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"PATHOPHYSIOLOGY OF AMYLOIDOSIS"- AN AYURVEDIC VIEW

Helen G Monica[1], Prashanth Jain[2], Geetha B Markande[3]

[1]3rd year PG Scholar, [2]HOD, Associate Professor, [3]Associate Professor
(Department of PG Studies in Roganidana Evum Vikruti Vigyan) Alvas Ayurveda Medical College and Hospital, Moodbidri, Karnataka, India

Email: monicajithayu@gmail.com

ABSTRACT

Amyloidosis is a group of diseases having common deposition of similar appearing proteins. Symptoms in patients with amyloidosis result from abnormal functioning of the involved organs. Amyloidosis occurs in about 3-13 per million people per year. The usual age of onset of the types of Amyloidosis is 55 to 60 years old. In the developed world about 1 per 1000 people die from Amyloidosis. Amyloidosis has been described since at least 1639.Fundamentally it is a disorder of protein misfolding as a result of immunologic mechanisms. Depending on the structure of the particular amyloid, the protein can accumulate in an isolated tissue or be widespread, affecting numerous organs and tissues. There are over 30 different amyloid proteins. Each amyloid protein is arranged in a structure called a fibril. Fibrils are low molecular weight proteins that are derived from precursor proteins. Fibrils of amyloid can float in the plasma of blood and deposit into tissues of the body. The Ayurvedic treatment of this condition is aimed at treating the presenting symptoms and preventing organ failure. For diagnosis of the disease understanding the disease in Ayurveda is utmost important. The understanding of the mechanism of amyloidosis in various viewpoint of Ayurveda helps us to understand better and treat accordingly.

Keywords: Amyloidosis, Immunology, Ojas

INTRODUCTION

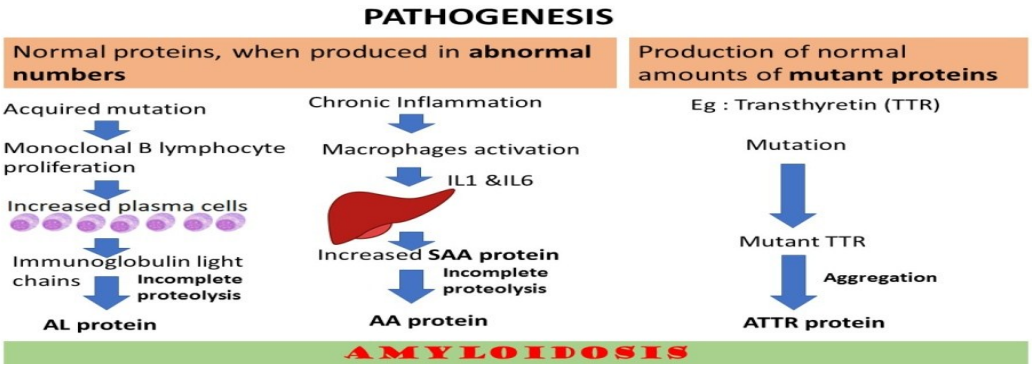
Immunologic mechanisms are suspected of contributing to many diseases. Among them amyloidosis is one. It is a systemic disease that involve components of immune system. Amyloid is the pathologic proteinaceous substance deposited between cells in various tissues and organs of the body in a variety of clinical settings. Amyloidosis is the term used for a group of diseases characterized by extracellular deposition of fibrillar proteinaceous substance called amyloid having common morphological appearance, staining properties and physical nature but with variable protein composition[1].

Pathogenesis:[2]

The basic mechanism in the pathogenesis of amyloidosis results from abnormal folding of proteins which are deposited as fibrils in extracellular tissues unstable and self-associate ultimately leading to the formation of oligomers and fibrils that are deposited in tissues. Under

normal circumstances these abnormal or misfolded proteins are degraded intracellularly in proteasome pathway and by macrophages extracellularly. In amyloidosis, these control mechanism fails or there may be mutations which favor misfolding which further leads to accumulation and aggregation to form fibrils.

Figure 1: (Pathogenesis of Amyloidosis)



The pathogenesis is broadly categorized into

- Acquired mutation
- Chronic inflammation.
- Production of normal amounts of mutant proteins.

Acquired Mutation: Acquired mutation lead to monoclonal B lymphocytes proliferation which in turn increase the plasma cells. As plasma cells are the one which synthesize immunoglobulins there will be increased production of immunoglobulin light chain. When there is abnormal number of normal proteins, they misfold abnormally leading to incomplete proteolysis which accumulate the amyloid protein (Amyloid light chain protein) or AL protein.

Chronic Inflammation: When there is chronic inflammation there will be activation of macrophages. These macrophages release IL1 and IL6 (Interleukin 1 and Interleukin 6). These IL1 and IL6 in the liver produce increased amount of acute phase protein (Serum Amyloid Associate Protein or SAA protein). When there is incomplete proteolysis these proteins lead to the accumulation of amyloid associated protein (AA protein).

Normal Amounts of Mutant Proteins: Production of normal amounts of mutant proteins e.g: Transthyretin (TTR) Whenever there is mutant of genes there will be mutant transthyretin. This mutant transthyretin is resistant to degradation. These lead to aggregation and inturn lead to accumulation of Amyloid ATTR protein.

Bio-Chemical Forms:[3]

Table 1: (Bio-Chemical Forms of Amyloid Protein)

AL Protein	AA Protein	β-Amyloid protein (Aβ)	Transthyretin (TTR)
Complete Ig light chains/amino terminal fragment of light chains/both	Non- immunoglobulin. They are acute phase proteins	Trans membrane glycoprotein	It is a normal serum protein
Secreted by mono-clonal population of plasma cells.	Derived from SAA protein which is synthesized from liver.	Derived from proteolysis of amyloid precursor protein	_
Causes Plasma cell tumors	Causes Chronic inflammatory disorders	Causes Alzheimer's disease	Mutant forms are deposited in familial amyloid polyneuropathies

			Normal form is deposited in heart of aged patients ie) Senile Cardiac amyloidosis.

Classification:[4]

Table 2: (Classification of Generalized/ Systemic amyloidosis)

Generalized/Systemic amyloidosis	Precursor protein	Fibril protein	Associated diseases
Primary amyloidosis	Ig light chain	AL	Multiple myeloma and other plasma cell dyscrasias
Secondary amyloidosis	SAA	AA	Chronic inflammation
Haemodialysis associated	β_2-m	Aβ_2-m	Chronic renal failure

Table 3: (Classification of Localized amyloidosis)

Localized Amyloidosis	Precursor protein	Fibril protein	Associated diseases
Senile Cerebral	APP	Aβ	Alzheimer's disease
Endocrine: Thyroid	Calcitonin	Acal	Medullary Ca Thyroid
Islet of Langerhans	Islet Amyloid Peptide	A_1APP	Type 2 diabetes

Table 4: (Classification of Localized amyloidosis)

Hereditary Amyloidosis	Precursor protein	Fibril protein	Associated diseases
Familial Mediterranean fever	SAA	AA	-
Familial Amyloidotic Neuropathy	Transthyretin	ATTR	-
Systemic Senile Amyloidosis	Transthyretin	ATTR	-

Generalized /Systemic Amyloidosis:[5]

- **Primary Amyloidosis:**

In primary amyloidosis the precursor protein is immunoglobulin light chain and the fibril proteins are AL type. It is often severe in heart, kidney, bowel, skin, respiratory tract, skeletal muscle and other organs.

- **Secondary /Reactive Aa Amyloidosis:**

It is also referred to as reactive systemic amyloidosis. The precursor protein in these conditions are serum amyloid associated (SAA) and fibril protein is AA type. It can occur at any age including children. It occurs typically as a complication of chronic infection. They are distributed in solid abdominal viscera like kidney, liver, spleen and adrenals. Seen in inflammatory conditions like pyelonephritis, chronic osteomyelitis, ankylosing spondylosis, rheumatoid arthritis etc

- **Haemodialysis Associated Amyloidosis:**

Patient on long-term dialysis for more than 10 years for chronic renal failure develop systemic amyloidosis. β_2-microglobulin is increased in the serum of dialysis patients. In the past β_2-microglobulin could not be filtered by dialysis, which lead to the deposition of Aβ_2 microglobulin. In the present era there are good dialysis filters which can filter the Aβ_2 microglobulin. Thus, there is decreased incidence of haemodialysis - associated amyloidosis.

- **Localized Amyloidosis:**

The amyloid deposits are limited to a single tissue or organ without involvement of any other site in the body.

- **Senile Cardiac Amyloidosis**: Senile cardiac amyloidosis is seen in 50% of people above the age of 70 years. The deposits are seen in heart and aorta.
- **Senile Cerebral Amyloidosis:** Senile cerebral amyloidosis is a heterogenous group of amyloid deposition. Deposits are seen as congophilic angiopathy, neurofibrillary tangles and senile plaques. Ex: Alzheimer's disease, Down's syndrome etc.
- **Tumour -Forming (Al):** Isolated tumour like formation of amyloid deposits are seen in lungs, larynx, skin, urinary bladder, eye. In most cases the amyloid type is AL.

- **Heredofamilial Amyloidosis:**
- **Familial Mediterranean Fever:** The amyloid fibril proteins are made up of AA proteins. This amyloidosis related to recurrent bouts of inflammation that characterize the disease. The most common example is an autosomal recessive condition called "Familial Mediterranean fever". It is widespread amyloidosis with precursor proteins is AA type.
- **Familial Amyloidotic Neuropathy:** It is an Autosomal dominant condition. Deposition of amyloid in peripheral and autonomic nerves. Fibrils are made up of mutant TTR's.

In Ayurveda different mechanisms that can account for amyloidosis are enlisted below:

1. *Ojas:* Amyloidosis is one among the immune disorders. Dis-equilibrium in immune system culminate in vast array of diseases. If immune system is over-active the body attacks and damage its own tissues. Hypersensitivity is a state of altered reactivity in which the body reacts with exaggerated immune response.

Persistent *Ashuddha Rasa Dhathu* causes formation of *Ashuddha Ojus (Apara)* in *Dhathus.*[6] A potent infection at this *Ashuddha Apara-Ojus* can cause *Dhathu-Paaka.* When inflammation develop due to *Upadhathu-Ojo-Vyapat* it cannot be metabolized and it form *Saama Rasa (Aama-Visha).* Auto-immune diseases are examples of *Upadhathu-Ojo-Vyaapat.* Decrease of *Upadhathu Ojus* is identified with infections or *Vyabicaari* causes. Alteration in *Ojo-Vyapat* leads to cancerous growth. *Dhathu-Leena Saama-Dosha* if didn't get metabolized remains in *Dhathu* itself and eventually lead to *Ojo-Vyaapat.*

Aama Visha in *Rasa Dhathu* causes inflammation which cannot be metabolized. *Aama Visha* plays the prime role in causing *Ojo-Vyapat* of *Upadhathu-Ojas*.

In सु.सु *Ojo Kshaya Lakshanas* are explained[7]

"मूर्च्छा मांसक्षयो मोह: प्रलापोऽज्ञानमेव च/

पूर्वोक्तानि च लिङ्गानि मरणं च बलक्षये//"

Fainting, depletion of muscles, unconsciousness, delirium, improper perception of knowledge, death are the symptoms of *Ojo Kshaya* which share the same symptoms with the disease amyloidosis.

2. *Dhatwagni:* *Agni Dusthi* is the prime cause for development of toxins in the body.[8]Proteins are supplied to all tissues in the body by *Rasa-Dhathu.* Tissue absorb protein with the help of *Samana Vayu* and *Dhatwagni. Dhatwagni* is kindled or enfeebled according to the metabolic needs of the tissue. Due to dysfunction of tissue metabolism will not be taking up the protein from the *Rasa Dhathu.* The *Dhatwagni* will not be able to utilize or metabolize the same. So more the agni-hypo functioning, samana dysfunction causes interference in transformation. In the tissue *Saama-Dosha* produces "accumulation of metabolic wastes" and causes dysfunction of tissue metabolism and obstruction in all channels. The partially or incompletely metabolized *Poshaka Dhathus* due to disturbance in *Dhatwagni* are known as "*Ama* and *Malas*".[9]

3. Aama: *Saama Dosha* or *Visha* get lodged in tissue (*Dhathu-Leena*-state of *Dosha/Visha*)[10] causing *Ojo-Dushti* producing *Balavyapat* of the tissue. Whenever *Dhatwagni* fails to transform Rasa-Dhathu rasa develops Guru-Sheetha-*Snigdha-Picchila* properties. As tissue cannot assimilate the *Apakva Rasadhathu* it impairs further metabolism lead to aama formation E.g.) the accumulated proteinaceous substance in amyloidosis.

- ***Kha-Vaigunya:*** According to *Vyaadhi-Nidana, Kha-Vaigunya* develops and *Saama-Dosha* gets lodged (*Sthaana Samshraya*) at the site of *Kha-Vaigunya.* The *Kha-Vaigunya* develops due to impairment of *Agni* resulting in obstruction to *Posaka Dhathus* leading to stasis of *Malas.*[11]The site where interaction take place is stated to be the region where process of disease is initiated. Localized Amyloidosis one among the classification of amyloidosis which comes under this concept.
- ***Aama-Visha:*** *Aama Visha* is toxic metabolites in *Rasa Dhathu. Aama Visha* is also the cause of autoimmunity/hypersensitivity/cancers. [12]*Aama Vishas* paves way for chronic inflammation of auto immune diseases like amyloidosis.
- ***Mala Sanchaya:*** ..... केचित् मल संञ्चयम्// (M.N 25/5)[13] **-** The term *Mala Sanchaya* is used to designate "*Ama".* These are the metabolic waste products that are not properly eliminated by the body. These accumulated waste products formed are also termed as *Kleda*. Accumulated *Kleda* in the body are called as "*Ama*" by certain authors.[14]

4. *Dhathu Paaka:*

Dhathu Paakam is the sudden destructive change in the *Dhathu.* In *Dhathu Paaka* there is stasis of metabolic waste resulting in destruction of *Ojas* in a tissue, which results in destruction. Destructive changes that take place in auto immune diseases is by *Dhathu Paaka.*[15]In living cells the proteins are hydrolysed into their constituent amino acids, and these molecules constantly break down to form new protein molecules. Some of the proteins molecules when not degraded normally form amyloid proteins. Amyloid protein is abnormal that the body cannot break down and recycle. This accumulation of amyloid protein in tissues lead to the disease amyloidosis. Same is explained in *Dhathu Paaka* where there is absence of sequence of replenishment of seven *Dhathus* which is important for maintaining the homeostatic condition of body[16]. Instead there is stasis of metabolic waste, reduced *Poshana* to *Dhathus* which lead to *Balakshaya* which shares similar clinical feature with amyloidosis.

5. ***Avarana:*** Whenever there is accumulation of *Kapha* there is *Dhathugata Mala Sanchaya.* Accumulation of unwanted metabolic waste also lead to *Dhathugata Mala Sanchayam.* Here the *Sanchitha Mala* behave equal to *Kapha Avaranam. Avarana* is not only the occlusion in *Srotas,* even the unwanted protein in the body shares the same scenario. Amyloid protein, α protein, β protein seen in amyloidosis is nothing but the accumulation of kapha.[17] The untreated *Avarana* progress the disease condition and lead to *Bala Kshaya.*

DISCUSSION

Ojas is responsible for health maintenance, health promotion, fight disease and prevent disease. Loss of *Ojas* amounts to the loss of life itself. It constitutes the essence of all *Dhathus* (tissues). The Elan Vital owes its existence to it. Low quality of *Dhathus* lead to low quality *Ojas.* If all the *Dhathus* are balanced in terms of quality and quantity the *Ojas* too will be formed and balanced in a good way. In the disease Amyloidosis the amyloid protein is embedded in the tissue causing obstruction to the flow of nutrition is a result of impaired immunologic mechanism. Effective extraction and absorption of nutrition is due to proper functioning of *Agni*. When the *Dhatwagni* is enfeebled produces "accumulation of metabolic waste" can be understood as the amyloid in the disease Amyloidosis. Amyloid deposition causes pressure on adjacent cells result in atropy. The amyloid deposition in blood vessels result in narrowing and increased permeability lead to the transudation of protein out of vessels. This *Mala Sanchaya* lead to *Avarana* which in turn lead to destructive changes in the tissue i.e.) *Dhathu Paaka. Kapha* in its natural state promotes strength in the form of *Ojas.* When in morbid condition takes the form of excrete as *Kapha Avarana*. The symptoms of the disease Amyloidosis are vague and is necessary to diagnose with recent advance techniques like biopsy, congored staining, SAP Scan and Genetic testing. This rare, uncommon disease have a median survival rate of two years with diagnosis. So, understanding the Pathophysiology of Amyloidosis in different views of Ayurveda is the need of the hour in this epoch for the better treatment regimen.

CONCLUSION

Amyloidosis is frequently discovered after significant organ damage. An early and definite diagnosis of this condition is very important. Precise diagnosis is important because treatment varies greatly, depending on specific conditions. Immune response and metabolic reaction are inter-related and proper functioning of one is dependent on the other. When *Doshas* remain latent in *Dhathus* it can lead to *Maha Rogas* or *Bala-Vyapat.* So, maintaining normal functions of *Dhatvangni* and *Ojas* thereby bringing back the affected *Dhathus* from *Dhathupaaka* by removing *Aama* and *Aavarana* from the body helps to overcome this deadly disease.

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