"PATHOPHYSIOLOGY OF AMYLOIDOSIS"- AN AYURVEDIC VIEW

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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 composition¹.

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 in turn lead to accumulation of Amyloid ATTR protein.

**Bio-Chemical Forms**

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

IAMJ: Volume 8, Issue 4, April - 2020 (www.iamj.in)
Normal form is deposited in heart of aged patients ie) Senile Cardiac amyloidosis.

### Classification:

#### Table 2: (Classification of Generalized/ Systemic amyloidosis)

<table>
<thead>
<tr>
<th>Generalized/Systemic amyloidosis</th>
<th>Precursor protein</th>
<th>Fibril protein</th>
<th>Associated diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary amyloidosis</td>
<td>Ig light chain</td>
<td>AL</td>
<td>Multiple myeloma and other plasma cell dyscrasias</td>
</tr>
<tr>
<td>Secondary amyloidosis</td>
<td>SAA</td>
<td>AA</td>
<td>Chronic inflammation</td>
</tr>
<tr>
<td>Haemodialysis associated</td>
<td>β2-m</td>
<td>Aβ2-m</td>
<td>Chronic renal failure</td>
</tr>
</tbody>
</table>

#### Table 3: (Classification of Localized amyloidosis)

<table>
<thead>
<tr>
<th>Localized Amyloidosis</th>
<th>Precursor protein</th>
<th>Fibril protein</th>
<th>Associated diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Senile Cerebral</td>
<td>APP</td>
<td>Aβ</td>
<td>Alzheimer's disease</td>
</tr>
<tr>
<td>Endocrine: Thyroid</td>
<td>Calcitonin</td>
<td>Acal</td>
<td>Medullary Ca Thyroid</td>
</tr>
<tr>
<td>Islet of Langerhans</td>
<td>Islet Amyloid Peptide</td>
<td>A1APP</td>
<td>Type 2 diabetes</td>
</tr>
</tbody>
</table>

#### Table 4: (Classification of Localized amyloidosis)

<table>
<thead>
<tr>
<th>Hereditary Amyloidosis</th>
<th>Precursor protein</th>
<th>Fibril protein</th>
<th>Associated diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial Mediterranean fever</td>
<td>SAA</td>
<td>AA</td>
<td>-</td>
</tr>
<tr>
<td>Familial Amyloidotic Neuropathy</td>
<td>Transthyretin</td>
<td>ATTR</td>
<td>-</td>
</tr>
<tr>
<td>Systemic Senile Amyloidosis</td>
<td>Transthyretin</td>
<td>ATTR</td>
<td>-</td>
</tr>
</tbody>
</table>

### Generalized /Systemic Amyloidosis:

- **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 spondylitis, rheumatoid arthritis etc

- **Haemodialysis Associated Amyloidosis:**
  Patient on long-term dialysis for more than 10 years for chronic renal failure develop systemic amyloidosis. β2-microglobulin is increased in the serum of dialysis patients. In the past β2-microglobulin could not be filtered by dialysis, which lead to the deposition of Aβ2 microglobulin. In the present era there are good dialysis filters which can filter the Aβ2 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. 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-Vyaapat of Upadhathu-Ojus. In चुरु चुरु "Ojo Kshaya Lakshanas are explained\(^7\)

"प्रत्यौर्गङ्गः मासाः योगः, प्रत्याङ्गःजाथमेव च/ पूर्वोपकारिः विहिनसां मयं च बलवते/"

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-Dushhti producing Balavayapat 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 Visha paves way for chronic inflammation of auto immune diseases like amyloidosis.

- **Mala Sanchaya:** ......... कृपया मल संचययम्/ (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. 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. 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. 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 atrophy. 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, congered 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 Dhatvagni 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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Source of Support: Nil
Conflict of Interest: None Declared

How to cite this URL: "Helen G Monica et al: Pathophysiology Of Amyloidosis"- An Ayurvedic View. International Ayurvedic Medical Journal {online} 2020 {cited April, 2020} Available from: