Diagnosis of autoinflammatory diseases[1–3]

1 Clinical exam[3]

Recurrent/persistent inflammatory manifestations, including **fever in the absence of infection**, particularly in children or young adults

Common manifestations:

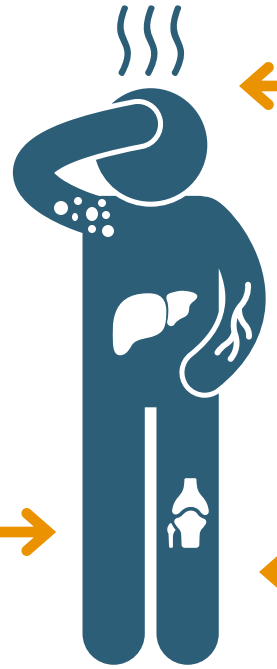
- Skin (rash)
- Musculoskeletal
- Hematopoietic
- Gastrointestinal
- Respiratory
- Nervous system

2 Routine laboratory parameters[3]

Examples include elevation in:

- ESR
- CRP
- Ferritin
- WBCs (possible)[4]

6 Suspected autoinflammatory disease



3 Genetic testing[2]

Next-generation sequencing:

- Whole exome/genome sequencing
- Targeted gene panel

4 Specific tests/biomarkers[3]

Examples include:

- Serum 100 protein
- Immunoglobulin D
- Serum amyloid A
- Urinary mevalonic acid

5 Functional analysis[1,3]

Examples include:

- Inflammasome analyses
- Cytokine profile
- IFN gene signature assay
- ADA2 enzyme activity
- Proteasome assays

- **Autoinflammatory diseases present with complex pathobiological features;** the ultimate diagnosis will depend on the differential analysis of the outcomes of each assessment[1,2]
- **Direct measurement of IL-1 is not a reliable diagnostic biomarker** because circulating IL-1β levels are typically low, and IL-1α levels are below the level of detection even in patients with severe autoinflammatory disease[5–8]

ADA2, adenosine deaminase 2; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IFN, interferon; IL, interleukin; WBC, white blood cell.

1. Kul Cinar O, et al. *Front Pediatr* 2022;10:867679; 2. Nigrovic PA, et al. *J Allergy Clin Immunol* 2020;146:925–937; 3. Zen M, et al. *Clin Rev Allergy Immunol* 2013;45:227–235;
4. Bonnekoh H, Krause K. *Curr Treat Options Allergy* 2015;2:235–245; 5. Broderick L, et al. *Nat Rev Rheumatol* 2022;18:448–463; 6. Lachmann HJ, et al. *J Exp Med* 2009;206:1029–1036;
7. Mantovani A, et al. *Immunity* 2019;50:778–795; 8. Monastero RN, et al. *Int J Inflam* 2017;2017:4309485.

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Diagnosis: Clinical signs and symptoms

Autoinflammatory disease should be suspected in those who present with:[2,3]

- **Fever**, **rash**, or recurrent **unexplained inflammation** in the absence of infection
- **Early age** of onset
- A **family history** of autoinflammatory disease

One size does not fit all

Clinical signs of autoinflammatory disease[1–3]

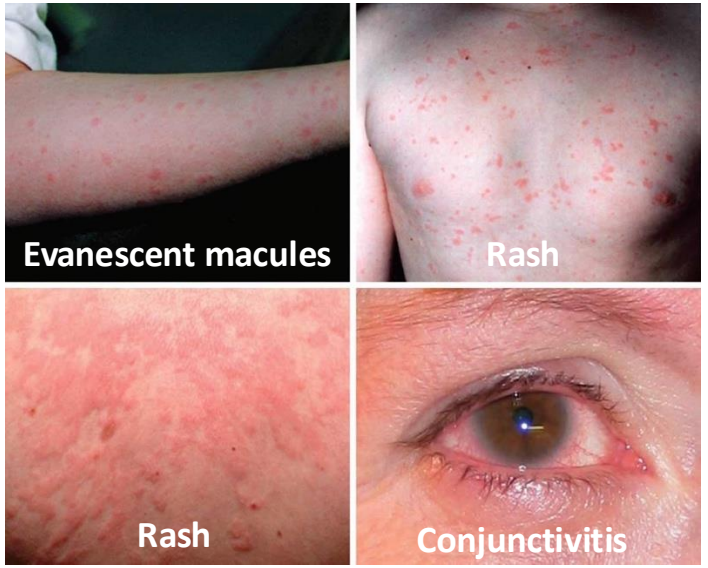
- Recurrent episodes of fever lasting a few hours to several weeks[2]
- Elevated inflammatory markers (e.g., CRP and ESR)[1,2]
- Skin rashes[2]
- Musculoskeletal, gastric, hematopoietic, ear, eye, and CNS symptoms[2]

Signs of multiorgan inflammation[2]:

- Myalgia/arthralgia
- Lymphadenopathy/splenomegaly
- Weight loss
- Fatigue
- Malaise
- Flu-like symptoms

Symptoms tend to recover with defervescence[2]

Typical symptoms of autoinflammatory disease[4]



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CNS, central nervous system; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

1. Nigrovic PA, et al. *J Allergy Clin Immunol* 2020;146:925–937; 2. Zen M, et al. *Clin Rev Allergy Immunol* 2013;45:227–235; 3. Gutierrez M, et al. *Rheum Dis Clin North Am* 2022;48:371–395;
4. Leslie KS, et al. *Arch Dermatol* 2006;142:1591–1597.

Diagnosis: Laboratory testing

Laboratory tests for a clinical workup of a patient with suspected IL-1–mediated autoinflammatory disease include:[1]

CRP **ESR** **SAA** **Ferritin** **S100**

Acute phase reactants

IL-1–induced biomarkers of systemic inflammation that correlate with disease activity in most patients[2–4,10]

CBC
(with differential)

Blood cell counts

An increase in WBCs associated with inflammation may correlate with disease flares[5]

Establishing the extent of inflammatory organ involvement or damage requires laboratory tests for markers of renal/hepatic/neurological function where clinically indicated[1]

Direct measurement of IL-1 is not a reliable diagnostic biomarker because circulating IL-1β levels are typically low, and IL-1α levels are below the level of detection even in patients with severe autoinflammatory disease[6–9]

CBC, complete blood count; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IL, interleukin; S100, serum 100 protein; SAA, serum amyloid A; WBC, white blood cell.

1. Romano M, et al. *Ann Rheum Dis* 2022;81:907–921; 2. Gattorno M, et al. *Ann Rheum Dis* 2019;78:1025–1032; 3. Chuamanochan M, et al. *World Allergy Organ J* 2019;12:100019; 4. Kuemmerle-Deschner JB, et al. *Ann Rheum Dis* 2017;76:942–947; 5. Gutierrez MJ, et al. *Rheum Dis Clin North Am* 2022;48:371–395; 6. Broderick L, et al. *Nat Rev Rheumatol* 2022;18:448–463; 7. Lachmann HJ, et al. *J Exp Med* 2009;206:1029–36; 8. Mantovani A, et al. *Immunity* 2019;50:778–795; 9. Monastero RN, et al. *Int J Inflam* 2017;2017:4309485; 10. Nirmala N, et al. *Curr Opin Rheumatol* 2014;26:543–552.

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Diagnosis: Genetic testing

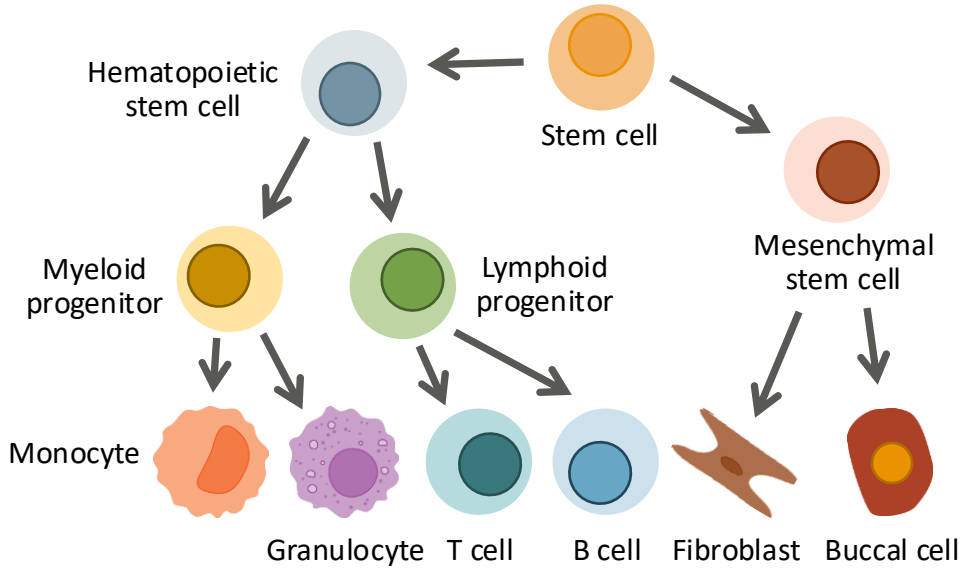
Genetic testing is a crucial component of an accurate diagnosis for **monogenic** autoinflammatory diseases[1,2]

- Monogenic autoinflammatory diseases can be familial or caused by *de novo* somatic mutations
- Somatic mutations may be difficult to detect by standard-coverage NGS and require deeper sequencing

~60% of patients with systemic autoinflammatory disease have no known pathogenic mutations[3–6]

Functional analyses (e.g., inflammasome analysis, cytokine assays, etc.)[7–9] to probe the pathogenicity of genetic VUS are becoming increasingly necessary in clinical practice[10]

Example: A myeloid-restricted somatic mutation manifesting as adult-onset CAPS



	Granulocyte	T cell	B cell	Fibroblast	Buccal cell
Subcloning	15.2%	0%	4.3%	0%	0.5%
Targeted sequencing	18.0%	0.9%	5.6%	0.1%	1.9%

Conventional sequencing was negative for *NLRP3* mutations; however, exome and deep sequencing revealed a mutation in monocytes (13.3–16.8%) and granulocytes (15.2–18.0%)[11]

Figure adapted from Zhou Q, et al. *Arthritis Rheumatol* 2015;67:2482–2486.
CAPS, cryopyrin-associated periodic syndrome; NGS, next-generation sequencing; VUS, variants of unknown significance.

1. Romano M, et al. *Ann Rheum Dis* 2022;81:907–921; 2. Broderick L, et al. *Nat Rev Rheumatol* 2022;18:448–463; 3. Harrison SR, et al. *JCI Insight* 2016;1:e86336;
4. Schnappauf O, et al. *Rheumatology (Oxford)* 2019;58(Suppl 6):vi44–vi55; 5. Papa R, et al. *Rheumatology (Oxford)* 2020;59:344–360; 6. Hoffman HM, Broderick L. *Arthritis Rheumatol* 2017;69:253–256;
7. Chirita D, et al. *Methods Mol Biol* 2022;2523:179–195; 8. Kuemmerle-Deschner JB, et al. *Rheumatology (Oxford)* 2020;59:3259–3263; 9. Tsuji S, et al. *Clin Exp Immunol* 2019;198:416–429;
10. Kul Cinar O, et al. *Front Pediatr* 2022;10:867679; 11. Zhou Q, et al. *Arthritis Rheumatol* 2015;67:2482–2486.

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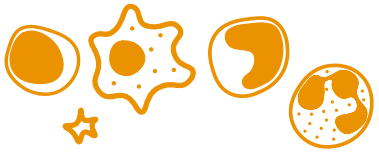
Pathophysiological effects of IL-1

Immunological



Immune cell recruitment and activation
Production of inflammatory mediators

Inflammation, tissue damage[1,2,9,11]

Liver

Induction of IL-6
Production of acute-phase reactants

Elevated acute-phase reactants, e.g., CRP, SAA[1,2,14]

CNS

Induction of PGE_2
Activation of the HPA axis

Fever, fatigue, loss of appetite, pain, production of cortisol[1,2,4–7]

Endothelium

Endothelial permeability
Vascular smooth muscle modulation

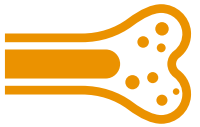
Skin rash, vasodilation, hypotension[1,3,15]

Musculoskeletal

Activation of synovial fibroblasts, chondrocytes, and osteoclasts; amino acid release from muscle

Cartilage degradation/ bone erosion,[8–10] muscle pain[16]

Bone marrow



Neutrophilia, thrombocytosis, anemia

Hematological abnormalities, hypercoagulation[1,11–13]

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CNS, central nervous system; CRP, C-reactive protein; HPA, hypothalamic–pituitary–adrenal; IL, interleukin; PGE_2, prostaglandin E2; SAA, serum amyloid A.

1. Rösen-Wolff A, et al. Cytokines in Autoinflammation In: Hashkes PJ, et al (Eds). Textbook of Autoinflammation. Switzerland. Springer; 2019:111–122; 2. Garlanda C, et al. *Immunity* 2013;39:1003–1018;
3. Dinarello CA. Interleukin-1-Induced Hypotension and the Effect of an Interleukin-1 Receptor Antagonist. In: Faist A, et al (Eds). Host Defense Dysfunction in Trauma, Shock and Sepsis. Berlin: Springer-Verlag; 1993:571–575;
4. Roerink ME, et al. *J Neuroinflammation* 2017;14:16; 5. Burfeind KG, et al. *Semin Cell Dev Biol* 2016;54:42–52; 6. Dinarello CA. *Eur J Immunol* 2011;41:1203–1217; 7. Ren K, et al. *Brain Res Rev* 2009;60:57–64;
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12. Nishmura S, et al. *J Cell Biol* 2015;209:453–466; 13. Vora SM, et al. *Nat Rev Immunol* 2021;21:694–703; 14. Sack GH. *Mol Med* 2018;24:46; 15. Fahey E, Doyle SL. *Front Immunol* 2019;10:1426;
16. Li W, et al. *Am J Physiol Cell Physiol* 2009;297:C706–C714.

The autoinflammatory disease patient journey can be lengthy and frustrating

Given the rarity of autoinflammatory diseases, median time to diagnosis is often delayed by:[1,2]

5 years for patients with **monogenic** autoinflammatory diseases

1 year for patients with **polygenic** autoinflammatory diseases

Diagnostic delays lead to insufficient treatment/disease progression, quality of life impairment, and higher morbidity/mortality for patients with autoinflammatory disease[1,3,4]

HCPs report that the key challenges in diagnosing autoinflammatory conditions include:[1]

- Atypical or no clinical symptoms at presentation
- Symptom overlap with other diseases or mosaicism
- Access to specialized testing

HCP, healthcare professional.

1. Chuamanochan M, et al. *World Allergy Organ J* 2019;12:100019; 2. Ozen S, et al. *Arthritis Care Res (Hoboken)* 2017;69:578–586; 3. Obici L, et al. *Autoimmun Rev* 2012;12:14–17; 4. Romano M, et al. *Ann Rheum Dis* 2022;81:907–921.

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