Amyloidosis

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Secondary article

Article Contents

The amyloidoses are a group of β-structure protein deposition diseases that may be systemic or localized, sporadic, hereditary or associated with chronic inflammation. Pathology is the result of displacement of normal tissue structures.

Introduction

Amyloidosis refers to a number of protein deposition diseases in which normal or variant forms of proteins aggregate and form insoluble fibrils measuring 75–100 Å in cross-section and with indeterminant length. These fibrils characteristically have β-structure, are resistant to proteolysis, and accumulate in extracellular spaces. While tissue deposits of amyloid appear amorphous on routine histology, the ordered structure of the fibrils causes the deposits to have the crystalline property of birefringence and to bind specific histochemical dyes such as Congo red and thioflavin (**Figure 1**). These properties are commonly used to identify the pathological amyloid deposits in tissue sections. There are several types of amyloidosis. At least 18 different proteins have been identified as subunit proteins of amyloid fibrils and each is associated with a different disease process. **Table 1** lists the generally accepted nomenclature for most of the known amyloid precursor proteins and their respective diseases. It should be noted that some forms of amyloidosis are systemic and others are localized. In the systemic forms of amyloidosis the precursor protein is synthesized by one or more tissues (bone marrow, liver, intestinal mucosa, lymph nodes) and then transported via the blood to other areas of the body where the amyloid deposits can form. Therefore, all vascular organs including liver, kidney, spleen, heart, joints, muscles and gastrointestinal tract are often involved in the systemic forms of amyloidosis. The brain, however, is usually not involved, except for vascular structures, because of the presumed blood–brain barrier to plasma proteins. Localized forms of amyloidosis are usually associated with synthesis of the amyloid precursor protein in a specific organ and deposition of fibrils within that same organ. Localized forms of amyloidosis include Alzheimer disease (β-peptide), the prionoses (PrP), medullary carcinoma of the thyroid (procalcitonin), type II diabetes mellitus (amyloid-associated polypeptide (IAPP) or amylin).

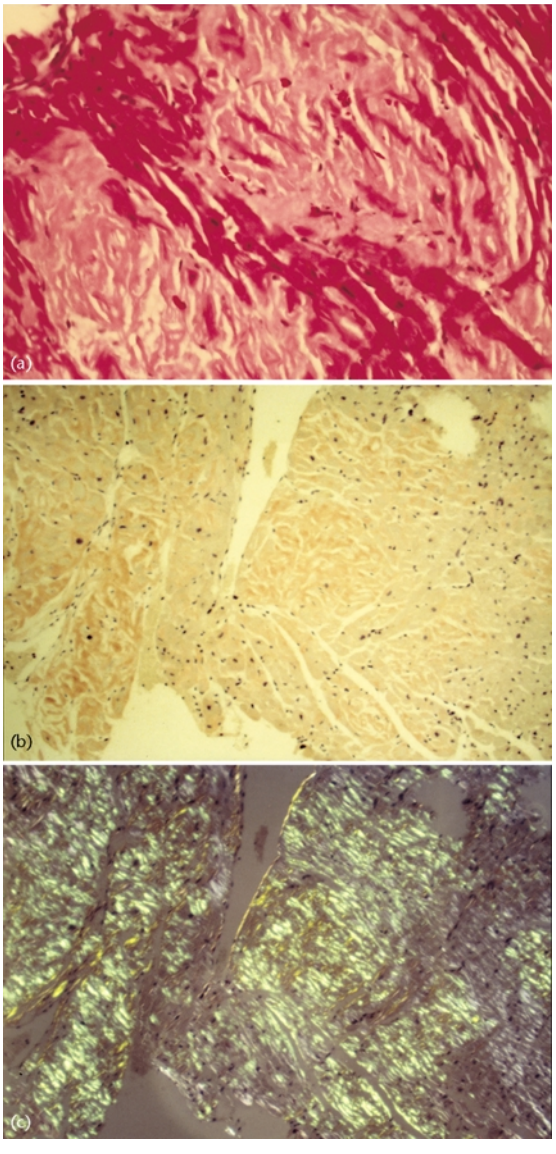

Figure 1 Histological sections of an endomyocardial biopsy from a patient with amyloid cardiomyopathy. (a) Amyloid deposits are eosinophilic and disrupt normal myocardial fibres (haemotoxylin and eosin). (b) Amyloid deposits have an affinity for Congo red. (c) Same section as in (b) in polarized light showing green birefringence characteristic of Congo red-stained amyloid fibril deposits.

Systemic Amyloidosis

There are four major types of systemic amyloidosis (**Table 2**). They represent a greater number of disease

Table 1 Standardized nomenclature for amyloid and amyloidosis

Amyloid protein[a]	Protein precursor	Protein type of variant	Clinical
AA[b]	SAA		Reactive (secondary), familial Mediterranean fever, familial amyloid nephropathy with urticaria and deafness (Muckle–Wells syndrome)
AL	Kappa, lambda (e.g. κIII)	Aκ, Aλ, (e.g. AκIII)	Idiopathic (primary), myeloma-associated or macroglobulinaemia-associated
AH	IgG 1 (γ1)	Aγ1	
ATTR	Transthyretin	e.g. Met30[c] e.g. Met111	Familial amyloid polyneuropathy (Portuguese) Familial amyloid cardiomyopathy (Danish), systemic senile amyloidosis
AapoAI	apoAI	Arg26	Familial amyloid polyneuropathy (Iowa)
AGel	Gelsolin	Asn187[d](15)	Familial amyloidosis (Finnish)
ACys	Cystatin C	Gln68	Hereditary cerebral haemorrhage with amyloidosis (Icelandic)
AFib	Fibrinogen Aα chain	e.g. Leu554	Hereditary renal amyloidosis
ALys	Lysozyme	e.g. His	Nonneuropathic hereditary amyloidosis
Aβ	β protein precursor (e.g βPP_{695}[e]) Gln693(22)		Alzheimer disease, Down syndrome, hereditary cerebral haemorrhage amyloidosis (Dutch)
$A\beta_2M$	β_2-microglobulin		Associated with chronic dialysis
AprP	PrP^c-cellular prion protein	PrP^{Sc}, PrP^{CJD}	Scrapie, Creutzfeldt–Jakob disease, kuru
		e.g. P102L, A117V, F198S, Q217R	Gerstmänn–Sträussler–Scheinker syndrome
ACal	(Pro)calcitonin	(Pro)calcitonin	Medullary carcinoma of the thyroid
AANF (atrial natriuretic factor)			Isolated atrial amyloid
AIAPP (islet amyloid polypeptide)			Islets of Langerhans, diabetes type II, insulinoma

[a] Nonfibrillar proteins, e.g. protein AP (amyloid P-component) excluded.
[b] Abbreviations not explained in table: AA, amyloid A protein; SAA, serum amyloid A protein; apo, apolipoprotein; L, immunoglobulin light chain; H, immunoglobulin heavy chain.
[c] ATTR Met30 when used in text.
[d] Amino acid positions in the mature precursor protein. The position in the amyloid fibril protein is given in parentheses.
[e] Number of amino acid residues.
Modified from Husby G, Araki S, Benditt EP *et al.* (1990) The 1990 guidelines for nomenclature and classification of amyloid and amyloidosis. In: Natvig JB, Forre O, Husby G *et al.* (eds) *Amyloid and Amyloidiosis 1990*, VIth International Symposium on Amyloidosis, August 5–8, 1990, pp. 7–11. Dordrecht, Netherlands: Kluwer Academic Publishers.

Table 2 Systemic amyloidoses

Type	Subunit protein	Distinguishing feature
Immunoglobulin (AL)	Ig light chains (κ or λ)	Monoclonal immunoglobulin
Reactive (AA)	Amyloid A	Inflammatory disease
β_2-Microglobulin (β_2M)	β_2-Microglobulin	Renal dialysis
Hereditary	Transthyretin	Autosomal dominant
	Apolipoprotein A-I	
	Gelsolin	
	Fibrinogen	
	Lysozyme	
	Cystatin C	

states, however, since hereditary amyloidosis may be caused by mutations in several different proteins, and each represents a separate disease entity (Benson, 1995). Each major type of amyloidosis has a unique aetiology, with varying pathophysiology, treatment and clinical prognosis. Therefore, each needs to be considered separately.

Immunoglobulin light chain (AL) amyloidosis

This is the most common type of systemic amyloidosis. It is a sporadic disease with increasing incidence with age; true incidence is difficult to estimate because diagnosis is often not made prior to death and post-mortem studies are now performed infrequently. The incidence, based on case studies in the United States, probably approaches 1 in 100 000.

AL amyloidosis is the result of amyloid fibril formation from fragments of monoclonal immunoglobulin light chain proteins (kappa or lambda) (Glenner, 1980). Fibril deposition, which is extracellular, may occur in any vascular organ and pathology is related to the organ involved and the degree of deposition. The most prevalent and morbid clinical syndromes are nephrotic syndrome followed by progressive azotaemia, restrictive cardiomyopathy with low output heart failure, and hepatomegaly with subsequent hepatic decompensation. Polyneuropathy, carpal tunnel syndrome, gastrointestinal haemorrhage, pulmonary nodules or infiltrates, macroglossia, purpura, and cardiac arrhythmias are also commonly seen in varying combinations.

AL amyloidosis is the result of a monoclonal immunoglobulin dyscrasia. It may occur in patients with multiple myeloma, Waldenström macroglobulinaemia or B-cell lymphoma, but most AL amyloid patients have a benign monoclonal gammopathy (BMG) or monoclonal gammopathy of unknown significance (MGUS). The basic requirement for amyloid is overproduction of monoclonal immunoglobulin with a light chain protein that is capable of forming β-structured fibrils (**Figure 2**). The monoclonal immunoglobulin synthesis may be the result of malignant transformation of a B-cell clone or expansion of a plasma-cell clone without malignant features. It is assumed that the overproduction of monoclonal immunoglobulin leads to cellular inability to adequately catabolize the protein, so that it is available for fibril formation. It is also assumed that the primary structure of the immunoglobulin light chain (LC) protein is an important factor in amyloid formation, since lambda (λ) LC proteins are more frequently associated with amyloid than are kappa (κ) light chains. Within the λ subgroups, λII and λVI proteins are more frequently found in amyloid cases than would be expected from the normal prevalence of these proteins in plasma. This classification of κ and λ LC proteins is based upon primary amino acid structure. Factors associated with AL amyloid deposition in specific organs have not been identified. Clinically, renal and cardiac amyloidosis

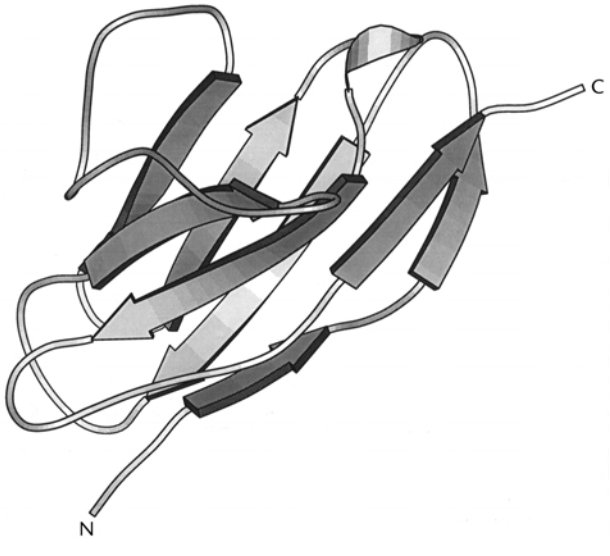

Figure 2 Computer graphic model of a κI amyloid light chain variable region protein (V_L) based on X-ray crystallographic diffraction data of V_L protein produced by recombinant DNA technology. This model has eight β strands in two planes with extensive hydrogen bonding.

are the most frequent, but organ involvement seems not to be related to structure of the LC protein. It is possible that individualized tissue factors may play a role in this phenomenon.

Lifespan after diagnosis of AL amyloidosis varies with extent and degree of organ involvement, but median survival in most series is 1–2 years. Five-year survival is approximately 20%. Nonspecific treatment of organ failure can significantly prolong the life of patients with cardiac failure, cardiac arrhythmias and renal failure, but the disease is usually progressive. Specific therapy is aimed at decreasing the aberrant plasma cell clone that produces the amyloid precursor protein. The most frequently used chemotherapy has been with an alkylating agent (usually melphalan) plus corticosteroid (prednisone) given orally in 4- to 7-day courses every 6 weeks for 2 years as tolerated. Definite response to this therapy may occur, but in only a minority of cases, and it cannot be predicted. Trials of high-dose intravenous melphalan with autologous stem cell rescue have shown promise of greater response. The extent of amyloid progression at the time of presentation dictates whether bone marrow transplantation is a therapeutic option. Many patients with severely impaired hepatic, cardiac, pulmonary or renal function cannot withstand the rigours of this procedure.

Reactive (secondary) amyloidosis

Reactive amyloidosis is the result of overproduction and incomplete catabolism of serum amyloid A protein (SAA). SAA is an apolipoprotein synthesized mainly by the liver. There are physiologically two types of SAA. SAA proteins of one type (SAA1 and SAA2) are part of the acute-phase response to tissue injury. Plasma concentrations may increase from less than 3 μg/ml to over 500 μg/ml during infections or inflammatory diseases. The second type of SAA (SAA4) is synthesized in a constitutive fashion without variation with inflammatory state. Only the acute-phase SAA1 and SAA2 provide substrate for amyloid fibril formation. Usually acute-phase SAA, which in the human has 104 amino acid residues in a single polypeptide chain, is degraded to give an amino-terminal fragment (residues 1–76) that serves as the basic constituent of amyloid fibrils. There is often considerable heterogeneity at the carboxyl end of the fibril peptide with shorter and longer AA peptides present in the same fibril isolate.

The pathophysiology of reactive (AA) amyloidosis is similar to that of AL amyloid. Fibril deposition is extracellular and organ dysfunction is the result of displacement of normal tissues. Renal, hepatic and splenic amyloid deposition is more consistent in *AA amyloidosis* and significant cardiac amyloid is unusual. Amyloid peripheral neuropathy, which is often a part of AL or hereditary amyloidosis does not occur in AA amyloidosis. Macroglossia is not part of the syndrome. Death is usually from renal failure but, if dialysis is used to prolong life, liver amyloid deposition progresses to give hepatic failure. Occasionally traumatic rupture of the liver or spleen related to the friable nature of the amyloid-infiltrated organs will cause fatal haemorrhage. Gastrointestinal haemorrhage is frequently seen in this disease.

Prognosis is variable. Sometimes AA amyloidosis runs a progressive course over 1–2 years, but often several years may pass before renal function deteriorates to the level of dialysis or death. The incidence of AA amyloidosis is not known. It probably varies with the type of inflammatory disease and the genetic background of the affected subject. It is now uncommon to see AA amyloidosis associated with chronic tuberculosis or osteomyelitis. A greater number of subjects with AA amyloidosis have rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, or granulomatous colitis as the predisposing condition. Occasionally it is seen with cystic fibrosis, Gaucher disease and systemic lupus erythematosus or no evidence of any chronic inflammatory condition. Random gastrointestinal biopsies in Japanese patients with rheumatoid arthritis have shown approximately 8% incidence of AA amyloidosis, but only a fraction of this number has clinically significant consequences from the amyloid deposition. AA amyloidosis occurs in a majority of Sephardic Jews with familial Mediterranean fever (FMF) but only a minority of Armenians with FMF. This clinical observation suggests a role for other genetic factors in the pathogenesis of the disease. Most mammalian species and some birds can have AA amyloidosis and these have been used extensively to study reactive amyloidosis. In particular, the murine model in which amyloid is induced by repeated injections of casein or endotoxin has revealed many of the features of acute-phase SAA synthesis and pathogenesis of fibril formation.

Treatment of AA amyloidosis starts with control of the inflammatory predisposing condition. This is not always easy to accomplish, but anti-inflammatory and cytotoxic therapies have been shown to have some efficacy. Chlorambucil in patients with juvenile inflammatory arthritis has given positive results. Azathioprine is often used to slow the disease in adults with rheumatoid or other inflammatory arthritis. Colchicine, which prevents attacks of FMF, has been shown to prevent the occurrence of AA amyloidosis in that condition. However, its efficacy in AA amyloidosis secondary to other diseases is not proven.

β_2-Microglobulin amyloidosis

β_2-Microglobulin (β_2M) amyloidosis occurs in subjects treated with dialysis for end-stage renal disease of any type. Most affected subjects have been treated with haemodialysis for 7 or more years. A few have been treated with peritoneal dialysis. The amyloid deposits, which have a predilection for bone and articular structures, may also be found in organs such as the intestine and muscle. Carpal

Table 3 Mutant proteins associated with autosomal dominant systemic amyloidosis

Protein	Mutation	Clinical features	Geographic kindreds
Transthyretin	72 known so far	PN[a], cardiomyopathy, nephropathy, vitreal deposits	Worldwide
Apolipoprotein AI	Gly26Arg	PN[a], nephropathy	United States
	Leu60Arg	Nephropathy	England
	Trp50Arg	Nephropathy	England
	del60–71 insVal/Thr	Hepatic	Spain
	del70–72	Nephropathy	South Africa
	Leu90Pro	Cardiomyopathy, cutaneous, laryngeal	France
	Arg173Pro	Cardiomyopathy, cutaneous	United States
Gelsolin	Asp187Asn	PN[a], lattice corneal dystrophy	Finland, United States, Japan
	Asp187Tyr	PN[a]	Denmark, Czech Republic
Cystatin C	Leu68Gln	Cerebral haemorrhage	Iceland
Fibrinogen	Arg554Leu	Nephropathy	Mexico
	Glu526Val	Nephropathy	United States
	4904delG	Nephropathy	United States
	4897delT	Nephropathy	France
Lysozyme	Ile56Thr	Nephropathy, petechiae	England
	Asp67His	Nephropathy	England

[a]PN, peripheral neuropathy.

tunnel syndrome due to amyloid deposition is commonly the presenting feature of the disease. The clinical syndrome most frequently seen includes shoulder and hip pain related to infiltrative, cystic, erosive lesions of the articular structures. Amyloid fibrils may be seen in synovial fluid. Occasionally, spinal vertebrae may be destroyed by amyloid deposition; this can lead to spinal cord impingement.

Pathogenesis of this type of amyloidosis is related to markedly elevated β_2M plasma levels. This protein, which is the light chain portion of the major histocompatibility antigen (HLA) on all cell surfaces, is not adequately cleared from the plasma of patients with chronic renal insufficiency. It therefore serves as substrate for amyloid fibril formation as does monoclonal immunoglobulin light chain in AL amyloidosis. It should be recalled that β_2M is derived from the ancestral immunoglobulin domain gene and has extensive β-sheet structure as do all immunoglobulin domains.

Treatment for β_2M amyloidosis is directed toward lowering the plasma β_2M concentration. Renal transplantation will do this if accomplished successfully. High-flux dialysis membranes are now commonly used, but their efficacy in preventing this disease will take years to determine.

Hereditary amyloidoses

Several diseases are included in the classification of hereditary amyloidosis (**Table 3**) (Benson, 1995). They are all inherited as autosomal dominant traits and each of the hereditary systemic amyloidoses is caused by a structural change in a specific plasma protein that is capable of forming β-sheet fibrils. In most cases the structural change is a single amino acid substitution, but a few have amino acid deletions or aberrant peptides resulting from nucleotide gene deletions and shift of reading frame for the mRNA. The presently known proteins associated with hereditary systemic amyloidosis are listed in **Table 3**.

Mutations in plasma transthyretin are the most frequent cause of hereditary amyloidosis. To date, 72 amyloid-associated mutations have been described. All are single amino acid substitutions except one (ΔVal122), which is the deletion of three nucleotides in the transthyretin gene and therefore a loss of one amino acid residue in the mature protein.

Transthyretin is a plasma protein synthesized predominantly by the liver but also by the choroid plexus of the brain and retinal pigment epithelium of the eye. Transthyretin is a single polypeptide chain of 127 amino acid residues (coded by a gene on chromosome 18) that folds to produce extensive β-structure. The plasma protein is a tetramer of four identical monomers and has the physiological functions of transporting thyroid hormone, which binds in a central channel of the tetramer, and retinal binding protein – vitamin A – which binds to the surface of the tetramer (**Figure 3**).

The pathophysiology of transthyretin amyloidosis may be related to alterations in protein structure that affect molecular aggregation or metabolism of this major plasma protein (200–400 mg L^{-1}), which has a plasma residence time of only 1–2 days. A limited number of studies have suggested equal expression of normal and variant transthyretin alleles in subjects heterozygous for amyloid-associated mutations, but it is not known whether equal amounts of the allelic protein products are secreted by hepatocytes. As with other types of amyloidosis, pathology is related to the location and extent of extracellular fibril deposits and the tissue dysfunction that these deposits cause.

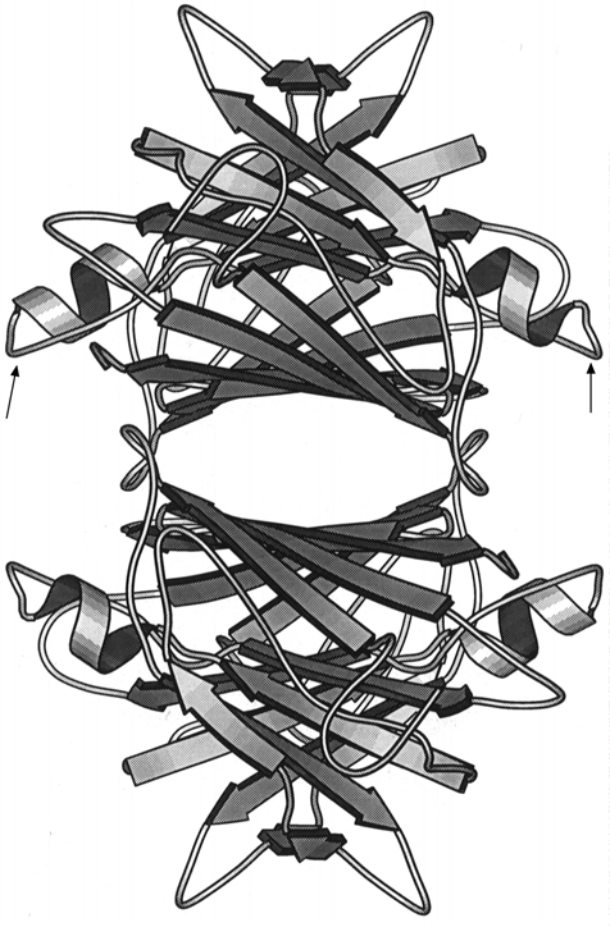

Figure 3 Computer graphic model of transthyretin tetramer. Thyroxine binds in the central channel and vitamin A–RBP binds on the surface of the tetramer. Each monomer has extensive β-sheet structure.

Clinically, transthyretin amyloidosis usually presents with progressive sensorimotor peripheral neuropathy affecting the longest fibres first. Carpal tunnel syndrome, a compression neuropathy at the wrist, may be an early indication of the disease. Restrictive cardiomyopathy is the most common cause of death, but some subjects die of renal amyloidosis or malnutrition due to bowel dysfunction. Liver and spleen are usually not significantly affected in this type of amyloidosis.

All of the transthyretin amyloid syndromes are adult-onset, most after age 50 years, but some present by age 30 and occasionally before age 20. Clinical disease course is usually 10–20 years with progressive organ dysfunction. Occasionally a rapid course of cardiac or renal failure may be seen, and some patients have fatal cardiac arrhythmia. Cardiac amyloidosis is most frequently seen and causes progressive restrictive cardiomyopathy, low-output failure and often supraventricular tachycardia late in the course. The terminal stage may be characterized by such low cardiac output that vital organs are not perfused sufficiently to sustain life.

The only specific treatment for transthyretin amyloidosis is liver transplantation. Since the sole source of plasma transthyretin is the liver, this procedure should be curative. There is, however, synthesis of transthyretin in the choroid plexus, which probably is the source of CSF transthyretin and therefore of leptomeningeal deposits, and in the retinal pigment epithelium, which probably leads to the frequently seen vitreal amyloid deposits. There is also concern that, after liver transplantation, normal transthyretin may be recruited to fibril formation on top of pre-existing deposits. There have been a few reports of senile cardiac amyloidosis caused by transthyretin amyloid deposition in the absence of a demonstrable transthyretin mutation, so the possibility of normal transthyretin continuing the fibril process after an affected individual has had liver transplantation is real. Since many individuals express transthyretin amyloidosis in later life (60–80 years), liver transplantation is often not a therapeutic option. Therefore, nonspecific therapy for the organ dysfunction caused by amyloid deposition is important. Cardiac pacing, renal dialysis and nutritional supplementation all may be necessary to enhance quality and duration of life. Most antiarrhythmic drugs have negative inotropic effects on the myocardium and may cause worsening of heart failure. They should be used only when absolutely necessary and then with caution. Maintenance of normal sinus rhythm, however, is important for diastolic filling and may require digitalis or electrical defibrillation. Predictive DNA testing and counselling are important for families with this disease

and can help contain the extensive clinical diagnostic testing that is often the result of difficulty in recognizing amyloid signs and symptoms.

The incidence of transthyretin amyloidosis is unknown, but may approach 1:100 000 in most populations. One mutation (Val30Met) is common in northern Portugal and northern Sweden population groups (perhaps 3%). Another mutation (Val122Ile) is present in nearly 4% of American blacks and is also present in some population groups in Africa.

Other types of hereditary amyloidosis give more defined clinical syndromes than does transthyretin. Mutations in gelsolin, a plasma actin-binding protein, cause lattice corneal dystrophy, cranial neuropathy and some degree of systemic amyloid deposition. The corneal amyloid deposits may appear in early adult life, but the disease in heterozygous individuals seems not to significantly shorten lifespan. A few homozygous subjects have been shown to have more severe rapidly progressing systemic amyloidosis with renal and cardiac involvement.

One mutation in cystatin C, a serine protease inhibitor, has been shown to cause leptomeningeal vascular amyloidosis that leads to death from repeated intracranial haemorrhage. Mild systemic amyloid deposition has been described. This disease is found principally in Iceland and has been named hereditary cerebral haemorrhage with amyloidosis (HCHWA).

Several mutations in apolipoprotein AI cause hereditary amyloidosis that usually affects the kidneys and liver. This is an autosomal dominant disease and all patients described so far have been heterozygous for a mutant form of apoAI. The amyloid deposits contain an amino-terminal peptide of apoAI (usually 83–93 residues) that evidently can assume β-structure to form fibrils. Native apoAI has mainly α-helix structure, so the pathogenesis of the disease must include major rearrangement of the fibril-forming peptide. The clinical course of apoAI amyloidosis may continue over a number of years. There is no specific therapy. ApoAI is synthesized by the liver and also the intestine, so the benefit of liver transplantation cannot be predicted. Renal dialysis has prolonged the life of some subjects.

Two mutations in lysozyme have been found to cause systemic amyloidosis. Hepatic and renal amyloid deposition and resultant organ failure are similar to the apoAI disease. Lysozyme is synthesized by polymorphonuclear leucocytes and macrophages. There is no specific therapy for this type of amyloidosis.

Four mutations in the gene for fibrinogen Aα chain are associated with amyloidosis that is predominantly expressed as nephropathy. Two are missense mutations that give single amino acid substitutions and two are single nucleotide deletions that cause a shift in reading frame of the mRNA and aberrant peptides. All are in the carboxyl portion of the Aα-chain protein. This is the protease-sensitive region of the protein, and it is assumed that the proteolytic peptide products containing 49–83 amino acid residues are capable of forming β-structure and being incorporated into fibrils.

The clinical syndrome is characteristic for this type of amyloidosis. First, there is hypertension, which may start in early adult life. This is followed by proteinuria and then progressive azotaemia usually over 5–10 years. If dialysis is instituted to save life, splenic and hepatic amyloid will progress. A few renal transplants have been performed in these patients. Amyloid appears in the grafted organ in as short a time as 1–2 years. The graft may function for 5–10 years. Two patients have received liver transplants with good results. Fibrinogen is synthesized exclusively by the liver and liver transplantation may well be curative. No data on incidence are available for this disease, but this diagnosis should be considered for any unknown type of hereditary amyloidosis with nephropathy in the absence of neuropathy and cardiomyopathy.

Diagnosis of Systemic Amyloidosis

The most important factor in making the clinical diagnosis of amyloidosis is to be aware of the various amyloid diseases. Unfortunately, this is rarely the case. Amyloidosis can cause a wide variety of syndromes that mimic part or all of the clinical features of other diseases. The combination of signs for multiple organ system abnormalities should raise the possibility of amyloidosis. Particularly the concomitant presence of cardiomyopathy and proteinuria or azotaemia in the patient should be suggestive. Peripheral neuropathy with cardiomyopathy, nephropathy or hepatic enlargement is frequently seen with systemic amyloidosis.

Diagnosis is made by biopsy of an affected tissue (e.g. heart, kidney, liver, nerve), but random intestinal biopsy (rectum, stomach, duodenum) will give the answer in 70–80% of cases. The majority of AL patients will have monoclonal immunoglobulin proteins detected by serum and urine electrophoresis. Most hereditary amyloid patients will have a family history of similar disease, although penetrance of the autosomal dominant amyloidoses is not 100%.

Localized Amyloidosis

Localized forms of amyloidosis include immunoglobulin light chain deposits in extramedullary plasmacytomas and in the respiratory and urinary tracts, β-peptide in Alzheimer plaques and blood vessels in the cerebral nervous system (Levy *et al.*, 1990), procalcitonin in medullary carcinoma of the thyroid, islet-associated amyloid peptide or amylin in islets of Langerhans of adult-onset diabetes mellitus and prion deposits in

Creutzfeld–Jacob and Gerstmann–Sträussler–Scheinker disease. There are also localized forms of amyloidosis in the pituitary (lactoferrin), cornea of the eye (keratoepithelium), aorta (apolipoprotein AI), cardiac atria (atrial natriuretic factor) and other conditions not yet characterized. Each is a separate pathological entity and are reviewed in the References and Further Reading. The amyloid fibril-forming process in each case probably represents a localized variation on the general theme of β-pleated sheet fibril synthesis, but with a unique amyloid precursor protein.

Summary

In summary, the amyloidoses should be considered as a variety of diseases or pathological states that share the common property of β-structured protein fibril deposition: the end result of the transition of homogeneous soluble protein to insoluble fibrils with ordered structure. Pathology is the result of displacement of normal tissues and disruption of their function. Diagnosis is by tissue biopsy. Treatment varies depending upon the type of amyloidosis but, unfortunately, is not often very gratifying for either the patient or the physician.

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