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Autoinflammatory Disease: Molecular Insights, Clinical Spectrum, and Emerging Therapies

Author(s)

Selen Duygu Arık, Bengisu Menentoğlu, Özlem Akgün

Affiliation(s)

İstanbul University, İstanbul Faculty of Medicine, Department of Pediatrics, Division of Pediatric Rheumatology, İstanbul, Türkiye

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Abstract

Autoinflammatory disease (AID) represents a heterogeneous group of disorders resulting from dysregulation of the innate immune system, independent of autoantibodies or antigen-specific T-cells. Clinically, AIDs are marked by recurrent or persistent systemic inflammation manifested by organ-specific involvement such as fever, rash, arthritis, serositis, mucocutaneous lesions, cytopenias, and neurological or gastrointestinal complications. This review provides a comprehensive overview of the major autoinflammatory syndromes categorized according to their underlying molecular mechanisms. It discusses the current understanding of the pathogenesis, clinical manifestations, diagnostic approaches, and treatment strategies of AID's, with particular-emphasis on genetically defined syndromes and their molecular classification. Understanding the genetic and molecular basis of these syndromes has led to significant advances in their diagnosis and management. However, variability in clinical presentation, incomplete genotype-phenotype correlations, and the rarity of many conditions continue to pose diagnostic and therapeutic challenges. Continued research into novel disease mechanisms, therapeutic targets, and long-term outcomes is essential to improve the care of individuals with these complex disorders.

Keywords: Autoinflammation, autoinflammatory disease, hereditary AIDs, periodic disease, recurrent fever

Introduction

Familial Mediterranean fever (FMF) represents the most prevalent autoinflammatory disorder worldwide; however, this review aims to provide a comprehensive overview of other autoinflammatory diseases (AIDs) beyond FMF. AIDs comprise a spectrum of disorders marked by inflammatory attacks that emerge in the absence of infections, autoantibodies, or autoreactive T-cells. These diseases arise from innate immune system abnormalities, leading to the uncontrolled activation of inflammatory pathways[1]. Clinically, AIDs often present as fever, rashes, joint pain,

Correspondence: Özlem Akgün MD, İstanbul University, İstanbul Faculty of Medicine, Department of Pediatrics, Division of Pediatric Rheumatology, İstanbul, Türkiye
E-mail: drozlemakgun@hotmail.com **ORCID:** 0000-0001-7216-0562

abdominal discomfort, and organ-specific involvement. Inflammatory episodes can occur spontaneously or be triggered by minor external factors. Diagnosing AIDS involves assessing clinical features, conducting genetic analyses, and evaluating inflammatory biomarkers[2]. Epigenetic modifications can regulate the expression of inflammatory genes and impact disease severity, while triggers such as infections, psychological stress, and environmental exposures can provoke inflammatory responses[3]. Treatment strategies focus on controlling inflammation and preventing long-term complications. Targeted biologics such as interleukin (IL)-1 and tumor necrosis factor (TNF)-α inhibitors, along with non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids (CS), effectively manage many autoimmune diseases and acute inflammation.

Highlights

- Autoinflammatory diseases primarily occur due to dysregulation of the innate immune system, characterized by the absence of autoantibodies or autoreactive T-cells.
- Autoinflammatory diseases often present with overlapping features such as recurrent fever, mucocutaneous lesions, arthritis, and systemic inflammation.
- Early recognition and molecular diagnosis of these conditions enable the use of targeted treatments.

I. Diseases of Inflammasomes and Related IL-1-family Cytokines

These pathological conditions are a category of AIDs resulting from the aberrant activation of the cytoplasmic protein inflammasome complex. Activation of these mechanisms produces inflammatory cytokines like IL-1β and IL-18, and triggers pyroptosis[4]. Diseases of inflammasomes and related IL-1-family cytokines are summarized in **Table 1**.

1. Pyrin Inflammasome

Pyrin is usually kept inactive through phosphorylation by RhoA kinase, which regulates cell migration. However, when RhoA is inactivated, the pyrin inflammasome is triggered[5,6]. Microtubules play a key role in its assembly, which may explain the therapeutic effectiveness of colchicine, a microtubule inhibitor.

i. Hyperimmunoglobulin D Syndrome

Variants in the *MVK* gene, responsible for producing mevalonate kinase, an enzyme crucial for cholesterol and isoprenoid biosynthesis, cause hyperimmunoglobulin D syndrome (HIDS), a rare autosomal recessive (AR) AID[7]. Complete loss of enzyme activity results in mevalonic aciduria, while partial activity (2-30%) leads to HIDS. MVK deficiency depletes geranylgeranyl phosphate, a molecule essential for the membrane targeting of RhoA. Without RhoA's inhibitory effect, the pyrin inflammasome becomes overactive, leading to excessive IL-1β production and recurrent inflammatory episodes[8]. In more than 90% of cases, symptoms begin during the first year of life.

Clinical Features

Inflammatory episodes characterize HIDS, though persistent disease has been reported in 14% of patients. Attacks generally recur every 4 to 8 weeks, with a duration of 3 to 6 days, and may be triggered by vaccinations, physical trauma, psychological stress, or infections[9]. During attacks, patients often have symptoms including high fever, swollen lymph nodes, abdominal pain, diarrhea, vomiting, mucocutaneous involvement, aphthous ulcers, maculopapular or urticarial rashes, morbilliform rashes, pharyngitis, myalgia, arthritis, and arthralgia[9]. Some may also develop neurological issues such as headaches and, in severe cases, cognitive impairment. Although rare, Amyloid A amyloidosis remains a serious but potential complication[10].

Diagnosis

Serum IgD levels increased during and between attacks. Still, this measurement is not used in diagnosis because it has low sensitivity and specificity and 20% of patients do not show an increase. In contrast, urinary mevalonic acid levels are typically elevated during episodes and can serve as a diagnostic biomarker for these conditions. According to the Eurofever/ Paediatric Rheumatology International Trials Organisation (PRINTO) HIDS classification criteria, the diagnosis requires the presence of pathogenic or likely pathogenic MVK variants (homozygous or compound heterozygous) and at least one of the following symptoms: gastrointestinal involvement, cervical lymphadenitis, or aphthous stomatitis[11].

Treatment and Management

HIDS does not respond well to colchicine, and statins are also ineffective. Patients can benefit from NSAIDs for symptomatic relief, but these generally do not provide a complete response. While patients usually show a strong response to steroids during flare-ups, anti-IL-1 treatments remain the most effective option for managing HIDS[11]. IL-6 blockers or anti-TNF agents may be used as maintenance therapy in patients who present frequent attacks and/or subclinical inflammation if anti-IL-1 treatments are insufficient. In cases of severe and refractory disease, hematopoietic stem cell transplantation (HSCT) represents a possible therapeutic approach[12].

ii. Pyrin-associated Autoinflammation with Neutrophilic Dermatosis

A single heterozygous mutation leads to pyrin-associated autoinflammation with neutrophilic dermatosis (PAAND), a chronic neutrophilic dermatosis marked by recurrent and prolonged inflammatory episodes[13]. Genetic alterations in the *MEFV* gene underlie the disease and contribute to heightened IL-1β secretion during episodes of fever. All reported cases have been linked to the dominant p.S242R mutation in the *MEFV* gene, and recently, the E244K mutation has been identified. Both mutations in exon 2 disrupt the phosphorylation site of the pyrin protein or its +2 position, impairing its

interaction with the 14-3-3 protein and ultimately leading to dysregulation of the inflammatory response[14].

The disease differs with prolonged fever episodes, severe neutrophilic skin inflammation (e.g., cystic acne, hidradenitis suppurativa, pyoderma gangrenosum), and musculoskeletal symptoms. Serositis and amyloidosis are unexpected features[15]. Laboratory findings mostly included anemia and elevated acute-phase reactants. Individuals with PAAND respond to colchicine, and IL-1β-targeting therapies have also been effective in keeping the remission state[16].

iii. Pyogenic Sterile Arthritis, Pyoderma Gangrenosum, and Acne (PAPA)

This AD disorder, known as pyogenic sterile arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome, is associated with alterations in the *PSTPIP1* gene, resulting in dysfunction of a protein involved in inflammatory signaling pathways[17]. These mutations are thought to disrupt PSTPIP1 binding to tyrosine phosphatase, leading to hyperphosphorylation of the mutant protein, decreased affinity for pyrin in the cytosol, and unregulated IL-1β production[18]. Typically beginning in early childhood, PAPA is marked by repeated episodes of destructive oligoarticular arthritis, most often involving the knees, ankles, or elbows[19]. Attacks

Table 1.
Diseases of inflammasomes and related IL-1-family cytokines

Mechanism	Disease	Gene	Heredity	Clinical findings	Target/treatment	Age of onset	Attack duration
1. Pyrin inflammasome	FMF	*MEFV*	OR/OD	Fever, pain (abdomen, chest, joint), rash	IL-1/colchicine	<20	1-3 days
	PAAND	*MEFV*	OD	Fever, myalgia, myositis, rash, abscess	IL-1/colchicine		
	HIDS	*MVK*	OR	Fever, abdominal and extremity pain, vomiting, rash	IL-1	<1	3-7 days
	PAPA	*PSTPIP1*	OD	Pyoderma gangrenosum, arthritis	IL-1, TNF		
	Hz/Hc	*PSTPIP1*	OD	Rash, hepatosplenomegaly, neutropenia	IL-1, TNF		
	PFIT	*WDR1*	OR	Fever, infection, perianal ulceration, oral inflammation	IL-18		
2. Cryopyrin inflammasome	FCAS	*NLRP3*	OD	Cold urticaria, extremity pain, conjunctivitis, fever	IL-1		<24 hours
	MWS	*NLRP3*	OD	Extremity pain, conjunctivitis, fever, hair loss, urticarial rash	IL-1		2-3 days
	NOMID	*NLRP3*	OD	CNS inflammation, urticaria, knee arthropathy, fever	IL-1	neonatal	Continuous with occasional flare-ups
	Majeed	*LPIN2*	OR	Osteomyelitis, fever, rash, dyserythropoietic anemia	IL-1	<2	
3. NLRC4 inflammasome	AIFEC	*NLRC4*	OD	Fever, arthritis, rash, enterocolitis	IL-1, IL-18		
	FCAS/NOMID	*NLRC4*	OD	Cold urticaria, extremity pain, fever, CNS disease	IL-1		
4. NLRP12 inflammasome	FCAS	*NLRP12*	OD	Cold urticaria, extremity pain, fever	TNF, IL-1		
5. NLRP1 inflammasome	NAIAD	*NLRP1*	OD	Eye-larynx-skin dyskeratosis, fever, arthritis	IL-1, TNF		
6. Receptor antagonist deficiencies	DIRA	*IL1RA*	OR	Pustular rash, osteomyelitis, periostitis, fever	IL-1		
	DITRA	*IL36RA*	OR	Pustular psoriasis, fever, malaise	TNF, IL-17/23		

IL: Interleukin, FMF: Familial mediterranean fever, PAAND: Pyrin-associated autoinflammation with neutrophilic dermatosis, PAPA: Pyogenic sterile arthritis, pyoderma gangrenosum, and acne, HIDS: Hyperimmunoglobulin D syndrome, PFIT: Periodic fever, immunodeficiency, and thrombocytopenia, FCAS: Familial cold autoinflammatory syndrome, MWS: Muckle-Wells syndrome, NOMID: Neonatal-onset multisystem inflammatory disease, AIFEC: Autoinflammation with infantile enterocolitis, NAIAD: NLRP1-associated autoinflammation with arthritis and dyskeratosis, DIRA: Deficiency of the IL-1 receptor antagonist, DITRA: Deficiency of the IL-36 receptor antagonist, TNF: Tumor necrosis factor, CNS: Central nervous system

usually occur spontaneously or after minor trauma. By early adolescence, most patients develop severe cystic acne, pyoderma gangrenosum, and sterile, pathergia-like abscesses at injection sites; hidradenitis suppurativa, particularly in the axilla and groin. In such cases, bone marrow suppression has been observed with exposure to sulfonamide drugs. Laboratory findings are often nonspecific; therefore, genetic testing is crucial for confirming a diagnosis. Glucocorticoids may be used for short-term disease control. Anti-TNF treatments are known to be more effective in skin manifestations, while anti-IL-1 treatments are better in joint involvement[20].

iv. Periodic Fever, Immunodeficiency, and Thrombocytopenia

In recent years, this rare AR disorder has been associated with homozygous loss-of-function mutations in the *WDR1* gene, which encodes a protein essential for actin cytoskeleton regulation and turnover[21]. These mutations lead to the accumulation of actin molecules, activation of pyrin, and excessive secretion of IL-18[22]. Patients with periodic fever, immunodeficiency, and thrombocytopenia present from birth with small platelets and thrombocytopenia, neutropenia with neutrophil dysfunction, recurrent fever, oral and perianal aphthous ulcers, and opportunistic infections. Disruption of the cytoskeleton affects the function of T-cells, antigen-presenting cells, and megakaryocytes, resembling the pathophysiology seen in Wiskott-Aldrich syndrome.

Treatment options are limited; CS and biologics offer partial benefits but also increase the risk of infection. To date, the only effective treatment reported has been allogeneic bone marrow transplantation[21].

v. Neonatal Onset of Pancytopenia, Autoinflammation, Rash, and Episodes of Hemophagocytic Lymphohistiocytosis Syndrome

CDC42 is a Ras-related GTPase that fundamentally plays a role in various biological activities, including cellular attachment, directional movement, polarization, growth, and malignant progression[23]. Mutations in this protein lead to mislocalization, causing peripheral blood mononuclear cells to produce excessive amounts of IL-1β and IL-18. Furthermore, increased activation of nuclear factor kappa B (NF-κB) has been observed in related studies. Episodes of neonatal pancytopenia, autoinflammation, rash, and hemophagocytic lymphohistiocystosis (HLH) characterize the disease[24]. IL-1 antagonists and interferon (IFN)-gamma blockade may provide partial clinical improvement; allogeneic bone marrow transplantation remains the sole option with curative potential[25].

2. NALP3/Cryopyrin Inflammasome

i. Cryopyrin-associated Periodic Syndrome

Gain-of-function AD mutations in the *NLRP3 (CIAS1)* gene cause cryopyrin-associated periodic syndrome (CAPS), a spectrum of AIDs. These pathogenic variants cause excessive IL-1β production, with most identified mutations clustered in exon 3[26]. The CAPS spectrum includes several distinct clinical entities, namely Familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and chronic infantile neurological cutaneous and articular syndrome (CINCA), also known as neonatal-onset multisystem inflammatory disease (NOMID)[27,28]. Within the spectrum of NLRP3-related diseases, FCAS represents the mildest form, while CINCA/NOMID is the most severe[29]. As CINCA syndrome is a chronic AID that begins in the neonatal period and is associated with a significant risk of long-term sequelae, early recognition and intervention are essential to mitigate permanent damage.

Clinical Features

FCAS is characterized by attacks lasting 1 to 2 days, cold-induced inflammation, and presents with fever, urticaria, arthralgia/arthritis, and transient conjunctivitis[30]. In most cases, avoiding cold exposure is sufficient to manage symptoms and prevent exacerbations. MWS is the most severe form, presenting with rash, arthralgia/arthritis, hearing loss, and ocular involvement; and approximately 25% of patients develop amyloidosis[28]. NOMID follows a chronic and persistent course, with patients experiencing persistent fever and rash, abnormal bone growth, and central nervous system (CNS) symptoms such as aseptic meningitis and increased intracranial pressure[31]. Joint involvement in CINCA/NOMID can be erosive, potentially leading to permanent sequelae. Ocular involvement, such as uveitis, papilledema, and optic atrophy, is more commonly reported in CINCA/NOMID, although it can also be seen, albeit less frequently, in MWS. Progressive hearing loss is primarily associated with CINCA/NOMID, but it can also occur, though less frequently, in MWS[32].

Diagnosis

Genetic analysis should be performed for diagnosis. It is recommended to test exon 3 with clearly pathogenic variants, such as R260W, D303N, L305P, E311K, T348M, L353P, A439V; and variants of unknown significance (VUS), such as V198M, for genetic testing of NLRP3[33]. According to the Eurofever/PRINTO classification criteria, the diagnosis of CAPS requires the presence of a pathogenic or likely pathogenic heterozygous variant in the *NLRP3* gene together with at least one of the following clinical features: Urticarial rash, red eyes, or neurosensory hearing loss. However, if a VUS is detected in the *NLRP3* gene, the CAPS classification requires the presence of at least two of three clinical criteria[10].

Treatment and Management

The primary pathogenic mechanisms underlying CAPS involve NLRP3 inflammasome engagement and IL-1 overproduction; therefore, treatment typically involves anti-IL-1 therapies[34,35]. Routine monitoring of patients should include auditory and ophthalmologic examinations[11]. Cognitive testing, lumbar puncture, skeletal imaging, and brain magnetic resonance imaging (MRI) may be necessary for comprehensive assessment and management.

ii. Majeed Syndrome/Lipin 2 (LPIN2)

Majeed syndrome is a rare AR disorder caused by inactivating mutations in the *LPIN2* gene, which plays a

key role in lipid metabolism. These mutations impair the regulation of the NLRP3 inflammasome, resulting in the overproduction of IL-1β and excessive inflammation[36,37]. Majeed syndrome is primarily characterized by fever, sterile osteolytic lesions, congenital dyserythropoietic anemia, and sometimes transient neutrophilic dermatosis. Persistent inflammation in affected individuals may result in recurrent fevers, growth delays, hepatosplenomegaly, and increased levels of acute-phase reactants[37]. IL-1 inhibitors have been effective in managing fever episodes and reducing inflammation in bone tissue[38].

3. NLRC4 Inflammasome

The *NLRC4* gene, composed of nine exons, is situated on the short arm of chromosome 2 at position p22.3. Gain-of-function mutations in the *NLRC4* gene create a wide range of autoinflammatory phenotypes, representing an expanding group of AIDs with an extensive clinical spectrum ranging from FCAS to NOMID[39]. In contrast to NLRP3, NLRC4 encompasses a caspase activation and recruitment domain, thereby facilitating its interaction with pro-caspase-1 independent of ASC for its activation.

Autoinflammation with Infantile Enterocolitis

Autoinflammation with Infantile Enterocolitis (AIFEC) is caused by pathogenic variants in NLRC4 and presents with systemic autoinflammation, including symptoms such as recurrent fever, fatigue, splenomegaly, vomiting, intermittent rash, and enterocolitis[40,41]. Extremely high serum IL-18 concentrations are present in AIFEC. The triggers of attacks, physical and emotional stressors, activation of the aberrant NLRC4 inflammasome, and the type three secretion system have been identified as possible facilitators. AIFEC flares share similarities with HLH, as both conditions exhibit IL-1β-associated symptoms (e.g., fever, tachycardia) and IFN-γ-associated histopathology (e.g., hemophagocytosis)[42]. A severe AIFEC attack can be misinterpreted as primary HLH due to the shared laboratory characteristics of hypertriglyceridemia, coagulopathy, cytopenia, increased soluble IL-2 receptor concentrations, and compromised *in vitro* cytotoxic activity. Unlike HLH, cytotoxic function in AIFEC returns to normal between attacks, suggesting that granule-related cytotoxicity remains intact. A key difference between HLH and AIFEC is gastrointestinal involvement: AIFEC, which commonly causes severe secretory neonatal diarrhea and enterocolitis, sometimes starts antenatally and often resolves after the first year, whereas diarrhea is rare in HLH. Notably, serum IL-18 levels remain elevated in AIFEC. In the context of therapeutic interventions, prophylactic administration of anakinra has demonstrated superior efficacy compared to low-dose CS and colchicine regarding the reduction of both the severity and occurrence of HLH-like attacks in AIFEC patients exhibiting mild gastrointestinal manifestations[40]. Recombinant IL-18 binding protein has shown dramatic efficacy in patients with neonatal AIFEC.

4. NLRP12 Inflammasome

Nucleotide-binding leucine-rich repeat-containing receptor 12 (NLRP12) is an intracellular protein with dual roles: it functions as an inflammasome and a negative regulator of inflammation[43]. It plays a crucial role in innate immunity, responding to pathogen- and damage-associated molecular patterns to modulate inflammatory processes[44]. Beyond its inflammasome activity, NLRP12 also inhibits the non-canonical pathway responsible for activating the proinflammatory transcription factor complex NF-κB[45]. This highlights how AIDs can involve overlapping proinflammatory pathways, further complicating immune regulation.

Familial Cold Autoinflammatory Syndrome 2

NLRP12-associated (NLRP12) AID arises from AD variants affecting the *NLRP12* gene. To date, no formal classification or diagnostic criteria have been established. It was named familial cold autoinflammatory syndrome 2 (FCAS2) because of its clinical similarities to FCAS. The disease typically presents with fever, elevated inflammatory markers, urticaria, arthralgia, and myalgia and is usually triggered by cold exposure[46]. Symptoms usually last one to seven days. Some patients may develop features resembling amyloidosis, sensorineural hearing loss, optic neuritis, and cryopyrinopathies. Approximately half of the patients present with cutaneous manifestations during attacks[47].

5. NLRP1 Inflammasome

The first scaffold protein discovered to facilitate inflammasome assembly was NLRP1 (nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 1). In contrast to other proteins that form inflammasomes, NLRP1 activation occurs through proteolytic cleavage[48]. Predominantly expressed in keratinocytes, NLRP1 mutations are linked to skin disorders such as multiple self-healing palmoplantar carcinoma and familial keratosis lichenoides chronica[49].

NLRP1-associated Autoinflammation with Arthritis and Dyskeratosis

The disease typically manifests within the first six months of life, presenting with a broad range of polymorphic mucosal and skin lesions. These may include papillary or filiform hyperkeratosis, pseudophrynoderma, human papillomavirus-negative condylomata, and candidiasis. In addition to recurrent fever episodes and polyarthritis, patients may exhibit abnormal bone growth[49]. NLRP1 inflammasome-activating mutations lead to an overproduction of IL-1, which subsequently contributes to the depletion of $CD27^+$ memory B-cells. Therapeutic interventions that consist of anti-TNF or anti-IL-1 inhibitors have been used to control the disease.

6. Receptor Antagonist Deficiencies

i. Deficiency of the IL-1 Receptor Antagonist

Pathogenic alterations in the IL1RN gene, responsible for producing IL-1 receptor antagonist (IL-1RA), underlie this AR disorder[50]. The inability to properly secrete this aberrant protein, leads to unregulated activation of the IL-1 receptor, which subsequently induces elevated responses of IL-1α and IL-1β. Typically presenting in early neonates, the disease is characterized by sterile multifocal osteomyelitis, periostitis, neutrophilic

pustulosis, and includes the possibility of heterotopic bone formation, nail dystrophy, oral lesions, vasculitis, lung disease, and atlantoaxial subluxation[50,51]. High fever is not typically observed, but patients exhibit markedly elevated acute-phase reactants. Notably, joint involvement in deficiency of the IL-1 receptor antagonist shows a strong therapeutic response to anti-IL-1 therapy[52].

ii. Deficiency of the IL-36 Receptor Antagonist (DITRA)

Deficiency of the IL-36 receptor antagonist (DITRA) is a potentially life-threatening AID originating from loss-of-function mutations in the IL-36 receptor. It typically presents with generalized pustular psoriasis (GPP), high fever, malaise, asthenia, and episodes of systemic inflammation[53]. Reports have also noted issues with the oral mucosa, nail dystrophy, and oligoarthritis, although oligoarthritis is reported rarely. Gastrointestinal symptoms are caused by the increased secretion of proinflammatory cytokines by the intestinal epithelium. The disease predominantly occurs in early childhood or adolescence and can be life-threatening, with severe skin rashes leading to sepsis-related complications. The estimated mortality rate is 4-7%[54]. Both familial and sporadic cases of GPP have been associated with the L27P mutation in the *IL36RN* gene, which leads to diminished activity of IL-36Ra. Due to its rarity, there are no established treatment guidelines for DITRA, however, case reports and small series demonstrate good clinical responses to methotrexate (MTX), oral retinoids, anti-TNF agents, and inhibitors of IL-17 and IL-12/23[54].

II. Diseases of Interferon Production and Signaling

1. Impaired Degradation or Processing of Endogenous Nucleic Acids

Aicardi-Goutières Syndrome

Aicardi-Goutières syndrome (AGS) is an uncommon genetic disease linked to gene defects responsible for nucleic acid metabolism and intracellular signaling pathways[55]. Gene products of TREX1, RNASEH2A/B/C, SAMHD1, ADAR, and IFIH1 are critically involved in regulating these biological processes[56]. Most disease-causing mutations follow an AR inheritance pattern, with *TREX1* and *RNASEH2B* mutations being the most frequently detected. Type 1 Interferonopathy is summarized in **Table 2**. AGS presents in two distinct clinical forms. In the early-onset form (22.8%), symptoms are present from birth and closely resemble congenital infections. Affected infants exhibit severe neurological impairment, psychomotor developmental delay, and liver abnormalities[57]. The late-onset form, emerging after initial normal development, is marked by slowed cranial growth, increasing spasticity, and significant cognitive and developmental impairments[58]. Neurological symptoms such as abnormal eye movements, nystagmus, deficient visual tracking are prevalent. A unique feature is an exaggerated startle response to minor sensory stimuli. Neuroimaging typically reveals

Table 2.
Type 1 interferanopathy

Mechanism	Disease	Gene	Heredity	Clinical findings	Target/treatment
1. Nucleic acid processing and degradation	Aicardi-Goutières syndrome	*TREX1, ADAR1, RNASEH2A/B/C, SAMHD1, IFIH1*	OR (OD: IFIH1)	Fever, encephalopathy, cerebral calcification, chilblains, autoantibody positivity, neurological retardation	JAK
	Monogenic syndrome	*DNASE1/2/1L3*	OR (OD: DNASE1)	Cytopenia, glomerulonephritis, rash, oral ulcer, arthritis, autoantibodies	JAK?
2. Nucleic acid sensing	SMS	*IFIH1, DDX58a*	OD	Calcification of the heart valve or aorta, osteopenia, acro-osteolysis, dental anomalies	JAK?
	SAVI	*TMEM137*	OD	Small vessel vasculitis, arthritis, chilblain rash	JAK
3. Proteasome	CANDLE/ PRAAS, PRAID	*PSMB4,8,9,10 PSMA3, PSMG2 POMP*	OR (POMP: OD)	Fever, joint contractures, HSM, lipodystrophy, growth retardation	JAK
4. IFN signaling	AGS-like	*USP18, ISG15, STAT2*	OR	Skin ulcers, convulsions, hydrocephalus, cerebral calcification, respiratory failure	JAK
5. Other	SPENCD	*ACP5*	OR	Skeletal dysplasia, cerebral calcification, cytopenia, autoantibody	?

IFN: Interferon, SAVI: Infancy-onset STING-associated vasculopathy, STING: Stimulator of interferon genes, CANDLE: Chronic atypical neutrophilic dermatitis with lipodystrophy and elevated temperature, AGS: Aicardi-Goutières syndrome, JAK: Janus kinase, HSM: Hepatosplenomegaly

intracranial calcifications, white matter destruction, and cerebral atrophy, analogous to the findings observed in congenital infections. Over time, symptoms tend to stabilize without further progression of the disease. Glaucoma, which occurs in the first six months of life, affects 6% of patients but is more common in those with SAMHD1 mutations (20%) and is notably absent from cases associated with ADAR or IFIH1 mutations.

Diagnostic evaluation of AGS includes measurement of IFN-stimulated gene expression scores to assess serum IFN activity; however, this may be normal in 30% of patients with isolated RNASEH2B mutations. Also, cerebrospinal fluid pterin levels indicate CNS IFN activity[59]. Prognosis varies depending on the genetic mutation involved, with the most significant mortality rates observed within the initial five years of life, particularly in cases associated with TREX1 mutations, which have the poorest outcome[60].

2. Enhanced Nucleic Acid Sensing

Stimulator of Interferon Genes Associated Vasculopathy with Onset in Infancy

Stimulator of interferon genes (STING) associated vasculopathy with onset in infancy (SAVI) constitutes a rare AID arising from heterozygous activating mutations within the *TMEM173* gene. This gene produces STING, essential for mediating type I IFN signaling[61]. These mutations lead to overactivation of the IFN pathway, resulting in chronic inflammation and severe damage to the skin and lungs. Dermatologic features include telangiectasia on the nose and cheeks, nodular formations, and atrophic plaques on the hands[62,63]. It presents with painful ulcerative lesions, loss of capillary loops, and distal capillary loss, particularly on the fingers, toes, ears, and nose. Lung involvement contributes significantly to morbidity and mortality in SAVI and leads to fibrotic interstitial lung disease accompanied by hilar or paratracheal lymphadenopathy. Neurological findings such as basal ganglia calcifications have been observed, but are less common than in other interferonopathies. Intermittent fever, polyarthritis, myositis, and developmental delay may be present. Autoantibody positivity, such as antinuclear antibodies (ANA), rheumatoid factor (RF), and anti-neutrophil cytoplasmic antibodies (ANCA), has also been reported in some cases[63]. Due to the pivotal involvement of IFN pathway abnormalities in SAVI, Janus kinase (JAK) inhibitors have been introduced as potential therapeutic agents[63].

3. Proteasome Dysfunction

Chronic Atypical Neutrophilic Dermatitis with Lipodystrophy and Elevated Temperature

This rare autoinflammatory condition, chronic atypical neutrophilic dermatitis with lipodystrophy and elevated temperature (CANDLE), is associated with pathogenic variants in several proteasome-related genes, including PSMB8, PSMA3, PSMB4, and PSMB9, which are involved in protein degradation and immune regulation[64]. Deleterious mutations in the *POMP* gene, which produces a protein essential for the maturation of the proteasome, can lead to a CANDLE-like immune dysregulation syndrome. CANDLE is characterized by high fever, arthritis, and a rash similar to pernio affecting the extremities. Common systemic features include progressive lipomuscular dystrophy, joint contractures, myositis with muscle atrophy, and hepatosplenomegaly[65]. Neurologic involvement, including basal ganglia calcifications, may occur. Inflammatory indicators are typically elevated. Increased triglyceride levels and elevated thyroid-stimulating hormone levels are also observed in association with various autoantibodies. Unlike many other AIDs, CANDLE does not respond well to traditional immunosuppressive therapies, including CS, MTX, or IL-1 inhibitors. However, JAK inhibitors are used in treatment[66].

III. Diseases of Nuclear Factor Kappa B and/or TNF Activity

1. Dysregulation of NF-Kß Signaling

i. Haploinsufficiency of A20/TNF-alpha-induced Protein 3 (TNFAIP3)

A20, encoded by the *TNF-alpha-induced protein 3 (TNFAIP3)* gene, is an enzyme that regulates protein function and degradation by adding and removing ubiquitin. Loss-of-function TNFAIP3 variants inherited in an AD pattern lead to A20 haploinsufficiency (HA20) by increasing NF-κB translocation to the nucleus[67]. Even a 50% reduction in A20 activity drives systemic inflammation by increasing NF-κB signaling.

HA20 is a rare AID defined by the manifestation of systemic inflammation that arises early in life with recurrent oral, genital, and gastrointestinal ulcers[68]. Clinical features include musculoskeletal and gastrointestinal symptoms, skin lesions, neurologic and cardiac involvement, and ocular symptoms. Laboratory findings show elevated acute-phase reactants and autoantibody positivity. HA20 shares many clinical features with Behçet disease but has distinct characteristics. These include autosomal dominant (AD) inheritance, and early childhood onset, scarring oral ulcers, recurrent fever, elevated acute-phase reactants, variable presence of autoantibodies, and a disease course that is often resistant to standard treatments. Treatment strategies include colchicine for ulcer management and anti-cytokine therapies such as anti-TNF, IL-1, and JAK inhibitors to control systemic inflammation. In severe and refractory cases, HSCT may be an option[68,69].

ii. Nuclear Factor Kappa B Essential Modulator

Ablation of the C-terminal domain of NF-κB essential modulator prevents its association with the inhibitory protein A20, thereby promoting uncontrolled activation of NF-κB[70]. As a result, affected individuals exhibit marked erythroderma and colitis early in life, and malabsorption typically occurs with systemic inflammatory responses. In some cases, individuals may also suffer from recurrent bacterial infections, likely due to intrinsic immune dysregulation. Therapeutic modalities vary: CS, infliximab, and HSCT have shown efficacy in selected individuals[71].

2. Aberrant TNF Activity

i. TNF Receptor-associated Periodic Syndrome

AD missense mutations in the *TNFRSF1A* gene, encoding the TNF receptor on chromosome 12, primarily within exons 2 to 4, have been identified as the underlying cause[72,73]. These mutations cause the accumulation of TNF receptor type 1 in the endoplasmic reticulum, leading to disruption in receptor clearance, an increase in reactive oxygen radicals, and the induction of TNF receptor-associated periodic syndrome (TRAPS)-related NF-κB, thus triggering innate immunity and IL-1β overproduction, leading to chronic inflammation. TNFRSF1A gene mutations are categorized into two main groups: structural and non-structural[74-76].

Clinical Features

The age of onset varies from early childhood to adulthood, with an average of 3-10 years. Attacks tend to last longer than other AIDs, typically persisting for 3-4 weeks, while attack intervals remain variable[77]. Symptoms begin with muscle cramps and pain that migrate from the trunk to the extremities, followed by fever and systemic symptoms. Patients commonly experience recurrent fever, myalgia, abdominal pain, urticarial rash, periorbital edema, conjunctivitis, oral ulcers, and lymphadenopathy[73]. The rash is migratory, pseudocellulitic in appearance, and typically affects the extremities or trunk in areas with muscle pain. It is tender, warm, and blanches with pressure. Renal amyloidosis, a serious complication, occurs in 25% of patients, often presenting with proteinuria.

Diagnosis

According to the TRAPS classification criteria proposed by Eurofever/PRINTO, the patient must have a pathogenic (or likely pathogenic) heterozygous TNFRSF1A gene variant, disease attacks lasting longer than 7 days and at least one of the following: myalgia, migratory rash, periorbital edema, or family history of TRAPS. If a TNFRSF1A (VUS) is detected, at least two of five clinical criteria for classification must be met[10].

Treatment and Management

For acute attacks, CS and NSAIDs help control symptoms, but steroids do not reduce the risk of amyloidosis[78]. Anti-TNF agents (except etanercept) are generally not used, and tolerance to etanercept develops over time[79]. In contrast, anti-IL-1 therapy has shown promising results in disease management.

ii. Deficiency of adenosine deaminase 2 (DADA2)

Adenosine deaminase 2 (DADA2) deficiency is a rare monogenic AID resulting from biallelic mutations in the *ADA2* gene[80]. The disease manifests with vasculitis, immune dysregulation, and hematologic abnormalities[81]. Researchers have identified over 100 ADA2 gene mutations that cause diverse clinical presentations, with severity and symptoms varying even among individuals with the same mutations.

Clinical Features

Vasculitic manifestations include fever, arthritis, myositis, and various genitourinary, dermatologic, neurologic, cardiac, pulmonary, gastrointestinal, and ocular complications. Patients may develop renal involvement (such as renal artery aneurysms, glomerulonephritis, or nephrocalcinosis), skin manifestations (leukocytoclastic vasculitis, livedo racemosa, or necrotic ulcers), neurologic complications (ischemic or hemorrhagic strokes, seizures, or peripheral neuropathy), cardiac abnormalities (cardiomyopathy, myocardial infarction, or pericarditis), pulmonary manifestations (such as pleuritis, ARDS), gastrointestinal involvement (pancreatitis, mesenteric ischemia, or bowel perforation), Raynaud phenomenon, and ocular involvement (uveitis, optic neuritis, or retinal vasculitis)[82]. Initial clinical signs typically emerge during early childhood, with an average onset between 5 and 7 years.

Immunodeficiency is a hallmark of DADA2 and predisposes patients to recurrent bacterial and viral infections. Patients often exhibit autoimmune neutropenia, eczema, and increased susceptibility to herpesvirus and other double-stranded DNA viruses. Hematologic abnormalities include pure red cell aplasia, pancytopenia, myelofibrosis and HLH. Less commonly, they include portal hypertension, hepatosplenomegaly, hepatic fibrosis, autoimmune lymphoproliferative syndrome-like features, Hodgkin lymphoma, or atypical cutaneous acute myeloid leukemia.

Unlike classic childhood polyarteritis nodosa (PAN), in which CNS involvement is rare, pediatric cases with PAN-like symptoms often present with arterial infarctions in the CNS. In addition, DADA2 can present with a combination of livedo reticularis and neurologic manifestations and may resemble Sneddon syndrome. Vascular abnormalities, including mesenteric and renal aneurysms, share striking similarities to those seen in PAN on both imaging and histologic examination, making diagnosis difficult.

Diagnosis

Elevated inflammatory markers are present. Plasma ADA2 enzyme activity below 5% of the standard value, along with the detection of a homozygous mutation in the *ADA2* gene, is critical for diagnosis. Brain MRI is used to assess stroke status.

Treatment and Management

Unlike high-dose glucocorticoids, conventional immunosuppressive therapies have generally been ineffective in managing the disease. The vasculitic manifestations, however, show a strong response to TNF-α inhibition[83]. HSCT has demonstrated potential in normalizing enzyme activity and resolving the vasculitic, hematologic, and immunologic symptoms associated with the disease. Diseases related to dysregulation of NF-κB signaling and/or TNF activity are summarized in **Table 3**.

Table 3.
Diseases of NF-kB and/or TNF activity

Mechanism	Disease	Gene	Heredity	Clinical findings	Target/treatment
1. Dysregulation of NF-Kß signaling	Haplo A 20	*TNFAIP3*	OD	Oral, gastrointestinal and genital ulcers, fever, arthritis, recurrent infection	TNF, IL-1, JAK?
	RELAhaploinsuf	*RELA*	OD	Cytopenia, lymphoproliferative disease, oral and gastrointestinal ulcers	TNF
2. Aberrant TNF activity	Blau	*NOD2*	OD	Granulomatous dermatitis, uveitis, arthritis	TNF
	TRAPS	*TNFRSF1A*	OD	Episodic fever, abdominal pain, headache, conjunctivitis, painful rash	IL-1, TNF
	DADA2	*ADA2*	OR	Systemic vasculitis, fever, rash, stroke, cytopenia	TNF, HSCT
3. Disorders of linear ubiquitination	ORAS	*OTULIN*	OR	Fever, panniculitis, diarrhea, arthritis	TNF
	LUBAC	*HOIL1, HOIP*	OR	Fever, recurrent infection, HSM, amylopectin-like deposits in muscles	TNF?

NF-kB: Nuclear factor kappa B, TNF: Tumor necrosis factor, IL: Interleukin, JAK: Janus kinase, HSCT: Hematopoietic stem cell transplantation, TRAPS: TNF receptor-associated periodic syndrome, DADA2: Deficiency of adenosine deaminase 2, ORAS: OTULIN-related autoinflammatory syndrome, LUBAC: Linear ubiquitin chain assembly complex, HSM: Hepatosplenomegaly

iii. Nucleotide-binding Oligomerization Domain Protein 2 - Blau Syndrome

The nucleotide-binding oligomerization domain 2 (NOD2) protein, encoded by the *NOD2* gene, belongs to the NOD-like receptor family and serves as a critical mediator of innate immune activation and inflammatory signaling[84]. Pathogenic variants that enhance the function of this gene result in heightened NF-κB activity, leading to dysregulated synthesis of proinflammatory mediators. The clinical picture typically includes rash, arthritis, and uveitis, with skin involvement appearing first between 1 and 2 years of age as a spreading maculopapular rash and possible erythema nodosum. Arthritis is polyarticular and symmetric, often causing severe arthritis with joint swelling. Ocular involvement, affecting 75-90% of patients within two years of onset, presents as granulomatous iridocyclitis and posterior uveitis that may progress to destructive panuveitis[85].

Since the primary affected organs are the skin, joints, and eyes, diagnostic evaluation includes tissue biopsy, ophthalmologic assessment, and imaging studies of the joints. Serum angiotensin-converting enzyme levels are usually normal. Genetic testing for NOD2 mutations can help confirm the diagnosis, but mutations may not be detected in all cases.

Treatment typically begins with CS; prednisolone is started at 1-2 mg/kg/day, tapered over 8-12 weeks, and maintained at the lowest effective dose for at least six months. MTX can be used at a dose of 10-15 mg/m² per week[86]. Patients with refractory disease may require additional immunosuppressive therapy, such as azathioprine, cyclophosphamide, cyclosporine, adalimumab, or infliximab, to control disease progression and prevent complications.

3. Disorders of Linear Ubiquitination

Ubiquitination, an essential post-translational modification, plays a key role in directing proteins for proteasomal degradation. Linear ubiquitin chains, in particular, are vital for regulating intracellular signaling pathways such as the TNF receptor and NF-κB. This specific form of ubiquitination is mediated by the linear ubiquitin chain assembly complex (LUBAC), which is crucial for maintaining effective signal transmission[87]. To maintain balanced LUBAC activity, the OTU deubiquitinase (OTULIN) selectively removes linear ubiquitin chains, preventing excessive LUBAC autoubiquitination and preserving cellular homeostasis.

i. OTULIN-related Autoinflammatory Syndrome

Homozygous OTULIN deficiency leads to excessive NF-κB signaling, resulting in a severe inflammatory condition that appears from the neonatal period onwards. Affected individuals present with persistent fever, systemic inflammation, diarrhea, sterile neutrophilic dermatitis, arthritis, and growth failure[88]. Treatment options include TNF inhibitors, which can help control inflammation, or bone marrow transplantation in severe cases[89].

ii. Deficiency of Linear Ubiquitin Chain Assembly Complex

A deficiency of LUBAC, resulting from homozygous deletions in either (heme-oxidized IRP2 ubiquitin ligase 1 or its interacting partner HOIP, leads to recurrent episodes of autoinflammation in affected individuals. Attacks typically present with prolonged fever lasting up to 2 weeks, invasive bacterial infections, hepatosplenomegaly, and amyloidosis. LUBAC deficiency, unlike other NF-κB-related disorders, impairs NF-κB signaling but paradoxically increases IL-1β sensitivity, indicating a complex and unclear pathogenesis[90].

IV. Autoinflammation Mediated by Miscellaneous Mechanisms

i. Coatomer Protein Complex Subunit Alpha Syndrome

The *coatomer protein complex subunit alpha (COPA)* gene encodes the α subunit of the COPI protein, which is essential for mediating vesicle transport from the Golgi apparatus to the endoplasmic reticulum (ER). This retrograde vesicular movement prevents the excessive accumulation of STING within the ER[91]. Pathogenic COPA variants disrupt this process, leading to overactive STING signaling and excessive production of type I IFNs. This mechanistic link explains the clinical similarities between COPA syndrome and SAVI. Interstitial lung disease, pulmonary hemorrhage, and inflammatory arthritis predominantly distinguish COPA syndrome. Affected children typically present with chronic cough and tachypnea within the first five years of life[92].

Many individuals with COPA syndrome exhibit autoantibody positivity, such as RF, anti-cyclic citrullinated peptide, ANA, and ANCA[92]. Treatment options include systemic CS, MTX, azathioprine, hydroxychloroquine, etanercept, and intravenous immunoglobulin.

ii. Autoinflammation and PLCG2-associated Antibody Deficiency and Immune Dysregulation

This AD autoinflammatory condition, called autoinflammation and PLCG2-associated antibody deficiency and immune dysregulation, results from mutations in the *PLCG2* gene and involves features such as immune dysregulation and impaired antibody production[93]. It is characterized by widespread inflammatory skin lesions, not triggered by cold. Patients may develop interstitial lung disease, ocular involvement, gastrointestinal inflammation, and mild immune deficiency[93]. Additionally, lymphoproliferative disorders and autoimmune manifestations may coexist. Glucocorticoids can be effective in managing symptoms.

iii. Cleavage-resistant Receptor-interacting Serine/Threonine Kinase 1 Induced Autoinflammatory Syndrome

Receptor-interacting protein kinase 1 (RIPK1) is a pivotal modulator of innate immune signaling, significantly activating NF-κB and other proinflammatory pathways[94]. Individuals presenting with biallelic loss-of-function mutations in RIPK1 demonstrate increased susceptibility to infections, progressive polyarthritis, and early-onset inflammatory bowel disease[94]. Most affected individuals experience recurrent febrile episodes with lymphadenopathy, occurring at one- to seven-day intervals every two to four weeks, typically within the first six months of life. Elevated acute-phase reactants mark these episodes, and skin rashes are absent. CS effectively controls disease flares, while IL-6 blockade has shown promising results in many patients[95].

Ethics

Informed Consent: The consent form was not needed due to the study design.

Footnotes

Author Contributions: Arık SD: Surgical and Medical Practies, Concept, Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing; Menentoğlu B: Surgical and Medical Practies, Concept, Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing; Akgün Ö: Surgical and Medical Practies, Concept, Design, Analysis or Interpretation, Writing.

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