 Risk factors for amyloid kidney disease (AKD) development in autoinflammatory diseases (AIDs).

Disease	Risk factors
FMF	Male gender, early onset, arthritis, persistent chronic inflammation, high recurrence of attacks, *MEFV* mutation: M694V (c.2080A > G; p.Met694Val), SAA1α/α genotype
MKD	*MVK* mutations: V377I (c.1129G > A; p.Val377Ile), and I268T (c.803 T > C; p.Ile268Thr)
CAPS	*NLRP3* mutation: R260W (c.784C > T; p.Arg262Trp)
TRAPS	*TNFRSF1A* mutation: T50M (c.236C > T; p.Thr79Met)
All	Increased SAA levels

Abbreviations: CAPS, cryopyrin-associated periodic syndromes; FMF, Familial Mediterranean fever; MKD, mevalonate kinase deficiency; SAA, serum amyloid A; TRAPS, TNF receptor-associated periodic fever syndrome.

on SAA plasma clearance in mice.[32,34] Also, the SAA1α isoform could strongly stimulate fibrilogenesis or be more susceptible to deposition and accumulation (Figure 1B).[32,33] However, the exact molecular mechanisms underlying the relationship between *SAA1α* and AKD are still elusive. Notably, genotypic background has no effect on SAA levels.[32] Regarding *MEFV*, M694V (c.2080A > G; p.Met694Val) homozygous mutations have been related to an increased risk of chronic renal disease.[35] Furthermore, several other independent predictors for the risk of AKD have been recognized, including male gender, early onset of disease, presence of arthritis, persistent chronic inflammation, high recurrence of attacks, and others.[24,33,35–37] However, in some cohorts of FMF patients, all homozygous individuals for *SAA1α* and M694V developed AKD.[33] Persistent proteinuria is an early sign of renal involvement in FMF patients, often representing the only finding, while haematuria is rarely seen. Meanwhile, several children with persistent proteinuria have minimal signs of AKD, while

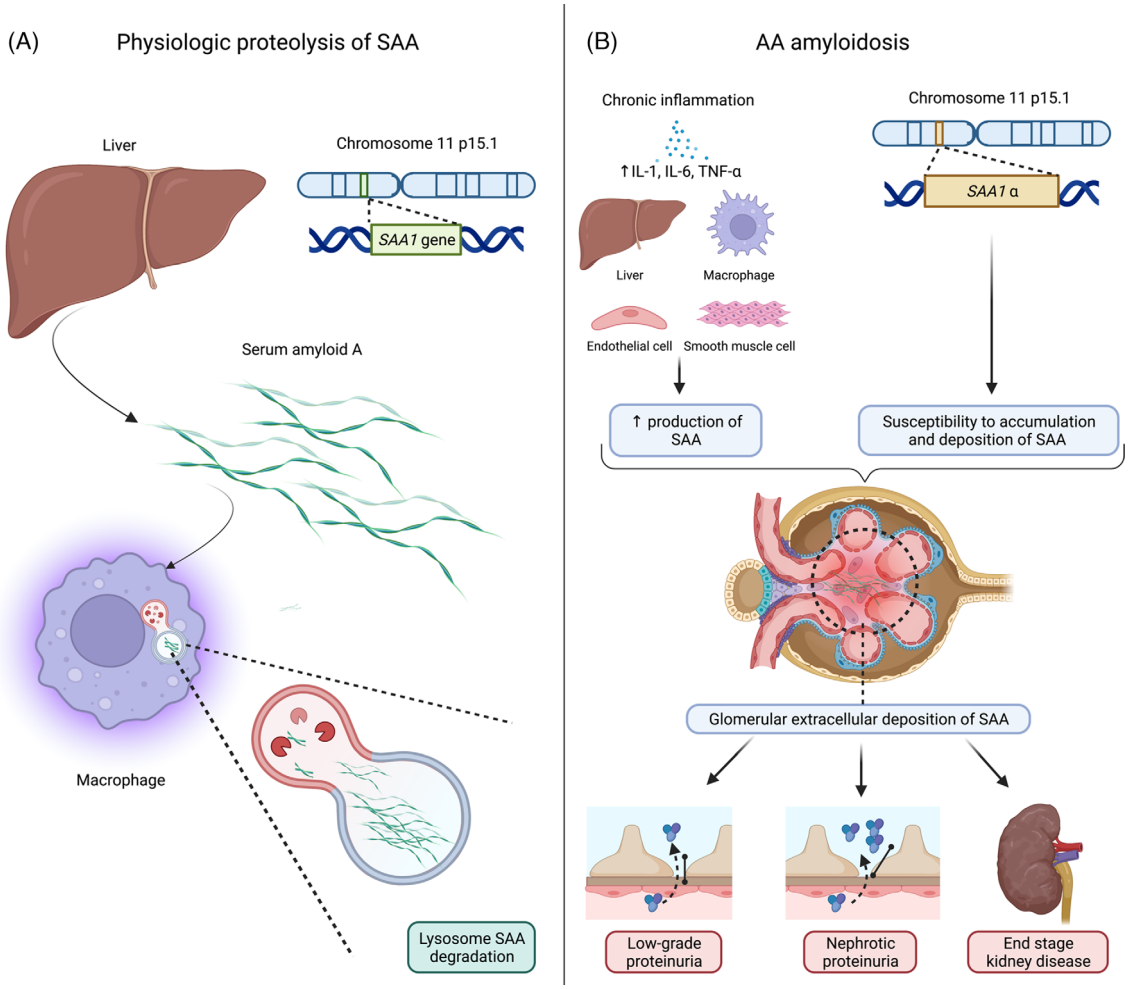

FIGURE 1 Metabolism and pathophysiology of serum amyloid A (SAA) (created with BioRender.com). (A) The most abundant SAA isoform is SAA1, which is encoded by the *SAA1* gene on chromosome 11p15.1. SAA is predominantly generated by the liver and processed by macrophage lysosomes. (B) SAA synthesis increases in response to pro-inflammatory cytokine stimulation. In the meantime, a genetic predisposition caused by certain SAA isoforms, mostly homozygous *SAA1α* variations, makes SAA more susceptible to extracellular deposition. Glomerular extracellular deposition of SAA causes amyloid kidney disease (AKD), which leads to proteinuria and chronic renal damage.

manifesting minimal change disease (MCD), focal segmental glomerular sclerosis (FSGS), MesPGN, IgA nephropathy (IgAN), crescentic GN, and renal vasculitis such as that of polyarteritis nodosa (PAN).[15,38] It has been reported that Henoch Schönlein purpura (HSP) and PAN are more prevalent in FMF patients than in healthy people.[15] Indeed, HSP is observed in 2.75%–7% of patients with FMF, while PAN has been reported in up to 2.1% of them.[15,39] In addition, PAN shows characteristic features when observed in FMF patients. Such patients have an earlier onset of disease and a higher frequency of perirenal hematoma, up to half of cases, with other rare overlap findings.[15,40] In a 10-year retrospective study evaluating renal bioptic features in patients with FMF and daily proteinuria greater than 0.5 g/24 h, up to 40% of patients (10/25) had histopathologic features related to NAKD, mostly FSGS, as reported by other studies.[15,41] As a result, the authors recommended that all FMF patients with proteinuria greater than 0.5 g/24 h undergo a renal biopsy.[41] Differently, other results suggest a lower frequency of NAKD in FMF patients.[38] In a recent study, 58 FMF patients underwent renal biopsy due to the presence of chronic kidney disease, with an AKD rate of approximately 89.6%.[42] In this cohort of patients with FMF and renal involvement, less than 35% avoided haemodialysis or death.[42] However, the prevalence of NAKD may vary across nations because of variations in affordability, adherence to therapy, and other environmental variables.[15] Large epidemiological studies investigating the frequency of NAKD in FMF patients are lacking, probably due to the poor use of renal biopsies and the satisfactory improvement with medical therapy. Although not specific to AKD, hypertension and proteinuria greater than 3 g/24 h are considered more common in AKD compared to NAKD.[15,41] However, urinary testing does not allow to discriminate between the two conditions.[41] Finally, chronic renal failure is more common in FMF patients with AKD than in those with NAKD.[28]

2.2 | Mevalonate kinase deficiency

AKD has been rarely described in patients with mevalonate kinase deficiency (MKD).[43–45] MKD is a rare autosomal recessive (AR) hereditary AID due to mutations of the *MVK* gene, located on chromosome 12q24.11 and encoding for mevalonate kinase (MVK).[46] MVK is an enzyme engaged in the isoprenoid biosynthesis pathway, catalysing the phosphorylation of mevalonate into 5-phosphomevalonate, which is required for cholesterol production.[47] Its defective function affects the prenylation and modulation of proteins involved in pyrin regulation, such as geranylgeranyl pyrophosphatase.[47] The clinical phenotype is largely dependent on the residual enzymatic function. When the enzyme activity is absent or lower than 1%, patients manifest mevalonic aciduria, growth delay, severe cognitive impairment, dysmorphism, and recurrent high-grade fever, often with arthritis. When some residual enzymatic activity is conserved, patients present with recurrent high-grade fever, serositis, hepatosplenomegaly, aphthous stomatitis, and cervical lymphadenopathy.[25,46] Some *MVK* mutations, such as V377I (c.1129G > A; p.Val377Ile) and I268T (c.803 T > C; p.Ile268Thr), have been reported to markedly increase the risk of AKD.[43] In a large cohort of 114 MKD patients, 4% of them had AKD, with a higher prevalence as compared to previous reports.[43,44] In such patients, the median disease duration before the diagnosis of AKD was 23 years.[43] A recent systematic review estimated a prevalence of MKD-associated AKD of about 6%, although the exact worldwide frequency of MKD is unknown.[45] In addition, all patients had disease onset within the age of 4 years, and five patients died of AKD, despite biologic therapy.[45] AKD was mainly revealed by nephrotic syndrome, chronic renal failure, or both.[45]

2.3 | Cryopyrin-associated periodic syndromes

Cryopyrin-associated periodic syndromes (CAPS) are a group of monogenic AIDs, comprising familial cold urticaria (FCAS), Muckle-Wells syndrome (MWS), and chronic infantile neurologic cutaneous articular syndrome/ neonatal onset multisystem inflammatory disease (CINCA/NOMID).[5,25] CAPS is a group of diseases that progress in severity from FCAS, the mildest form, to CINCA/NOMID, the most severe. CAPS are caused by mutations in the *NLRP3* gene, which encodes cryopyrin, the main sensor protein of a broad family of inflammasomes.[25] Pathogenic mutations in *NLRP3* lead to systemic hyperinflammation with recurrent fever and typical skin involvement (https://infevers.umai-montpellier.fr/web/search.php?n=4). Patients with FCAS present with cold-induced attacks of sterile inflammation with recurrent fever, urticarial rash, and serositis. In addition to recurrent fever, rash and serositis, both uveitis and progressive sensorineural hearing loss are feared complications in MWS patients.[25] CINCA/NOMID is characterized by the early onset of recurrent fever, urticarial rash, sterile serositis, severe arthropathy, growth delay, macrocephaly, and thick extremities.[25] AA amyloidosis is frequently observed in CAPS due to persistent inflammation and the elevated levels of pro-inflammatory cytokines, mainly IL-1β.[16] Renal involvement is associated with glomerular deposition of SAA β-fibrils, which accumulate in the extracellular subset, resulting in impaired filtration and nonspecific glomerular injury, which promotes proteinuria and chronic renal failure over time.[16] Thus, AKD is a significant complication in patients with CAPS, described in up to 4% of FCAS, 25% of MWS, and in a large number of CINCA/NOMID cases.[5] The most frequent *NLRP3* mutation in patients with AKD is R260W (c.784C > T; p.Arg262Trp), which is considered a probable risk factor for AA amyloidosis.[48]

3 | TNF RECEPTOR-ASSOCIATED PERIODIC FEVER SYNDROME

TNF receptor-associated periodic fever syndrome (TRAPS) is a rare autosomal dominant (AD) disease caused by mutations of the *TNFRSF1A* gene. Heterozygous mutations of *TNFRSF1A* affect the function of the TNF receptor 1 (TNFR1), causing a complex clinical phenotype characterized by recurrent high-grade fever, erythematous skin rash, arthralgia, myalgia, serositis, and organ inflammation.[12,25,49] The molecular mechanisms underlying TRAPS consist of a defective TNFR1, which does not adequately move to the cell membrane, hence triggering a particular stress response and overexpression of IL-1.[11] However, the genetic background of

TRAPS is heterogeneous, and several pathogenic mutations have been reported, mostly R92Q (c.362G > A; p.Arg121Gln) and T50M (c.236C > T; p.Thr79Met), according to the EuroFever registry (https://infevers.umai-montpellier.fr/web/search.php?n=2). AA amyloidosis is a serious complication of TRAPS, leading to high rates of mortality.[11,49] The most important pathogenic *TNFRSF1A* variants observed in AA amyloidosis are missense substitutions that disrupt structurally important cysteine-cysteine disulphide bonds in the extracellular domain.[49] T50M is the most important of these missense *TNFRSF1A* mutations, encoding one of the cysteine residues involved in disulphide bonds.[11] Specifically, the T50M mutation leads to an abnormally highly conserved hydrogen bond, necessary for protein folding.[12] Differently, despite being the most frequent pathogenic mutation, R92Q is not associated with AA amyloidosis in patients with TRAPS.[49] Approximately 25% of TRAPS patients seem to develop AA amyloidosis, even in the presence of subclinical inflammation.[11] In a series of 158 TRAPS patients from the EuroFever international registry, AA amyloidosis occurred in 10% of patients at a median age of 43 years with a long disease course.[49] Furthermore, in a recent systematic literature review, 41 patients with AKD and TRAPS were reported; of them, 61% needed a renal transplant or died after a median follow-up of almost 2 years.[11,50]

4 | TYPE I-INTERFERONOPATHIES

Genetic overproduction of type I interferon (IFN-I) may generate a sterile chronic systemic inflammation, resulting in a lupus-like immune complex GN. In such disorders, podocytopathy-like lesions are observed due to the ability of IFN-I to induce programmed cell death.[51,52] Type 1 interferonopathies represent a rare class of monogenic AIDs, characterized by enhanced IFN-I signalling pathways. Several diseases among type I interferonopathies may affect renal health, and there is growing interest in their molecular basis and renal histopathologic features.[51] Among them, Aicardi-Goutières syndrome (AGS), coatomer subunit-α syndrome (COPA), monogenic systemic lupus erythematosus (SLE) due to DNASE1L3 deficiency, stimulators of interferon genes (STING)-associated vasculopathy of infancy (SAVI), spondyloenchondrodysplasia (SPENCD) due to *ACP5* biallelic mutations, and deficiency of adenosine deaminase 2 (DADA2) have been associated to renal damage, with different biopsy findings.[51,53] In renal diseases, plasmacytoid dendritic cells may produce substantial levels of IFN-I, although resident cells are likely the primary source.[51] Type I interferonopathies are complex clinical entities, but several clinical characteristics may be regarded as red flags: severe growth impairment, developmental delay, skeletal dysplasia, intracranial calcifications, therapy-resistant inherited "idiopathic" arthritis in childhood, early-onset necrotizing vasculitis, non-infectious interstitial lung disease, panniculitis, and lipodystrophy.[53,54] Renal features at biopsy are heterogeneous: collapsing glomerulopathy, a rare renal disease characterized by vascular collapse, parietal epithelial cell proliferation, and podocyte loss has been found in AGS and SAVI.[16,51] Instead, immune-mediated kidney injury (including membranous nephropathy, MesPGN, and lupus-like GN) is most often seen in COPA, SPENCD and monogenic SLE due to *DNASE1L3* impairment.[51,53,54] Vascular lesions such as renal vasculitis, PAN-like presentation, and thrombotic microangiopathy are typical features of DADA2 (Figure 2).[51]

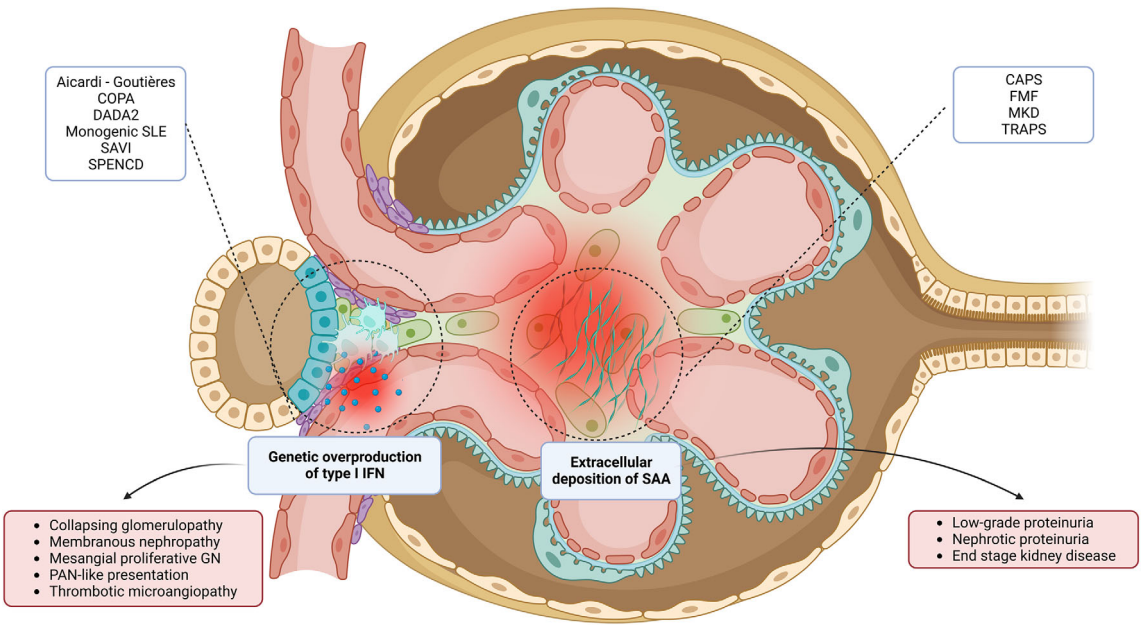

FIGURE 2 Mechanisms of renal damage in autoinflammatory diseases (AIDs) (created with BioRender.com). Histopathologic manifestations of AIDs are heterogeneous: inflammasomopathies result in amyloid kidney disease (AKD) owing to extracellular deposition of serum amyloid A (SAA). In addition, familial Mediterranean fever may potentially be responsible for a significant number of non-amyloid kidney diseases (NAKD), as shown in Table 2. Type-I interferonopathies result from an overproduction of interferon (IFN), leading to various forms of renal damage.

5 | TREATMENT STRATEGIES

Colchicine reduces AKD risk and represents a key treatment in FMF, thanks to its low cost, effectiveness, and safety.[24] In addition, colchicine might be effective for FMF patients with non-amyloid renal involvement, including MesPGN and IgAN.[15,55] Colchicine inhibits neutrophil migration and extravasation by reducing their flexibility via tubulin degradation and microtubule instability, hence preventing the activation of the pyrin inflammasome.[56] Persistent diarrhoea and increased liver transaminases are the most important side effects (observed in up to 10.8% and 6% of patients, respectively), and various other drugs should be avoided with colchicine, including macrolides, omeprazole, and statins.[57] A lifelong treatment with colchicine should be delivered to all FMF patients to avoid chronic renal failure, since the risk of AKD is strongly decreased in treated individuals.[24,57] The starting dosage of colchicine should be 0.5 mg/day in children less than 5 years of age, 0.5–1 mg/day in patients with 5–10 years of age, and 1–1.5 mg/day after 10 years of age (up to 2 mg/day in children).[57] However, up to 5%–10% of FMF patients are resistant or intolerant to colchicine.[58] Different approaches have been adopted for assessing the colchicine response, mainly based on the number of attacks per month but rarely considering subclinical inflammation and chronic renal disease.[57,59] Nevertheless, colchicine-resistant (crFMF) and intolerant individuals, often owing to diarrhoea, are successfully treated with IL-1 inhibitors.[24,60] Canakinumab is a long half-life selective IL-1β blocker, and anakinra is a subcutaneous IL-1β receptor antagonist with a brief duration of action.[60,61] Nevertheless, recent evidence suggests that canakinumab is not effective in reducing proteinuria in FMF patients with pre-existing renal impairment, and it should be administered early to avoid renal complications.[62] Both the efficacy and safety of canakinumab and anakinra have been extensively investigated in the literature, leading to their recent approval for crFMF by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA). According to the recent European League Against Rheumatism (EULAR) recommendations, IL-1 inhibitors should be used together with colchicine when systemic inflammation is not well controlled to reduce the risk of AKD and NAKD in children and adults with FMF.[59] Because colchicine is ineffective in MKD, and IL-1 inhibitors and TNF-blockers are only partially effective, patients with AKD frequently require a kidney transplant.[45] However, early diagnosis and biologic treatment are essential in MKD to avoid chronic renal failure.[45] IL-1 inhibitors are also effective in patients with CAPS, with good renal improvement and a 50% decrease in proteinuria in almost 90% of cases.[48] In addition, future perspectives are focusing on proton pump inhibitors (PPIs) for their anti-inflammatory properties, with good results in preliminary studies.[63] In most patients with TRAPS, therapy with biologics improved renal function or halted the course of disease.[11,50] These findings are consistent with previous studies that found an improvement in renal function in AKD patients treated with anakinra, as well as evidence that IL-1 blockers are more effective in TRAPS than TNF-inhibitors.[11,64] The current therapeutic strategies in interferonopathies are based on glucocorticoids and immunosuppressive drugs, including antiproliferative agents, mycophenolate mofetil, IFN blockers and Janus kinase inhibitors (JAKi).[53,65,66]

6 | CONCLUSIONS

Prevention of renal AA amyloidosis is mandatory in all paediatric patients with AIDs, in order to avoid long-term complications. Adequate treatment of the underlying disease is of key importance, along with accurate surveillance through periodic assessment of inflammatory markers, including SAA and albuminuria. However, despite the strong impact that AKD may have in AIDs, AA amyloidosis is often undiagnosed and ignored until the onset of late organ deterioration signs.[11,12] In addition, NAKD represents an uncommon but serious complication in patients with AIDs, often with a severe disease course. Thus, understanding the molecular mechanisms, histological features, and clinical manifestations of renal involvement in AIDs is crucial for early diagnosis and therapy in order to minimize long-term renal consequences and improve the disease prognosis.

AUTHOR CONTRIBUTIONS

Saverio La Bella, Armando Di Ludovico, Giulia Di Donato, and Giovanna Scorrano had the idea for the article, performed the literature search, wrote the manuscript, and realized tables and figures. Marina Vivarelli, Luciana Breda, and Francesco Chiarelli coordinated and approved the final version of the manuscript and critically revised the work. The final version was seen and approved by all authors.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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