



Clinical Features, Diagnosis and Treatment of amyloidosis: A Review

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Abstract

The name Amyloid is derived from the word "Oid", which means semi-starch, which is a protein that transforms into the shape or amyloid state when a distortion or a change occurs in its secondary structure as it becomes insoluble, shaped, and assembled as beta folded sheets. The structure of the amyloid protein can be seen by the electronic microscope as a group of non-branched fibers, with unspecified lengths and cross-sections between (7.5–10) nanometers. Also, the distinguished structure (the folded beta sheets) is clearly seen, and this structure is responsible for the unique pigmentation that is shown by the amyloid proteins with the Congo red stain.

Keywords: Amyloidoses, AL amyloidosis, Light chain amyloidosis, Transthyretin Amyloid, $\beta 2$ microglobulin

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I. INTRODUCTION

The German botanist Matthias Schleiden used the term "amylon" in 1834 to refer to the waxy starch found in plants. The term "amyloid" was subsequently created by Rudolph Virchow in 1854 to characterize tissue deposits that, when exposed to iodine, stained like cellulose (Sipe *et al.*, 2010). Using the Congo red stain, which was first developed in the 1920s, pathologists now know that amyloid exhibits apple-green birefringence under polarized light and looks pink in normal daylight. Light microscopy is unable to discriminate between the different forms of amyloid. Since the type of protein responsible for amyloidosis can have a significant impact on therapy and prognosis, it is imperative that the pathologist do further investigations to determine with certainty what kind of protein is implicated (Merlini and Bellotti, 2003). Light microscopy or immunogold electron microscopy can be used to speciate amyloid following (Kyle, 2001). Amyloidosis comes in different forms, all of which are brought on by the accumulation and aggregation of certain proteins in bodily tissues and organs. These proteins are found in an aberrant form resembling fibers (amyloid fibrils, amyloid deposits), which accumulate and gradually impair the organs' ability to function normally. (Lachmann *et al.*, 2002). Various proteins are associated with distinct forms of amyloid, and the appropriate identification of the specific amyloid protein is crucial for its management (Comenzo *et al.*, 2006). The condition is known by its general term, amyloidosis, and the aberrant

protein deposits that build up in the body are known as amyloid (Vrana *et al.*, 2009).

The name Amyloid is derived from the word "Oid", which means semi-starch, which is a protein that transforms into the shape or the amyloid state when a distortion or a change occurs in its secondary structure as it becomes insoluble, (Ribes *et al.*, 2022) shaped and assembled as beta folded sheets (Tycko, 2016).

II. AMYLOID PROTEIN

The Amyloid protein structure can be seen by the electronic microscope as a group of non-branched fibers, with unspecified lengths and cross-sections between (7.5-10) nanometers. as shown in Figure 1, Also the distinguished structure (the folded beta sheets) is seen clearly and this structure is responsible for the unique pigmentation that is shown by the amyloid proteins with the Congo red stain. More specifically, amyloid protein consists of 95% of fibrous proteins and 5% of glycoproteins (Chen *et al.*, 2017).

Until now, about 25 types of amyloid proteins were identified and the chemical structure of 15 of them only was distinguished. The most common of these are:

A. AL or Amyloid light chain

It is derived from the plasma cells and they include chains of light immunoglobulins, most of which are of the kappa and lambda types (Esparvarinha *et al.*, 2017) but less than the

former. This type is associated with the diseases resulting from the reproduction of lymphocytes.

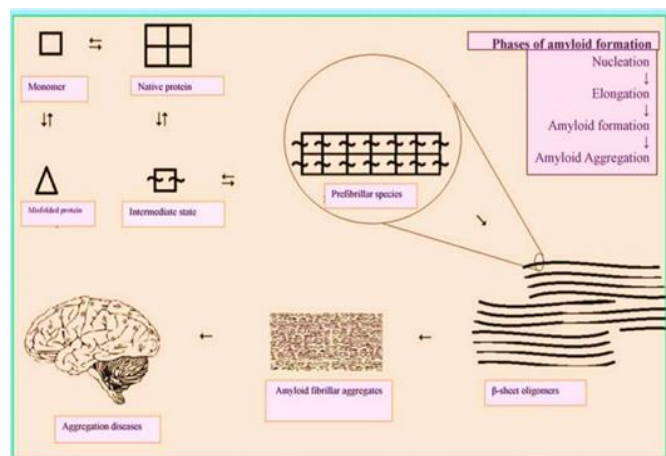


Figure 1. Amyloid proteins structure (Ashraf *et al.*, 2014)

B. AA or Associated Amyloid

They are proteins that don't include immunoglobulins and they are produced in the liver. Their molecular weight is about (18.5) Dalton and they are made up of 76 amino acids and their existence is associated with amyloid disease (Lachmann *et al.*, 2007).

C. βA or Beta Amyloid

They take the shape of beta sheets with a molecular weight of (4000) Dalton and they precipitate in the neural cells and cause Alzheimer disease (Sehar *et al.*, 2022).

D. ATTR or Transthyretin Amyloid

It is called the Transthyretin and it is a mutant form of a plasma protein, which associates and transports the thyroxine and retinol and in deposits in the neural cells and the cells of the heart muscle (Hamilton and Benson, 2001)

E. $A\beta 2 M$ or $\beta 2$ microglobulin

It is a type of natural proteins that exists in the immune system and it was observed that is formed in the patients who have hemodialysis, which is an artificial operation to exclude the wastes and the surplus fluids in the body and it is necessary for the kidneys when they don't function properly (Mallus and Rizzello, 2023).

F. Prion Related Protein (PRP)

This is associated with the Prion disease, which is one of the epidemics resulting from infectious epidemic proteins such as bovine spongiform encephalopathy. The prions can be called infectious protein molecules (Joshi and Ahuja, 2023). Doctor Stanley Brodskis, who is a Nobel prize winner, suggested its name due to his researches and discoveries related to the prions. These prions are made up of protein only, i.e. without any genetic matters (DNA or RNA). This protein exists naturally, and it is not harmful, in all the mammal's membranes and its function is to transport the ions through the cell membranes. When the structure of the

protein changes it becomes harmful and can cause disease. The general structure of the protein might change due to the genetic changes (mutations) or when a harmful protein gene is caught from an external source. In this case, the protein molecules don't suffer proteolysis in the body and they accumulate in the neural cells causing their death (Weigel and Colot, 2012).

The amyloid is associated with more than (50) diseases in humans and these are known as Amyloidosis. It plays an important role in some neural degeneration and some of these disorders (Buxbaum *et al.*, 2022) which basically considered individual and some case are genetic, while some other are totally genetic. Some of them result from using a medication including one of the infectious amyloids, which is called the prion as it can act as a template that transforms other non-infectious proteins into an infectious one.

Amyloid might precipitate on a wide scale in the body, as is the case of Amyloidosis or might precipitate in the organs with a limited level. For instance, it precipitates in the pancreas and causes type-2 diabetes (Alrouji *et al.*, 2023), precipitates in the central neural system and causes, Alzheimer, Parkinson, Huntington or bovine spongiform encephalopathy (Race *et al.*, 2018).

III. AMYLOIDOSIS

This disease results from the precipitation of abnormally-folded proteins and amyloid fibers that accumulate in the different tissue and organs and they sometimes lead to a dysfunction of the organs, failure and death (Picken, 2013). Amyloidosis is regarded as of the challenging diseases that is still a medical riddle in terms of the formation of the amyloids, their types and their treatment in spite of the advances that took place recently in this respect.

the disease is called amyloidosis due to the dye of amyloid protein is similar to starch dye and amyloid is formed from protein, which consists of very thin filaments, which are stiff, non-branched, insoluble and non-biodegradable. If a continuous increase in their quantity and size occurs inside the body, they precipitate outside the cells in one location or several locations and organs in the body (Ow and Dunstan, 2014).

IV. CAUSES OF AMYLOIDOSIS

Amyloidosis results from a dysfunction in the metabolism of one of the proteins derived from Alpha globin, which is called amyloid (starch analogue) and this dysfunction leads to a large increase in producing it in the body and this makes it precipitate in one or more than one organ in the body. Recently, it was observed that there is a complication and great difficulty in classifying the amyloids and the diseases they cause (Sinnige, 2022).

All the types of amyloidosis have a protein, which is abnormally folded (all the proteins are long chains of molecules that are folded in a certain way). Folded proteins agglomerate in an abnormal way together and accumulates

in various tissues. These accumulations of amyloids precipitations are called the amyloid fibrils. There are different proteins that can be folded abnormally and can form amyloid precipitations. All these proteins are produced in the body and they don't come from the dietary system (Ikura *et al.*, 2022).

Some proteins are mutated copies of the natural proteins, while the rest of them are natural but they simply tend to be abnormally folded. The production of some amyloids proteins occurs due to certain chronic or infectious diseases (Galkin and Sysoev, 2021).

V. GENESIS OF AMYLOIDOSIS

The human bone marrow produces red blood cells, white blood cells and blood platelets in addition to certain proteins that are called the antibodies (Boes and Durham, 2020).

It is known that these antibodies play their role in resisting the inflammation and the various microbes and after fulfilling their task, the body destroy them and reproduce them again to resist other microbes and infections. Amyloidosis occurs when the bone marrow produces the antibodies that can't be destroyed by the body after they accomplish their task and so they increase in the blood stream gradually and this makes them precipitate in one or more than one organ of the body (Shi *et al.*, 2022) like the heart, kidneys, liver, spleen, skin, mucus membranes, striated muscles, brain, nerves, joints, respiratory, or digestive system and this leads to a disorder and dysfunction in the function of the infected organ and symptoms of the disease begin to appear (Zerdan *et al.*, 2023).

VI. CLASSIFICATION OF AMYLOIDOSIS

Amyloids precipitations are of two types according to the infection location:

A. Systemic amyloid deposits

They spread in all the locations of the body and they might infect more than one organ in more than one location. The systemic amyloid disease is represented by a type of light amyloid series and it results from abnormal plasma cell reproduction as shown in Figure 3 and leads to some diseases such as myelomatosis and osteoarthritis in the thigh bone (Milani *et al.*, 2017). This type also causes high portions of immune globulin in the blood and this problem can lead to infection with leukemia or some autoimmune diseases including lupus erythematosus, collagen, rheumatoid arthritis, ulcerative colon inflammation and other diseases (Jin *et al.*, 2020).

Crohn's disease, ulcerative colitis, tuberculosis celiac disease are considered among systemic amyloidosis in addition to the spine illnesses like ankylosing spondylitis, Mediterranean fever and familial mediterranean fever (Barahona-Correa *et al.*, 2021).

Systemic amyloidosis is branched also to amyloidosis that is related to blood dialysis due to the precipitation of globulin-

derived fibers as this type accumulates for the patients who suffer from kidneys failure due to the blood dialysis for prolonged periods. the disease targets also joints and bones (Scarpioni *et al.*, 2016).

B. Local amyloid deposits

Local amyloidosis occurs when the amyloid precipitates in certain organs or tissues. For example, the amyloids accumulate in the brain for Alzheimer patients and it is thought that it plays an important role in terms of causing this disease. Also, some amyloids precipitations might occur in the skin or the digestive or the respiratory track or the bladder (Morelato *et al.*, 2021).

The intensity of the disease appears depending on the organ infected with the amyloids precipitations. Genetic and non-genetic forms of amyloidosis and it is currently classified chemically. The chemical classification of the amyloids is the current criterion and this can be done through a thorough examination of biopsy of the tissue to detect the type of the protein that is considered the unique description of the relevant disease (Hemminki and Försti, 2021).

Three types of amyloidosis can be identified and each of these types begins with the letter "A" from the word (Amyloidosis) and the second letter denotes the name or the type of the precipitated protein (the antibodies) (Picken, 2020). These types are:

- **Primary Amyloidosis - Amyloid light chain (AL)**

It is the most common and it represents (80%) of the cases diagnosed. The incidence occurs when the bone marrow produces strange non-degradable antibodies, which precipitate and the amyloid also precipitate in the tissues and this causes a disorder in the body functions and the reason is always a tumor in the marrow. This type can affect the heart, kidneys, nerves and the tongue (Figure 2) (Baker, 2022).



Figure 2. Effect of the primary Amyloidosis on the tongue (Babburi *et al.*, 2013).

The proteins precipitated in the body, in the case of this type, are the immune globulin proteins (Chain Protein Light). This type of amyloidosis is treated using chemical therapy (Bianchi *et al.*, 2021).

- **Secondary amyloidosis -Associated Amyloid (AA)**

It occurs due to severe chronic infection like rheumatoid arthritis or inflammatory bowel syndrome and the protein

responsible for it is the protein of the serum SAA that is produced in the liver due to the death of some cells as a result of contaminations or chronic diseases such as tuberculosis and some types of cancer (Adams *et al.*, 2019). This type appears in several tissues like the liver, kidney, and adrenal gland, heart and the peripheral nervous system (Ihne *et al.*, 2020). This type is treated mostly through the surgical intervention, which improves the health of the patient considerably and halts the progress of the disease (Salem *et al.*, 2021).

• Familial amyloid

It is a rare type of amyloid that results due to mutations in the gene responsible for the decoding of transthyretin protein. This protein is essentially produced in the liver and this type could also be called senile systemic amyloidosis, which occurs due to abnormal folding of the protein that connects the thyroxine that precipitates in various organs and various tissues (Tao *et al.*, 2023).

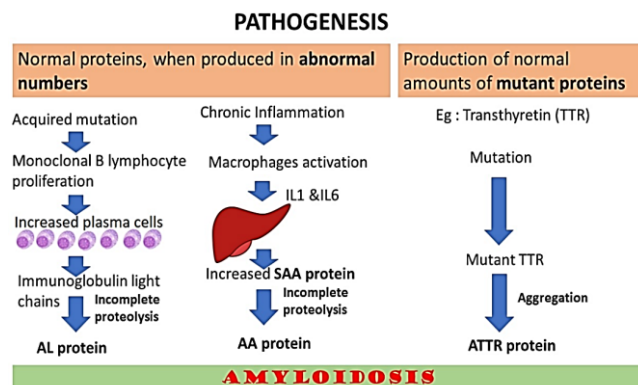


Figure 3. Pathogenesis of amyloidosis (Shankar, 2017)

VII. SYMPTOMS OF AMYLOIDOSIS

The large amounts of amyloid precipitations lead to defects in the natural functions of several organs and there are few symptoms for some patients, whereas others are infected with a severe disease that threatens their lives (Wilkinson *et al.*, 2017). The symptoms of amyloidosis are presented by fatigue and weight loss and other symptoms are associated with the location in which the precipitation of amyloid is formed (Vaxmana and Gertza, 2020).

When the precipitations are in the heart, a patient might suffer from difficulty of breathing, weakness or faint. When the precipitations are formed in the nerves, then the patient suffers from tingling or numbness in the fingers or toes or feels dizzy when he stands up (Sandstrom, 2014). Moreover, when precipitation is in the kidneys, the patient may suffer from swelling in the feet and legs and sometimes in the belly, but when it is in the skin bruises appear commonly and this can happen around the eyes and the tongue swelling (macroglossia) as well in certain occasions (Senecal *et al.*, 2023).

There are some symptoms that can be identified, which confirm the infection with amyloid, they are:

- Continuous feeling with exhaustion and unjustified fatigue
- Bruises in the body
- Peripheral edema
- Difficulty in breathing
- Unjustified weight loss
- Numbness in the limbs
- Weak hearing
- (Macroglossia) swelling of the tongue
- Treatment

With the development of new chemotherapeutic drugs within the past ten years, the management of amyloidosis has undergone a significant shift. Although overall survival has increased as a result, there are still issues with advanced disease, where the median survival rate is still extremely low.

Blood indicators, such as brain natriuretic peptides and troponin, influence the choice and length of approaches to therapy (Perrone *et al.*, 2022).

Although treatments will continue to evolve, early detection is always the major goal.

diagnosis prior to the occurrence of end-stage organ failure. Extending the amyloid-exclusive immunotherapeutic targeting of amyloid deposits in the therapeutic landscape show potential for modify the course of amyloidosis (Ikura *et al.*, 2022).

VIII. CONCLUSION

A very uncommon disorder called amyloidosis is brought on by the build-up of different types of normal and aberrant proteins in different body tissues. Correct identification of the kind of amyloid is necessary before initiating effective therapy. A wide range of subspecialists must carefully coordinate their care in order to treat these complex patients. Since successful treatments for AL and other forms of amyloidosis have been developed, and since the efficacy of therapeutic intervention depends on the earliest possible diagnosis, this has become even more crucial.

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