Hereditary periodic fever syndromes (HPF) are a group of diseases characterised by recurrences of fever and inflammation separated by symptom-free intervals. Familial Mediterranean fever (FMF) is the most frequent entity within this group of disorders which further consists of hyperimmunoglobulinaemia D and periodic fever syndrome (HIDS), tumour necrosis factor receptor-associated periodic syndrome (TRAPS) and cryopyrin-associated periodic syndrome (CAPS). In recent years the causative genes have been identified. Reactive amyloidosis is a severe complication of HPFs. This is caused by deposition of fibrils that consist of the proteolytically cleaved acute-phase protein serum amyloid A (SAA). Several factors have been identified that modulate the risk for developing amyloidosis, including SAA concentrations, polymorphisms in the SAA gene and ethnic origin. Furthermore, the risk of developing amyloidosis varies widely between the different HPFs. Colchicine is the cornerstone in the management of FMF, as it reduces the severity and frequency of attacks and is also effective in preventing amyloidosis. In the other HPFs, the introduction of anti-cytokine-based therapies is a promising new option in treating these inflammatory conditions and they potentially can prevent amyloidosis.

Key words Amyloidosis • SAA • FMF • TRAPS • HIDS • CAPS • Periodic fever

Introduction

Hereditary periodic fever (HPF) syndromes are a group of genetic diseases clinically characterised by recurrent febrile attacks lasting in length from a few days to a few weeks. By definition, these episodes of fever are separated by symptom-free intervals of variable duration. During attacks patients have vigorous inflammation, with leukocytosis and elevated concentrations of acute phase proteins such as C-reactive protein (CRP) and serum amyloid A (SAA) [1].

So far, at least 4 different genetic HPFs have been well defined at the clinical and genetical level. The best known HPF is familial Mediterranean fever (FMF), but three other entities have been identified as well: hyperimmunoglobulinaemia D and periodic fever syndrome (HIDS), tumour necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS) and the cryopyrin-associated periodic syndrome (CAPS), which encompasses Muckle-Wells syndrome (MWS), familial cold autoinflammatory syndrome (FCAS), and chronic infantile neurological cutaneous and articular syndrome (CINCA).

The most devastating complication of the HPFs is reactive (type AA) amyloidosis [2]. This is caused by accumulation of amyloid fibrils in the extracellular spaces of var-

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ious organs and tissues, most notably the kidneys, liver and spleen, leading to organ failure [3]. Not all patients with elevated SAA concentrations will develop amyloidosis. Several genetic and environmental factors modify the risk for reactive amyloidosis.

In this review we will focus on amyloidosis in the group of HPF and genetic and clinical aspects of the HPFs.

AA amyloidosis

Pathogenesis of AA amyloidosis

Amyloidosis is a general denominator for a group of diseases that are characterised by extracellular deposition of fibrils of aggregated proteins [4]. These fibrils consist of polymers in a β sheet configuration of a precursor protein. To date, at least 21 different proteins have been described that have the ability to form amyloid fibrils, including Aβ42 in Alzheimer’s disease and immunoglobulin light chains in AL amyloidosis [5]. The amyloidosis type in HPF is reactive amyloidosis, also known as AA amyloidosis. The precursor protein in reactive amyloidosis is SAA. SAA is an acute phase protein that is mainly produced in the liver upon stimulation with various pro-inflammatory cytokines. It is found in plasma as an apolipoprotein of HDL cholesterol. During active inflammation serum concentrations beyond 1000 mg/l can be reached, which is 1000-fold higher than the constitutional concentration [6–8]. The conserved homology of the protein among a wide range of species suggests that SAA has an important biological function [9]. SAA has been implicated in leukocyte chemoattraction [10, 11] opsonisation of Gram-negative bacteria [12], and cholesterol metabolism [13–15]. However, to date, the exact function of SAA remains speculative.

Although the size of the SAA protein produced by the liver is 104 amino acids, amyloid fibrils found in patients with AA amyloidosis mainly consist of an accumulation of the 76 N-terminal amino acids of this protein [16–18], although proteins of different length have been reported [19, 20]. The C-terminal portion of SAA is cleaved off by macrophages. After dissolution of HDL, SAA is absorbed by macrophages and transported to the lysosome [21–24] where it is cleaved by a group of enzymes called cathepsins [25–27] (Fig. 1). In normal circumstances SAA is completely degraded. In patients with amyloidosis, the process of degradation is thought to be impaired, leading to the accumulation of the 76-amino acid intermediate [28]. The acidic environment of the lysosome facilitates the formation of these intermediates into a β sheet structure and subsequent polymerisation.

After deposition of these accumulated intermediates in the extracellular space, several glycosaminoglycans, serum amyloid P and lipid components bind to the fibril, and confer resistance to proteolysis [29–31].

Clinical manifestations of AA amyloidosis

Clinical symptoms of reactive amyloidosis are usually non-specific and depend on the organ involved. Several organs can be affected by AA amyloidosis, but the kidneys are most frequently involved. Reactive amyloidosis therefore usually presents as proteinuria with or without renal impairment. Renal involvement is found in >90% of patients [32, 33]. If the underlying process cannot be controlled, renal failure will ensue, necessitating renal replacement therapy or kidney transplantation. Gastrointestinal involvement is seen in about 20% of patients with reactive amyloidosis, and may present as diarrhoea, malabsorption or gastrointestinal pseudo-obstruction [32–34]. This has become more common with the availability of haemodialysis and renal transplantation, which has increased the life expectancy and thus duration of amyloid accumulation in these patients. Amyloidotic goitre, hepatomegaly, splenomegaly and polyneuropathy are less frequently encountered features of reactive amyloidosis [32, 35–37]. In contrast to other types of amyloidosis, cardiac involvement is rare in reactive amyloidosis [38].