Hereditary systemic amyloidosis with renal involvement

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ABSTRACT: Hereditary systemic amyloidosis is caused by deposition of genetically variant proteins as amyloid fibrils. The types that present with renal disease are usually associated with mutations in the genes for either apolipoprotein AI, apolipoprotein AII, lysozyme or fibrinogen A α-chain. These diseases are inherited in an autosomal dominant manner with variable penetrance, and can present clinically at any time from the teen years to old age, though usually in mid-adult life. Hereditary amyloidosis is uncommon, but its precise characterization has major implications for patient management and genetic counseling, and it has been an extremely valuable model for elucidating the pathogenesis of amyloid deposition generally. The amyloidogenic variant proteins associated with hereditary amyloidosis are less stable than their normal wild type counterparts and even under physiological conditions can populate partly unfolded states, involving loss of tertiary or higher order structure, which readily aggregate with retention of β-sheet secondary structure into protofilaments and fibrils. The clinical phenotype of hereditary renal amyloid is non-specific and is readily misdiagnosed as acquired AL amyloidosis. Indeed, we have lately demonstrated that five percent of patients with apparent sporadic amyloid have hereditary fibrinogen A α-chain amyloidosis associated with the valine 526 variant. Penetrance of this particular mutation is extremely low in most families obscuring the genetic etiology, but the renal histology is very characteristic showing substantial accumulation of amyloid within enlarged glomeruli, but none in blood vessels or the interstitium. DNA analysis is now performed routinely in UK National Amyloidosis Centre in patients with systemic amyloidosis in whom AA or AL fibril type cannot be definitively verified.

Key words: *Amyloid, Amyloidosis, Hereditary, Familial, Renal*

INTRODUCTION

Amyloidosis is a disorder of protein folding in which normally soluble proteins are deposited as abnormal, insoluble fibrils that progressively disrupt tissue structure and cause disease (1). Some 20 different unrelated proteins can form amyloid *in vivo*, and clinical amyloidosis is classified according to the fibril protein type. In systemic amyloidosis, deposits may occur in all tissues other than the brain, and are present to some extent in blood vessels throughout the body. Systemic amyloidosis is potentially fatal although its prognosis has been improved by hemodialysis, kidney, liver and heart transplantation, and by increasingly effective treatment of the various conditions that underlie amyloid deposition. There are also various localized forms of amyloidosis in which the deposits are confined to specific foci or to a particular organ or tissue. These may be clinically silent or trivial, or they may be associated with serious disease, such as hemorrhage in local respiratory or urogenital tract AL amyloid. In addition there are important diseases associated with local amyloid deposition in which the pathogenetic role of the amyloid is still unclear, for example, Alzheimer's disease, the prion disorders and type II diabetes mellitus. Although these conditions will not be discussed here, it should be noted that therapeutic strategies aimed at inhibiting amyloid fibrillogenesis and/or promoting regression of amyloid deposits in systemic amyloidosis may also be applicable to localized amyloidosis and *vice versa*.

In addition to the fibrils, amyloid deposits always contain the normal plasma protein serum amyloid P component (SAP), because it undergoes specific calcium-dependent binding to amyloid fibrils (2). SAP contributes to amyloidogenesis (3), and radiolabeled SAP is a specific, quantitative and highly informative tracer for scintigraphic imaging of systemic amyloid deposits (4, 5). The treatment of amyloidosis comprises measures to support impaired organ function, in-

cluding dialysis and transplantation, along with vigorous efforts to control underlying conditions responsible for production of fibril precursors (6). Serial SAP scintigraphy has demonstrated that reduction of the supply of amyloid fibril precursor proteins leads to regression of amyloid deposits and clinical benefit in many cases.

Pathogenesis

Amyloidogenesis involves substantial refolding of the native structures of the various amyloid precursor proteins enabling them to autoaggregate in a highly ordered manner to form fibrils with a characteristic β-sheet structure (7, 8). Amyloid deposition occurs *in vivo* under several conditions. Firstly, when a normal protein is present for sufficient time at an abnormally high concentration, for example serum amyloid A protein (SAA) and $\beta_2$microglobulin (β_2M) during chronic inflammation and renal failure respectively. Secondly, in the presence of a ordinary concentration of a normal, but inherently weakly amyloidogenic protein over a very prolonged period, such as in the case of transthyretin in senile cardiac amyloidosis which is extremely rare before 70 years of age. Thirdly, when there is an acquired or inherited variant protein with abnormal amyloidogenic structure, such as certain monoclonal immunoglobulin light chains and variant lysozyme, etc.

Hereditary amyloidosis

Hereditary systemic amyloidosis is caused by deposition of genetically variant proteins as amyloid fibrils, and is associated with mutations in the genes for either transthyretin, cystatin C, gelsolin, apolipoprotein AI, apolipoprotein AII, lysozyme or fibrinogen A α-chain. These diseases are all inherited in an autosomal dominant manner with variable penetrance, and present clinically at various times from the teens to old age, though usually in middle adult life. By far the commonest hereditary amyloidosis is caused by transthyretin variants, which usually presents as familial amyloid polyneuropathy with peripheral and autonomic neuropathy, often with prominent or predominant cardiac involvement. Cystatin C amyloidosis presents as cerebral amyloid angiopathy with recurrent cerebral hemorrhage and clinically silent systemic deposits, and has been reported only in Icelandic families. Gelsolin amyloidosis is also extremely rare and presents with corneal lattice dystrophy and cranial neuropathy; although there are substantial renal amyloid deposits these are usually clinically silent.
Apolipoprotein AI, apolipoprotein AII, lysozyme and fibrinogen A α-chain amyloidosis almost always present as non-neuropathic systemic amyloidosis that can affect any or all the major viscera, but with renal involvement typically being prominent. These latter conditions are readily misdiagnosed as acquired AL amyloidosis, and are less rare than previously thought (9).

Familial amyloidotic polyneuropathy

Familial amyloidotic polyneuropathy (FAP) is caused by point mutations in the gene for the plasma protein transthyretin and is an autosomal dominant syndrome with variable penetrance. Symptoms typically present between the third and seventh decades (10). The disease is characterized by progressive and disabling peripheral and autonomic neuropathy, and varying degrees of visceral amyloid involvement. Severe cardiac amyloidosis is common. Deposits within the vitreous of the eye occur in a proportion of cases and are very characteristic, but thyroid, spleen and adrenals deposits are usually asymptomatic. Renal amyloid deposits are common but are usually only associated with renal impairment relatively in patients who have undergone the stress of liver transplantation. There are well-recognized foci of the disease in Portugal, Japan and Sweden but FAP has been reported in most ethnic groups throughout the world. There is considerable phenotypic variation in the age of onset, rate of progression, involvement of different systems and disease penetrance, generally, even within families. More than 80 variant forms of transthyretin are associated with FAP, the most frequent of which is the substitution of methionine for valine at residue 30. Transthyretin alanine 60 is the most frequent cause of FAP in the British population, and usually presents after age 50 years, often with predominant cardiac amyloidosis. Transthyretin isoleucine 122 occurs in four percent of black African-Americans and may give rise to a clinical picture resembling senile cardiac amyloidosis, but up to 10-20 years earlier than in subjects with wild-type transthyretin.

Hereditary systemic amyloidosis with prominent nephropathy

Ostertag first described the syndrome of hereditary systemic amyloidosis in a German family in 1932. He reported 2 families with autosomal dominantly inherited renal amyloidosis without neuropathy. It is now known that almost all individuals with this clinical picture are heterozygous for mutations in the genes for either lysosyme, apolipoprotein AI or fibrinogen A alpha chain. A family with this phenotype has also been reported with mutation in the gene for apolipopro-

tein AII in which loss of a stop codon results in a 21-residue extension at the *C*-terminus of the protein (11).

Lysosyme amyloidosis

Hereditary non-neuropathic systemic amyloidosis has been described in association with three lysozyme variants, the substitution of histidine for aspartic acid at position 67, threonine for isoleucine at position 56, and arginine for tryptophan at position 64 (12, 13). Penetrance is high but is incomplete, and patients with hereditary lysozyme amyloidosis may present at any age after the second decade. Most patients present in middle age with proteinuria and very slowly progressive renal impairment that can take decades to reach end-stage. Hepatosplenomegaly due to amyloid deposition is common but often asymptomatic, and petechial rashes are associated with the lysozyme threonine 56 variant. Intriguingly, although lysozyme histidine 67 amyloidosis usually presents with nephropathy, it presented with acute hepatic rupture in 3 generations of one particular kindred (14). Cardiac amyloid and neuropathy are not features of lysozyme amyloidosis. Virtually all patients have substantial gastrointestinal amyloid deposits, and although these are often asymptomatic, they are important since gastrointestinal haemorrhage or perforation are frequent causes of death (15).

Apolipoprotein AI amyloidosis

Apolipoprotein AI is a major constituent of high density lipoprotein. Eleven amyloidogenic variants are known, eight of which are single amino acid substitutions, two are deletions and one a deletion/insertion (16-25). Depending on the mutation, patients can present with massive abdominal visceral amyloid involvement, predominant cardiomyopathy or an FAP-like syndrome. Penetrance in hereditary apolipoprotein AI is high, but very substantial visceral amyloid deposits may be present for decades before symptoms develop. The majority of patients eventually develop renal failure, but despite extensive hepatic amyloid deposition liver function usually remains well preserved. Neuropathic involvement is virtually restricted to certain patients and families with the arginine 26 variant (16). Several variants, including proline substitutions at residues 90, 173 and 175 and histidine 178, are associated with hoarseness due to laryngeal amyloid deposits which may be misdiagnosed as localized AL type. Normal apolipoprotein AI amyloid is itself weakly amyloidogenic, and is the precursor of small amyloid deposits that occur quite frequently in aortic atherosclerotic plaques (26). Deletion of lysine at residue 107 has been associated with increased susceptibility to amyloid deposition in the aortic intima and ischemic heart disease.

Fibrinogen A alpha chain amyloidosis

Fibrinogen A alpha chain was first isolated from amyloid fibrils in 1993 (27). Four amyloidogenic mutations have been described in eight unrelated kindreds. These include two frame shifting deletion mutations, and a leucine for arginine substitution at codon 554 (28-31). However, much the commonest mutation results in the substitution of valine for glutamic acid at position 526 (32). This mutation has been reported in several families of European descent in which it had high penetrance, but we have lately shown that this variant is the cause of amyloid deposition in five per cent of patients referred to the UK National Amyloidosis Centre with an apparent diagnosis of acquired AL amyloidosis (9). Fibrinogen A alpha chain valine 526 is thus a surprisingly frequent cause of amyloidosis in the northern European population, and overall, the mutation has very low penetrance. Indeed, the typical patient with this form of hereditary amyloidosis does not give a family history. Most patients present in middle age with proteinuria or hypertension, and progress to end-stage renal failure within 4-8 years. Amyloid deposition occurs predominantly in the kidneys, but deposits in the spleen and sometimes the liver may also occur.

DIAGNOSIS OF HEREDITARY AMYLOIDOSIS

A hereditary etiology must be considered and a detailed family history sought in all patients with systemic amyloidosis of non-AA type. Immunohistochemistry using antibodies to serum amyloid A protein is a vital initial investigation in all patients with amyloidosis that can reliably confirm or exclude amyloid of AA type. However, immunohistochemistry is frequently non-diagnostic in AL amyloidosis and the mere presence of a monoclonal gammopathy does not prove that the fibrils are of immunoglobulin light chain type. Thirty one out of the 34 patients in whom hereditary amyloidosis was misdiagnosed as AL amyloidosis in our own series of 350 cases had amyloid of either variant transthyretin or fibrinogen A α chain type (9). Hereditary transthyretin amyloidosis presented with polyneuropathy and/or amyloid cardiomyopathy in each case, and we recommend that the gene for transthyretin should be sequenced in all patients with this phenotype. Clues to variant fibrinogen A α chain amyloidosis were its almost exclusively renal presentation coupled with a distinctive appearance on renal biopsy. This type of amyloid accumulates very selectively and substantially within the

glomeruli, but is characteristically absent from blood vessels and the interstitium. In marked contrast to AL amyloidosis, echocardiographic features of amyloid were not present in any patient with fibrinogen A α chain Glu526Val amyloidosis. Immunohistochemical staining of transthyretin, lysosyme, apolipoprotein AI and fibrinogen A alpha chain fibril proteins may require pre-treatment of sections with formic acid, alkaline guanidine or deglycosylation, and, even then, may not give definitive results in some cases. In addition, appropriate tissue and absorption controls are required to ensure specificity, and these are not generally available in most hospital laboratories. DNA analysis is therefore frequently required to confirm or exclude a diagnosis of hereditary amyloidosis, and is now performed routinely in patients attending the UK National Amyloidosis Centre. However, it remains essential to corroborate DNA findings by confirming one way or another that the respective protein is indeed the main constituent of the amyloid.

Treatment of hereditary amyloidosis

Hepatic transplantation is effective in familial amyloid polyneuropathy associated with transthyretin gene mutations since the variant amyloidogenic protein is produced mainly in the liver (33). Successful liver transplantation has now been reported in hundreds of patients with this condition and although the peripheral neuropathy usually only stabilizes, autonomic function can improve and the associated visceral amyloid deposits have been shown to regress in many cases. Important questions remain about the timing of the procedure but, so far, early intervention seems advisable. Disappointingly, there is evidence that wild-type transthyretin, an inherently but weakly amyloidogenic protein, may in some cases continue to be deposited after liver transplantation on an existing 'template' of amyloid in the heart and in the vitreous (34).

Fibrinogen is also synthesized only in the liver and hepatic transplantation therefore has a potential role in the management of hereditary fibrinogen A alpha chain amyloidosis (35). Successful, and most likely curative, liver transplants have been performed in a small number of these patients who have had unusually severe and early onset disease. However, renal support including renal transplantation offers most patients with hereditary fibrinogen A alpha chain amyloidosis an excellent quality of life.

The most common forms of hereditary apolipoprotein AI amyloidosis present with slowly progressive renal disease, which is probably managed optimally by renal transplantation. Although this does not alter the supply of the amyloidogenic precursor protein, which is produced in the liver and small intestine, renal and cardiac grafts are rarely damaged by 'recurrent' amyloid deposition in the medium to long-term (23, 36). Combined liver and renal transplantation was performed with very successful outcome in a patient with apolipoprotein AI arginine 26 who had liver and renal failure, the procedure providing unique confirmation that 50 percent of apolipoprotein AI and its variant are produced in the liver (37).

Hereditary lysozyme amyloidosis usually runs an exceptionally slow course, and patients with renal failure merit strong consideration for renal transplantation (38).

New therapeutic approaches

Improved understanding of the protein folding mechanisms underlying amyloid fibrillogenesis, and recognition that relative instability of the precursor molecules is a key factor in amyloidogenesis, have identified novel therapeutic possibilities. These include investigation of small molecules, peptides, and glycosaminoglycan analogues that bind to and stabilize fibril precursors, or interfere with refolding and/or aggregation into the cross-β core structure common to amyloid fibrils. Some of these agents have already been shown to be effective in experimental murine AA amyloidosis. Our own efforts to develop specific therapy are focused on the avid binding of SAP to amyloid fibrils which significantly contributes to pathogenesis of amyloidosis (3). The removal of SAP from amyloid deposits may facilitate their clearance, and we have identified a pharmacological compound that inhibits the SAP–fibril interaction, and which is presently being evaluated in clinical trials at the Royal Free Hospital (39).

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