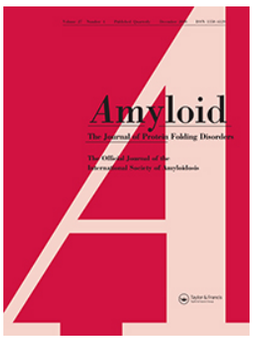

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NOMENCLATURE ARTICLE

Amyloid nomenclature 2020: update and recommendations by the International Society of Amyloidosis (ISA) nomenclature committee

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ABSTRACT

The ISA Nomenclature Committee met electronically before and directly after the XVII ISA International Symposium on Amyloidosis, which, unfortunately, had to be virtual in September 2020 due to the ongoing COVID-19 pandemic instead of a planned meeting in Tarragona in March. In addition to confirmation of basic nomenclature, several additional concepts were discussed, which are used in scientific amyloid literature. Among such concepts are cytotoxic oligomers, protofibrils, primary and secondary nucleation, seeding and cross-seeding, amyloid signature proteins, and amyloid plaques. Recommendations for their use are given. Definitions of amyloid and amyloidosis are confirmed. Possible novel human amyloid fibril proteins, appearing as 'classical' *in vivo* amyloid, were discussed. It was decided to include fibulin-like extracellular matrix protein 1 (amyloid protein: AEFEMP1), which appears as localised amyloid in portal veins. There are several possible amyloid proteins under investigation, and these are included in a new Table.

KEYWORDS

Amyloid; fibril protein; nomenclature; aggegation; oligomer; inclusion

Introduction

The Amyloidosis Nomenclature Committee of the International Society of Amyloidosis meets in association with the International Symposia of Amyloidosis. These symposia initially appeared irregularly but are now organised every second year. This year, 2020, was an exception due to the COVID-19 pandemic which caused the symposium to be postponed then converted to a virtual electronic format. Thus, Nomenclature meetings were held in spring and summer 2020 either by e-mail or *via* Zoom directly after the ISA Symposium. As previously, these Meetings have resulted in the present update of the amyloid nomenclature including recommendations.

Amyloid

The word 'amyloid' was introduced by Rudolf Virchow in 1854 describing a pathologic substance initially believed to be related to cellulose or starch but soon shown to be of protein nature. For more than 100 years, the word amyloid was almost explicitly used in human and veterinary medicine with little mechanistic insight. It was known as an extracellular substance that varied highly in distribution and properties and, if any, in clinical manifestations. This heterogeneity led to several early classifications, the most well-known probably that of Reimann et al. [1] dividing the diseases in 1. Primary, 2. Secondary, 3. Tumour-forming, and 4. Myeloma-associated amyloidosis. This classification has had a very long survival but is with our increasing knowledge outdated and should not be used.

Modern research on amyloid started with the demonstration of a sub-microscopic fibrillary structure of a substance that histologically appeared amorphous. Seminal X-ray diffraction studies of the fibrils revealed a generic cross-β structure of amyloid fibrils of different origin. The molecular nature of different amyloid fibril proteins was established by amino acid sequence analyses with the subsequent conclusion that they were derived from non-fibrillar precursors. At the second International Symposium on Amyloidosis, held in Helsinki, Finland in 1974, the chemical nature of the first two amyloid fibril proteins were identified and it was at this symposium an embryo of a modern amyloid fibril classification was born.

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Amyloid fibril

The basic structure of all amyloid is the fibril. An amyloid fibril is built up by twisted protofilaments. An amyloid protofilament is a stack of protein layers in β-sheet structure, which when twisted about identical stacks, forms an amyloid fibril. Amyloid fibrils may be formed from 2, 3, 4, or many such protofilaments, or in some cases from a single protofilament. Protofilaments are bound to each other in a parallel fashion *via* their sidechains.

Amyloid protofilaments and fibrils can be generated *in vitro* from protein purified from *ex vivo* deposits but also from synthetic or recombinant peptides. Such fibrils exhibit characteristic ultra-structural, X-ray crystallographic diffraction patterns, and the binding of dyes such as Thioflavin T and Congo red. Recently it has become clear that fibrils generated *in vivo* may be different from those derived from the same precursor obtained in the test tube [2].

In 2018, the Nomenclature Committee agreed on a general definition of the name 'amyloid' which earlier was used differently by varying groups of researchers. In medicine it was used only for pathologic deposits of specific fibrillary protein aggregates with distinct microscopic properties, particularly affinity for the dye Congo red with typical birefringence. Thus, in medicine amyloid was regarded as abnormal, an opinion which became unsustainable when the concept of 'functional amyloid' was introduced. Chemists, increasingly used the word amyloid for β-sheet protein fibrils of any kind, including synthetic or naturally appearing fibrils. The committee agrees that the term 'amyloid fibril' should be used for any cross β-sheet fibril [3]. It is recommended that when the word 'amyloid' is used, its nature and origin should be clear.

Functional amyloid

In nature, β-sheet fibrils are adapted to many purposes. Certain polypeptide hormones are stored in β-sheet conformation, perhaps not as regular fibrils; melanin is bound to the β-sheet fibrillar carrier (p-mel) in melanosomes. The strength of β-sheet fibrils is used by many lower animals in the production of extra-corporal structures like silk. Bacteria make several different structures, such as biofilms that have β-sheet fibrillary compositions. All these are examples of what we now accept as functional amyloid.

Amyloid fibril classes

Early observations assumed that amyloid fibrils are of similar or identical appearance despite varying protein origin. Moreover, it has been found that fibrils formed *in vitro* from recombinant protein (usually in short time frames) can differ profoundly from *in vivo* fibrils formed from the same precursor (frequently over a long period of time). With the wide definition of 'amyloid' it is necessary to talk about different amyloid fibril classes:

1. *In vivo* and *ex vivo* disease-related fibrils
2. *In vivo* and *ex vivo* functional fibrils
3. Recombinant fibrils of disease-related proteins and of functional amyloid proteins
4. Fibrils of synthetic or non-disease related peptides
5. Fibrils from condensates and hydrogels that give the cross-β diffraction pattern

Additional components in amyloid

It is well known that amyloid deposits always contain additional molecules. At least heparan sulphate proteoglycan (HSPG) and serum amyloid P-component (SAP or AP) are always present but there may be others. How these additional proteins are integrated in the amyloid deposit is presently unknown. Protein AP, which is identical with the plasma protein serum amyloid P (SAP) is bound in a calcium-dependent fashion to the fibrils. Its importance in amyloid pathogenesis is incompletely understood although there is evidence that it acts as an inhibitor of fibril degradation [4]. HSPG is clearly involved in the pathogenesis of AA amyloidosis and its ubiquitous presence in other amyloid deposits indicates a universal function in amyloidogenesis. Both these components belong to the so called 'amyloid signature proteins', see below.

Conceptions used in publications on amyloid and amyloidosis

Appearance of amyloid

Plaque is a word that often is used in scientific literature to describe the spread, small extracellular Aβ deposits in the cerebral cortex, particularly of patients with Alzheimer's disease. This is an incorrect description of the Aβ deposits which are more globular than flat. However, the wording is so commonly used in Alzheimer vocabulary it is difficult to eradicate but, at least, the word 'plaque' should not be used for other amyloid forms.

Amyloid properties

In medical practice amyloid is recognised microscopically by its amorphous structure, affinity for the dye Congo red and its increased birefringence under polarised light after such staining. The quality of the birefringence is usually described as green or even 'apple-green'. As has been underlined in several papers by Dr. Howie [5], the colour is highly mixed and varying, green being just one, albeit one looked for. In reality, red, green and yellow are commonly seen depending on how the tissue is cut with respect to the orientation of the fibrils *in situ*. Green may be very weak and difficult to see. It is therefore recommended that the findings should be described in detail in order to avoid statement that is not fully correct.

The use of crossed polarisers is also often described in peculiar ways, such as 'crossed-polarised light'. Such light does not exist. It should be stated that the specimen is placed between two polarisers.

Amyloid signature proteins

As mentioned above, amyloid deposits not only consist of the key fibril protein but other components are always present. The best studied are HSPG and SAP. Both these are implicated in the pathogenesis of several types of amyloid. With the use of mass spectrometry (MS) in typing amyloid deposits it became clear that several other proteins are often found at higher concentration than in the parent normal tissue. Such proteins are, in addition to SAP and HSPG, apolipoprotein (apo-) AI and apo-AIV, apo-E and others. The importance of these proteins in amyloidogenesis or if they are real components of the deposits are still not known but finding them at MS can help the identification of studied material as amyloid and are therefore often called 'amyloid signature proteins'.

Nucleation and secondary nucleation

In amyloid research the designation nucleation (primary) is used for a concentration-dependent stochastic event by which misfolded proteins bind to each other, thereby shifting the equilibrium and allowing the attraction of additional structurally identical/related molecules. This creates a protofilament which grows by addition of new identical molecules to fibril ends. The process templates identical misfolding of the subunits. Secondary nucleation, on the other hand, is a somewhat less understood influence of fibril surface to concentration-dependently induce nucleation of an amyloid-prone protein. The resulting fibrils do not necessarily adopt the exact same misfolding as the parent fibril.

Seeding and cross-seeding

These processes are related to the mechanisms in the previous paragraph. Addition of fibrils to a protein solution of same composition abolishes the nucleation lag phase and starts fibril elongation immediately. Although the mechanism has been studied in detail only *in vitro*, it is the accepted way by which prion diseases are transmitted. Cross-seeding in strict sense means that elongation of fibrils occurs for a peptide different from that in the fibril. In a broader sense cross-seeding is used to describe acceleration of fibrillogenesis when the mechanism is more unclear, possibly secondary nucleation.

(Cyto)toxic oligomers and protofibrils

Non-fibrillar amyloid protein aggregates are suspected to generate many of the effects on cells in the pathogenesis of tissue damage. The majority of studies have been performed *in vitro* and studies on (possible) *ex vivo* oligomers are sparse, except perhaps in Alzheimer's disease. Oligomers are in this context small non-fibrillar amyloid protein aggregates. The delineation towards protofibrils is not absolutely clear. The concepts of cytotoxicity, oligomer and protofibril are vague and vary between studies. Therefore, the use of these concepts always needs a thorough operational description as stated by P.W. Bridgman: 'In general, we mean by any concept nothing more than a set of operations; the concept is synonymous with the corresponding set of operations' [6].

Amyloid and amyloidosis in medical practice

Amyloidosis

While amyloid is the deposited material, amyloidosis is the disease caused by amyloid fibrils or during the process of their formation. Thus, this term is only used for the consequences of a pathologic protein aggregation from which human and animals may suffer. Amyloidosis is used for the different potentially lethal systemic diseases but also for a limited number of localised deposits, particularly localised AL amyloidosis. Several other diseases for which amyloid or other amyloid protein aggregates (cytotoxic oligomers, protofibrils) are characteristic, are presently not named amyloidoses although they may become so in the future. Alzheimer's disease (amyloid protein: Aβ), Parkinson's disease (amyloid protein: AαSyn) and type 2 diabetes (amyloid protein AIAPP) belong to these diseases. Although there is strong evidence for all three peptides to be involved in the pathogenesis, these diseases are rarely called localised amyloidoses. One reason is that for all of them there are researchers who doubt the central role of the components in the development of disorders. Furthermore, oligomeric aggregates rather than mature fibrils may be central in pathogenesis.

Amyloid protein nomenclature

The principles of the nomenclature have been given in earlier versions and for history, please see [3]. All amyloid fibril proteins are called protein A + the specific protein as a suffix, e.g. AL (L = immunoglobulin light chain) or ATTR (TTR = transthyretin). Further specification can be given after the protein name, e.g. ATTRwt or ATTRv (wt = wild-type and v = variant). If suitable, the specific mutation can replace v, e.g. ATTRV30M. Please observe that the Nomenclature Committee recommends the use of mature proteins in numbering of amino acid residues, i.e. without leader sequences. Numbering of the full precursor may be included as well but then in parenthesis after the mature protein, e.g. TTRV30M (*p. TTRV50M*). It should also be underlined that the abbreviations are for the proteins, not the diseases. For these, the protein name followed by 'amyloidosis' should be used. More specified disease designation can be used, e.g. ATTRv cardiomyopathy or ATTR polyneuropathy.

So far known human amyloid fibril proteins are given in Table 1. Presently, 18 proteins appearing as systemic amyloidosis and 22 as localised forms have been identified. Please note that some proteins can appear both as systemic and as localised amyloid deposits. Many of the amyloid types shown in Table 1 are rare or very rare.

Table 1. Amyloid fibril proteins and their precursors in human[a].

Fibril protein	Precursor protein	Systemic and/or localised	Acquired or hereditary	Target organs
AL	Immunoglobulin light chain	S, L	A, H	All organs, usually except CNS
AH	Immunoglobulin heavy chain	S, L	A	All organs except CNS
AA	(Apo) serum amyloid A	S	A	All organs except CNS
ATTR	Transthyretin, wild type	S	A	Heart mainly in males, lung, ligaments, tenosynovium
	Transthyretin, variants	S	H	PNS, ANS, heart, eye, leptomeninges
Aβ2M	β2-microglobulin, wild type	S	A	Musculoskeletal system
	β2-microglobulin, variants	S	H	ANS
AApoAI	Apolipoprotein A I, variants	S	H	Heart, liver, kidney, PNS, testis, larynx (C terminal variants), skin (C terminal variants)
AApoAII	Apolipoprotein A II, variants	S	H	Kidney
AApoAIV	Apolipoprotein A IV, wild type	S	A	Kidney medulla and systemic
AApoCII	Apolipoprotein C II, variants	S	H	Kidney
AApoCIII	Apolipoprotein C III, variants	S	H	Kidney
AGel	Gelsolin, variants	S	H	Kidney PNS, cornea
ALys	Lysozyme, variants	S	H	Kidney
ALECT2	Leukocyte chemotactic factor-2	S	A	Kidney, primarily
AFib	Fibrinogen α, variants	S	H	Kidney, primarily
ACys	Cystatin C, variants	S	H	CNS, PNS, skin
ABri	ABriPP, variants	S	H	CNS
ADan[b]	ADanPP, variants	L	H	CNS
Aβ	Aβ protein precursor, wild type	L	A	CNS
	Aβ protein precursor, variant	L	H	CNS
AαSyn	α-Synuclein	L	A	CNS
ATau	Tau	L	A	CNS
APrP	Prion protein, wild type	L	A	CJD, fatal insomnia
	Prion protein variants	L	H	CJD, GSS syndrome, fatal insomnia
	Prion protein variant	S	H	PNS
ACal	(Pro)calcitonin	L	A	C-cell thyroid tumours
		S	A	Kidney
AIAPP	Islet amyloid polypeptide[c]	L	A	Islets of Langerhans, insulinomas
AANF	Atrial natriuretic factor	L	A	Cardiac atria
APro	Prolactin	L	A	Pituitary prolactinomas, aging pituitary
AIns	Insulin	L	A	Iatrogenic, local injection
ASPC[d]	Lung surfactant protein	L	A	Lung
ACor	Corneodesmosin	L	A	Cornified epithelia, hair follicles
AMed	Lactadherin	L	A	Senile aortic, media
AKer	Kerato-epithelin	L	A	Cornea, hereditary
ALac	Lactoferrin	L	A	Cornea
AOAAP	Odontogenic ameloblast-associated protein	L	A	Odontogenic tumours
ASem1	Semenogelin 1	L	A	Vesicula seminalis
AEnf	Enfurvitide	L	A	Iatrogenic
ACatK[e]	Cathepsin K	L	A	Tumour associated
AEFEMP1[e]	EGF-containing fibulin-like extracellular matrix protein 1 (EFEMP1	L	A	Portal veins Aging associated

[a]Proteins are listed, when possible, according to relationship. Thus, apolipoproteins are grouped together, as are polypeptide hormones.
[b]ADan is the product of the same gene as ABri.
[c]Also called amylin.
[d]Not proven by amino acid sequence analysis.
[e]Full amino acid sequence to be established.

The possibility of using hATTR (h = hereditary) instead of the recommended name ATTRv has been suggested, particularly of legal reasons. If absolutely necessary, this may be acceptable in exceptional cases but then the reason for the choice as well as the recommended name should be given.

Additions to amyloid fibril protein lists since previous nomenclature

Human fibulin-like extracellular matrix protein 1

EGF-containing fibulin-like extracellular matrix protein 1 (EFEMP1), also known as fibulin 3 and several other names is a 476 aa (mature protein, without a 17 aa signal peptide) extracellular matrix protein with several proposed functions. In a paper by Tasaki et al. [7] there is strong evidence that the venular gastrointestinal amyloid, originally described as portal amyloid [8] is derived from EFEMP1. This type of amyloid seems to be a common localised form in aging people (16 out of 110 patients, 85 years and older in the study by Röcken et al.) but obviously overlooked. The study by Tasaki et al. indicates that the amyloid fibril protein is a 10 kDa C-terminal EFEMP1 fragment but the exact sequence is not known. The amyloid fibril component has been added as protein AEFEMP1 (Table 1).

Calcitonin

Calcitonin (or procalcitonin) was the third protein to be identified as an amyloid fibril component in human. It was

characterised from amyloid in medullary thyroid carcinoma (MTC) and has been regarded as a strictly localised form. However, calcitonin amyloid deposits in the glomeruli have been described in patients with metastatic MTC by two independent groups [9,10]. In one of the reports ACal was identified also in subcutaneous fat tissue. Therefore, calcitonin has to be added to systemic amyloid proteins.

Potential amyloid fibril proteins under investigation

Human glucagon

Glucagon has been described as the major amyloid protein in a patient with a glucagon-producing pancreatic tumour ('glucagonoma') [11]. Glucagon has earlier been found to form amyloid fibrils *in vitro* [12]. Glucagon (or proglucagon) nature of the tumour amyloid was determined by MS followed by IH. Whether or not there were protein modifications such as fragmentation, was not shown. Therefore, it was decided to list as a putative amyloid fibril protein under investigation (Table 2).

Rat lipopolysaccharide-binding protein (LBP)

Amyloid is very rare in rat but can be found in mammary tissue and tumours. Murakami et al. [13] studied the nature in such amyloid and found evidence for lactadherin in some types of deposits while one specific morphological kind of amyloid, which they called needle-shaped, contained lipopolysaccharide binding protein (LBP). LBP is a 481 aa (including a 25 aa signal peptide) acute phase protein, expressed by mammary epithelial cells. The study did not exactly define which part of the protein that is associated with amyloid fibril formation. LBP was therefore added to the list of putative amyloid fibril proteins under investigation (Table 2).

Retraction from the human amyloid fibril protein list

Galectin-7, a 122 aa protein expressed by squamous epithelium was described as the fibril protein in [14] localised amyloid in association with epidermal cancer *in situ* (Bowen's disease). Westermark et al. [15] found the same protein in amyloid of two patients with lichen amyloidosus/macular amyloidosis. This finding was reported in abstract form only. Now, Chapman et al. [16] have performed laser capture dissection followed by MS and not found evidence for galectin-7 in subepidermal localised amyloid. They found basal epidermal cell keratins but could not definitely say that the amyloid is of keratin origin.

Due to the ambivalence galectin-7 is added to a list of proteins for which verification as *in vivo* amyloidogenesis is needed. The protein has been moved to Table 2.

Amyloid proteins in animals

The number of animal amyloid fibril proteins has not increased and is still 10, see Table 3. As seen above, one more is under investigation.

Intracellular inclusions

As mentioned above there are several intracellular inclusions of which several show at least some typical amyloid fibril properties, Table 4. To this list are now two added.

Transcription factor p53

P53 is a 393 aa tetrameric DNA-binding protein which regulates gene expression and is important for DNA stability. Malignant tumours are very often associated with mutations in the transcription factor p53. Variant p53 can misfold and

Table 2. Proteins under investigation.

Protein	Species	Protein nature	Associated disease	Type of aggregate
Glucagon	Homo sapiens	Islet hormone	Islet tumour	Extracellular amyloid
Lipopolysaccharide- binding protein	Rattus norvegicus	Acute phase protein	Mammary tumours	Extracellular amyloid
Galectin 7	Homo sapiens	Galectin	Forms of localised dermal amyloid	Extracellular amyloid
Desmin	Homo sapiens	Intermediate filament	Myopathies	Intracellular, not fully characterised

Table 3. Amyloid fibril proteins and their precursors in animals.

Fibril protein	Precursor protein	Systemic and/or localised	Affected organs or syndrome	Species
AL	Immunoglobulin Light Chain	S,L	Plasmacytoma	Cat, Horse
AA	(Apo) Serum Amyloid A	S	Chronic Inflammation or Infections	Many mammalian and avian species: mouse, cat, cow, dog, duck, guinea pig, etc.
AApoAI	Apolipoprotein AI	S	Age-related	Dog
AApoAII	Apolipoprotein AII	S	Age-related	Mouse
ATTR	Transthyretin	S	Age-related	Vervet monkey
AFib	Fibrinogen Aα	S	Spleen, Liver	Stone marten
Aβ	Aβ precursor protein	L	Age-related	Dog, sheep, wolverine
AIAPP	Islet Amyloid Polypeptide	L	Islets of Langerhans, Insulinoma	Apes, cat, racoon
AIns	Insulin	L	Islets of Langerhans	Octodon degus
ACas	A-S2C casein	L	Mammary gland	Cow

Table 4. Intracellular inclusions with known biochemical composition, with or without amyloid properties.

Inclusion name	Site	Protein nature	Examples of associated disease
Lewy bodies	Neurons intracytoplasmic	α-synuclein[a,b]	Parkinson's disease
Huntington bodies	Neurons intranuclear	PolyQ expanded huntingtin	Huntington's disease
Hirano bodies	Neurons	Actin	Neurodegenerative disorders
Collins bodies	Neurons	Neuroserpin	Forms of familial presenile dementia
Not specified	Neurons, many different cells	Ferritin	Form of familial neurodegenerative disorder
Neurofibrillary tangles	Neurons intracytoplasmic	Tau[b]	Alzheimer disease, fronto-temporal dementia, aging, other cerebral conditions
Russel bodies, Dutcher bodies, Mott cell inclusions	Plasma cells	Monoclonal immunoglobulin	Several conditions, incl. multiple myeloma
Crystal-like inclusions	Plasma cells, proximal tubule cells, histiocytes	Monoclonal light ig chains usually kappa rarely lambda	Monoclonal kappa light chain diseases
Not specified	Tumour cells	P53	Tumour cells

[a]Simplified. Additional components may exist.
[b]Also included in Table 1 since deposits may appear extracellularly.

aggregate intracellularly and thereby loose its normal function. Such aggregates have some properties characteristic of amyloid, e.g. cross β-sheet structure and seeding ability, for review, see [17].

Desmin

Desmin is a 470 aa muscle intermediate filament protein. The protein has been suggested to be involved in the pathogenesis of myofibrillar myopathies. Intracellular inclusions are common and contain desmin as a major protein but not as a sole constituent. *In vitro* experiments have supported desmin fragments as possible amyloid component [18]. Intracellular muscle inclusions have been added to Table 4 with desmin as a possible ingredient.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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