

The paramount importance of pattern recognition in auto-inflammatory diseases in reducing time to diagnosis

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Diagnosis of Familial Mediterranean Fever (FMF) is often delayed, as illustrated by Hageman et al.¹ The authors' message that the diagnostic delay in Amsterdam is comparable with the that in Mediterranean regions where the disease is more prevalent is somewhat reassuring for clinicians working in the Netherlands. However, the delay to diagnosis is still long, more than eight years. In the reported manuscript, the disease severity score was mild in more than half of the patients studied (55%), the majority (more than 90%) reported peritonitis, and more than 30% of patients underwent unnecessary abdominal surgery. Only one patient reported chronic sequela (amyloidosis). If recognized, treatment with colchicine, the inexpensive first-line treatment for FMF, was effective.

The long-term complication rate in the reported study by Hageman et al.¹ was low, which may reflect the relatively mild disease severity in the population studied. However, if left unrecognized, and in more severe disease cases, the chronic sequelae of FMF can be devastating. Amyloid deposition may lead to end-organ damage such as kidney failure and cardiomyopathy. None of the FMF patients reported in the study of Hageman et al.¹ needed second-line therapy. In case of failure of or intolerance for colchicine, second-line therapy, such as anti-interleukin-1 (IL-1) is generally effective.²

FMF is the most common auto-inflammatory disease. These conditions are caused by genetic mutations in molecules involved in regulating the innate immune response. Kastner et al. defined the concept of auto-inflammation as an "abnormally increased inflammation, mediated predominantly by the cells and molecules of the innate immune system, with a significant host predisposition".³ Initially-recognized auto-inflammatory diseases include, in addition to FMF, other periodic fever syndromes such as TNF-receptor-

associated periodic fever syndrome (TRAPS), hyperIgD with periodic fever syndrome (HIDS), and cryopyrin-associated periodic syndrome (CAPS).³ These entities share the clinical hallmarks of fever and other signs and symptoms such as rash, arthralgia, myalgia, and lymphadenopathy with an autosomal inheritance and the feared complication of amyloid deposition. Among these diseases, the efficacy of anti-IL-1 treatment suggests a major role of IL-1 in their pathogenesis.⁴ More recently, improved genetic sequencing has led to the discovery of a spectrum of auto-inflammatory syndromes, in which fever may be less pronounced and aspects of auto-immunity or immunodeficiency are part of the phenotype, broadening the clinical and immunological phenotypic spectra seen in these disorders.⁵ For example, a genetic defect through which macrophages are skewed towards a pro-inflammatory state underlies the phenotype adenosine-deaminase 2 (ADA2) deficiency, a spectrum of vascular and inflammatory phenotypes, ranging from early-onset recurrent stroke to systemic vasculopathy or vasculitis and immune deficiency.⁶

Early and correct diagnosis is sometimes difficult in auto-inflammatory disease given the variety of clinical signs and symptoms which also often overlap. Auto-inflammatory genetic screening panels help in defining the disease. Furthermore, mosaicism analysis indicates that a lower proportion of mutated alleles is of clinical importance in auto-inflammatory diseases, such as CAPS.⁷

International resources in the field of auto-inflammatory diseases are the International Society of Systemic Auto-Inflammatory Diseases (ISSAID), which, among others, organizes biannual meetings to share insights in the recognition of new disease entities; the EUROFEVER project, <https://www.printo.it/eurofever/>, which aims at

classifying auto-inflammatory diseases,⁸ providing insight into the burden of disease and in supports increased awareness; and INFEVERS (Internet periodic FEVERS), a registry of hereditary auto-inflammatory disorders mutations, <https://infevers.umai-montpellier.fr/web/>. From the patients' perspective, the Auto-inflammatory Alliance promotes awareness and improved care for people with auto-inflammatory diseases, <http://www.autoinflammatory.org/>.

Pattern recognition is of paramount importance in reducing the time to diagnosis in auto-inflammatory diseases. The competence of physicians able to recognize disease based on a pattern is to a large extent determined by their clinical experience.⁹ Being exposed to auto-inflammatory disease phenotypes through studies like Hageman et al¹ is therefore essential for physicians.

REFERENCES

1. Hageman MG, Visser H, Veenstra J, Baas F, Siegert EH. Familial Mediterranean fever (FMF): a single centre retrospective study in Amsterdam. *Neth J Med.* 2019;77:177-82.
2. Jesus AA, Golbach-Mansky R. IL-1 blockade in autoinflammatory syndromes. *Ann Rev Med.* 2014;65:223-44.
3. Kastner DL, Aksentijevich I, Goldbach-Mansy R. Autoinflammatory disease reloaded: a clinical perspective. *Cell.* 2010;140:784-90.
4. Ozen S, Bilginer Y. A clinical guide to autoinflammatory diseases: familial Mediterranean fever and next-of-kin. *Nat Rev Rheum.* 2014;10:135-47.
5. Maghaddas F, Masters S. The classification, genetic diagnosis and modelling of monogenic autoinflammatory disorders. *Clin Sci (Lond).* 2018;132:1901-24.
6. Zhou Q, Yang D, Ombrello AK. Early-onset Stroke and vasculopathy associated with mutations in ADA2. *N Eng J Med.* 2014;270:911-20.
7. Labrousse M, Kevorkian-Verguet C, Boursier G, et al. Mosaicism in autoinflammatory diseases: Cryopyrin-associated periodic syndromes (CAPS) and beyond. A systematic review. *Crit Rev Clin Lab Sci.* 2018;55:432-42.
8. Gattorno M, Hofer M, Federici S, et al. Eurofever Registry and the Paediatric Rheumatology International Trials Organisation (PRINTO). Classification criteria for autoinflammatory recurrent fevers. *Ann Rheum Dis.* 2019 Apr 24. pii: annrheumdis-2019-215048. doi: 10.1136/annrheumdis-2019-215048.
9. Sanders L. Every patient tells a story. Medical mysteries and the art of diagnosis. Broadway Books, New York, 2009.