Rare Types of Amyloidosis and their Pathogenesis:
Targets for Innovative Therapy

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Abstract

Amyloidosis light chain (AL) which is caused by abnormal immunoglobulin storage with idiopathic feature or is precipitated by B cell or plasma cell tumors often occurs throughout the body as the most frequent type of amyloidosis. There are also other kinds which are the result of genetic disorders or other acquired abnormalities such as infections, chronic inflammation, or other tumors. These disorders may cause abnormal storage at limited sites which may be handled with local treatment. However, the storage sites may also be distributed through systemic involvement. Chemotherapy or other therapies have not been successful in the treatment of these types. Prevention of complications from the disease is an important issue of concern. Studying the mechanisms of the disease leads to innovations that can be used in targeted therapy which may be more effective in reducing the accumulation of abnormal proteins.

Keyword: amyloidosis, targeted therapy, genetic disease

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Introduction

Amyloidosis is a syndrome in which there is an abnormal accumulation of a natural human protein derivative termed amyloid which infiltrates the extracellular component of body organs. It was first recognized and recorded 400 years ago but Virchow was the first to use this term in 1854 CE. It is related to the word describing the starch in plants that can be stained with iodine dye to differentiate it from cellulose powder. Amyloid can be dyed in the same way. It is tolerant to normal proteolysis and forms itself into a three dimensional β-pleated sheet. It weighs 5–25 kilodaltons and is currently found as 25 subtypes in humans and 8 in animals.1

This disease is not actually rare since in western countries it is as common as Hodgkin disease.5 Its incidence has been reported to be 12 per million per year but this figure might actually be higher if autopsies had been conducted on all potential cases.2 Amyloidosis is rarely hereditary but it is common as an acquired type. The latter can be sub-divided further into primary amyloidosis (AL), and secondary amyloidosis3 which results from other causes such as tumors, chronic infections, and inflammatory autoimmune diseases. In addition, its subtypes can be classified in other fashion as a local type that is mostly diagnosed by autopsy in asymptomatic cases, and a systemic type that is more frequently found with an obvious clinical appearance. The localized type constitutes a quarter of all occurrences. Each variant among the primary and secondary types can express their symptoms either with the limited or generalized involvement of body systems. More detail is mentioned later in this review and concluded in table 1.

The important reason to review these types of amyloidosis is to warrant the readers to recognize them as which differ from more common type AL upon
prognosis and treatment. Their rarity can make us unfamiliar to treatment. The differential diagnosis between types is important to use its specific treatment other than chemotherapy like as AL. As other diseases, the progression of treatment is accorded to more understanding of their pathogenesis. There are now innovative interventions that will be reviewed later in the content to change the conventional as passive style to be more efficacious.

**Hereditary Amyloidosis (Table 1)**

**Local type**
Firstly, the localized skin type could present with infiltration of keratin fibrils resulting in multi-sized macular or papular rashes on the skin. This is caused by genetically controlled precipitation of cutaneous lichen amyloidosis or it might be found as part of multiple endocrine neoplasia (MEN) type II.4 Ocular regions in the cornea could be involved, with symptoms ranging from corneal turbidity to a mass. This involvement could be found within systemic lattice dystrophy type II, a disorder in the group termed familial Finnish type which has the mutant Gelsoline gene5 or vitreous amyloidosis which has mutant transthyretin (TTR) molecules.6 Cardiac amyloidosis also has an abnormal TTR gene which mostly results in local accumulation in the heart. A previous study reported that 350 patients who had first suspected AL had no family history related to amyloidosis were later found to have a genetic disorder which was mostly TTR and α fibrinogen A mutation with a value of 9.7%7 Cerebral amyloidosis8 is caused mostly by congenital disorders because of the difficulty of acquiring storage across the blood brain barrier. Alzheimer’s disease,9 which affects 12 million people worldwide, is an example of this type of disorder. The process may start at an early age, with aging being an important factor in the development of this disease. The symptoms are memory impairment, dementia, and behavior change. This autosomal dominant (AD) disease is caused by point mutation on chromosome (Chr) 21 at the β-amyloid precursor protein (APP), which results in abnormal cerebral storage of this protein. These pathologic cerebral findings are not usually concordant with the symptoms. Furthermore, there are other diseases involving the cerebral areas such as the Icelandic type which produces cystatin C, and the Dutch type which produces β-Amyloid. Both are AD mutations which cause neurological disorders and cerebrovascular accident in middle age.10 Other diseases could be related to mutations of the prion region on Chr 20. Twenty mutations have already been found which cause Gersatzfeld–Jakob disease and Gerstmann–Straussler–Scheinker syndrome. The latter had symptoms of cerebellar insufficiency in the early phase which then progressed to dementia. It has been discovered to be related to Prion protein gene (PRNP) defect and transmit with AD manner.11 Another disease, transmissible spongiform encephalopathy, which involves Kuru amyloids, can trigger an encephalopathy episode.

**Systemic type**
It can be grouped into 4 subtypes. Familial amyloid polyneuropathy (FAP) is an AD transmitted disease which has been found in Swedish, Japanese and Portuguese patients. Most patients had symptoms during the early adult period with peripheral, autonomic neuropathy, and systemic organ involvement. The symptoms and abnormal storage increased with time. The length of survival was approximately 10 years after diagnosis. This disease had point mutations on the gene which coded for the TTR protein on Chr 18 and it has already been found in more than 100 mutations. This congenital mutation is the most common form in the USA. It is equally common in both sexes and causes infiltration predominantly in the heart. FAP predominantly involving cranial neuropathy is most commonly found in Finnish patients and affects the middle–aged. The survival rate is the same as that of the general population. It is also AD inheritance with an abnormal gene at Chr 9 which has been increasing in actin–modulating protein or gelsolin. Secondly, hereditary non–neuropathic systemic amyloidosis which
has no neurological involvement is responsible for the abnormal production of ApoAI, lysozyme and fibrinogen α–chain protein. It begins in early adulthood with AD penetration. Skin, gastrointestinal and liver might be involved in this disease. The patients could be affected later with hypertension and renal failure. The third form which had abnormal fibrinogen deposits occurred most in England and northern Europe. The last form was systemic Familial Mediterranean fever (FMF). It is an autosomal recessive penetrating disease with the following symptoms: intermittent fever, abdominal pain, pleuritic chest pain, and arthritis for 2–4 days. It could provoke renal failure. Without treatment, this type could lead to systemic AA.

**Acquired Amyloidosis (Table 1)**

A change in natural protein degradation can occur in normal populations due to increasing age. Senile amyloidosis is an example of local infiltrating β–amyloid occupying cerebral vessels, cartilage and joint capsules, β2–microglobulin (β2M) in the corpora amylacea of the prostate, and lastly atrial natriuretic peptide in the cardiac

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**Table 1. Amyloid Proteins and Their Precursors.**

<table>
<thead>
<tr>
<th>Distribution</th>
<th>Amyloid Protein</th>
<th>Precursor</th>
<th>Type</th>
<th>Syndrome or Involved Tissues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localize</td>
<td>Aβ</td>
<td>Aβ protein precursor</td>
<td>Acquired Hereditary</td>
<td>Sporadic Alzheimer’s disease, Aging Prototypical hereditary cerebral amyloid angiopathy, Dutch type</td>
</tr>
<tr>
<td></td>
<td>APrP</td>
<td>Prion protein</td>
<td>Acquired Hereditary</td>
<td>Sporadic (iatrogenic) CJD, new variant CJD (alimentary?)</td>
</tr>
<tr>
<td></td>
<td>AA</td>
<td>Serum Amyloid A</td>
<td>Acquired</td>
<td>Secondary, reactive and chronic infection including hereditary periodic fever</td>
</tr>
<tr>
<td></td>
<td>AApOAI</td>
<td>Apolipoprotein A–I</td>
<td>Hereditary</td>
<td>Liver, Kidney, Heart</td>
</tr>
<tr>
<td></td>
<td>AApOAI</td>
<td>Apolipoprotein A–II</td>
<td>Hereditary</td>
<td>Kidney, Heart</td>
</tr>
<tr>
<td></td>
<td>ACys</td>
<td>Cystatin C</td>
<td>Hereditary</td>
<td>Icelandic hereditary cerebral Amyloid angiopathy</td>
</tr>
<tr>
<td></td>
<td>AFib</td>
<td>Fibrinogen Aα chain</td>
<td>Hereditary</td>
<td>Kidney</td>
</tr>
<tr>
<td></td>
<td>AGel</td>
<td>Gelsolin</td>
<td>Hereditary</td>
<td>Finnish type hereditary amyloidosis</td>
</tr>
<tr>
<td></td>
<td>ALys</td>
<td>Lysozyme</td>
<td>Hereditary</td>
<td>Kidney, Liver, Spleen</td>
</tr>
<tr>
<td></td>
<td>ATTR</td>
<td>Transthyretin</td>
<td>Hereditary</td>
<td>Prototypical familial Amyloid polyneuropathy</td>
</tr>
<tr>
<td></td>
<td>Aβ2M</td>
<td>Beta–microglobulin</td>
<td>Acquired</td>
<td>Chronic hemodialysis Joint</td>
</tr>
<tr>
<td></td>
<td>ATTR</td>
<td>Transthyretin</td>
<td>Acquired</td>
<td>Senile heart, Vessels Tenosynovium</td>
</tr>
</tbody>
</table>

* Data were adapted from reference 1, 64 and 65. CJD denotes Creutzfeldt–Jakob disease, and GSSD denotes Gerstmann–Sträussler–Scheinker disease.
atrium. Senile cerebral amyloidosis, which occurs in elderly people, is caused by abnormal infiltration of cerebral vessels that are then likely to experience a cerebral vascular accident (CVA).

TTR infiltration into coronary vessels, cardiac muscles and walls is a characteristic of AA with systemic involvement. This type had survival rates better than AL as 75 to 11 months in whom even had cardiac involvement reported by a previous study. Its manifestation usually does not include renal failure which might be used to differentiate this disorder from any other genetic disease which has similar symptoms and has been found in African Americans. The discrimination of mimic features among types is warrant cause of the difference of their prognosis.

APUD tumors (cell that produce amine, precursor uptake and decarboxylase – an enzyme for conversion of precursors to amines) produce a hormone that could be metabolized later to amyloid and infiltrated into gland stroma. Some disorders of this type were found in medullary thyroid carcinoma that was caused by procalcitonin and insulinoma by islet amyloid polypeptide (IAPP) deposit.

Having hemodialysis for 5 years or more could result in the abnormal storage of β2M. Since it is frequently stored in joints, they become stiff while the involved bones have the potential to be fractured. It is also associated with peritoneal dialysis and has been reported in 1 million patients around the world.

Acute phase proteins in chronic inflammations, chronic arthritis such as rheumatoid arthritis (RA), or chronic infections such as tuberculosis, leprosy, and osteomyelitis, could cause reactive AA. It is also related to cancers such as Hodgkin lymphoma and renal cell carcinoma. Most patients have symptoms that are related to the affected organs and finally experience end stage renal disease within 5 years of the diagnosis. AA might have another abnormal protein which causes disorder.

Apolipoprotein (AP) is stimulated by interleukin 1, 6 (IL-1, IL-6) and tumor necrotic factor (TNF) which is related to inflammatory processes and bonding of macrophage to high density lipoprotein.

Pathogenesis (Figure 1)

In addition to abnormal amyloid deposits in body tissue, there is also the resistance to elimination by natural proteolysis. Infiltration of these abnormal proteins leads to organ degeneration and dysfunction. The disorder occurred among normal proteins going to take place in structure change as secondary structure as antiparallel β sheet structure. While proteins are folded at the cytoplasm of the cell into funnel-like pathways, abnormal proteins such as amyloid are miss-folded even in the normal process of protein generation and are likely to infiltrate abnormal tissue. Proteolysis of APP which is impaired by Alzheimer’s disease also demonstrates an imbalance in the storage of extracellular matrices as reported by a previous study. The instability of proteins in TTR and lysozymes produces more abnormal folding in their derivatives. Additionally, charged residues which function as gatekeepers to allow protein accumulation are an important key to initiating protein storage. Any disorder could lead to pathologic processes during the infiltration. Other environments such as low intracellular pH, oxygen, high temperature, high urea and other ions, could facilitate misfolding of amyloid. Glycosaminoglycans (GAGs) are the other key point since they acted as cell membrane receptors for advanced end-products (RAGE) that are used for admitting proteins into cells. Disorder could lead to the instigation of pathological processes. Recently, free calcium ions and its channel have also been found to affect this step. Its signal initiated for tissue damage and organ dysfunction and also for RAGE’s. An Aβ substance which can be found in Alzheimer’s disease and TTR mutation is a soluble oligomeric intermediate which causes cytotoxicity in cells through oxidative stress and apoptotic pathways. The serum amyloid P (SAP) component that was the basement of protein network is a new diagnostic tool using radiolabeling techniques to demonstrate the storage of amyloid.
Figure 1. Pathological processes of Amyloidogenesis which had specific intervention treatments

<table>
<thead>
<tr>
<th>Steps</th>
<th>Targets and such treatments</th>
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</thead>
<tbody>
<tr>
<td>Mutation of DNA</td>
<td>Gene therapy??</td>
</tr>
<tr>
<td>Translation</td>
<td>Antisense oligonucleotide</td>
</tr>
<tr>
<td></td>
<td>Small interfering RNA</td>
</tr>
<tr>
<td>Abnormal Amyloid</td>
<td>Liver transplantation: ATTR, Fibrinogen and ApoA</td>
</tr>
<tr>
<td></td>
<td>Inflammation: Immunosuppressant</td>
</tr>
<tr>
<td></td>
<td>Colchicine: FMF</td>
</tr>
<tr>
<td></td>
<td>Vaccines</td>
</tr>
<tr>
<td>Abnormal lysis</td>
<td>Diflunisal: TTR</td>
</tr>
<tr>
<td>Miss folding</td>
<td>Secretase γ: Alzheimer’s disease</td>
</tr>
<tr>
<td></td>
<td>Statins</td>
</tr>
<tr>
<td>Calcium channel</td>
<td>Eprodisate: AA</td>
</tr>
<tr>
<td>GAGs</td>
<td>4′-ido-4′ Deoxydoxorubicin</td>
</tr>
<tr>
<td>SAP</td>
<td></td>
</tr>
<tr>
<td>Free radicals</td>
<td>Antioxidants</td>
</tr>
<tr>
<td>Cytotoxic to cells</td>
<td>Statins</td>
</tr>
</tbody>
</table>

* Data were derived from reference 40, 66 and 67; ATTR denotes Transthyretin; ApoA denotes ApoAolipoprotein AI Amyloidosis; FMF denotes Familial Mediterranean Fever; and AA denotes Serum Amyloid A.
the construction of the protein network. These components which are related to the protein network are targets since they can prevent amyloid accumulation in normal tissue. Adequate treatments to correct or prevent further organ dysfunction are the last keys to amyloid treatment. Inhibition of further abnormal storage and the potential for proteolysis such as liver transplantation to decrease amyloid fibril precursor in hereditary amyloidosis are the other two keys in this new treatment.

Investigation

For subtypes that could involve the whole body, extensive systemic work up as in AL should be performed for every patient to evaluate their definitive diagnosis, organ involvement and health status upon vital organ dysfunction. Immunofixation now yields most valuable laboratory to determine abnormal protein level. Tissue pathology to evaluate for immunohistochemistry should be obtained if possible to differentiate the types. In addition to basic pathology, fibrinogen, lysozyme and APP type A staining could be added to individuals who have negative results for kappa and lambda traditional staining which is used to confirm the diagnosis of other types of AL. Cardiac function examined by echocardiogram or its marker such as troponin T and NT-pro BNP are warranted. Kidney function is required to evaluate and prepare to prevent further complications. SAP scanning for detection of the P component can determine the total body amyloid deposit with a specificity of 93% and a sensitivity of 90% for AA and AL but has less sensitivity for hereditary ATTR. Often SAP scanning is not useful in diagnosing diseases involving the heart. However, there are other conventional tools that can be used. Therefore, experts reserve this scan only for positive cases for evaluation of amyloid extension.

Treatments (Table 2)

Recently, studies and trials for many diseases were conducted to be dependent on disease basis or molecular level. The new interventions according to these concepts were generated. Unfortunately, there is not much research on amyloidosis because of its rarity. The trend in treatments for this disorder has shifted away from the supportive treatments of the past as a result of a new understanding of disease mechanism, to active management to prevent further diminishment of normal organ function. It is important to differentiate AL from other subtypes in order to minimize the risk posed by its toxicity and the ineffectiveness of chemotherapy for types other than AL amyloidosis. This review will only mention the treatments for the latter form.

To decrease pathologic production

In a similar way to the aim of chemotherapy treatment for AL, the first principle is to decrease concurrent production of the amyloid which is related to inflammation and genetic disorders. AA disease, which is a result of these causes, requires the control of the underlying inflammation using immunosuppressive drugs and TNF inhibitors. Colchicine is used in FMF to decrease fever symptoms and the production of inflammatory proteins which lead to AA. The use of liver transplantation in the treatment of TTR Amyloid aims to eradicate the source which produced the abnormal protein. ATTR Val30Met has been found to be successfully treated with this procedure. It is also used to treat fibrinogen and ApoA types. Treatment of antisense oligonucleotide and small interfering RNA to decrease amyloidogenic proteins by inhibition of the replication of abnormal polymorphism that produces abnormal proteins, is also possible. However, there are still knowledge limitations concerning its specificity for the defective gene and the quantity needed for adequate blocking. Most current research on this type of intervention is in animal models. In some of them, ALN–TTR01 has already been undergoing phase I clinical trials.
To decrease pathologic structure

The second target is to limit protein folding by using specific ligands, for example, the use of diflunisal for TTR disease. The third target is to inhibit abnormal protease enzyme which precipitates alternative proteolysis as abnormal amyloid as β- and γ-secretase in Alzheimer's disease. The alpha type was considered to have potential as a possible treatment but it had limitations in the form of side effects and the numbers of clinical trials. Statins were also found to have an effect on this mechanism.

To prevent abnormal storage

The prevention of storage and initiation of fibril nuclei deposits by natural ligands and SAP has potential to be an intervention which is universal as it applies to all types and also succeeds in trials in human. Iodinated anthracycline (4'-iodo-4' deoxydoxorubicin) is a template that can bind specifically to natural amyloid fibrils and then diminish the formation of fibrils but this drug is not under active consideration at the current time. Furthermore, eprodisate which can bind with GAGs and inhibit pro-amyloidogenic interactions with it and AA during fibril formation, has been demonstrated to decrease amyloid in AA patients. It was able to prevent deterioration of creatinine clearance. One aspect that can be treated is the prevention of amyloid cytotoxicity using free radical scavengers or antioxidants, and by suppression of the signals of cell damage at cell receptors.

New targeted therapy

The last part of treatment is the use of vaccines to stimulate the immune system to eliminate amyloid by infusion of full length or fragment of its peptides into the body. Another option is passive immunotherapy which involves giving patients the anti-amyloid antibodies directly to interact with abnormal protein. This intervention was used mostly in the early phase of the study in a vaccine trial for Alzheimer's disease but some of the passive antibodies are now in phase III. One study reported complications involving encephalitis in some participants. Recently, it was reported that a regimen of IL–6 and other immunotherapy drugs diminishes the production of AA protein. A trial of new treatment for RA showed that an IL–6 receptor inhibitor could decrease amyloid significantly and had an effect on many aspects of this disorder. Another cytokine, anti–TNF both to the ligand and its receptor have been demonstrated to prohibit C–reactive protein and AA protein in chronic inflammatory diseases by 50% in overall responses and for the same criteria as IL–6 in a recent study.

Local modalities

For localized amyloidosis in the respiratory tract, local surgery can be undertaken. Skin involvement can be treated with lasers, Nd Yag, and local medication. Radiotherapy has a role in unresectable cases. Dimethyl sulfoxide (DMSO) by passing with cystoscopy can treated urethra and urinary bladder lesion. Oral preparation of this drug has been shown to have a demonstrated effect on AA.

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