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Review

Amyloidosis in autoinflammatory syndromes

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ABSTRACT

AA amyloidosis may still dramatically impact on the outcome of patients with autoinflammatory diseases, particularly when diagnosis is delayed. Clinicians should maintain a high level of attention to identify early this severe complication. Initial signs mostly reflect kidney damage, with proteinuria, with or without renal failure, being the more frequent presenting feature. If SAA levels are not rapidly normalized, progression toward end-stage kidney disease and dialysis invariably occurs. Over time, multiple organ failure, including heart, autonomic and adrenal insufficiency usually complicates the disease course. Limited tools are still available to predict the occurrence of AA, therefore close monitoring of at risk patients is required to detect promptly the "early red flags" through periodic search for preclinical amyloid deposits and regular assessment of proteinuria and SAA concentration. Effective control of the underlying inflammatory process may halt disease progression and even reverse damage. Anti-cytokine agents are becoming the mainstay of therapy to prevent and treat AA, including patients with FMF that do not respond or do not tolerate adequate colchicine dosages. Renal transplantation can be considered in selected patients progressing to end-stage kidney disease. Novel treatments are under development, targeting key molecular events in the fibrillogenesis process.

Contents

1. Introduction

Systemic AA amyloidosis may complicate the course of hereditary autoinflammatory syndromes in a variable but significant percentage of patients. This potentially life-threatening disease results from the extracellular deposition of proteolytic cleavage products of the acute phase reactant serum amyloid A (SAA) as insoluble cross-β-sheet fibrils. AA amyloid fibrils first accumulate in the spleen, the kidneys and the liver. In untreated patients, the peripheral and autonomic nervous systems, the testis, the thyroid, the adrenal glands and the heart almost invariably become involved over time. The clinical presentation at onset mostly consists of signs and symptoms of kidney damage, including glomerular proteinuria of 0.5 g/day or more, nephrotic syndrome and/or progressive loss of renal function. In some patients a marked splenomegaly occurs in the early phases of the disease. The main prognostic factor affecting progression to end-stage kidney disease (ESKD) and survival is the concentration of the amyloidogenic precursor SAA [1].

SAA is an apolipoprotein of high-density lipoproteins that circulates in plasma at a concentration of 1–3 mg/L in physiological conditions, but may rise by one-hundred to one-thousand fold following an inflammatory stimulation. Sustained SAA levels are a prerequisite for

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amyloid fibrillogenesis, promoting a cascade of pathophysiological events that include protein misfolding, proteolysis and aggregation into highly ordered amyloid fibrils [2]. Tissue glycosaminoglycans are well known to accelerate the formation and local deposition of AA fibrils [3], making these molecules potential targets for novel therapeutic approaches [4].

Hereditary autoinflammatory diseases are characterized by a vigorous increase in SAA levels during inflammatory bouts, which often persist also in between attacks. Early recognition and effective treatment of any of these conditions are therefore pivotal for preventing the occurrence of AA amyloidosis. Once it occurs, AA may still dramatically impact on the quality of life and prognosis of patients with autoinflammatory syndromes [5]. However, prompt anti-inflammatory treatment combined with a tailored supportive therapy may reverse organ damage at an early stage or halt progression toward renal failure.

2. Who is at higher risk of developing AA?

The prevalence of AA amyloidosis varies among the different autoinflammatory diseases if patients are not treated (Table 1). Once an autoinflammatory disorder has been diagnosed, prevention of AA amyloidosis can be challenging in patients in whom the inflammatory response cannot be completely suppressed by standard treatment. Although only a subset of patients presenting with sustained SAA levels ultimately develops clinically overt AA amyloidosis, genetic and/or environmental factors that affect susceptibility are still largely unknown, making it difficult to estimate the individual risk and adapt treatment accordingly.

SAA1 genotype has been proved to significantly impact on the risk of development of AA in FMF [6], as well as other chronic arthritides [2]. In Caucasians, homozygosity for *SAA1.1* is associated with a significant increase in AA risk. *SAA1* alleles differ for two SNPs located in exon 3, that results in amino acid changes at positions 52 and 57 respectively. It has been proposed that the presence of an alanine residue at position 57 may confer to SAA1.1 an increased susceptibility to proteolysis by matrix metalloprotease 1 (MMP-1), promoting the release of N-terminal peptides and accounting for the higher amyloidogenicity of this isoform [7].

In FMF, arthritis and homozygosity for the M694V variant are additional independent risk factors for development of amyloidosis [6]. Moreover, family history of amyloidosis combined with consanguinity resulted in 6.04 fold increased risk of developing this complication [8]. Finally, a population-related variability in AA risk appears also to play a role. A seminal study in over 2000 FMF patients showed that country of recruitment, encompassing both ethnic background and environmental factors, was the leading risk factor for amyloid nephropathy, being superior to disease duration and *MEFV* genotype [9].

Table 1
Prevalence of AA amyloidosis in specific autoinflammatory diseases in the absence of treatment.

Disease	Prevalence of AA amyloidosis
FMF	~50% (pre-colchicine)
TRAPS	10–20%
HIDS	<10%
CAPS	
FCAS	<10%
MWS	~25%
NOMID	Unknown
PFAPA	None

FMF, familial Mediterranean fever; TRAPS, TNF receptor-associated periodic syndrome; HIDS, Hyper-IgD syndrome; CAPS, cryopyrin-associated periodic syndromes; FCAS, familial cold autoinflammatory syndrome; MWS, Muckle–Wells syndrome; NOMID, neonatal-onset multisystem inflammatory disease; PFAPA, periodic fever adenitis pharyngitis and aphthous stomatitis.

SAA1.1 homozygosity is consistently associated with a significantly higher risk of AA in patients with TRAPS (Obici et al., unpublished data). Overall, in our view, multiple evidence support assessment of SAA genotype in Caucasian patients with autoinflammatory diseases to guide treatment choices in respect to AA risk.

3. Monitoring development of AA

Subclinical amyloid deposits are known to anticipate clinically overt AA amyloidosis [2]. Although the progression from asymptomatic to clinically overt amyloid disease is yet unpredictable, periodic search for subclinical deposits might help to identify subjects at higher risk for kidney dysfunction [10]. Serial abdominal fat aspirates or duodenal biopsies are routinely performed in at risk patients in some centers [10,11]. SAP scintigraphy is similarly able to detect asymptomatic visceral amyloid deposits showing high sensitivity and specificity [12]. However, the availability of this technology is limited. Patients with a positive tissue biopsy or SAP scan without evidence of organ damage should be considered at higher risk. Close monitoring of SAA levels is thus recommended and treatment should be adapted to maintain SAA concentration within the reference range.

Together with a periodic search for subclinical amyloid deposits, attention should be paid every 4–6 months to the occurrence of proteinuria >0.5 g/day, renal failure, splenomegaly and/or an increase in alkaline phosphatase with or without liver enlargement. Additional signs that should raise a clinical suspicion of AA are a progressively enlarging thyroid, carpal tunnel syndrome and the occurrence of bowel abnormalities, with constipation usually preceding diarrhea.

4. Managing AA amyloidosis in patients with autoinflammatory syndromes

An autoinflammatory disease is still diagnosed in a significant number of patients after renal AA amyloidosis has occurred. If treatment is established before development of renal failure, damage can potentially be reversed and amyloid deposits eventually re-absorbed [1].

Treatment must aim at rapidly normalizing SAA levels, possibly into the lower reference range [1]. Renal outcome and survival are strictly dependent on the residual inflammatory activity, with concentrations persistently over 50 mg/L being associated with disease progression and worse prognosis. Close monitoring of circulating SAA concentration is therefore mandatory to detect even slight elevations that may still occur in the absence of symptoms. In patients with end-stage kidney disease undergoing dialysis, suppression of SAA levels is of outmost importance to prevent occurrence or progression of cardiac amyloidosis, autonomic dysfunction, adrenal insufficiency and potentially life-threatening gastrointestinal or bladder bleeding.

Treatment choice should be guided accordingly. Colchicine at a daily dose of 1.5–2 mg may control chronic inflammation and renal damage in most FMF patients with AA. However, colchicine may not be tolerated at recommended doses or renal failure may limit adequate treatment. Anakinra has been proved to be effective in halting disease progression in this context, without significant safety issues [13]. Recently, anti-TNF agents have also been successful in managing FMF and amyloidosis when spondylitis also coexists [14].

In patients with AA amyloidosis secondary to TRAPS, CAPS or mevalonate kinase deficiency, continuous anti-cytokine treatment should always be considered, even when the number and duration of inflammatory episodes are low, to obtain stable suppression of SAA levels [15]. Recently, treatment with biological agents has been associated with reduced progression to end-stage kidney disease and improved prognosis in patients with RA and amyloidosis, supporting similar benefit over non-biological treatments also in patients with autoinflammatory diseases [16].