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Diagnostic problems of rare diseases - amyloidosis. A case report

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Abstract

The presented case study focuses on the complexities and challenges in diagnosing one of the forms of amyloidosis, where abnormal protein (amyloid) deposits in various organs and tissues lead to affection of many organs, especially the heart, kidneys, liver, spleen, and occasionally the central nervous system. Its aetiology remains largely unknown, making diagnosis and treatment particularly challenging.

This report details the case of an 88-year-old patient, disabled for months (with a modified Rankin Scale score of 4), who presented to the Neurology Department with sudden right limb paresis and speech disorders. Initial assessments indicated suggested ischemic stroke, and patients received thrombolysis. Further laboratory tests and imaging, including serum protein electrophoresis and computer tomograph (CT) scans, suggested transthyretin amyloidosis (ATTR), which was later confirmed through genetic testing.

This case underscores the rapid, multi-organ progression of amyloidosis and its devastating impact, highlighting the necessity for early diagnosis and a multidisciplinary treatment approach.

Despite ongoing research, the pathogenesis of amyloidosis remains elusive, and current treatment options are primarily symptomatic. This study aims to shed light on the diagnostic difficulties and the urgent need for timely intervention in amyloidosis cases.

Key Words: cardiac amyloidosis; amyloid, heart failure, ischemic stroke, amyloidosis AL, amyloidosis treatment

Introduction

Amyloidosis is a group of diseases characterized by the extracellular accumulation of in-soluble fibrillar proteins, called amyloid, in tissues and organs. Extracellular deposition of these proteins in the form of soluble or insoluble cross-β sheets interferes with the function-ing of essential organs.[1]. For long time the amyloidosis was considered an idiopathic disease and impossible to diagnose in life. Over time, knowledge about this disease has deepened and we are now able to distinguish several subtypes of amyloidosis and present the differences between them.[2] Amyloidosis, is a group of diseases characterized by the extracellular accumulation of insoluble fibrillar proteins, called amyloid, in tissues and organs. Extracellular deposition of these proteins in the form of soluble or insoluble cross-β sheets disrupts the functioning of important organs. More than 27 different precursor proteins have the propensity to form amyloid fibrils. The precursor protein that misfolds to form amyloid fibrils determines the type and predicts the patient's clinical course [1]. The cause of the above condition is not fully known.[3] The disease often co-occurs with chronic inflammation, such as rheumatoid arthritis, Crohn's disease, juvenile idiopathic arthritis, or chronic abscesses.[4] The manifestation of symptoms most often affects the heart, kidneys, spleen, liver and

rarely central nervous system. The forms of amyloidosis differ not only in the structure of the proteins that make up amyloid fibers, but also in their presentation and clinical course. There are five subtypes of amyloidosis. AL (light chain) amyloidosis, also called primary amyloidosis occurs in monoclonal gammopathies. The AA amyloidosis (secondary), otherwise called reactive, occurs during chronic inflammatory conditions such as Sjogren's syndrome, systemic lupus erythematosus, etc. Secondary amyloidosis also presents in the course of chronic bacterial infections, e.g. tuberculosis, predisposing diseases or cystic fibrosis. The third form is Aβ2M amyloidosis, which may transpire as a consequence of long-term dialysis therapy. In the case of LECT2 amyloidosis the source of amyloid fibers is leukocyte chemotactic factor 2.[2] The fifth form is the Transthyretin amyloidosis (ATTR), which is a very rare form of the disease, with the true incidence and prevalence currently unknown, with some racial disparities in prevelance suggested. [5,6] Studies suggest that's ATTR affects 11-13% of patients with heart failure with preserved ejection fraction. [7] Moreover, in about 15% of patients with aortic stenosis (AS) undergoing transcatheter aortic valve replacement, nuclear scintigraphy results are consistent with transthyretin amyloidosis cardiomyopathy (ATTR-CM). [7] Furthermore, it has been noted that variant ATTR (particulary the TTR V122l variant) is a relatively prevalent cause of heart failure among individuals of Afro-Caribbean heritage. [7] Additionally, individuals affected by polyneuropathy associated with transthyretin (ATTR-PN) may develop symptoms related to sensory-motor and/or autonomic neuropathy. Among these symptoms are paraesthesias, hypoesthesias, motor deficits affecting the hands or feet, disturbances in position or vibration sensation, orthostasis, and other symptoms of dysautonomia. In some patients with the variant form of ATTR (v-ATTR), changes in the eye associated with amyloidosis, such as vitreous opacities or glaucoma, may also occur. Carpal tunnel syndrome is a common symptom in both v-ATTR and transthyretin-related wild-type ATTR (wt-ATTR) disease. Additionally, patients with wt-ATTR may have a history of lumbar spinal stenosis, tendon rupture, or other orthopedic conditions.The component protein of amyloid is the protein transthyretin (TTR), also known as prealbumin, which is produced in the liver, choroid plexus of the pigment epithelium of the brain and the retina of the eye. [7] Transthyretin is a single polypeptide chain consisting of 127 amino acid residues. [8] It is also divided into two subtypes: ATTR - where the amyloid

component is transthyretin with a normal structure, and TTR - in which the main role is played by a familial gene mutation resulting in structurally abnormal transthyretin.[1]

The most common manifestation of TTR amyloidosis is cardiomyopathy with a clinical picture of heart failure, although other organs may also be affected.[9] Patients are often referred to the Cardiology Department with an erroneous diagnosis of sarcomeric hypertrophic cardiomyopathy. Transthyretin amyloidosis most often takes the form of restrictive hypertrophic cardiomyopathy and as the disease progresses it manifests itself as diastolic heart failure with maintained left ventricular ejection fraction. The prognosis depends on the degree of cardiac involvement, and the stage of the disease determines the choice of therapy. [10,11] amyloidosis is suspected based on clinical symptoms associated with amyloid accumulation in organs such as unexplained nephrotic syndrome or cardiomyopathy, hepatosplenomegaly, peripheral neuropathies, with one of the most common – carpal tunnel syndrome - chronic unexplained diarrhea and malabsorption syndromes. [12, 13] Familial occurrence of neuropathy, kidney disease, vitreous opacities and cardiovascular diseases suggest familial amyloidosis. What makes it very difficult is the development of the disease in question over a long period of time or the local advancement of the disease.[14] The diagnosis of amyloidosis requires histological identification of amyloid deposits. Congo red staining method gives amyloid deposits a salmon-colored staining under light microscopy with a distinctive apple-green birefringence after applying polarized light conditions. Additionally, immunohistochemical staining of precursor proteins helps determine the type of amyloidosis. Ultimately, immunogold electron microscopy and mass spectrometry provide the greatest sensitivity and specificity for amyloid typing.[1] Systemic AL amyloidosis should be distinguished from other diseases involving the deposition of misfolded proteins and from other forms of systemic amyloidosis. In case of failure to determine the nature of the amyloid deposits genetic testing should be conducted to diagnose hereditary amyloidosis. [15] The combination of a positive scintigraphy result using bone markers and the absence of monoclonal protection in follow-up procedures or non-invasive diagnosis of ATTR.[16] In the case of key treatment that follows the diagnosis of the disease with attention to the fact that the build-up of amyloid deposits is a

consequence of proper functioning and adversely affects the prognosis. The diagnosis of amyloidosis is made based on patient's symptoms, physical examination and follow-up tests. Data from tests in the TTR subtype include echocardiography, in which unexplained left ventricular hypertrophy, accompanied by QRS main voltage on the ECG, is a characteristic feature of amyloid cardiomyopathy. The test that allows us to obtain the effect of ten types of amyloidosis is technetium-labeled diphosphonate bone scintigraphy (99mTc-DPD). [17] In magnetic resonance imaging, after contrast agent administration, in addition to the morphological features of the heart there is an image of scattered, subendocardial late enhancement ofgadolinium. [9] Alternative sources and widely used tests that cannot be forgotten are cardiac biomarkers (troponin, NT-proBNP).[10] Amyloidosis is treated primarily in the form of symptomatic therapy and rehabilitation. The goal of treatment is the remission of plasma cell dyscrasias or inhibition of the progression and disfunctions of the organs that are fighting amyloidosis.[18] Currently, there is no method to cure this condition but diagnostic and therapeutic treatment of the underlying disease is equally important.[1] In the sources of systemic amyloidosis, strategies are currently being developed to address effects not resulting from the formation of amyloid deposits, including chemotherapy to eradicate the plasma cell clone in the context of light chain amyloidosis. [19,20] Equally important research directions include the development of therapies to eliminate already-formed amyloid deposits. These include the administration of doxycycline, which interfered with the formation of amyloid deposits and abolished the direct cardio effect triggered by the dissolution of light chains,as was observed in preclinical studies. [21,22] Tafamidis therapy seems modern and promising as this medication stabilizes tetramers of transthyretin when connected to amyloid-degrading fibers. The drug acts selectively and does not have an anti-inflammatory effect. Tafamidis was approved for treating cardiomyopathy caused by transthyretin amyloidosis by the US Food and Drug Administration in 2019 and in 2020 by European Agency.[16]

Case study

An 88-year-old patient was admitted to the Department of Neurology due to sudden weakness of the right limbs and speech disorders; he was seen the last time without the symptoms a few hours earlier in the morning. The patient showed signs of non-fluent aphasia, total gaze paresis, deviation of the central damage to the seventh nerve on the right side and limb plegia of right upper limb and severe paresis of the right lower limb, reduced muscle tone and weakened deep reflexes in the right limbs. In addition, the examination revelased deformation of the right knee-joint, atrophy of the nail of the first toe of the right foot, an ulcer on the right foot and a pressure ulcer near the sacral bone. The stroke assessment scale of National Institutes of Health (NIHSS) was applied in the diagnostic and therapeutic procedures and a score of 15 was obtained defining a moderate stroke.

Before onset of the disease, the patient's general condition deteriorated during the last two months, and the patient stopped walking; he changed his lifestyle to primarily sitting and lying down. Moreover, he required the assistance of a caregiver with everyday activities. In a modified Rankin Scale (mRS) [21-23] - tool for assessing patients' disabilities and their dependence on others, the results may range from zero to six, where zero indicates no symptoms, five represents complete physical dependence, and six indicates death- he scored 4. The interview revealed also other significant comorbidities of the patient, such as the condition after deep vein thrombosis 9 years earlier, chronic lower limb ischemia (currently monitored by Angiosurgery Clinic where the patient was checked in half a year earlier). Moreover, the patient was diagnosed with hypertension arterial disease, ischemic heart disease, prostatic hypertrophy and urinary tract infection 5 months before the current admission. The patient's family history revealed a sudden cardiological death of the son (41 years old), with indication towards amyloidosis in post mortem examination.

Diagnosis

Computer tomography (CT) and basic laboratory tests were performed in acute conditions. A CT scan of the head, which showed imaging hyperdense initial section of one of the M2 branches of the left middle cerebral artery (LMCA), indicating the possible presence of a blood clot in a given area. Moreover, the

study showed moderate cortical-subcortical brain atrophy and periventricular leukoaraiosis of significant severity, previous vascular lesion in the left cerebellar hemisphere and calcifications atherosclerosis of intracranial arteries. In the conducted angio-CT examination, no obstructions in the initial section of the LMCA were confirmed. The patient received thrombolysis with improved strength of the right limbs. In the basic laboratory tests, the only deviation from the norm was a lower level of haemoglobin.

Based on the clinical symptoms and the above CT findings, the ischemic stroke diagnosis was stated. The patient received thrombolysis with an improvement of speech and the strength of the right limbs.

During the subacute phase of the hospitalization further workup of the underlying cause of the stroke was performed, which included control non-contrast head CT, ultrasound of cephalic arteries, echocardiography, ultrasound of upper and lower limbs, blood pressure monitoring using analogue and digital devices (Holter type) - Holter RR, Holter ECG followed by specialist consultations including cardiology. Follow-up computed tomography revealed two hypodense lesions of a total size of 2.3 cm located in the caudate nucleus, confirming the diagnosius of ischemic stroke. After the echocardiography, which revealed a left ventricle with concentric wall hypertrophy of second degree diastolic dysfunction, degenerative changes in the aortic valve causing a complex defect (moderate regurgitation, moderate stenosis), mild regurgitation of mitral and tricuspid valve, dilated aortic arch and root and aneurysmally dilated ascending aorta, very suggestive for amyloidosis further detailed laboratory examinations were performed. The abnormalities in laboratory test are presented in **Tables 1**. In addition the urinary tract infection was diagnosed (**Table 2**).

Table 1. Serum protein electrophoresis, identification of a monoclonal protein and Lambda light chain level

Beta-2-globulins	5.39g/l (normal 2.1 – 4.9g/l)
Beta-2-globuin %	9.3% (normal 3-7%)
Gamma-globulins	20,8% (10-2-%)
The remaining components have no deviations from the norm	
Beta-2-globulin %	7.7% (normal 3-7%)
Gamma- globulin %	22% (normal 10-20%)
Serum immunofixation	Serum immunofixation showed no monoclonal protein
Lambda	2,24 g/l (normal 0,9-2,1 g/l)

Table 2. General urine examination

Bacteria	Numerous
Erythrocytes	350/ul (normal 0-10/ul)
Blood	Present (+++)
Leukocytes	Present (+++)
Leukocyte clusters	157/ul (normal 0-1/ul)
Leukocytes WBC	2943/ul (normal 0-15/ul)
Clarity	Very turbid

Other abnormalities found in laboratory test were increasing values of urea during examination (could be due to CT contrast administration or antibiotics used during hospitalization)

The Holter ECG showed a low-voltage P wave with sinus rhythm, occasionally absent visible P wave, which also corresponds to the image of amyloidosis. Neurography and EMG were also performed, which revealed mixed axonal polyneuropathy with predominance of changes in sensory fibers with overlapping bilateral demyelination damage to the median nerve in the wrist-forearm section and multi-level injuries cervical radicular lesions, which also corresponds to the picture of amyloidosis.

Genetic research was performed, and the results were positive for TTR Amyloidosis.

Treatment

The patient, which was admitted to the hospital during the therapeutic time window and had no known contraindications for the treatment, was qualified in the acute phase for intravenous thrombolytic of the ischemic stroke. The patient received a total of 50 mg of alteplase, of which 5 mg was administered as a bolus, followed by 45 mg on the pump.

Considering the limitation of the patient's daily functioning (mRS 4) and doubts about the patency of a large vessel (results of CT and angio-CT were not consistent), the patient was not qualified for treatment with mechanical thrombectomy.

The patient saw gradual improvement in his neurological condition with the completion of alteplase administration. Initially, the tendency to turn and look to the left disappeared. The paresis of the right limbs also decreased and then disappeared entirely. In the following hours, the speech disorders also disappeared. During hospitalization, empirical antibiotic therapy was initiated, and a positive reaction to the treatment was obtained. The patient was given antiplatelet drugs, and antihypertensive treatment was modified because patients with amyloidosis

generally do not tolerate commonly used antihypertensive drugs (inhibitors angiotensin-converting enzymes, beta blockers). The ECG showed suspicion of third-degree atrioventricular block, which a cardiologist consulted. Due to the lack of blockage in the patient's follow-up, ECG treatment was monitored and the treatment was modified by discontinuing amiodarone and bisoprolol.

No specific treatment for TTR amyloidosis was offered to the patient.

Discussion

Still unclear pathogenesis, multifactorial aetiology, difficulties in diagnosis, and the particular rarity of TTR amyloidosis prompted discussion of this issue's clinical case example. Determining the diagnosis of amyloidosis is based on analyzing the symptoms reported by the patient, physical examination and additional tests. Because amyloidosis is a disease uncommon and causing non-specific symptoms, its diagnosis is not easy. Amyloidosis is a chronic disease, and curing it completely is not possible. Therapy's goal is to control the symptoms and slow down the course of the disease. Amyloid is identified based on a biopsy e.g. of subcutaneous abdominal fat tissue, organs affected by ATTR-FAP (e.g. nerves, heart, kidneys) or another unoccupied place, e.g. gums, rectal mucosa, salivary glands. Genetic testing can complement diagnostic methods used to identify deposits amyloid. Accurate determination of mutations in DNA using genetic testing is possible, important for prognosis and treatment. In the case in question, a genetic test was performed which confirmed the genetic mutation responsible for transthyretin amyloidosis of autosomal dominant inheritance. For this reason, it is advisable to perform genetic testing for this disease in other family members. In the course of amyloidosis, it occurs as amyloid deposition in various tissues. If the heart is affected, it leads to cardiomyopathy amyloidosis. This complication develops in approximately 50% of patients with AL amyloidosis and in 10% of patients with AA amyloidosis. [23] It is much less frequently observed in familial cardiomyopathy amyloid ATTR. Although the incidence of transthyretin amyloidosis cardiomyopathy (ATTR-CM) is not quite clear, studies suggest that's ATTR affects 11-13% of patients with heart failure with preserved ejection fraction. [7] Moreover, in about 15% of patients with aortic stenosis (AS) undergoing

transcatheter aortic valve replacement, nuclear scintigraphy results are consistent with transthyretin amyloidosis cardiomyopathy (ATTR-CM). [7] Furthermore, it has been noted that variant ATTR (particularly the TTR V122l variant) is a relatively prevalent cause of heart failure among individuals of Afro-Caribbean heritage. [7] Regardless of the type of amyloidosis, it accumulates amyloid, which in the case of cardiac localization leads to thickening of the walls and enlargement of the cavities, ventricular restriction and diastolic dysfunction, as well as rhythm and conduction disorders. With the patient discussed in this case, cardiac ultrasound revealed left ventricle with concentric wall hypertrophy and the second-degree diastolic dysfunction, degenerative changes of the aortic valve causing its complex defect: moderate regurgitation and other abnormalities that make up the characteristic picture of echocardiography, which may suggest amyloidosis. In older people who are treated with antihypertensive drugs such as inhibitors angiotensin-converting enzymes, beta blockers, at some point, the blood pressure drops and intolerance to the treatment appear, which is what happens to be a signal that we may be dealing with amyloidosis. Due to progressive dysfunction of the autonomic nervous system in the advanced phase of amyloidosis, these drugs greatly intensify hypotension and fainting in this mechanism. In a few cases beta blockers are needed in heart rhythm control, but they must be used with caution. [24] Basic preparations used in the symptomatic treatment of heart failure in patients with transthyretin amyloidosis are loop diuretics. Cardiac involvement significantly worsens prognosis because those patients usually survive less than 6 months.[24] In the case in question, serum protein electrophoresis was also performed which showed abnormalities in beta and gamma globulin values. This is another diagnostic method that allows observation of monoclonal proteins but due to low sensitivity it is not used as test confirming the initial diagnosis. During the patient's stay in the hospital, full diagnostics process was performed including numerous imaging tests. Thrombolytic treatment of ischemic stroke was administered due to the known time of symptom onset and the lack of absolute contraindications for its administration in order to improve the clinical condition, in particular, to eliminate symptoms of right limb paresis and speech disorders. The right limb paresis disappeared completely, and speech disorders decreased significantly. In Poland, so far only a dozen or so families with TTR amyloidosis are known, and many patients remain undiagnosed.[25] Until recently, the sole recognized method

to stop the advancement of hereditary TTR amyloidosis was through liver transplantation. [25, 26] This procedure involves replacing the liver, the source of the mutated TTR, with the less amyloidogenic wild-type TTR. However, a new approach has emerged in the form of Tafamidis meglumine. This carefully designed benzoxazole derivative, unrelated to NSAIDs, binds strongly and selectively to TTR. It works by kinetically stabilizing the tetramer, slowing down the monomer formation, misfolding, and amyloidogenesis processes. Notably, Tafamidis is the first medication sanctioned to decelerate the progression of peripheral neurologic impairment in TTR familial amyloid polyneuropathy. [26] Significantly, among various groups of patients with TTR amyloidosis who were treated with tafamidis, including those with heart-related issues and a small subset with kidney problems, the adverse events (such as urinary tract infections, respiratory infections, diarrhea, headache, pain, and vomiting) were generally of mild to moderate severity. Importantly, no major safety concerns were identified. Generally, a daily dose of tafamidis at 20mg proved safe and well-tolerated. In patients with heart-related issues undergoing open-label tafamidis treatment, the measures of disease progression did not significantly worsen over 12 months. [26]

While tafamidis may offer advantages to individuals dealing with nerve or heart-related problems, it's improbable that oral tafamidis therapy would effectively address central nervous system manifestations of TTR amyloidosis, such as ocular amyloidosis. This is because the drug doesn't penetrate extensively into the eye, as observed in rat studies. [26]

Our patient was not qualified for any other specific treatment due to his disability stage.

Conclusions

Despite ongoing research and attempts to identify the cause of amyloidosis, its pathogenesis is still unknown and available treatment is only symptomatic. In case of suspicious abrasives, the implementation of rapid diagnostics seems to be undoubtedly the most important step, as the build-up of amyloid deposits

progresses over time. It has a key influence on patient's prognosis and course of treatment. Amyloidosis is a devastating disease that advances rapidly. It is progressive, painful and ends in premature death, as well as presents with a multi-organ symptom so it undoubtedly requires interdisciplinary treatment. Patients being treated correctly have a chance to enjoy a long and fully valuable life. To improve the diagnosis and of TTR amyloidosis the awareness and transfer of knowledge should start at the medical school level, even if the future doctor will never face this disease during their practice.

Declarations

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Author contributions

Conceptualization, H.S, P.G.; Methodology I.M, H.S; Validation, P.G, P.B.; Formal Analysis, A.M. ; Investigation, H.S, I.M. ; Resources H.S, P.G., N.J. ; Data Curation, A.S; Writing – Original Draft Preparation, A.S, P.B., Z.M. ; Writing – A Case report & Editing, H.S., A.M; Visualization, P.B,A.S ; Supervision, A.M, N.J ; Project Administration, A.S, P.G., Z.M.

Conflicts of interest

The authors have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this manuscript.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Data availability

The data have not been made public, but are kept with the authors, if necessary.

Ethics approval

Written informed consent for publication was obtained from the patient. We complied with the policy of the journal on ethical consent.

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