Baska Aleksandra, Kazik Jakub, Bojczuk Daria, Racinowski Mariusz, Leis Kamil, Mazur Ewelina, Kałużny Krystian, Gałązka Przemysław. Cardiac amyloidosis: a review. Journal of Education, Health and Sport. 2019;9(3):333-338. eISNN 2391-8306. DOI http://dx.doi.org/zenodo.2597569
http://ojs.ukw.edu.pl/index.php/johs/article/view/6711

The journal has had 7 points in Ministry of Science and Higher Education parametric evaluation. Part B item 1223 (26/01/2017).
1223 Journal of Education, Health and Sport eISSN 2391-8306 7

The authors declare that there is no conflict of interests regarding the publication of this paper.

Received: 18.02.2019. Revised: 18.02.2019. Accepted: 18.03.2019.

CARDIAC AMYLOIDOSIS: A REVIEW

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Abstract: Cardiac amyloidosis is a type of amyloidosis in which one of the affected organs is the heart. The disease is characterized by the formation of protein aggregates between the cells of the organ, namely amyloid, which disables its function. The following types of amyloidosis can be distinguished: systemic senile amyloidosis (wild-type ATTR), light chain amyloidosis (AL) and hereditary transthyretin-related amyloidosis. The symptoms include, e.g., systolic dysfunction or arrhythmia. The treatment is focused on the therapy with melphalan and, additionally, stem cells transplant and chemotherapy with dexamethasone or cyclophosphamide. In the advanced stage of the disease, a heart transplant is necessary. The diagnosis is made on the basis of laboratory testing, electrocardiogram changes, and echocardiography.

Keywords: cardiac amyloidosis; amyloid; heart failure

Introduction

The amyloidoses belong to a group of diseases that cause disorders characterized by protein flaccidity. In these diseases it is possible to occupy more than one organ by amyloid deposits. The organ which is occupied by amyloid and the type of amyloid affects on the prognosis of the disease. [1] Light-chain (AL) amyloidosis belongs to rare and unfortunately often fatal disease.Its leading cause is light chains misfolding, which form soluble toxic aggregates that deposit as fibrils (amyloid) in tissue and organs. It results in significant and permanent organ dysfunction. Practically every organ can be affected by AL amyloidosis but approximately 70% of patients amyloid deposits in the cardiac myocytes. As a result, ventricular wall thickens, and that leads to restrictive cardiomyopathy and subsequent congestive heart failure. [2]

Cardiac AL - amyloidosis

Amyloid is a fibrillar proteinaceous material which spread out in extracellular space of the heart in cardiac amyloidosis. The most common type of amyloid protein that occupies the heart are the immunoglobulin-derived light chain and transthyretin (TTR; previously called prealbumin). TTR is a type of transporting proteins which is thyroid and retinal (vitamin A) protein. It is essential to precisely define the precursor protein causing amyloidosis because it affects the clinical manifestation of the disease and choice of therapies. It is significant to recognize that cardiac amyloidosis as a part of a systemic illness. [1] Patients with cardiac amyloidosis have a poor prognosis with eventual development of congestive heart failure, angina, and arrhythmias. [3] In the past amyloidosis was perceived as a rare condition, often only diagnosed at autopsy, and was untreatable. Over the last decade, huge progress has been made, both in diagnosis and treatment of cardiac amyloidosis. The disease first symptoms appear from the fifth to seventh decade. However, it can occur at any age from the fourth decade onward. [1]

Cardiac involvement is characteristic of three types of primary amyloidosis: hereditary transthyretin, acquired monoclonal light-chain and systemic senile amyloidosis. The heart is rarely affected in secondary amyloidosis, and it is clinically non-significant. [4]

Hereditary transthyretin-related amyloidosis

This familial type of cardiac amyloidosis is associated with autosomal dominant TTR gene mutation found on chromosome 18 (18q23). There are over 100 different mutations encoding variant TTR described and they concern a single nucleotide polymorphism. [4,5] The most common mutation regards substitution of valine with methionine at position 30. [4,7,8] The new variant of a transport protein (TTR) has destabilized tetramers which dissociate forming monomers. They tend to misfold and form the aggregates of amyloid fibrils. Carriers of the mutation have no amyloid deposition until adulthood for the development of the disease is probably associated with aging. The onset of the disease varies significantly across different populations, usually between 20-90 years old. [4,5,7,8]

Light-chain amyloidosis (AL)

Light-chain amyloidosis occurs in 8.9 per million people per year and is the most common and the most severe form of cardiac amyloidosis. AL occurs approximately evenly in men and women. [6,9] Small plasma cell clones are involved in this type of amyloidosis. They produce monoclonal immunoglobulin light chains, which are secreted extracellularly (either as a fragment or an entire molecule) and form fibril composed of monoclonal kappa or lambda LCs. These abnormal proteins misfold instead of forming the α-helical structure and, as a result, produce amyloid. [4,6,10] This process is responsible for systemic toxicity, the devastation of the organ and cardiac failure. [9]

Systemic senile amyloidosis (wild-type ATTR)

The prevalence rate of systemic senile amyloidosis (SSA) is at about 10% in patients aged >80 years. Furthermore, estimations show that half of the population aged >90 years may suffer from SSA. Systemic senile amyloidosis has a higher morbidity rate in men than in women. [4] In spite of the 'systemic disease' term, the heart is usually the only affected organ. Wild-type transthyretin builds up in the heart tissue while TTR mutations are absent. [8] Those deposits are structurally unstable, leading to expansion of misfolded intermediates which then aggregate and form amyloid. Wild type ATTR may contribute to heart failure with preserved ejection fraction. [11]

Symptoms

Cardiac amyloidosis, independently of type, appears as restrictive cardiomyopathy defined by continuous progress of diastolic and subsequently systolic dysfunction and arrhythmia of both cardiac ventricles. [12] Diagnosis is frequently delayed as a result of its numerous nonspecific manifestations. The spectrum of possible presentations may be very different and range from asymptomatic stage to NYHA IV heart failure. Commonly fatigue, exertional dyspnea, hepatic congestion or pedal edema are early findings. [12,13] The other frequent symptoms include – lightheadedness, angina pectoris, ascites and right upper quadrant pain attributable to congestive or infiltrative hepatomegaly. [13,14] Rarely present chest pain can be attributed to amyloid infiltration of small inner vessels of the heart. [14,15,16] Atrial and ventricular arrhythmias are common findings. The most frequent early arrhythmia is atrial fibrillation, with ventricular fibrillation emerging in a later stage of the disease. [15] Syncopal episodes may derive from autonomic neuropathy as well as electromechanical dissociation and ventricular arrhythmias. Exertional syncope could stem from the insufficient cardiac output in these patients with decreased ability to adequately increase the heart rate. [12,14] Syncope due to autonomic neuropathy, bradycardia or heart block does not prognosticate well and is equivalent to a high risk of death. Multiple other noncardiac symptoms such as dry mouth, purpura, bleeding, defecation abnormalities, paresthesias, and hoarseness may accompany especially in AL type of cardiac amyloidosis. The pathognomic features of AL amyloidosis – macroglossia and periorbital ecchymosis are present only in the minority. [12,14] AL amyloidosis cardiomyopathy is restrictive therefore chest x-ray (CXR) may not show any abnormalities. [17]

Classically, a patient with AL cardiac amyloidosis suffers from symptoms caused by rapid expansion of congestive diastolic heart failure and subsequent right-sided systolic dysfunction produced by right ventricular wall thickening secondary to amyloid deposition. [13] However, because of the overlapping manifestations it is imprudent to rely solely on clinical symptoms. [14]

Diagnosis of amyloidosis

Amyloidosis is a disease that is relatively difficult to diagnose. The most common method is a heart muscle biopsy which enables identification of proteins forming amyloid. The biopsy specimen is evaluated immunohistochemically and histologically by use of

thioflavin and Congo red. In case of a negative result, another tissue needs to be sectioned to confirm amyloidosis. [18,19,21] Immunohistochemical tests have lower sensitivity than histological ones due to the structure of amyloid.

In some cases for diagnostic confirmation of amyloidosis amyloid sequencing and serum amyloid P scintigraphy are required, but those methods have little diagnostic value as a large amount of blood is present in both atria and ventricles which may result in a false outcome. [19,21]

Electrophoresis is another diagnostic method which helps to observe the monoclonal protein. Due to its low sensitivity, it is not used as a diagnosis confirmation. [19,21]

Laboratory testing is significant in the process of diagnosis. It reveals proteinuria, increased level of creatinine and alkaline phosphatase. The necrosis of cardiomyocytes probably causes a high concentration of troponins. The necrosis is a consequence of heart cells ischemia because of amyloid deposition or vessel occlusion with amyloid fiber. BNP concentration is also high as ventricles are filled with blood during blood pressure increase. BNP and troponin I bespeak a poor prognosis of amyloidosis course. [20]

CXR shows a physiological cardiac silhouette, or it is slightly enlarged. On electrocardiogram the QRS complex is low-amplitude as a result of healthy cardiomyocytes mass decrease, changes ensuing heart attack, atrial fibrillation, heart axis deviation, first-degree atrioventricular block and ventricular tachycardia. [20]

Echocardiography exhibits granular, spotty heart walls which are considerably enlarged just as the size of atria, thickness of interatrial and interventricular septa. The size of ventricles is unchanged. The symptoms of diastolic, restrictive heart failure are present. When the disease is advanced, there are also signs of systolic heart failure. [20] Cardiac amyloidosis diagnosis criteria according to Gertz et al. from 2005 include heart wall enlargement >12mm found in echocardiography and lack of other possible causes of hypertrophy. [21]

In the course of cardiac amyloidosis ‘square root sign’ is present. It is characterized by a significant fall in pressure in the first phase of diastole with a subsequent sudden rise. This sign is also present in constrictive pericarditis, but the slower filling of left ventricle in the first phase in amyloidosis allow to differentiate these diseases. [20]

Treatment

The progress and intensification of cardiac AL amyloidosis treatment depend on the clinical state of a patient. The therapy strategy is modified individually; therefore, the earlier diagnosis is made and the treatment implemented, the greater the therapeutic success.

Currently, the treatment of choice is melphalan in high doses (HDM) combined with autologous stem cells transplant (ASCT). Patients with >10% of plasma cells in their bone marrow are advised to undergo induction chemotherapy (bortezomib + cyclophosphamide + dexamethasone) with following ASCT. This method has relatively high efficiency and allows to avoid burdensome continuous chemotherapy.

Unfortunately ASCT is not possible in all patients. High-risk patients, who would not survive such a strong cytotoxic therapy due to, e.g., end-stage heart failure, are recommended oral treatment with melphalan and dexamethasone (MDex). So far, ASCT has not been proven to have a greater efficiency than MDex. Certain conditions need to be fulfilled to meet the transplant qualification terms, so most of the patients (about 80-85%) undergo the second option of treatment. [22,27]

Another important alternative to transplant is proteasome inhibitors. The proteasome is an enzymatic complex that takes part in most of the processes of proteins degradation (including amyloid) in eukaryotic cells, leading to intracellular homeostasis maintenance. [23] It was confirmed that using proteasome inhibitors in monotherapy cause light chain amyloid decline and clinical improvement among those patients. The combination of

cyclophosphamide with dexamethasone (CVD) is at the moment the first-line treatment for patients with cardiac AL amyloidosis who are not qualified directly to ASCT. This method is also used as induction or consolidation just after or before HDM with ASCT. Study on ixazomib, an oral proteasome inhibitor, is ongoing and phase I and II results are promising. However, the final results are not available yet and are going to be released in August 2022. [24,27,28]

Recurrent and resistant AL amyloidosis is treated with good results with thalidomide, lenalidomide, and pomalidomide. However, thalidomide and lenalidomide are not frequently used, because of their low-profile safety. Research on pomalidomide, on the other hand, provided us with auspicious data. Study on the positive impact of doxycycline is being carried out because it was proven that patients taking this drug as infection prophylaxis after stem cells transplant achieve better hematologic response and higher survival rates than with penicillin therapy. [28]

One of the wild-type ATTR and ATTRm treatment methods are liver or liver and heart transplant. Due to limited organs availability and chronic immunosuppression after surgery, the therapy has little value, and there is a need for an alternative treatment. One of them is transthyretin synthesis inhibition. Patisiran, a small interfering RNA (siRNA), binds specific sequences on messenger RNA, silence them and inhibits protein synthesis. Antisense nucleotides and their ability to specifically bind to RNA and inhibit transthyretin translation are being analyzed. However, these results are not as positive as the previous ones. [25]

Another drug, Tafamidis, which binds to transthyretin and inhibit amyloidogenesis looks promising. Phase III of the study, showed a significant decrease in the number of both, hospitalizations due to cardiovascular reasons, and mortality in a group of patients with transthyretin amyloid cardiomyopathy taking Tafamidis versus placebo. [26,28,29]

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