Paediatric Autoinflammatory Diseases: Conceptual, Clinical and Mechanistic Dimensions

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I. Wekell P, Friman V, Balci-Peynircioglu B, Yilmaz E, Fasth A, Berg S. Familial mediterranean fever – an increasingly important childhood disease in Sweden. Acta Paediatrica (2013) 102: 193-198.

II. Brown KL*, Wekell P*, Osla V, Sundqvist M, Sävman K, Fasth A, Karlsson A, Berg S. Profile of blood cells and inflammatory mediators in periodic fever, aphthous stomatitis, pharyngitis and adenitis (PFAPA) syndrome. BMC Pediatrics (2010) 10:65.

III. Sundqvist M, Wekell P, Osla V, Bylund J, Christenson K, Sävman K, Foell D, Cabral DA, Fasth A, Berg S, Brown KL, Karlsson A. Increased intracellular oxygen radical production in neutrophils during febrile episodes of periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis syndrome. Arthritis and Rheumatism (2013) 65: 2971-2983.

IV. Wekell P*, Björnsdottir H*, Björkman L, Sundqvist S, Christenson K, Osla V, Berg S, Fasth A, Welin A, Bylund J, Karlsson A. Neutrophils from patients with SAPHO syndrome show no signs of aberrant NADPH-oxidase dependent production of intracellular reactive oxygen species. (Submitted manuscript)
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ABSTRACT

This thesis focuses on three paediatric autoinflammatory diseases in Sweden today; familial Mediterranean fever (FMF), periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) and synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO). In addition to describing autoinflammation with reference to these diseases, the thesis explores the concept of autoinflammatory disease by examining four existing definitions. A modified definition is then proposed in the light of this analysis.

The aim of the first study (paper I) was to characterize FMF in western Sweden. Patients with autoinflammatory diseases were continuously registered at five hospitals and case records were analysed retrospectively. Population data on immigration were retrieved from Statistics Sweden. Thirty-seven patients with FMF were identified in the records from the years 2000 to 2008. For the majority of patients, disease onset occurred during childhood. In western Sweden, the prevalence of FMF among immigrants from the eastern Mediterranean Basin was of the same order as for their country of origin.

The second and third study (papers II and III) aimed to advance the pathophysiological understanding of PFAPA, as an initial step towards identification of molecular and cellular mechanisms important in disease pathogenesis, as well as facilitating the definition of biomarkers. Levels of blood cells, serum cytokines and functional features of neutrophils were investigated during afebrile and febrile phases in children with typical PFAPA episodes. The results show oscillations in the concentration of blood cells between the afebrile and febrile phases of PFAPA. Upon onset of fever, there were modest levels of pro-inflammatory serum cytokines, together with increased levels of the IFN-γ-induced chemokine IP10/CXCL10. Further, neutrophils were analysed for functional features such as apoptosis, production of reactive oxygen species (ROS) and priming status (paper III). The results show that neutrophils from patients with PFAPA are primed, show decreased apoptosis and generate increased amounts of intracellular ROS during febrile attacks, whereas the afebrile phase was characterized by increased apoptosis. How these molecular and cellular features may affect disease pathogenesis is discussed in the thesis.

The fourth study (paper IV) investigated whether deficiency in neutrophil intracellular production of NADPH-oxidase-derived ROS is a disease mechanism in SAPHO, as suggested in a previous case report. Cells from four patients with SAPHO showed normal production of ROS, both intracellularly and extracellularly, contradicting the previous finding and showing that the SAPHO syndrome is not necessarily associated with deficient neutrophil intracellular ROS production.

This thesis gives new insights into a group of diseases that has been largely overlooked in the context of immune function, as each disease involves newly defined mechanisms important for innate immune regulation. The thesis also attempts to advance the definition of autoinflammatory diseases, complementing the previous definitions with the possible activation of the adaptive immune system and an association with other immune dysfunctions.

Keywords: child, fever, inflammation, cytokines, familial Mediterranean fever, neutrophils

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