From renal amyloid deposits to the identification of the culprit genes

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ABSTRACT: Hereditary amyloidoses with renal involvement are classified in two groups. The first group is a growing family of autoinflammatory disorders characterized by recurrent fever attacks. Amyloidosis is caused by the deposition of amyloid A (AA) protein, which is a degradation product of a normal serum acute-phase protein: serum amyloid A (SAA). The prototype is familial Mediterranean fever (FMF). TNF Receptor Associated Periodic Syndrome (TRAPS) is a recently recognized periodic fever syndrome, differing from FMF in several characteristics: autosomal-dominant transmission, longer duration of attacks, and lack of response to colchicine prophylaxis. The second group comprises a variety of disorders, each characterized by the deposition of a specific mutant protein. The prototype is transthyretin amyloidosis (TTR).

Identification of the form of amyloidosis has clinical implications. Therefore, in a patient with a history of recurrent fever attacks and AA amyloidosis, a diagnosis of FMF or TRAPS dictates appropriate genetic counseling and management. In patients with renal amyloidosis without a history of fever, identification of the mutant protein is therapeutically crucial; therefore, when the cell type that produces the precursor is (exclusively or mainly) the hepatocyte, a liver transplantation is to be considered.

Key words: *Amyloidosis, Familial Mediterranean fever, TNF receptor associated periodic syndrome, Transthyrethin*

INTRODUCTION

The term "amyloidosis" is used to describe a number of protein deposition diseases. It was coined by Virchow in 1854 because the deposited substance stained with iodine in a way similar to starch and cellulose. Although the protein content of amyloid was subsequently recognized, the term "amyloid" persisted (1). There are many different forms of amyloidosis, each characterized by the nature of the deposited protein. The common property of these proteins is their ability to aggregate into fibrils, measuring 75-100 A in cross-section, having an indeterminate length and a β-pleated sheet structure (2). This peculiar structure accounts for their selective affinity to certain histochemical dyes, i.e. Congo red. By electron microscopy, all amyloid deposits appear as linear, randomly oriented, nonbranching fibrils, 8-10 nm in diameter. Staining with specific antibodies allows the identification of the deposited protein (usually by immunofluorescence microscopy).

Amyloid fibrils accumulate in extracellular spaces of involved tissues with subsequent cell dysfunction and death. Signs and symptoms of the disease depend on the location and size of the deposits. Some forms of amyloidosis are confined to a single organ (for example, the brain in Alzheimer's disease), whereas others are systemic, deriving from circulating precursors (2). Systemic amyloidoses can be acquired (i.e. immunoglobulin light chain-related amyloidosis) or can be hereditary. Only the systemic hereditary amyloidoses with renal involvement are considered here. They can be classified in two groups. The first group is a growing family of autoinflammatory disorders characterized by recurrent fever attacks. Amyloidosis is caused by the deposition of amyloid A (AA) protein, which is a degradation product of a normal serum acute-phase protein: serum amyloid A (SAA) (3). The prototype is familial Mediterranean fever (FMF) (Tab. I). The second group comprises a variety of disorders, each characterized by the deposition of a specific mutant protein. The prototype is transthyretin amyloidosis (TTR) (Tab. II).

Hereditary AA amyloidoses associated with recurrent fever syndromes

FMF is the only systemic hereditary amyloidosis transmitted as an autosomal recessive trait (with rare exceptions) (4, 5). It is seen most frequently in individuals of Mediterranean origin. The disease is characterized by periodic episodes of fever, which can be accompanied by peritonitis, synovitis, pleuritis or an erythematous rash. The attacks usually resolve within 2-4 days. Treatment with colchicine prevents the febrile attacks and subsequent amyloidosis (6). A high percentage of FMF patients develop systemic amyloidosis with prominent renal involvement (7). The susceptibility to amyloidosis was found to be influenced, independently, by the type of mutation, the SAA1

TABLE I - AA RENAL AMYLOIDOSIS ASSOCIATED WITH FAMILIAL RECURRENT FEVER SYNDROMES

	FMF	TRAPS	MWS	FCAS
Ethnic geographic background	Sephardic Jews Armenians Turkish	Europe	Europe	USA
Inheritance	Autosomal recessive	Autosomal dominant	Autosomal dominant	Autosomal dominant
Gene	MEFV (16p13)	TNFRSF1A (12p13)	CIAS1 (1q44)	CIAS1 (1q44)
Protein	Pyrin / marenostrin	55kd TNF receptor	Cryopyrin	Cryopyrin
Age at onset	Childhood	Variable	Variable	Childhood
Duration of fever episodes (days)	3-4	7-21	1-2	1-2 (cold-induced)
Abdominal pain	++	++	+	+
Arthritis	++	+	+	+
Skin	+/- rash	++ erysipeloid	++ urticaria	++ urticaria
Deafness	-	-	+	-

FMF: familial Mediterranean fever. TRAPS: TNF receptor associated periodic syndrome. MWS: Muckle-Wells syndrome. FCAS: familial cold autoinflammatory syndrome.

TABLE II - AMYLOIDOSES WITH RENAL INVOLVEMENT DUE TO THE DEPOSITION OF A MUTANT PROTEIN

	Transthyretin	Apolipoprotein A1	Apolipoprotein A2	Fibrinogen Aα - chain	Lysozyme
Geographic background	Europe USA Japan	Europe USA	USA	Europe USA	Europe
Inheritance	Autosomal Dominant	Autosomal Dominant	Autosomal Dominant	Autosomal Dominant	Autosomal Dominant
Main other clinical manifestations	Neuropathy Cardiopathy	Neuropathy Hepatopathy	–	–	Gastro-intestinal

genotype and sex (8).
TNF Receptor Associated Periodic Syndrome (TRAPS) is a recently recognized periodic fever syndrome, differing from FMF in several characteristics: autosomal-dominant transmission, European ancestry, longer duration of attacks and lack of response to colchicine prophylaxis (9-12). Amyloidosis developed in about 20% of reported cases, with the risk skewed toward individuals with cysteine substitutions (13). Muckle-Wells syndrome (MWS) is characterized by day-long episodes of fever with abdominal pain, arthritis, urticarial rash and progressive sensorineural hearing loss. Approximately 25% of patients develop renal amyloidosis (14). Familial cold autoinflammatory syndrome (FCAS) is characterized by cold-induced attacks of fever, urticarial rash and arthritis. MWS and FCAS recently proved to be due to distinct mutations in the same gene (15).
Interestingly, the proteins involved in these four disorders (pyrin for FMF, 55 kD TNF receptor for TRAPS and cryopyrin for MWS and FCAS) are all involved in inflammation control, probably by regulating apoptosis in a subset of leucocytes involved in the early stage of the inflammatory cascade. Mutations in one of these proteins can favor an abnormal amplification of the inflammatory reaction (14).

Hereditary amyloidosis due to the deposition of a mutant protein

The most common form of amyloidosis, due to the deposition of a mutant protein, is associated with variants of plasma transthyretin (TTR). The major clinical manifestation is peripheral neuropathy. In the Portuguese-type TTR-associated amyloidosis, renal involvement is not exceptional (16).
Among the other, rarer, systemic amyloidoses due to the deposition of a mutant protein (Tab. II), those associated with a variant of apolipoprotein A1, apolipoprotein A2, fibrinogen Aα-chain and lysozyme present with renal involvement as the most prominent clinical manifestation (17-20).

Current insights and unanswered questions

Recent advances in the knowledge of systemic hereditary amyloidoses have clinical and pathophysiological implications. Therefore, in a patient with a history of recurrent fever attacks and AA amyloidosis and a diagnosis of FMF or TRAPS appropriate genetic counseling and management is essential. In renal amyloidosis patients without a history of fever, identification of the mutant protein (Tab. II) is therapeutically crucial; therefore, when the cell type that produces the precursor is (exclusively or mainly) the hepatocyte, a liver transplantation is considered (21-23).
Understanding the role of culprit genes and corresponding proteins in recurrent fever syndromes with AA amyloidosis provides new insights into the control mechanisms of the normal inflammatory process (14). Identification of the many proteins able to produce amyloid fibrils in their mutated form can enlighten our understanding of other, non-inherited conditions, for example, the aging process, since several of them can also aggregate as amyloid fibrils in their wild form with age (i.e. as normal transthyretin in cardiac amyloidosis) (24).
This progress in our knowledge of systemic hereditary amyloidosis leaves us with many unanswered questions. One is the reason for the large variability in the development and progression of amyloidosis, not only between families, but also within the same kindred. Although some risk factors for susceptibility to amyloidosis have been recently identified in FMF (8) and TRAPS (13), the mechanisms underlying fibrillogenesis, tissue distribution of amyloid and impact on organ function remain largely unknown.

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