The diagnosis, natural history and treatment of amyloidosis.

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Amyloidosis is a heterogeneous disease characterised by extracellular deposition of certain proteins in a distinctive abnormal fibrillar form. The term amyloid is derived from the Greek for 'starch-like' and was coined in 1838 by Schleiden, a German botanist. Virchow described human disease as amyloid in 1858, noting at autopsy the starch-like properties of tissues from patients with what had previously been called 'waxy infiltration' or 'lardaceous disease'. Amyloid retained its name despite Freidreich and Kekulé identifying its largely proteinaceous composition the following year. Interestingly, Congo red staining, which has remained the histological gold standard, was used by Divry back in 1927 during studies on the cerebral amyloid plaques of Alzheimer's disease. The characteristic ultrastructure of amyloid fibrils was identified by Cohen and Calkins in 1959, since when enormous progress has been made with respect to the chemical composition, pathogenesis and properties of amyloid, which has led to significant advances in its clinical management.

Amyloid can be acquired or hereditary and the deposits can be focal, localised or systemic. Small amounts of amyloid may be incidental but systemic amyloidosis and some local forms have serious sequelae and are often fatal. Amyloid deposits consist mainly of protein fibrils, the peptide subunits of which differ in the different forms of the disease (Tables 1 and 2). The core structure and biophysical properties of all types of amyloid fibril are remarkably similar despite much chemical heterogeneity among their respective precursor proteins. Glicosaminoglycans, predominantly of heparan sulphate and dermatan sulphate type, are invariably associated with the fibrils. In addition, all amyloid deposits contain a minor non-fibrillar constituent, amyloid P component, a glycoprotein derived from the normal plasma protein serum amyloid P (SAP) component. SAP binds specifically to amyloid fibrils via a calcium-dependent interaction which is the basis for our development of radiolabelled SAP as a diagnostic nuclear medicine tracer.

Clinically significant amyloidosis is not rare. Cerebral amyloid deposits are a hallmark of Alzheimer's disease, whilst amyloid in the islets of Langerhans may contribute to the pathogenesis of type II diabetes mellitus. Symptomatic amyloid deposition in bones, joints and soft tissues eventually affects most individuals on long-term haemodialysis. Acquired systemic amyloidosis of AL type (formerly known as primary amyloidosis) arising in patients with monoclonal plasma cell dyscrasias, and of AA type (formerly known as secondary amyloidosis) associated with chronic inflammation, are important because of the difficulty in making the diagnosis and because effective treatments have become increasingly available. Hereditary amyloidosis is extremely rare, but is important as a model for studying the pathogenesis of amyloid.

Although no treatment is yet available that specifically causes amyloid deposits to regress, measures that reduce the supply of the respective amyloid fibril precursor protein can preserve organ function and improve a patient's survival. There have also been occasional case reports of regression of amyloid following control of underlying conditions. These observations, coupled more recently with the results of systematic serial radiolabelled SAP scintigraphy, indicate that amyloid is, in fact, a remarkably dynamic process and suggest that mobilisation of the deposits may be the usual mechanism through which clinical improvements occur.

The management of amyloidosis depends on the type, distribution and clinical effects of the deposits in each case. Supportive therapy, including dialysis and occasionally organ transplantation, is vital whilst every means to reduce the supply of the respective fibril protein precursor is considered. Under favourable circumstances further amyloid deposition will be prevented, existing deposits will regress and organ function will improve.

Pathogenesis of amyloidosis

The key event in amyloid fibril formation is a change in conformation of the respective precursor protein which facilitates its autoaggregation into the characteristic fibrils. In many situations the precursor proteins are evidently produced in abnormal abundance and/or with abnormal primary structure. Many of these proteins can form amyloid fibrils in vitro and in some instances the fibrils in vivo are composed of...
Table 1. Acquired amyloidosis syndromes.

| Clinical syndrome                                                                 | Fibril protein                                                                 |
|----------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| Systemic AL amyloidosis, associated with immunocyte dyscrasia, myeloma, monoclonal gammopathy, occult dyscrasia | AL fibrils derived from monoclonal immunoglobulin light chains                  |
| Local nodular AL amyloidosis (skin, respiratory tract, urogenital tract, etc) associated with focal immunocyte dyscrasia | AL fibrils derived from monoclonal immunoglobulin light chains                  |
| Reactive systemic AA amyloidosis, associated with chronic active diseases         | AA fibrils derived from serum amyloid A protein (SAA)                           |
| Senile systemic amyloidosis                                                       | Transthyretin (TTR) derived from plasma TTR                                     |
| Focal senile amyloidosis: atra of the heart                                       | Atrial natriuretic peptide                                                      |
| aldbrain                                                                            | β-protein                                                                       |
| joints                                                                             | Not known                                                                       |
| seminal vesicles                                                                  | Seminal vesicle exocrine protein                                                |
| prostate                                                                          | β2-microglobulin                                                                |
| Non-familial Alzheimer’s disease, Down’s syndrome                                 | β-protein derived from β-amyloid protein precursor (APP)                        |
| Sporadic cerebral amyloid angiopathy                                              | β-protein derived from β-amyloid precursor protein (APP)                        |
| Sporadic Creutzfeldt–Jakob disease, kuru (transmissible spongiform encephalopathies, prion diseases) | Prion protein (PrP) derived from prion protein precursor                        |
| Type II diabetes mellitus                                                         | Islet amyloid polypeptide (IAPP), amylin, derived from its precursor protein   |
| Endocrine amyloidosis, associated with APUDomas                                   | Peptide hormones or fragments thereof (eg precalcitonin in medullary carcinoma of thyroid) |
| Haemodialysis-associated amyloidosis; localised to osteoarticular tissues or systemic | β2-microglobulin derived from high plasma levels                                |
| Primary localised cutaneous amyloid (macular, papular)                            | ? Keratin-derived                                                              |
| Ocular amyloid (cornea, conjunctiva)                                              | Not known                                                                       |
| Orbital amyloid                                                                   | Not known; AH fibrils derived from immunoglobulin heavy chain in one case      |

intact whole precursor molecules. More often the precursors undergo partial proteolytic cleavage, although it is not known whether this occurs before, during or after they have formed amyloid fibrils.

Although the amino acid sequence of fibril precursor proteins appears to be an essential determinant of their amyloidogenicity, little is known about the factors that govern the anatomical distribution of the deposits or their clinical effects, and why certain forms of amyloid are deposited in some individuals but not in others. For example, only a minority of patients with chronic inflammatory disease ever develop AA amyloidosis, and this may occur at any time from about 18 months to many decades after the onset of the underlying disorder. In experimental murine AA amyloidosis, in which mice given inflammatory stimuli for three to six weeks consistently develop amyloid, the latent period can be reduced to two days in animals that have received an extract of amyloidotic tissue by intravenous injection. The precise nature of ‘amyloid-enhancing factor’ (AEF) has eluded characterisation, but it clearly promotes the off-pathway folding of fibril precursors into the abnormal amyloid conformation. Since amyloid is inherently rich in AEF, the conditions necessary for amyloid formation in vivo may be self-perpetuating once an initial core of amyloid material has been laid down, depending only on the continued supply of the respective fibril precursor protein.

Amyloidosis is usually progressive and this, along with evidence that the fibrils are relatively resistant to proteolytic degradation in vitro, has given rise to the popular assumption that amyloid deposition is irreversible. However, systematic radiolabelled SAP imaging studies in over 1,000 patients (see below) have lately shown that this is far from the truth and, in reality, amyloid deposits often regress quite rapidly if the supply of fibril precursors is reduced. Presumably, therefore, amyloid deposits are continuously turned over, but, without treatment, the rate of deposition usually exceeds the capacity for its removal.

Amyloid deposits probably exert most of their pathological effects directly through their physical presence. The normal tissue architecture is disrupted, impairing organ function or, occasionally, producing space-occupying effects. It remains conceivable that amyloid may also have cytotoxic effects, possibly by inducing apoptosis; this would be compatible with its damaging consequences in certain situations, such as Alzheimer’s disease and the prion disorders, in which amyloid is scanty, and also with the notable absence of necrosis and inflammation in amyloidotic tissue.
Amyloid P component and serum amyloid P component

All amyloid deposits contain a non-fibrillar glycoprotein constituent, amyloid P component (AP), which is identical to the normal circulating plasma protein SAP and remains in a dynamic equilibrium with it in vivo. SAP/AP is a calcium-dependent ligand-binding protein that binds avidly and specifically to DNA, to chromatin, to certain glycosaminoglycans, and to all types of amyloid fibrils including those produced in vitro from synthetic peptide. The three-dimensional structure of SAP has been solved at 2A resolution. Remarkably, the arrangement of β-strands in the SAP subunit is very similar to the subunit fold of concanavalin A and pea lectin, despite the absence of sequence homology. The structure of SAP is consistent with its known resistance to proteinases.

No deficiency or polymorphism of SAP has been identified and it has been highly conserved in evolution. SAP is produced only by hepatocytes and its plasma level of around 28 mg/l is tightly regulated, even during massive amyloid deposition. SAP is cleared from the circulation with a half-life of 24 hours that is not influenced by non-amyloid disease processes, and is catabolised only by hepatocytes. Once associated with amyloid fibrils in vivo, SAP persists unaltered until it dissociates from them and is replaced by another SAP molecule, returns to the plasma and becomes available for uptake and degradation in hepatocytes or for re-incorporation into amyloid. SAP may possibly protect amyloid fibrils from recognition and digestion by macrophages and other cells, and we have lately demonstrated that in vitro binding of SAP to amyloid fibrils does indeed confer on them striking resistance to proteolysis. This can be abrogated simply by dissociating SAP from the fibrils, suggesting a novel therapeutic approach.

Diagnosis of amyloidosis

The diagnosis of amyloidosis is made challenging by the diversity of its clinical features. Confirmation of the diagnosis traditionally rests upon Congo red

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Table 2. Hereditary amyloidosis syndromes.

| Clinical syndrome | Fibril protein |
|-------------------|----------------|
| Predominant peripheral nerve involvement, familial amyloid polyneuropathy (FAP). Autosomal dominant | Transthyretin (TTR) genetic variants (most commonly Met30, but over 50 others described) |
| Predominant peripheral nerve involvement, familial amyloid polyneuropathy (FAP). Autosomal dominant | Apolipoprotein AI (apoAI) N-terminal fragment of genetic variant Arg26 |
| Predominant cranial nerve involvement with lattice corneal dystrophy. Autosomal dominant | Gelsolin, fragment of genetic variant Asn187 or Tyr187 |
| Non-neuropathic, prominent visceral involvement (Ostertag-type). Autosomal dominant | ApoAI, N-terminal fragment of genetic variants Arg26, Arg50, Arg60, etc |
| Non-neuropathic, prominent visceral involvement (Ostertag-type). Autosomal dominant | Lysozyme genetic variant Thr56 or His67 |
| Non-neuropathic, prominent visceral involvement (Ostertag-type). Autosomal dominant | Fibrinogen α-chain, fragment of genetic variants Leu554 or Val526 |
| Predominant cardiac involvement, no clinical neuropathy. Autosomal dominant | TTR genetic variants Thr45, Ala60, Ser84, Met111, Ile122 |
| Hereditary cerebral haemorrhage with amyloidosis (cerebral amyloid angiopathy). Autosomal dominant | Cystatin C, fragment of genetic variant Glu68 |
| Icelandic type (major asymptomatic systemic amyloid also present) Dutch type | β-protein derived from genetic variant APP Gln693 |
| Familial Alzheimer’s disease | β-protein derived from genetic variant APP Ile717, Phe717 or Gly717 |
| Familial Creutzfeldt–Jakob disease, Gerstmann–Sträussler–Scheinker syndrome (hereditary spongiform encephalopathies, prion diseases) | β-protein derived from genetic variant APP Asn670, Leu671 |
| Familial Mediterranean fever, prominent renal involvement. Autosomal recessive | Prion protein (PrP) derived from genetic variants of PrP precursor protein 51-91 insert, Leu102, Val117, Asn178, Lys200 |
| Muckle–Wells syndrome, nephropathy, deafness, urticaria, limb pain | AA derived from SAA |
| Cardiomyopathy with persistent atrial standstill | AA derived from SAA |
| Cutaneous deposits (bullous, papular, pustulodermal) | Not known |
| Not known | Not known |
histology. Immunohistochemistry is useful for typing the amyloid, although it may not give a definitive result in AL amyloidosis. However, biopsies are usually small and provide little information on the extent of amyloid deposits generally or their natural history. The development of radiolabelled SAP for quantitative scintigraphy and metabolic analyses has therefore been welcome and has provided important new insights into the natural history of amyloidosis and its response to treatment.

Radiolabelled SAP as a specific tracer in amyloidosis

Radio-iodinated SAP binds to all types of amyloid fibril in a specific and reversible manner that enables amyloid deposits to be evaluated quantitatively and repeatedly in vivo (Fig 1). The tracer does not accumulate in healthy subjects or patients with non-amyloid diseases, in whom it is rapidly catabolised and the label excreted. However, in patients with amyloidosis, labelled SAP localises rapidly and specifically to the amyloid deposits, in proportion to their quantity, and persists there for long periods. Essentially, the localisation of labelled SAP to amyloid is a specific dilution phenomenon, in which circulating SAP and amyloid-associated SAP remain in equilibrium. In tracer studies, radiolabelled SAP is distributed proportionately between the 100 mg or so of SAP that is normally in the plasma and the typically far greater quantity, sometimes exceeding 20,000 mg, that is concentrated within the amyloid deposits. The reversible nature of the SAP–fibril interaction, and the ensuing constant equilibrium of SAP within amyloid and plasma, means that ligands for radiolabelled SAP are always available on amyloid fibrils, irrespective of whether amyloid is being deposited or mobilised, or is in a steady state.

Highly purified SAP is readily labelled with $^{125}$I for scintigraphic imaging, and the long half-life isotope $^{125}$I for metabolic turnover studies. $^{131}$I has also been used for extended metabolic studies, but is less desirable for scintigraphy. Uptake of tracer into individual organs can be measured and, together with metabolic data on the plasma clearance and whole body retention of activity, the progression or regression of amyloid can be serially quantified and monitored (Table 3). Radiation doses are well within accepted

| Table 3. Applications of SAP scintigraphy. |
|------------------------------------------|
| Diagnosis and quantification of systemic and some local forms of amyloidosis |
| Identifying tissue distribution of amyloid deposits – may indicate type |
| Screening at-risk individuals for sub-clinical amyloid |
| Monitoring clinical and sub-clinical disease, ie natural history |
| Evaluating effects of therapy |

Fig 1. $^{125}$I-SAP scintigraphy in two young adults with systemic amyloidosis. On the left is an anterior whole body scan of a 26 year old man showing uptake of tracer into substantial liver, spleen and bone marrow amyloid, a distribution diagnostic of systemic AL amyloidosis. On the right is a posterior whole body scan showing AA amyloid deposits in the spleen, adrenals and kidneys of a 34 year old woman with rheumatoid arthritis. The presence and type of amyloid were corroborated histologically in both cases.
safety limits (effective dose equivalent ~3.5 mSv), and more than 1,500 studies have now been carried out on patients without adverse effects at Hammersmith Hospital and some 20 other centres).

Histology and SAP scintigraphy are complementary methods for demonstrating the presence of amyloid. SAP scintigraphy is non-invasive and provides a macroscopic survey of the whole body, whereas histology can reveal microscopic deposits but cannot quantify the whole body amyloid load or be used for monitoring changes in the deposits.

Management of amyloidosis

Until there is a treatment that specifically causes amyloid deposits to regress, therapy aims to reduce the supply of amyloid fibril precursor proteins in the hope that this will retard the progression of disease. However, few clinical trials have been performed and the approach to treatment remains somewhat empirical. Radical approaches may be justified when the prognosis is poor (Table 4), and substantial responses can be obtained in terms of preservation/restoration of organ function and improved survival. Speculation that amyloid deposits may regress under these circumstances has been confirmed using SAP scintigraphy in AA, AL, AA1516, AL1517,20, β₂-microglobulin (β₂M)22 and variant transthyretin (TTR)19 amyloidosis. Since the regression of amyloid is gradual, clinical improvement after therapy may be delayed for many months.

Supportive therapy remains critical for prolonging survival whilst therapy can be directed against the underlying process. Renal dialysis may be necessary and cardiac and other transplant procedures are indicated in selected cases. Surgical resection of amyloidotic tissue is occasionally beneficial but, in general, a conservative approach to surgery, anaesthesia or any invasive procedure is best. Meticulous attention to blood pressure and fluid balance is essential, especially in patients with renal and/or cardiac involvement. Amyloidotic tissues may heal poorly and are liable to haemorrhage. Diuretics and vasoactive drugs can reduce cardiac output substantially in cardiac amyloidosis.

Reactive systemic (AA) amyloid

AA amyloid fibrils are derived from serum amyloid A (SAA) protein and AA amyloidosis may occur in any patient with a sustained acute phase response. Many chronic inflammatory, infective and neoplastic disorders have been implicated but in the United Kingdom inflammatory rheumatic disease is the commonest predisposing condition. Five to ten per cent of patients with rheumatoid arthritis (RA) and juvenile chronic arthritis (JCA) are affected and the few treatment studies of AA amyloidosis that have been performed are in this setting25-27. The aim of therapy is to suppress the underlying disease and hence reduce acute phase synthesis of SAA. This will involve a range of medical and even surgical treatments in different diseases and frequent estimation of the plasma SAA level is highly desirable.

Scintigraphy with 123I-labelled SAP is extremely sensitive and specific in AA amyloidosis13. In 150 cases the spleen was always involved at an early stage and renal amyloid was visualised at presentation in most patients. Adrenal amyloid deposits were evident in about 40% of cases. Hepatic involvement is a late feature that carries a poor prognosis. Serial studies have confirmed that AA amyloidosis is progressive in most patients whose inflammatory disease remains active, albeit at remarkably variable rates. In some patients with persistent inflammatory disease, the amyloid load can level out, a phenomenon that may occur before the deposits have produced any overt clinical features.

Among patients whose inflammatory disease remitted, follow-up scans over two to three years have shown that AA amyloid deposits are fairly stable in up to one-half of cases but decrease, often substantially, in the remainder16. Although the amount of amyloid in an organ correlated poorly with impairment of function, regression of the deposits was usually associated with clinical improvement unless organ failure was very advanced. In particular, renal failure progressed inexorably in most individuals whose serum creatinine concentration exceeded 200–250 mmol/l before treatment.

These results indicate that amyloid turns over rapidly

### Table 4. Reducing the supply of fibril precursors in systemic amyloidosis.

| Disease                     | Aim of treatment                                      | Example of treatment                                      |
|-----------------------------|-------------------------------------------------------|-----------------------------------------------------------|
| AA amyloid                  | Suppress acute phase response                         | Immunosuppression in rheumatoid arthritis, Still’s disease (chlorambucil). Colchicine for familial Mediterranean fever, even if clinical episodes not fully suppressed. Surgery for osteomyelitis, and rare cytokine-producing tumours |
| AL amyloid                  |Suppress production of monoclonal immunoglobulin light chains | Chemotherapy for myeloma and monoclonal gammopathy         |
| Hereditary amyloidosis      | Eliminate source of genetically variant protein       | Orthotopic liver transplantation for variant transthyretin-associated familial amyloid polyneuropathy |
| Haemodialysis amyloidosis   | Reduce plasma concentration of β₂M                   | Renal transplantation                                      |
in some individuals. However, even in patients whose amyloid does not regress appreciably following prolonged remission from inflammatory activity, the function of affected organs may return to normal. Occult amyloid deposits may have important implications in such patients should they become pregnant, undergo surgery or acquire serious infections, because of the continued risk of bleeding, poor tissue healing and susceptibility to developing acute renal failure.

Monoclonal immunoglobulin (AL) amyloidosis

In AL amyloidosis the fibrils are derived from monoclonal immunoglobulin light chains. Most patients have relatively subtle monoclonal gammopathies, which in one-fifth of cases may completely evade characterisation; only about 15% of the 250 patients seen in our unit fulfilled the criteria for multiple myeloma. Most patients with AL amyloid are over 50 years of age, but young adults are occasionally affected. Almost any organ other than the brain can be directly involved. Significant cardiac involvement is frequent and most patients die of heart failure, renal disease or some other effect of amyloid within 6–24 months of diagnosis. Contrasting sharply with AA amyloidosis, clinical involvement of the skin, muscles, nerves, joints and gut is common.

Treatment is aimed against the underlying plasma cell dyscrasia but there are many difficulties. Subtle plasma cell dyscrasias may respond poorly to myeloma-based chemotherapy regimens and many patients have advanced multi-system disease. An early response to treatment cannot be measured in patients whose monoclonal gammopathies are too subtle to quantify. As a result, many patients die before traditional low intensity cytotoxic regimens can produce their beneficial effects. About 20% of patients with AL amyloidosis respond well to one year’s treatment with monthly cycles of low dose melphalan and prednisolone given by mouth. Dose-intensive chemotherapy regimens such as vincristine, doxorubicin (Adriamycin) and dexamethasone (VAD), and autologous peripheral blood stem-cell transplantation, are presently being evaluated, with more promising early results (Fig 2).

Among 250 patients with systemic AL amyloidosis, labelled SAP studies have shown that the deposits are much more heterogeneous than the AA type with respect to their distribution and quantity. Diagnostic scans were obtained in 85% of patients, most negative results being obtained when the deposits were scanty, for example in peripheral nerves, or were mainly confined to the heart or to diffuse structures such as the skin and muscles. Follow-up studies, performed six-monthly for at least one year, were obtained in 44 patients, of whom 40 underwent chemotherapy (low intensity oral alkylating drugs, 21 cases; dose intensive regimens, principally VAD, 19 cases). The amyloid deposits were stable in over three-quarters of the

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**Fig 2.** Serial posterior whole body SAP scans in a man who presented with nephrotic syndrome and renal impairment due to systemic AL amyloidosis. The renal amyloid deposits visualised at presentation (left) had regressed substantially three years later (right) following VAD (vincristine, Adriamycin, doxorubicin) chemotherapy, associated with recovery of normal renal function. The remainder of the images represents a normal blood-pool background signal, the level of which is inversely proportional to the whole body load of amyloid.
treated patients overall, and regressed in one-third of the intensively treated cases.

Cardiac transplantation should be considered in patients who have severe cardiac amyloidosis, but who otherwise have a good prognosis. Our approach to this problem was influenced by the favourable clinical course of a physician colleague, Professor Reginald Hall, who underwent cardiac transplantation for AL amyloidosis in 1984. Despite the presence of amyloid in his liver and kidneys, the procedure was successful and he subsequently underwent a modified 'ABCM' myeloma chemotherapy regimen. The resulting prolonged remission of his sublte underlying plasma cell dyscrasia facilitated substantial regression of his systemic amyloid deposits. Nearly 10 years after the transplant he delivered a unique account of his case at the Hammersmith Hospital Staff Round. Cardiac transplantation can therefore provide a vital window of opportunity in selected patients during which chemotherapy can produce its desired effect. We believe that preserved function of other vital organs and the absence of myeloma are more important factors than evidence of extra-cardiac amyloid deposits per se in considering whether cardiac transplantation might be appropriate in patients with amyloidosis.

**Dialysis-related (β₂M) amyloid**

Almost all patients on long-term haemodialysis develop β₂M amyloidosis. β₂M is normally metabolised in the kidney, and since the protein is not cleared significantly during dialysis, its plasma concentration rises substantially in patients with renal failure. The prevalence of symptomatic dialysis-related amyloidosis (DRA) increases with the duration of dialysis, affecting virtually all patients after 20 years. Older patients develop symptoms more rapidly. The amyloid deposits are predominantly osteoarticular and are associated with carpal tunnel syndrome, arthralgia, soft tissue masses, bone cysts and pathological fractures. Fatal systemic β₂M amyloidosis can occur. DRA also occurs in patients on continuous ambulatory peritoneal dialysis and has even been reported in patients with progressive renal failure who have never been dialysed.

Arthralgia due to β₂M amyloidosis may respond partially to non-steroidal anti-inflammatory drugs or corticosteroids, but even the most severe symptoms usually melt away after successful renal transplantation. The mechanism underlying such rapid improvement is not clear and, certainly, there is no evidence that the amyloid deposits regress over so short a time. Although anti-rejection steroid therapy may have a role, symptoms of DRA continue to improve in most transplanted patients even when steroids are eventually withdrawn. Although β₂M amyloid has been identified histologically many years after renal transplantation, and the associated radiological bone cysts persist, follow-up SAP scintigraphy has shown that the progression of articular amyloid is halted and that after five years some regression of β₂M amyloid can be found in nearly all cases.

**Hereditary amyloidosis and familial amyloid polyneuropathy**

Familial amyloid polyneuropathy (FAP) is the commonest form of hereditary amyloidosis. The amyloid is composed of variant forms of TTR, associated with 59 different TTR mutations. FAP is an autosomal dominant syndrome with onset at any time from the second decade, characterised by peripheral and autonomic neuropathy and varying degrees of visceral amyloid involvement. Major foci of FAP occur in Portugal, Japan and Sweden and occasional kindreds have been reported throughout the world. Although there is much variation in age of onset, rate of progression and involvement of different organ systems, FAP is almost always fatal within 5-15 years.

Treatment of FAP has lately been revolutionised by liver transplantation. Knowledge that the liver was probably the main source of circulating TTR prompted the group in Umeå, northern Sweden, to perform the first orthotopic hepatic transplant in a patient with FAP in 1990. Variant TTR disappeared from the plasma and, within one to two years, three out of the first four transplanted patients experienced improved general well-being, walking ability and bowel function. Successful liver transplantation for FAP has since been reported in hundreds of patients by many other centres. Autonomic function often improves substantially although the peripheral neuropathy usually only stabilises. Rehabilitation may be very slow and postoperative renal dysfunction occurs in up to 20% of cases.

SAP scintigraphy in over 50 patients with FAP has shown that although the small neural amyloid deposits could not be imaged, almost all patients had significant visceral amyloid involvement, usually affecting the kidneys and sometimes the spleen and adrenal glands. Amyloid regressed at varying rates in nine out of ten transplanted patients. Important questions remain about the timing and long-term outcome of the procedure but, so far, early intervention seems advisable.

**Cerebral amyloidosis, Alzheime’s disease and transmissible spongiform encephalopathy**

The brain is a common and important site of amyloid deposition although it is not directly affected in any form of acquired systemic amyloidosis. In FAP, clinically silent cerebrovascular deposits may occur and hereditary dementia with ataxia and spasticity has lately been reported in association with meningocerebrovascular TTR Gly18 amyloidosis. Conversely, all forms of brain amyloid are confined to the brain and cerebral blood vessels with the single exception of...
cystatin C amyloid in hereditary cerebral haemorrhage with amyloidosis, Icelandic type.

Intracerebral and cerebrovascular amyloid deposits are neuropathological hallmarks of Alzheimer’s disease. Most cases are sporadic but hereditary forms are caused by mutations in either the gene for the cerebral amyloid precursor protein, β-amyloid precursor protein (APP)\(^1\), or the recently characterised presenilin genes \(S182\) and \(STM2\). All of these mutations lead to increased abundance of the amyloidogenic A\(β\) 1-42 fragment of APP. However, the pathogenesis of Alzheimer’s disease is far from understood and it remains unclear whether or how the APP per se, or the amyloid fibrils formed by its A\(β\) fragment, contribute to the neuronal damage.

The neuropathology of the transmissible and, in some cases, hereditary spongiform encephalopathies also sometimes includes intracerebral amyloid plaques and cerebral amyloid angiopathy. These fatal disorders, Creutzfeldt–Jakob disease, Gerstmann–Sträussler–Scheinker syndrome and kuru, are closely related to the animal diseases: scrapie of sheep and goats, transmissible encephalopathy of mink, elk and male deer, and bovine spongiform encephalopathy\(^5\). The agents that cause these diseases are known as prions. The prion precursor protein (PrP\(^c\)) is a normal widely distributed molecule that can undergo a change in conformation to become a protease-resistant amyloid form, designated PrP\(^\text{sc}\). This material is the transmissible agent of the spongiform encephalopathies and may accumulate sufficiently to be identified histologically as amyloid. The change from normal autologous PrP\(^c\) to pathogenic PrP\(^\text{sc}\), which may occur by chance in sporadic prion disease, is promoted either by inoculation with transmitted PrP\(^\text{sc}\) or by genetic variants of PrP\(^c\). The mechanism(s) by which this process causes the disease are not known and may include interference with the as yet undefined normal role of PrP\(^c\).

Conclusions and prospects for the future

Despite the major progress in biochemical and clinical knowledge of amyloidosis, there is still no treatment that specifically disperses amyloid deposits. Supportive measures therefore remain an essential mainstay of management in systemic amyloidosis, particularly with respect to renal and heart failure, which are frequent causes of death. Encouragingly, however, scintigraphy with labelled SAP has confirmed that amyloid deposits regress in a substantial proportion of patients in whom the supply of the respective amyloid fibril precursor protein can be reduced, and this is often associated with improvement in the function of affected organs. Since this strategy is not possible in some types of amyloidosis and may fail in others, new approaches to inhibit the formation, persistence and/or effects of amyloid deposits are urgently required. The recent surge of interest in cerebral amyloidosis may hasten the fulfilment of these goals.

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