

Recent Advances in Systemic Amyloidosis

Bhavani.G

Bachelor Of Dental Surgery
Saveetha Dental College

Abstract

Aim :To update the new diagnostic method , new prognostic factors and new treatment modalities of systemic amyloidosis .

Objectives:To describe the clinical presentation, diagnosis, classification, grading, evaluation of prognosis, and treatment of amyloidosis.

Methods: PubMed , Science direct , google scholar and MEDLINE databases (2000 to 2014) and internet will be searched for the key word amyloidosis and will be evaluate on the basis of the authors' own clinical experience and work on the topic.

Background :Amyloidosis is an uncommon group of diseases in which soluble proteins aggregate and deposit extracellularly in tissue as insoluble fibrils, leading to tissue destruction and progressive organ dysfunction.It is often difficult to recognize because of the myriad symptoms and vague nature of the clinical presentation. Symptoms include fatigue, dyspnea, edema, paresthesias, and weight loss.

Reason : The main reason of this review is to gather recent advance in systemic amyloidosis .

Key words : amyloidosis ,diagnosis , treatment , symptoms

INTRODUCTION

Amyloidosis is a protein-folding disease characterized by extracellular deposition of a specific soluble precursor protein that aggregates in the form of insoluble fibril(1).When proteins that are normally soluble in water fold to become amyloids, they become insoluble and deposit in organs or tissues, disrupting normal function(2)The classification of amyloidosis is based on the chemical characterization of the precursor protein. Deposition of amyloid is localized or systemic. The 4 main types of systemic amyloidosis are AL, AA, ATTR, and A β 2M type. Amyloid fibrils are insoluble in vivo i.e under physiological conditions of PH and ionic strength , forming non branching fibrils that are 7.5-10nm in diameter and between 3000 and 100,000 nm in length(3).Symptoms can vary greatly depending on where the amyloid protein is collecting in the body. It is important to note that the symptoms described below may be due to a variety of different health problems. General symptoms such as Changes in skin color, Clay-colored stools ,Fatigue, Feeling of fullness, Joint pain, Low red blood cell count , Shortness of breath, Swelling of the tongue, Tingling and numbness in legs and feet, Weak hand grip, Weakness, Weight loss.(4) β 2-m-adsorbing columns have demonstrated some benefit in dialysis-related amyloidosis. This addition to long-term dialysis may reduce inflammation and accumulation of fibrils without major adverse effects(5).Immunotherapy A β immunotherapies have shown some promise in the treatment of Alzheimer disease. Agents with great potential include the passive monoclonal antibodies bapineuzumab(6) and solanezumab(7).

SYSTEMIC AMYLOIDOSIS

AL AMYLOIDOSIS:

Primary systemic or light chain amyloidosis (AL) is characterized by a clonal population of plasma cells in the

bone marrow that produce monoclonal light chain of kappa or lambda type. Amyloidogenic light chains misfold forming a highly ordered beta pleated sheet configuration which is the structure that defines amyloid fibrils of any type (including light chain, hereditary, senile systemic or secondary). Contiguous beta pleated sheets wind together into a fibrillar configuration instead of the typical alpha helical pattern of most proteins (8).Although AL amyloidosis is the most common form of systemic amyloidosis, up to 10% of patients may present with secondary amyloidosis and an incidental monoclonal gammopathy of undetermined significance rather than AL amyloidosis(9).

Clinical Characteristics :

All organs can be affected in systemic AL amyloidosis , except for central nervous system. The common symptom are asthenia and Dyspnea(10).Amyloid deposition in the kidneys can cause nephrotic syndrome, which results from a reduction in the kidney's ability to filter proteins. The nephrotic syndrome occurs with or without elevations in creatinine and blood urea concentration(11).The diagnosis of renal amyloidosis relies on the pathological demonstration of renal amyloid and/or, when a kidney biopsy is not available, on histological evidence from another tissue with proteinuria ≥ 0.5 g/day predominantly composed of albumin (12).Amyloid deposition within the myocardium results in thickening of ventricular and atrial walls leading to restrictive cardiopathy responsible for progressively increasing asthenia, dyspnoea and lower limb oedema(13).

Signs And Symptoms :

AL Amyloidosis is commonly affects kidney, symptoms of kidney disease and renal failure can include fluid retention, swelling, and shortness of breath(14). In addition to kidneys, it also affects the heart, peripheral nervous system, gastrointestinal tract, blood, lungs and skin. Heart complications, which affect more than a third

of AL patients, include heart failure and irregular heart beat. Other symptoms are stroke, gastrointestinal disorders, enlarged liver, diminished spleen function, diminished function of the adrenal and other endocrine glands, skin color change or growths, lung problems, bleeding and bruising problems, fatigue and weight loss(15).

Diagnosis :

The diagnosis of AL amyloidosis requires demonstration of amyloid in tissue and demonstration of a plasma cell dyscrasia. Tissue amyloid deposits demonstrate apple-green birefringence when stained with Congo red and viewed under polarizing microscopy (16). The sensitivity of bone marrow biopsy for the detection of AL amyloidosis has been estimated at ~50%–60%(17). The recently introduced serum free-light-chain (FLC) assay, a nephelometric immunoassay, has a sensitivity for circulating free light chains that is reportedly >10-fold that of immunofixation electrophoresis. Because the FLC assay is quantitative, it has utility not only in diagnosis but also in following disease progression or response to treatment(18).

Treatment:

Therapy for AL amyloidosis is based on anti-myeloma therapy that suppresses the underlying plasma cell dyscrasia along with supportive measures to manage the amyloid-related complications(19). AL amyloidosis can occur in a localized form that is most often identified in the upper respiratory, urogenital and gastrointestinal (GI) tracts, the skin and the orbit. The course of the disease is relatively benign in most patients, but severe damage to the affected organ can ultimately occur(20). Treatment is generally confined to local surgical intervention according to symptoms. Selected patients may benefit from local radiotherapy. Effective treatment for AL amyloidosis was oral melphalan and prednisone. Recent advances of treatments are High-dose melphalan and autologous stem cell therapy, immunotherapy, Novel agent such as thalidomide which is explored for AL amyloidosis due to its efficacy in multiple myeloma(21). A phase I/II dose escalation trial using thalidomide in patients previously treated with melphalan and dexamethasone found the agent to have activity but with significant toxicity and the starting dose in AL amyloidosis should be no higher than 50 mg(22).

AA AMYLOIDOSIS:

AA amyloidosis is characterized by the abnormal the deposited protein is serum amyloid A protein (SAA), a acute phase protein which is normally soluble and its plasma concentration is highest during inflammation(23) It is synthesized as a precursor by hepatocytes in response to transcriptional stimuli from various proinflammatory cytokines, such as interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF) alpha (24). Sustained abnormally SAA is normally found in serum which is essential for the growth of amyloidosis, Amyloid fibrils are not only composed of the N-terminal segment of SAA, but also of the serum amyloid P component (SAP), which is derived from a normal circulating plasma protein of the pentraxin family. The SAP binds to all types of amyloid precursors in a

calcium-dependent manner and stabilizes their tertiary structure. Heparin sulfate and glycosaminoglycan (GAG) chains from the extracellular matrix are also crucial for amyloid fibrillogenesis (25). Recently some case report described combination therapy with steroids, methotrexate and intravenous hyperalimentation benefiting GI symptoms in a patient with RA and intestinal AA amyloidosis(26).

Clinical Characteristic:

Frequent clinical manifestation like proteinuria which leads to nephrotic syndrome and renal insufficiency is the earliest that should raise suspicion of AA amyloidosis in patients with chronic inflammatory conditions(27). Although amyloid deposits are common in the liver and spleen, their clinical significance is relatively minor in the early stages of the disease(28). The advanced stages are hepatosplenomegaly and adrenal insufficiency. The gastrointestinal tract may also be affected, causing malabsorption, intestinal pseudo-obstruction, diarrhea, or bleeding. Peripheral polyneuropathy, restrictive cardiomyopathy leading to heart failure, and skin and soft tissue involvement, such as macroglossia, are extremely uncommon, especially when compared with other types of systemic amyloidosis(29).

Diagnosis:

Diagnosis cannot be confirmed based on the finding of amyloid deposits in indirect biopsy in the absence of clinical organ involvement or in the presence of a predisposing condition, even with highly elevated amyloidogenic proteins in serum and no histological evidence of organ damage(30). Recently Westermarck and Stenkvis described that subcutaneous abdominal fat tissue aspiration is the best site for biopsy, noninvasive technique, and this has now become the preferred initial option in most centers throughout the world(31). Numerous studies supports the Rectal mucosa biopsy which is use of a biopsy of the rectal mucosa and submucosa, with a sensitivity of ~75%–85% for the detection of amyloid deposits(32). Minor salivary gland biopsy is a technique offers sensitivity of ~83%–100% for the diagnosis of both AL amyloidosis and AA amyloidosis and also useful for the detection of mutated transthyretin(33). Amyloid material is also identified based on its metachromatic properties with aniline dyes, such as gentian violet, thioflavin T, or Congo red(34). Adding phenol to the classic Congo red dye and using fluorescence microscopy or electronic microscopy may help improve the sensitivity of this technique for the detection of amyloid deposits(35).

Treatment :

Treatment with TNF- α inhibitors and IL-1 inhibitors which lowering the incidence of amyloidosis without increasing mortality and is effective in controlling the progression of renal amyloid in patients with inflammatory arthritides and hereditary periodic fevers(36). High-dose colchicine (1.5–2 mg/day) is effective in controlling systemic inflammation in autoinflammatory syndromes, such as FMF, and has been able to induce remission of associated AA amyloidosis. Biologic agents such a Tocilizumab (anti-IL6 receptor antibody) used in juvenile idiopathic arthritis, and Infliximab, an anti TNF antibody, have been used to

successfully reduce inflammation and thereby induce SAA reduction in AA amyloidosis(37).

CONCLUSION :

This article focuses on recent advancement of systemic amyloidosis especially on area of diagnosis and treatment. In the recent year various investigations have been undertaken on this topic and achieved certain level of understanding and also new therapies for amyloidosis researches and other aspects of amyloidosis research is going on . This article focuses on encouraging more researchers to further investigate other aspects of this topic.

REFERENCE :

- Sanchorawala V, Wright DG, Rosenzweig M, et al: Lenalidomide and dexamethasone in the treatment of AL amyloidosis: results of a phase 2 trial. *Blood* 2007, 109:492-6.
- Murakami, T; Ishiguro N; Higuchi K (March 2014). "Transmission of Systemic AA Amyloidosis in Animals". *Veterinary Pathology* 51 (2): 363-371. doi:10.1177/0300985813511128. PMID 24280941
- Joel N. Buxbaum and Reinhold P.linke (18 January 2012) "A molecular history of the amyloidoses" *Journal of Molecular Biology* 412,142-159. doi :10.1016/j.jbm.2015.01.024
- www.webmd.com/a-to-z-guides/amyloidosis-symptoms-causes-treatments
- Eli Lilly and Company. Lilly Provides Update on Next Steps for Solanezumab. Lilly. Available at <http://newsroom.lilly.com/releasedetail.cfm?ReleaseID=726309>. Accessed 6th March 2014.
- Schenk D. Amyloid-beta immunotherapy for Alzheimer's disease: the end of the beginning. *Nat Rev Neurosci.* Oct 2002;3(10):824-8. [Medline].
- Senior K. Dosing in phase II trial of Alzheimer's vaccine suspended. *Lancet Neurol.* May 2002;1(1):3. [Medline].
- Bhat A, Selmi C, Naguwa SM, Cheema GS, Gershwin ME: Currents concepts on the immunopathology of amyloidosis. *Clin Rev Allergy Immunol* 2010, 38:97-106
- Comenzo RL, Zhou P, Fleisher M, Clark B, Teruya-Feldstein J: Seeking confidence in the diagnosis of systemic AL (Ig light-chain) amyloidosis: patients can have both monoclonal gammopathies and hereditary amyloid proteins. *Blood* 2006, 107:3489-91.
- GertzMA, ComenzoR, FalkRH, FermandJP, HazenbergBP, HawkinsPN, MerliniG, MoreauP,RoncoP, SanchorawalaV, SezerO, SolomonA, Grateau G: Definition of organ involment and treatment response in immunoglobulin light chain amyloidosis (AL): a consensus opinion from the 10 the international symposium on amyloid and amyloidosis, Tours, France,18-22April2004. *AmJHematol*2005,79:319-328.
- Falk, Rodney H.; Comenzo, Raymond L.; Skinner, Martha (25 September 1997). "The Systemic Amyloidoses". *New England Journal of Medicine* 337 (13): 898-909. doi:10.1056/NEJM199709253371306
- Dubrey SW, Hawkins PN, Falk RH: Amyloid diseases of the heart: assessment, diagnosis, and referral. *Heart* 2011, 97:75-84.
- Selvanayagam JB, Hawkins PN, Paul B, Myerson SG, Neubauer S: Evaluation and management of the cardiac amyloidosis. *J Am Coll Cardiol* 2007, 207(50):2101-2110.
- UNC Kindey Center. "AL Amyloidosis". UNC. Retrieved 22 November 2011
- Dember LM: Emerging treatment approaches for the systemic amyloidoses. *Kidney Int*68 :1377- 1390,2005 CrossRefMedline
- "Amyloidosis". University of Maryland Medical Center. Retrieved 23 November 2011.
- Libbey CA, Skinner M, Cohen AS: Use of abdominal fat tissue aspirate in the diagnosis of systemic amyloidosis. *Arch Intern Med*143 :1549- 1552,1983 CrossRefMedline
- Ansari-Lari MA, Ali SZ: Fine-needle aspiration of abdominal fat pad for amyloid detection: A clinically useful test? *Diagn Cytopathol*30 :178- 181,2004 CrossRefMedline
- Picken MM. Immunoglobulin light and heavy chain amyloidosis AL/AH: renal pathology and differential diagnosis. *Contrib Nephrol* 2007; 153:135-155. This is a comprehensive updated review of pathology and differential diagnosis of amyloidoses with emphasis on renal amyloidoses. Current diagnostic standards are reviewed, including interpretation of Congo red stain and alternative methods as well as proposed recommendations for amyloid typing.
- Lachmann HJ, Booth DR, Booth SE, et al. Misdiagnosis of hereditary amyloidosis as AL (primary) amyloidosis. *N Engl J Med* 2002; 346:1786-1791.
- Comenzo RL, Zhou P, Fleisher M, et al. Seeking confidence in the diagnosis of systemic AL (Ig light chain) amyloidosis: patients can have both monoclonal gammopathies and hereditary amyloid proteins. *Blood* 2006; 107:3489-3491.
- Lachmann HJ, Goodman HJ, Gilbertson JA et al. (June 2007). "Natural history and outcome in systemic AA amyloidosis" (PDF). *New England Journal of Medicine* 356 (23): 2361-71. doi:10.1056/NEJMoa070265. PMID 17554117
- Obici L, Perfetti V, Palladini G, Moratti R, Merlini G. Clinical aspects of systemic amyloid diseases. *Biochim Biophys Acta.* 2005;1753(1):11-22.
- Urieli-Shoval S, Linke RP, Matzner Y. Expression and function of serum amyloid A, a major acute-phase protein, in normal and disease states. *Curr Opin Hematol.* 2000;7(1):64-69.
- Shimoyama M, Ohtahara A, Fukui H, Okamura T, Shimizu H, Miyamoto M, et al. Acute secondary gastrointestinal amyloidosis in a patient with rheumatoid arthritis. *Am J Med Sci.* Sep 2003;326(3):145-7. [Medline].
- Immonen K, Finne P, Grönhagen-Riska C, et al. A marked decline in the incidence of renal replacement therapy for amyloidosis associated with inflammatory rheumatic diseases – data from nationwide registries in Finland. *Amyloid.* 2011;18(1):25-28.
- Jung O, Haack HS, Buettner M, et al. Renal AA-amyloidosis in intravenous drug users –a role for HIV-infection? *BMC Nephrol.* 2012;13:151.
- Lachmann HJ, Goodman HJ, Gilbertson JA, et al. Natural history and outcome in systemic AA amyloidosis. *N Engl J Med.* 2007;356(23):2361-2371.
- Westermarck P, Stenkvist B. A new method for the diagnosis of systemic amyloidosis. *Arch Intern Med.* 1973;132(4):522-523.
- van Gameren II, Hazenberg BP, Bijzet J, Van Rijswijk MH. Diagnostic accuracy of subcutaneous abdominal fat tissue aspiration for detecting systemic amyloidosis and its utility in clinical practice. *Arthritis Rheum.* 2006;54(6):2015-2021.
- Hachulla E, Grateau G. Diagnostic tools for amyloidosis. *Joint Bone Spine.* 2002;69(6):538-545.
- Caporali R, Bonacci E, Epis O, Bobbio-Pallavicini F, Morbini P, Montecucco C. Safety and usefulness of minor salivary gland biopsy: retrospective analysis of 502 procedures performed at a single center. *Arthritis Rheum.* 2008;59(5):714-720.
- Howie AJ, Brewer DB. Optical properties of amyloid stained by Congo red: history and mechanisms. *Micron.* 2009;40(3):285-301.
- Cooper JH. An evaluation of current methods for the diagnostic histochemistry of amyloid. *J Clin Pathol.* 1969;22(4):410-413.
- Bohle A, Wehrmann M, Eissele R, et al. The long-term prognosis of AA and AL renal amyloidosis and the pathogenesis of chronic renal failure in renal amyloidosis. *Pathol Res Pract.* Apr 1993;189(3):316-31. [Medline].
- Booth DR, Booth SE, Gillmore JD, et al. SAA1 alleles as risk factors in reactive systemic AA amyloidosis. *Amyloid.* Dec 1998;5(4):262-5. [Medline].
- Buck FS, Koss MN, Sherrod AE, et al. Ethnic distribution of amyloidosis: an autopsy study. *Mod Pathol.* Jul 1989;2(4):372-7. [Medline].