Human brain amyloidoses

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Introduction

Several diseases affecting the central nervous system (CNS) of humans result from the formation of a substance, named amyloid. Amyloid currently identifies aggregates of an insoluble protein which (i) generally occupy the extracellular space, (ii) are birefringent under polarized light, (iii) react with the Congo red histological stain, (iv) have a β-sheet secondary structure, (v) are fibrillary with an extensive antiparallel β-sheet strands quaternary structure, and (vi) are associated with other proteins presumed to be chaperones [1]. At least five biochemically distinct amyloids are known to affect the human CNS (Table 1). The amyloidoses due to the aggregation of the amyloid β peptide (Aβ), which include Alzheimer’s disease (AD), Down’s syndrome (DS) and the hereditary cerebral haemorrhage with amyloidosis (HCHWA)-Dutch type, and the amyloidoses due to aggregation of the prion protein (PrP), which include the Gerstmann–Sträussler–Scheinker disease (GSS), some variants of the Creutzfeldt–Jakob disease (CJD) and Kuru, are by far the most common. However, amyloidomas and transthyretin amyloidosis have also been reported. Recent advances in the understanding of neurodegenerative diseases such as Parkinson’s disease, amyotrophic lateral sclerosis and Huntington’s disease, and several forms of complex systemic degenerations, point to an amyloidogenic process as the central event in the pathogenesis of these diseases [2–5]. Therefore, the chapter of the human brain amyloidoses is likely to expand and to include many degenerative diseases of the nervous system in the near future.

This review summarizes the salient clinical and pathological features of the brain amyloidoses with special emphasis on the data obtained by our group. Some of the mechanisms involved in the pathogenesis of AD and prion disease are also briefly discussed.

Brain amyloidomas

Amyloid may deposit in the brain in the form of relatively large aggregates acting like space-occupying lesions, called amyloidomas [6–16]. Twelve cases have been reported to date (Table 2). The mean age at presentation is 54 years (range 28–76 years). The common clinical presentation is characterized by cognitive decline, seizures and signs of increased intracranial pressure. One case remained asymptomatic [10]. The location within the brain is variable but it is most commonly supratentorial and it involves the frontal and occipital lobes. In one case, the amyloidomas were located in the cerebellum and pons [11]. The amyloidomas may be single or multiple and present sizes that may vary between 0.5 and 8 cm in diameter. In the subject observed by us, the amyloidomas formed nodular masses of variable sizes far in excess of those detected with the magnetic resonance imaging (MRI) examination [11]. The amyloidomas were surrounded by cells identified as microglia which often showed intimate contact with the amyloid through digitating processes projecting into the amyloidoma [11]. Plasma cells were often seen around but not in contact with the amyloid. Immunocytochemistry indicated that the plasma cells contained λ light chains, and immunoelectrophoresis of the cerebrospinal fluid (CSF) demonstrated a monoclonal IgG-λ with free λ light chains, consistent with the presence of an aberrant clone of plasma cells within the CNS [11]. Immunohistochemistry as well as amino acid sequence analysis of amyloid fibrils purified from the amyloidomas demonstrated that the amyloid protein is an unusual immunoglobulin λ light chain, starting at

### Table 1. Amyloidoses of the central nervous system

<table>
<thead>
<tr>
<th>Disease</th>
<th>Amyloid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amyloidomas</td>
<td>Multiple myeloma-associated AL</td>
</tr>
<tr>
<td>Oculoleptomeningeal A</td>
<td>Transthyretin</td>
</tr>
<tr>
<td>Meningocerebrovascular A</td>
<td>Transthyretin</td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td>Amyloid β protein</td>
</tr>
<tr>
<td>Down’s syndrome</td>
<td>Amyloid β protein</td>
</tr>
<tr>
<td>HCHWA-Dutch type</td>
<td>Amyloid β protein</td>
</tr>
<tr>
<td>HCHWA-Icelandic type</td>
<td>Cystatin C</td>
</tr>
<tr>
<td>Transmissible spongiform</td>
<td>Prion protein</td>
</tr>
<tr>
<td>encephalopathy</td>
<td></td>
</tr>
</tbody>
</table>

*Hereditary cerebral haemorrhage with amyloidosis.
Table 2. Intraparenchymal amyloidomas

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yr)</th>
<th>Presentation</th>
<th>Location</th>
<th>Amyloid type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saltykow [6]</td>
<td>NR</td>
<td>Psychiatric</td>
<td>Cortex and white matter</td>
<td>ND</td>
</tr>
<tr>
<td>Harris and Rayport [7]</td>
<td>28</td>
<td>Focal seizures</td>
<td>Frontal white matter</td>
<td>ND</td>
</tr>
<tr>
<td>Spaar et al. [8]</td>
<td>46</td>
<td>Visual loss</td>
<td>Occipital white matter</td>
<td>ND</td>
</tr>
<tr>
<td>Townsend et al. [9]</td>
<td>28</td>
<td>Focal seizures</td>
<td>Frontal white matter</td>
<td>ND</td>
</tr>
<tr>
<td>Case 1</td>
<td>47</td>
<td>Cognitive decline</td>
<td>Frontal white matter</td>
<td>ND</td>
</tr>
<tr>
<td>Hori et al. [10]</td>
<td>50</td>
<td>Visual field defect</td>
<td>Occipital white matter, basal ganglia</td>
<td>ND</td>
</tr>
<tr>
<td>Cohen et al. [11]</td>
<td>60</td>
<td>Asymptomatic</td>
<td>Extensive white matter, including left</td>
<td>AL</td>
</tr>
<tr>
<td>Eriksson et al. [12]</td>
<td>60</td>
<td>Seizures</td>
<td>Right parietal</td>
<td>AL</td>
</tr>
<tr>
<td>Linke et al. [13]</td>
<td>61</td>
<td>Mental deterioration seizures</td>
<td>Frontal white matter</td>
<td>AL</td>
</tr>
<tr>
<td>Lee et al. [14]</td>
<td>70</td>
<td>Hemiparesis, hemiataxia</td>
<td>Right parieto-occipital region</td>
<td>AL</td>
</tr>
<tr>
<td>Schroeder et al. [15]</td>
<td>71</td>
<td>Hemiparesis</td>
<td>Lateral ventricle above thalamus</td>
<td>ND</td>
</tr>
</tbody>
</table>

NR, not recorded.

Residue five of the variable domain [17]. The amyloid protein had a mol. wt of 10–30 kDa. The higher molecular weights probably arose from the polymerization of the 10 kDa subunit or sequential proteolytic cleavage of the light chain, or both [17]. Together, these data indicate that the amyloidomas in our observation contain primary myeloma-related amyloid (AL) which is most likely the product of an amyloidogenic plasmacytoma of the brain. This was the first identification of the protein component of a brain amyloidoma. AL amyloid has been found in subsequent cases of brain amyloidomas, suggesting that it may be the component of most if not all brain amyloidomas [12,13,15].

Transthyretin amyloidosis of the central nervous system

Autosomal dominant mutations in the gene of the plasma protein transthyretin (TTR), previously called pre-albumin, account for the majority of the human familial amyloidoses [18]. Over 60 distinct mutations resulting either in single or double amino acid substitutions have been reported [19–21]. By far the most common phenotype associated with mutations in the TTR gene is a condition identified as familial amyloidotic polyneuropathy [23]. Involvement of the CNS in TTR amyloidosis is very rare. Eight distinct mutations of the TTR gene have been reported to be associated with a familial amyloidosis which is characterized by amyloid deposition predominantly in the CNS and its coverings [22]. This disease entity has been designated familial oculeoleptomeningeal amyloidosis when the eye is also affected, or meningo-cerebrovascular amyloidosis when there is no eye involvement (Table 3) [23–25]. The involvement in most of these mutations is limited to the meninges, dura mater and/or leptomeninges and their vessels as well as the vessels of the brain, especially those at the or near to the surfaces (Table 3). Amyloid deposits in the brain parenchyma have been observed in only three TTR gene mutations. We had the opportunity to identify one of these three mutations, a point mutation resulting in the substitution of valine with glycine, and to study the disease phenotype in one affected kindred [22]. Clinically, the distinctive characteristics in this kindred are episodes of progressive motor deficits such as hemiparesis and ataxia, associated with progressive cognitive impairment, abnormal behaviour, seizures and headache. Decreased vision due to vitreous opacities is almost invariably present. Histopathologically, the hallmark is the presence of TTR amyloid deposits in the subependymal region, in the leptomeninges and in the wall of the subarachnoid blood vessels. The subependymal amyloid deposits are associated with a glial reaction resulting in the alteration of the ventricular wall and narrowing of the ventricular lumen, especially at the level of the aqueduct. The meningeal and vascular deposits are likely to be the cause of the multiple infarcts and hypoxic–ischaemic changes present in virtually the entire CNS. In contrast, amyloid deposits in the peripheral nerves are rare. Small amyloid deposits are present in the retina and retinal vessels. The peripheral nerves are minimally affected. Clinical and pathological features similar to those of the present kindred have been observed in other kindreds reported under the label of oculoleptomeningeal amyloidosis [26–29]. However, the nature of the amyloid and the presence of a mutation in the TTR gene have not been established in these families. Recently, a Hungarian kindred carrying a mutation in the TTR gene resulting in the replacement of asparagine with glycine (D18G) has been reported [30]. Clinically, affected subjects are reported to have memory loss, decreased hearing, signs of cerebellar and pyramidal dysfunction with episodic confusion and hallucinations. Pathologically, TTR amyloid deposits were observed in ‘meningeal vessels and subpial areas’; however, no other details are given [30].
The mechanism leading to the involvement of the CNS parenchyma, blood vessels and intracranial meninges, as opposed to the peripheral nervous system (PNS), in TTR amyloidosis remains obscure. The TTR molecule has an extensive β structure. The TTR monomer has eight β-chains arranged in antiparallel configuration in two planes [19]. Such a configuration is likely to predispose the TTR molecule to aggregate and form amyloid fibres as a result of a destabilizing change such as the presence of a mutation [19]. The V30M mutation, which is commonly associated with peripheral neuropathy, causes the increase of the sheet to sheet separation which, in turn, may result in altered disulfide bond formation and the subsequent formation of aggregates [31,32]. The V30A mutation as well as the V30G mutation that we observed might also be expected to reduce the sheet to sheet distance due to the smaller size of the residues. It is of interest, in this regard, that our kindred and the other kindred with the TTR phenotype characterized by clinical and histopathological involvement of meninges and brain parenchyma are both associated with a mutation resulting in the presence of a glycine residue in the N-terminal region of the TTR molecule [30].

The major phenotypic difference between the affected individuals with the V30G and those with the V30M mutations appears to be in the clinical features more than in the amyloid distribution. In the V30G-affected subjects, the signs of CNS involvement are prominent while those of PNS involvement are minimal or absent. The opposite applies to the phenotype of the V30M mutation. Nevertheless, amyloid deposits are present in the peripheral nerve and in the brain and intracranial meninges with both mutations. V30G-affected subjects also have significant brain parenchymal damage apparently secondary to the vascular amyloidosis which has not been observed in symptomatic V30M subjects. The distribution of the amyloid deposits in the leptomeninges and in the wall of the ventricles is highly consistent with the notion that, contrary to the TTR of the blood plasma that is synthesized in the liver, the TTR present in the CSF is synthesized by the epithelium of the choroid plexi and the vitreous TTR by the retinal pigmentated epithelium [33]. Thus, different TTR gene mutations might selectively affect not only the amount but also other features such as conformation, relating to the pathogenicity of the mutant TTR molecule synthesized in the different compartments. Whether the clinical and pathological features of the present kindred are due to a more abundant or more cytotoxic mutant TTR expressed in the choroid plexi or to other factors remains to be clarified.

**Hereditary cerebral haemorrhage with amyloidosis-Icelandic type (HCHWA-I)**

HCHWA-I is an autosomal dominant disease associated with a point mutation in codon 68 of the cystatin-C gene located in chromosome 20, resulting in the substitution of glutamine with leucine [34]. The cystatin C protein (CC) is composed of 120 amino acids with two disulfide bridges near the C-terminus. The protein is a member of the family 2 cystatins which are cysteine proteinase inhibitors. The amyloid form contains a 12 kDa truncated form of the mutant C protein, missing the 10 N-terminal residues [34]. X-ray analysis demonstrated that the Leu68 residue is buried in the hydrophobic core of the protein that seems to be the proteinase-binding region. As for TTR, the choroid plexus is considered to be the major site of CC synthesis, and patients with HCHWA-I have significantly lower CSF concentration of CC than normal subjects [35]. Several families as well as individual cases from apparently asymptomatic families in Iceland are affected [34,36,37]. The disease generally begins in the third and fourth decades and has a duration of ~10 years. The clinical presentation includes cerebral haemorrhage and minor infarctions associated with, and occasionally preceded by, cognitive impairment [34,37]. Pathologically, cystatin C amyloid is deposited in the leptomeningeal and intraparenchymal medium and small size vessels of cerebral grey and white matter which hyalinized and thickened walls [37]. The cerebral parenchyma shows infarctions, generally haemorrhagic, of various size and age.
Cystatin amyloid deposits are also present in the superficial dermis [37].

Alzheimer’s disease and other amyloidoses

One of the distinctive features of AD is that the phenotype is remarkably uniform despite the multiple aetiology of the disease. In addition to the sporadic form in which the aetiology is unknown, the AD phenotype is also associated with distinct genetic conditions which include the trisomy 21 or Down’s syndrome (DS) and different familial forms of AD (Table 4) [38]. The presence of AD in DS is attributed to the increased dosage of DNA, including the genomic DNA of the β amyloid precursor protein (βAPP), caused by the presence of an extra chromosome or, more rarely, of extrachromosomal material resulting from a translocation [39]. The DNA increased dosage results in a 4- to 6-fold increase in the expression of APP [39]. Familial forms of AD are linked to numerous distinct mutations in the BAPP gene on chromosome 21, in the genes of two transmembrane proteins, called presenilin-1 and presenilin-2, which are located on the chromosomes 14 and 1, respectively. The relative uniformity of the disease phenotype in the presence of this aetiological diversity strongly suggests that there is a common pathogenic pathway or cascade of events common to all these AD forms. This brief review focuses on some early events that may lead to the formation of the amyloid deposits and that can be shared by all forms of AD. Several recent reviews deal with all the other aspects of AD [38,40].

The invariable lesion and the histopathological hallmark of all forms of AD is the presence of amyloid deposits or plaques in the parenchyma and often in the vessels of the CNS and the leptomeninges [40]. In most subjects, there also is a neurofibrillary degeneration of neuronal cell bodies and their processes. The amyloid plaques are of two basic types. The so-called mature plaques are composed of deposits with the tonorial characteristics of the amyloid, i.e. positive with Congo red staining and apple green birefringent at polarized light, and with a target-like arrangement, i.e. a core surrounded by a concentric crown (Figure 1). The crown also contains distorted neuronal cell processes as well as reactive glial cells. The plaques of the second type, referred to as diffuse plaques, are made of aggregated material that does not display the characteristics of the amyloid and are associated with minimal or undetectable structural alterations of the brain parenchyma. The deposits present in the diffuse plaques have been named pre-amyloid, implying that the diffuse plaque is the precursor of the mature plaques. This assumption is supported by the finding that in the early stages of the disease the plaques are predominantly of the diffuse type [40] and cases have been reported in which the presence of a significant number of diffuse plaques is asymptomatic. If the diffuse plaques precede the mature plaques, then in AD amyloid formation is preceded by a condition in which the amyloidogenic protein is aggregated but does not form β-pleated sheets. Although these pathogenic events seem very logical and attractive, they have not been proved definitely to date. Regardless of whether they are in the form of amyloid or pre-amyloid, the deposits present in all plaques of AD contain primarily peptides of variable length identified as amyloid β peptide (Aβ) which, in turn, derives from a larger protein named amyloid β precursor protein (APP). APP is a transmembrane glycoprotein generated in several isoforms by alternative splicing of a single gene located on chromosome 21 (Figure 2) [38]. The Aβ is an internal sequence of APP, partially embedded in the membrane, which is thought to derive from cleavage of APP by at least three still unidentified proteases named secretases α, β and γ [40]. Normally, the α secretase cleaves APP between residue 16 and 17 of the Aβ region. This cleavage, which probably occurs at the membrane, results in the secretion of the APP fragment containing the N-terminal region, whereas the intracellular C-terminal fragment is likely to be degraded in intracellular compartments. Intact Aβ is thought to be produced by the cleavage at its N- and C-termini of β and γ secretases, respectively. There are several isoforms of Aβ which have been demonstrated in brains and CSF of subjects with AD [41]. Two major Aβ isoforms can be distinguished according to whether they end at the C-terminal residue 40 or 42, and are identified as Aβ40 and Aβ42 [38]. Considerable indirect evidence has been accumulated that Aβ, especially the Aβ42 isoform, plays a critical role in the β amyloid formation of AD. In addition to being the main component of both mature and diffuse plaques, Aβ42 has also been found to be increased in the plasma and in fibroblasts of subjects with genetic forms of AD, and Aβ42 in culture is secreted in increased amounts by cells carrying genetic mutations associated with AD [38]. Moreover, Aβ40 and even more Aβ42 are highly amyloidogenic and neurotoxic in vitro, probably following a change in conformation [42]. Therefore, it is believed that an increased amount of Aβ, especially Aβ42, is the common pathogenetic event shared by all forms of AD. However, no evidence for this has been obtained in the brain tissue.

In collaboration with Jan Teller, Massimo Tabaton and others, we have carried out the first search on the water-soluble Aβ (sAβ), i.e. Aβ not stably associated with amyloid and pre-amyloid deposits, in the brain.
Fig. 1. (A) Neuritic plaque showing numerous agryrophilic degenerating neurites forming a crown and a poorly stained core of amyloid (silver stain). (B) The amyloid core of a neuritic plaque is intensely stained green by an amyloid stain.

Fig. 2. Diagrammatic representation of amyloid precursor protein (APP). The cleavage sites of the α, β, and γ proteases (secretases) and the amyloid β (Aβ) peptide are indicated.

parenchyma of subjects with AD, subjects with DS and appropriate controls [43,44]. A large amount of sAβ was present in the AD brains (Figure 3). This finding was expected since in virtually all amyloidoses the protein forming the amyloid deposits is in equilibrium with the soluble form. The finding that sAβ was undetectable in brains free of Aβ plaques was less expected since sAβ is secreted by cells in culture and it is commonly stated that Aβ is normally present in the brain parenchyma. We then examined the presence of sAβ in the brain tissues of subjects with DS who came to autopsy at various ages. Virtually all subjects with DS develop AD between the age of 20 and 40 years [44]. Therefore, by examining the brain parenchyma in these subjects, one may identify changes preceding the formation of plaques. Analyses of DS brains showed that sAβ is present in significant amounts from birth and increases dramatically when diffuse or mature plaques appear. In contrast, sAβ was undetectable in brains free of plaques, from age-matched individuals with various pathologies (AD and DS excluded) in 35 out of 37 cases. Therefore, the presence of abnormal amounts of sAβ precedes the appearance of diffuse and mature plaques in DS. On gels, sAβ from either AD or DS brains separates into three bands, indicating the presence of at least three distinct isoforms [45]. Further characterization of sAβ showed that the upper band corresponds to the full-length sAβ made of residues 1–42 either as an unmodified form or as a form in which the aspartate residue (Aβ) peptide is racemized or isomerized; the intermediate and lowest bands are both made of sAβ isoforms containing pyroglutamate and ending at residue 42. In these two bands, the pyroglutamate modifies residue 3 and 11, respectively, which are also the starting residues of these two sAβ isoforms. Moreover, the amount of the pyroglutamate-modified sAβ3_42 appears to increase progressively with age in DS brains. Non-denaturing gel filtration and chromatography show that although water-soluble, the sAβ we examined is in aggregates which include all three isoforms [45]. Finally, sAβ is apparently unrelated to the insoluble Aβ since insoluble Aβ was present in similar amount in plaque-free brains from controls, which did not contain any detectable...
Aβ, and in plaque-free DS brains, which instead contained a significant amount of sAβ [45]. Recently it has been shown that in culture cells, sAβ42 is processed through a cellular pathway different from that of sAβ40, suggesting that in DS brain, probably because of overexpression of APP, the sAβ42-generating metabolic pathway is favoured [46].

In conclusion, post-translationally modified forms of sAβ are normally present in plaque-free DS brains which are bound to develop amyloid plaques at later ages. This finding indicates that the presence of sAβ1-42 and its modified forms precedes and perhaps is an essential step in the pathogenesis of amyloid plaque formation in DS-associated AD, and perhaps in other forms of AD.

HCHWA-Dutch type (HCHWA-D) is an autosomal dominant disease, caused by deposition of β amyloid in the leptomeningeal arteries and cortical arterioles, leading to fatal strokes in the fifth or sixth decade of life [47,48]. Only diffuse plaques are found in the parenchyma and only in older patients is it possible to find some congophilic plaques. Amyloid angiopathy has never been detected in spinal cord or its meninges [49]. The disease is due to a point mutation at codon 693 of the APP gene that codifies a glutamine for a glutamic acid at position 22 of Aβ.

**Prion diseases**

Prion diseases, also called transmissible spongiform encephalopathies, are fatal neurodegenerative disorders that affect humans and animals. They have the unique characteristic of being at the same time inherited and infectious [51]. Although not yet universally accepted, the dominant pathogenetic hypothesis, also referred to as the prion hypothesis, postulates that the central event shared by all forms of prion diseases is a change in conformation resulting in the conversion of a normal glycoprotein located mostly in the plasma membrane, named cellular prion protein (PrPc), into a conformer that has the same amino acid sequence and post-translational modifications as PrPres but differs in conformation, resistance to digestion with proteases, and pathogenicity. Three forms of prion diseases are commonly distinguished: inherited, sporadic and acquired (Table 5). According to the prion hypothesis [50], the change in conformation of PrPc into PrPres would be (i) an almost invariable consequence of the instability of PrP in the presence of a mutation in the familial or inherited form, (ii) the result of a spontaneous, random event in the sporadic form; or (iii) induced by the exposure to exogenous PrPres in the prion diseases transmitted by infection. The propagation of the disease would occur through the interaction between PrPc and PrPres. The PrPres acting as a template would convert the PrPc molecule into another PrPres molecule. The dissociation of the complex would then release the previously formed and the newly formed PrPres molecules, which would continue the conversion process in an autocatalytic chain reaction.

Table 5. Classification of prion diseases

<table>
<thead>
<tr>
<th>Form</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inherited</td>
<td>Creutzfeldt–Jakob disease (CJD)</td>
</tr>
<tr>
<td>Sporadic</td>
<td>Fatal familial insomnia (FFI)</td>
</tr>
<tr>
<td>Acquired by an infectious</td>
<td>Gerstmann–Sträussler–Scheinker (GSS)</td>
</tr>
<tr>
<td>mechanism</td>
<td>Heterogeneous</td>
</tr>
<tr>
<td>Acquired by an infectious</td>
<td>CJD</td>
</tr>
<tr>
<td>mechanism</td>
<td>Kuru</td>
</tr>
<tr>
<td>Acquired by an infectious</td>
<td>Iatrogenic CJD (iCJD)</td>
</tr>
<tr>
<td>mechanism</td>
<td>New variant of CJD (vCJD)?</td>
</tr>
</tbody>
</table>
tentorial characteristics of the amyloid, they are associated with structural damage of the cerebral parenchyma and, therefore, they are detectable not only following immunostaining but also with routine histological stains. Thus, they share many of the features of the mature plaques of AD. The second type of PrP\textsuperscript{res} deposits are detectable only following immunostaining and not with routine histological stains. They do not have the tentorial characteristics of the amyloid, they may be present without obvious damage of the parenchyma immediately adjacent to them and, therefore, they are reminiscent of the diffuse plaques of AD. However, the parenchyma usually shows widespread profound changes, as an amyloidogenesis-like process occurring in AD. In DS, we have demonstrated for the first time that the formation of amyloid and non-amyloid aggregates of the AD type is in turn preceded for many years by the abnormal presence of the amyloidogenic peptide in water-soluble form. Whether this pathogenetic event is also present in the other forms of AD and in other amyloidoses remains to be determined.

The chapter of the brain amyloidoses is undergoing profound changes, as an amyloidogenesis-like process seems to play a critical role in the pathogenesis of several neurodegenerative diseases.

Conclusions

Cerebral amyloidoses, although histopathologically diverse, have, not surprisingly, similar mechanisms of conversion of the amyloidogenic protein into amyloid deposits. The pivotal event in all of the amyloidoses appears to be a change in conformation which enhances the amyloidogenicity of the protein involved in the amyloid deposits. The conformational change is caused by the presence of a mutation in the amyloidogenic or amyloid precursor protein in the inherited amyloidoses, is supposedly spontaneous in the sporadic forms, and is transmitted through contamination in the forms of prion diseases acquired by an infectious mechanism.

In AD, prion diseases and probably other amyloidoses, the deposition of true amyloid is preceded by the presence of non-amyloid soluble aggregates which may remain asymptomatic or are associated with the disease.

In TTR amyloidosis, the entire protein participates in the formation of the amyloid deposits; in prion diseases, the entire protein participates in the non-amyloid soluble aggregate formation, but apparently only internal fragments are involved in amyloid formation; in AD, an internal fragment, Aβ, plays a central role in the formation of both non-amyloid and amyloid aggregates.

In DS, we have demonstrated for the first time that the formation of amyloid and non-amyloid aggregates of the AD type is in turn preceded for many years by the abnormal presence of the amyloidogenic peptide in water-soluble form. Whether this pathogenetic event is also present in the other forms of AD and in other amyloidoses remains to be determined.
of human plasma transthyretin. *Biochim Biophys Acta* 1992; 1139:9–16


