

Amyloid. History and Amyloid Update^X

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SUMMARY

In summary, amyloid research in the 20th century was decisively shaped by the work of Divry, Romhányi, Benditt, Cohen, Westermark and Linke. The Congo red staining method introduced by Bennhold in 1922 has remained a fundamental investigative technique for protein deposits to this day. Whereas only four types of amyloid were known in the early 1950s, 47 distinct types are now recognised. From a therapeutic perspective, accurately determining the origin of amyloid poses a significant diagnostic challenge, which can be addressed through immuno- histochemical, mass spectrometry and molecular genetic analyses. The main objective of the biennial amyloid forums is to standardise diagnosis and treatment.

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Over the past few decades, numerous new findings have emerged regarding the pathogenesis, diagnosis and treatment of various types of amyloidosis. György Romhányi's research into amyloidosis, spanning several decades, has contributed significantly to this [1-10].

Amyloidosis is a pathohistological lesion characterised by deposits of ballast proteins, with a multifactorial aetiology and a varied submicroscopic structure, which most often develops against the background of some chronic underlying condition (secondary amyloidosis), but may also occur without an underlying condition (primary amyloidosis). A distinction is made between localised and systemic forms.

Amyloidoses are storage diseases (thesaurismoses) that arise in the body due to the misfolding of certain physiological proteins, which, consequently cannot be properly metabolised or broken down. They therefore remain in the body, polymerise into microfibrils, aggregate with other substances to form pathological proteins known as amyloids, and are deposited in the extracellular space. By disrupting the function of the affected organs and tissues, their presence leads to various clinical and therapeutic consequences. Early, accurate diagnosis and the correct classification of amyloid deposits are of great importance, as both quality of life and mortality are linked to this.

Amyloids represent a group of diseases with different aetiologies, the common feature of which is a particularly strong affinity for Congo red staining, with double refraction and a green polarisation colour, provided the optimal section thickness is between 2 and 4 µm [11-15]. Its structure is characterised by a fibrillar arrangement

and β -sheet folding [16-20]. The common properties of amyloid are shown in Table 1 [20]. In recent decades, numerous new findings have emerged regarding the different types of amyloid, their pathogenesis and diagnosis, whilst their treatment still depends on the underlying disease.

Table 1: Westermark's Concept of Amyloid [20] Common Characteristics of Amyloid-Like Deposits

- Extracellular deposition
- Amyloid stained with Congo red exhibits double refraction and a green polarisation colour
- Characteristic ultrastructure
- Transversely β -folded fibrils (X-ray diffraction)

The History of Research into Amyloidosis

In 1639, Nicolaus Fontanus performed an autopsy on a young man who presented with ascites, jaundice, a liver abscess and splenomegaly. According to Kyle, his post-mortem findings are regarded as the first description of amyloidosis [21]. The term 'amyloid' was coined in 1839 by the German botanist *Schleiden* to describe a starch-like substance found in plants [22,23]. This plant substance was in fact cellulose, which was first identified by the French industrial chemist Payen [24,25]. In 1842, Carl von Rokitansky, a Viennese pathologist, was among the first to describe the pathological changes in organs characteristic of amyloidosis. He characterised the macroscopic changes in the liver and spleen as 'fatty and waxy' [26].

In 1854, Virchow examined the so-called corpus amylaceum of the brain. As they reacted with iodine and sulphuric acid, he concluded that they were a substance similar to plant cellulose [27-29]. Shortly afterwards, he had the opportunity to examine a spleen, which 'appeared to have the same pale, slightly lustrous, apparently soft structure as the corpus amylaceum of the brain'. In his further analyses, he attempted to describe this substance:

'It shares with cellulose the property of reacting to iodine and sulphuric acid, but differs from starch in its lack of an iodine reaction.' Virchow attempted to name it: the choice was between 'paramylon' and 'amyloid'; as most botanists had abandoned the term 'plant amyloid', he considered this name to be the most appropriate. Thus, as Virchow established, amyloid possesses properties similar to those of starch [29, 30].

Friedrich and Kekulé also investigated the question of amyloid; in their view, amyloid deposits are protein-like [31]. They were thus the first to establish the presence of proteins in amyloid. In 1930, *Weber* published the first case of amyloidosis occurring in multiple myeloma, without considering the possible link between the two conditions [32]. In 1931, Magnus-Levy hypothesised that there must be a link between proteinuria and amyloid in myeloma, and posed the question: 'Could the Bence Jones protein be the precursor of amyloid?' [33].

The first histochemical method for amyloid staining probably originated with Heschl, who used a mixture of Leonhardi's purple, aniline blue, aniline red and glycerine to prepare permanent histological sections. In 1875, Cornil (Paris), Heschl (Vienna) and Jürgens (Berlin) independently analysed aniline dyes for the examination of amyloid [34].

Böttiger first wrote about Congo red in 1883; it was initially used for dyeing cotton [25]. Although amyloidosis had been recognised as a disease for at least 80 years, in 1922, Bennhold was the first to realise that Congo red could also be used in the diagnosis of amyloidosis, specifically for the staining of post-mortem microscopic sections, thereby introducing Congo red staining-the 'gold standard'-into the diagnosis of amyloidosis [35]. Bennhold pointed out that Congo red disappears more rapidly from the blood in patients with amyloidosis than in the control group. This test remained the standard procedure for the diagnosis of amyloidosis until the late 1960s, whilst Congo red staining has been part of routine histological diagnosis since the 1950s.

Divry and Florkin were the first to describe double refraction and its intensification following Congo red staining, whilst examining senile plaques and experimental mouse amyloid [36, 37]. Divry was involved in the analysis of formalin-fixed frozen sections and recognised that the unstained plaques exhibit weak double refraction, whilst the iodine reaction enhances this double refraction. This implied that the cores of senile plaques were of an amyloid nature, which led them to stain the sections with Congo red and examine them under a polarising microscope (using linearly polarised light). They hypothesised that the observed double refraction was related to the crystalline structure of the amyloid.

Romhányi was able to demonstrate the positive double refraction of unstained amyloid using imbibition analysis and thus analyse its submicroscopic structure. Following Congo red staining, he observed an anisotropic effect that was five times stronger, which he explained by the parallel orientation of the Congo red dye molecules on the surface of the amyloid fibres, as Wälchli had also observed in his studies of cellulose and amyloid micelles [1-4, 38]. *Romhányi's* discovery took place between 1939 and 1941; he finally described the submicroscopic structure of human amyloid in October 1942, independently of Divry [1]. He was not even aware of Divry's data until 1953; he first read about these findings in the literature in a publication by Missmahl and Hartwig [36,37,39].

Missmahl and Hartwig concluded that the double refraction was not caused by the amyloid deposits, but by the collagen fibres located there [39]. *Romhányi's* response in 1956 was as follows: the double refraction of the collagen fibres can be eliminated by a phenol reaction (Ebner's phenol reaction), and following Congo red staining, the double refraction of the amyloid is indicated by a green polarisation colour under linearly polarised light [4]. Interestingly, Missmahl wrote the following in 1964: 'I have demonstrated that Congo red binds in an ordered manner to amyloid, thereby causing double refraction', overlooking the fact that in 1953 it was precisely he who had questioned *Romhányi's* findings [39-41].

Ladewig had already noted as early as 1945 that amyloid stained with Congo red changed colour twice, from yellow to green, when the preparation containing the amyloid was rotated by 360°. He was the first to observe and describe these colour changes [42]. Stiller and Katenkamp, in 1975, refer to the research of Wolman and Bubis, who also emphasised that the thickness of the section is of paramount importance in interpreting the green polarisation colour of amyloid stained with Congo red [43,44]. Missmahl, however, was the first to state that, following Congo red staining, only the 'green polarisation colour' is essential for the diagnosis of amyloid [41, 45-48]. In 1964, at the Leopoldina Amyloid Colloquium in Halle (Halle an der Saale), he gave a presentation entitled 'Structural Analysis of Amyloid' in place of *Romhányi* [40, 41]. *Romhányi*, who had been invited to give this presentation, was unable to attend the meeting due to illness. Missmahl repeatedly carried out the imbibition analysis of amyloid published by *Romhányi* [1-3]. He stated that amyloid deposits stained with Congo red appeared intensely green under crossed polarising filters observed in polarised light [40, 41]. It was on this basis that the dogma of 'green double refraction', or 'apple-green double refraction', emerged [47, 48]. The author of these lines has categorically rejected this term in his papers presented at several amyloid fora. Together with Westermark, he formulated the properties of amyloid in 2012, including the fact that, following Congo red staining, amyloid exhibits birefringence with a green polarisation colour [20]. *Romhányi* stated in 1966 and 1968 that the term 'apple-green birefringence' was incorrect and unscientific. Following Congo red staining and under crossed polariser beams, amyloid exhibits green polarisation colour birefringence if the section thickness is optimally between 2 and 4 µm [4, 5, 12, 44, 49, 50]. The polarisation colour is dependent on the thickness of the section [5, 12, 14, 46, 47, 51-54].

The Ultrastructure and Most Common Types of Amyloid

In 1959, Cohen and Calkins used electron microscopy to describe the ultrastructure of amyloid, which until then had appeared amorphous under a light microscope [55]. They found rigid, thin, non-branched fibrils with a diameter of 7–14 nm and an indeterminate length. Glenner used X-ray diffraction analysis and infrared spectroscopy to demonstrate that the amyloid fibrils consist of polypeptide chains arranged in a folded, perpendicular orientation along the axis of the filament [56].

For this reason, Glenner later termed amyloidoses 'β-fibrilloses' [57].

Romhányi introduced a new method in 1968 for distinguishing between secondary and primary amyloid: primary amyloid deposits are resistant to potassium permanganate + trypsin digestion, whilst secondary deposits are digested [6, 8, 9]. Wright, who visited *Romhányi's* institute, described a similar effect

following treatment of amyloid with potassium permanganate, and emphasised that this method allows the two types of amyloid deposits to be distinguished [58].

Makovitzky and Romhányi reported in 1971 that senile amyloid deposits in the aorta are resistant to the above treatments; Congo staining and double refraction persist after treatment with potassium permanganate, just as they do after treatment with potassium permanganate plus trypsin. The potassium permanganate solution must always be prepared fresh [50]. Benditt et al. found that the A-amyloid protein is unstable with regard to Congo red binding at an alkaline pH (11.5), whilst the B-amyloid protein retains its Congo red staining under such conditions [59-61]. These two discoveries represented milestones in amyloid research. The author of the present work analysed amyloid deposits [5, 49, 53, 62] using the Romhányi, Fischer, Módis methods and the topo-optical reactions described by himself, as well as isolated human amyloid fibrils and prion fibres, the amyloid deposits in animals, and bacterial amyloid [63]. He described how the fibrillar and non-fibrillar components of amyloid possess an ordered structure, and can be selectively detected [49, 53, 64-66]. The sugar and glycosaminoglycan components of the amyloid protein complex form a lipid-oriented system and link together to form the amyloid fibril. Makovitzky demonstrated the helical structure of unstained and Congo red-stained amyloid fibrils in 2005 based on polarisation analysis, which was confirmed by Pomozi and Steinbach using confocal laser scanning fluorescence microscopy [49, 67-69].

The Most Common Forms of Amyloidosis

To date, 42 amyloidogenic proteins have been identified in humans (Amyloid Forum 2022, Heidelberg). Amyloid deposits may be localised or systemic. In the former case, the deposits are present in a single organ, whilst in the latter they affect various organs. Exclusively localised amyloid deposits have been associated with at least 19 protein types, whilst in the case of systemic amyloidosis, at least 14 protein types (and many more variants) have been identified to date. Interestingly, however, at least three protein types (primarily AL/AH amyloidosis, arising from the light and heavy chains of immunoglobulin, respectively; ATTR amyloidosis; and A β 2M amyloidosis, arising from β 2-microglobulin) can occur in the form of both localised and systemic deposits. The AA and AL types are among the most common forms of multisystemic amyloidosis in clinical pathology. Mass spectrometry allows for the precise analysis of amyloid deposits [18].

- AA amyloidosis (precursor: 'serum amyloid A protein'): secondary amyloidosis in the narrower sense. It occurs as a consequence of persistent inflammatory activity or chronic diseases (the so-called 'higher principle', or 'übergeordnetes Prinzip' in German, according to Virchow).
- AL amyloidosis: the kappa or lambda type, formed from fragments of the light chains of immunoglobulins.
- ATTR amyloidosis (familial or hereditary amyloidosis): this type of amyloid accumulates, for example, in the liver and heart.
- DRA (dialysis-related amyloidosis): a type detected following at least 5 years of haemodialysis; its precursor is B2-microglobulin.
- Organ-specific amyloidosis (OA): only the skin, lungs, liver, brain and kidneys are affected.
- Localised amyloidosis: amyloid deposits in the meniscus, the Achilles tendon, the femoral head, the os labrum and the ligamentum flavum. Amyloidoma: accumulation of 'tumour-

like amyloid', for example in the breast, the brain or the lungs. Accumulation of 'tumour-like amyloid', for example in the breast, brain or lungs.

The Pathological Significance of Amyloidosis

Dorfman disease. However, in approximately 5% of cases of AA amyloidosis, no underlying disease has been AA amyloidosis may develop as a secondary condition in disorders associated with chronic inflammation, or as a complication of numerous underlying diseases, as listed in Table 2 [50, 67, 70-74]. Rarer causes include malignant diseases such as renal cell carcinoma, Hodgkin's and non-Hodgkin's lymphomas, and mesothelioma; it is occasionally observed even in Rosai-identified [70,75].

The incidence of diseases associated with AA amyloidosis clearly varies geographically. In recent decades, inflammatory rheumatic diseases have been the most common causes of AA amyloidosis in Western countries (in 66-76 per cent of cases). In countries where Mediterranean fever is common, such as Turkey, this is the main cause of AA amyloidosis. In the developing world and on the Indian subcontinent, however, tuberculosis and leprosy are the most common causes of the disease.

In AA amyloidosis, the parenchymal organs – such as the spleen, kidneys and liver - are most commonly affected [71]. The kidneys are of normal or enlarged size; however, in advanced stages, parenchymal atrophy and renal failure tend to develop, which account for 40-60 per cent of deaths. The liver, spleen and adrenal glands may also become enlarged. These organs retain their function over a prolonged period. Amyloid deposits may also occur in the gastrointestinal tract [76].

Hrabovszky et al. reported a case series describing a combination of a torpid crural ulcer and amyloidosis [77]. The patient was admitted to the clinic in a pre-uraemic state with proteinuria, which suggested amyloidosis. This was ultimately confirmed by histopathological examination, which revealed AA-type amyloid in characteristic locations (kidney, spleen, intestine).

Amyloid precursors (serum amyloid A, SAA proteins) were isolated and characterised more than 50 years ago. These proteins are short (104 amino acids) and show a remarkable association with the acute-phase reaction, whilst their serum levels can rise up to 1,000-fold within 24 hours. The SAA proteins are encoded by a family of closely related genes and have been remarkably well conserved throughout the entire evolution of vertebrates. The N-terminal fragments of SAA are capable of forming highly organised, insoluble fibrils which accumulate in 'secondary' amyloid diseases.

The best-known component of pathological secondary amyloid fibrils is the 'AA' polypeptide derived from SAA, but other molecules also exist. Heparan- and dermatan-sulfated glycosaminoglycans and proteoglycans are bound non-covalently [78,79]. Furthermore, all amyloid fibrils contain the plasma glycoprotein serum amyloid P (SAP, which is 51 per cent sequence-homologous to C-reactive protein and highly conserved phylogenetically), a member of the pentraxin protein family. SAP contains a calcium-dependent ligand-binding site which recognises an as yet unidentified feature that appears to be common to all types of amyloid fibrils.

AL amyloidosis is a rare monoclonal plasma cell disorder, with an incidence reported as 8 per 1,000,000 per year [80]. Glenner et al. discovered that this form of amyloidosis is characterised by

the deposition of immunoglobulin light chains (κ - or λ -chains) or their N-terminal fragments [81]. Accordingly, AL λ - and AL κ -amyloidosis can be distinguished. Monoclonal gammopathies based on the neoplastic proliferation of plasma cells (malignant transformation of plasma cells) are the most common cause. In approximately 15 per cent of patients with myeloma multiplex, amyloid deposits can be detected in various organs during the course of the disease [82]. Even non-secretory myeloma multiplex is capable of inducing amyloidosis; its prevalence accounts for 1-5% of all classic myeloma multiplex cases.

The Clinical Presentation of Amyloidosis

The clinical presentation of amyloidosis is characterised by progressive deterioration in the function of the affected organs. In this context, we reported on a 49-year-old female patient in whom we confirmed a very rare combination of AL amyloid deposits in the ribs, lungs and breast, occurring in the form of non-secretory multiple myeloma [63, 83]. The patient was successfully treated for 8 years.

AL-type systemic amyloidoses were previously referred to as primary amyloidoses. As various organs may be affected, the clinical symptoms are also highly variable. Fatigue and weight loss are the most commonly observed subjective symptoms. In approximately 40 per cent of patients with AL amyloidosis, carpal tunnel syndrome can be diagnosed; this condition also frequently occurs in its inherited form, localised in the wrist. It can be treated surgically.

Other symptoms caused by AL-amyloid infiltration may include restrictive cardiomyopathy, joint disorders, splenomegaly, skin manifestations and peripheral or autonomic neuropathy. Macroglossia is less common but is considered pathognomonic [84, 85]. Bilateral periorbital purpura (so-called 'cat's eyes'), caused by amyloid infiltration of the small blood vessels, is characteristic [82, 86]. Colonic stricture caused by amyloidosis may, in rare cases, be the first symptom of multiple myeloma [87]. The formation of amyloid and its dynamics were summarised by Merlini and Bellotti [Tab 2,88].

Table 2: Main Factors Influencing the Formation and Progression of Amyloid

- The primary and secondary structure of the precursor protein – The so-called germline mutation
- Polymorphisms in non-amyloidogenic proteins
- Abnormally elevated local or systemic concentrations of the precursor protein
- The presence of a nidus
- Altered proteolysis of the precursor protein
- Delayed degradation of amyloid

Diagnosis of Amyloidosis

It is rarely diagnosed because, as a secondary condition, it develops against the background of numerous other chronic conditions, the symptoms of which may mask or mislead the diagnosis. Characteristic organ lesions can be detected by histological, laboratory or imaging investigations.

- Among laboratory tests, markers of the acute phase of inflammation and indicators of parenchymal organ function (liver, thyroid and kidney function) are important; serum protein electrophoresis (paraproteinaemia) is essential.
- Tissue biopsies may be taken from the rectum, abdominal wall adipose tissue or bone marrow; however, oral mucosal

biopsies or examinations of other affected tissues (such as liver and kidney biopsies) may also be used [89,90].

- The nature and classification of amyloid deposits must be determined by immunohistochemical staining. This is of crucial importance for the choice of treatment. Monoclonal gammopathy is diagnosed by detecting monoclonal immunoglobulin in serum and/or urine using electrophoresis, immunoelectrophoresis or immunofixation.
- A bone marrow biopsy, showing an increased plasma cell count, and the detection of osteopenia typical of myeloma using imaging techniques provide further information about the disease.
- Imaging techniques (echocardiography, contrast-enhanced cardiography, and magnetic resonance imaging of parenchymal organs-such as the kidneys, liver, spleen, heart, lungs—and tissues).

The diagnostic work-up for systemic amyloidosis appears straight-forward, but there are sources of error. Amyloid is sometimes deposited unevenly, and a negative biopsy does not necessarily mean that the patient does not have the disease [91]. The staining method generally used for amyloid is alkaline Congo red, but unfortunately this is often not carried out properly, which can lead to false-positive findings.

Bély and Makovitzky recommend staining with a 0.1 per cent Congo red solution, as described by Romhányi, followed by mounting with gum arabic; under linearly polarised light, only the amyloid appears birefringent, specifically with a green polarisation colour [11,5]. This method is preferable to all other Congo staining techniques, as it does not produce 'false-positive' reactions.

Romhányi and Makovitzky and Romhányi emphasised the importance of section thickness, which is responsible for the green polarisation colour. The optimal section thickness is 2–4 μm [5,50].

Treatment of Amyloidosis

Given its diverse aetiology, there is no specific treatment for amyloidosis. The prognosis of the secondary (AA) form depends on the underlying condition. The aim of AA treatment is, on the one hand, to block the synthesis of the SAA precursor and, on the other hand, to support the function of the affected organs [72]. For the treatment of AL, conventional chemotherapy (melphalan and prednisolone according to the Alexanian regimen), high-dose chemotherapy and autologous haematopoietic stem cell transplantation are recommended [92,93].

Table 3: Principles and Main Options for the Pharmacological Treatment of Amyloidosis [94]

- Inhibition of amyloid precursor synthesis through management of the underlying disease AL amyloidosis: chemotherapy for plasma cell neoplasia, stem cell transplantation AA amyloidosis: enhanced anti-inflammatory therapy
- Use of protease inhibitors
- Inhibition of GAG binding to the protein core (eprodizate) [94]
- Small molecules that inhibit stabilisation (diflunisal, tafamidis)
- Removal of SAP from amyloid deposits using a palindromic
- Removal of amyloid deposits G) Anti-SAP
- antibodies GAG = glycosaminoglycan; SAP = serum amyloid P

The main aim of treatment is the prophylactic management of the underlying disease. If amyloidosis is already present, attempts

should be made to suppress SAA levels through aggressive treatment. It is of paramount importance to protect the kidneys and to avoid hypoperfusion, infections and nephrotoxic substances. Haemodialysis may be considered if renal function deteriorates. As a targeted therapy, treatment with eprodizate (a negatively charged molecule with a structure similar to heparan sulphate) is also indicated; this inhibits the binding of glycosa-minoglycans to the protein core. The use of carboxypyrrolidine-hexa-nonyl-pyrrolidine-carboxylic acid (CPHPC), which inhibits SAP binding, may be recommended. Finally, success has been achieved with anti-SAP antibodies, which may result in a slowing of amyloid deposition [95-98].

Kreutzkamp and Einsele report on newly diagnosed patients with multiple myeloma aged under 65, in whom the prognosis proved favourable following autologous stem cell transplantation (ASCT) and high-dose chemotherapy [99]. The prognosis of systemic AL amyloidosis depends predominantly on cardiac involvement, which occurs in 70-80 per cent of cases. Whilst the average survival time for patients without decompensated heart failure is 30 months, patients with this condition die approximately 4-6 months after diagnosis [100, 101]. In approximately 65 per cent of cases, more severe organ damage may occur in the kidneys; less commonly in soft tissues (15 per cent), the liver (15 per cent), nerve cells (10 per cent) or the gastrointestinal tract (5 per cent). Early diagnosis is important to ensure that patients receive appropriate treatment in good time [102].

Amyloidosis in Other Organ Localisations

Endocrine amyloidosis in two forms:

- Amyloid deposition in the interstitial space between tumour cells; its production may take place within the epithelial cells. Analysis of amyloid-producing, endocrinologically active tumours shows that amyloid is deposited
- Marked subendothelial deposition. Amyloid is found in the stroma of neuroendocrine tumours (APUDomas). In medullary thyroid carcinomas, amyloid fibrils composed of procalcitonin exhibit a characteristic pattern. In tumours of the endocrine islets of the pancreas (insulinoma), as well as in type 2 diabetes, deposits of amyloid peptide/amylin can be observed [103].

Localised Amyloidoses

According to Glenner, amyloidosis can also occur in a localised or organ-specific form [56]. Isolated amyloids occur exclusively in localised areas, for example on one eyelid, the vocal cords, the cornea, the breast or in both lungs. Due to their morphological appearance, they raise suspicion of a tumour. They may cause functional disturbances and are removed surgically where possible. If clinical symptoms are absent, amyloids may often remain undiagnosed [82].

Organ-limited amyloidoses may be confined to the lymph nodes, the skin, the brain, the respiratory system and the urogenital tract.

Organ-limited cerebral amyloidosis is caused by the deposition of A β protein in the cerebral cortex, which can lead to Alzheimer's-type dementia. Other diseases arising from the A β protein include cerebral amyloid angiopathy and Down's syndrome. Amyloidosis of the heart's atria and the aorta occurs relatively frequently; these conditions arise from atrial natriuretic peptide (ANP) and lactadherin, respectively.

Amyloid deposits localised to the head and neck region and the respiratory tract have been described in the salivary glands, the oral cavity, the pharynx, the paranasal sinuses, the larynx, the trachea, the bronchi and the lungs [96, 104-106]. Amyloid deposits have been observed in the Achilles tendon, the meniscus, the synovial membrane, the os labrum, in cases of gonarthrosis, and in the ligamentum flavum [8,13,80, 89, 90,107].

Hereditary Amyloidosis

ATTR amyloidosis is the most common hereditary amyloid disease, occurring in clusters in Portugal, northern Sweden and certain regions of Japan. Transthyretin (TTR; formerly: prealbumin) is a transport protein consisting of 127 amino acids, which binds retinol and thyroxine in plasma; its plasma half-life is approximately 50 hours. TTR is predominantly synthesised in the liver, with small amounts also produced in the retina and the choroid plexus. The gene is located in the 18q11.2-q12.1 chromosomal region. To date, more than 100 amyloidogenic TTR variants are known [30, 31, 72]. Pathogenic mutations can currently be identified using genetic diagnostic methods. The significance of this is that the deposition of the mutant protein can be reduced using tetramer-stabilising drugs (diflunisal, tafamidis) [Table 4,93].

Table 4: Therapeutic Options for ATTR [93]

- Suppression of ATTR synthesis: liver transplantation, gene silencing
- (siRNA, ASO)
- Use of tetramer stabilisers: tafamidis, diflunisal,
- SOMO226
- Degradation of amyloid fibrils
- Anti-SAP therapy
- Anti-amyloid mAb
- Doxycycline-TUDCA

ASO = antisense oligonucleotide; ATTR = transthyretin amyloidosis;

mAb = monoclonal antibody; SAP = serum amyloid P; siRNA = silencing

ribonucleic acid; TUDCA = tauroursodeoxycholic acid

TTR gene mutations are characterised by various phenotypes: neuropathy, cardiomyopathy, nephropathy and eye problems [18, 72]. ATTR amyloidosis is the most common hereditary amyloid disease. The mode of inheritance is autosomal dominant; the condition occurs not only in young people but is also known to manifest particularly late in life.

For the hereditary form of ATTR, liver transplantation was for a long time the only therapeutic option capable of eliminating the main source of the pathological precursor.

For a long time, liver transplantation has been the only therapeutic option for the hereditary form of ATTR, by which the main source of the pathological precursor can be eliminated. If the transplantation is carried out early enough in the course of the disease, mean survival rate is less than 20 years [93].

Amyloid Deposition Following Long Covid-19 Infection

Amyloidosis has recently and unexpectedly returned to the spotlight in connection with the SARS-CoV-2 pandemic. Tzankov detected ATTR amyloid deposition in 9 out of 70 autopsied cases of so-called 'long COVID-19' infection, of which 6 cases involved cardiac amyloidosis [108]. Burkhardt reported 51 fatal cases following mRNA vaccination. In addition to the immunohistochemical presence of the 'spike protein' underlying these severe adverse

effects and deaths, he also found amyloid deposits in various organs that gave negative immunohisto-chemical reactions [109]. The significance of these findings can only be assessed following more extensive studies.

The Future of Amyloid Research

As a result of the amyloid forums organised biennially by the International Amyloidosis Society (IAS) since 1967, we are currently able to distinguish 42 types of amyloid, which are identified in accordance with established guidelines. The international nomenclature reflects the latest research findings, with the most recent revision taking place in 2022 [110]. Diagnostic methods have become standardised in recent years, largely thanks to the discussions held at amyloid conferences. Testing procedures aimed at determining the aetiology of the disease have become increasingly precise and reliable, but have also become rather expensive and complex over the past 20 years; at the same time, they form the basis for the use of effective targeted therapies.

To conduct detailed investigations into this relatively rare group of diseases, and to trial new treatment methods, clinical amyloidosis centres have been established in the USA, Canada, Brazil and several European countries, including Germany and Hungary. As a result, the diagnosis and classification of amyloidosis, as well as the application of the most appropriate treatments for each type, are becoming increasingly standardised

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