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REVIEW ARTICLE

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AMYLOIDOGENIC PROTEINS AND OCCURRENCE OF DIFFERENT AMYLOIDOSIS IN DIFFERENT ANIMAL SPECIES

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ABSTRACT

Amyloidosis is a poly-systemic disease caused by extracellular deposition of biologically inactive amyloid proteins, most often in kidneys, liver, nervous system, thyroid, spleen and heart. Depending on the site of production and deposition they can be classified into causing localised (organ-limited) and systemic amyloidosis. Disturbances in functioning of individual organs occur with an increase of the amount of accumulated protein what in turn may lead to the death of the affected individual. The occurrence of amyloidosis has been reported in human, but in animals, the most common form is AA amyloidosis, while AL amyloidosis is the least common. Due to the fact that symptoms of amyloidosis vary and often resemble those occurring in the course of other diseases, it is difficult to diagnose. Treatment of amyloidosis is aimed at improving functioning of the affected organs, yet the disease is incurable.

Key words: amyloid proteins, localized amyloidosis, systemic amyloidosis

INTRODUCTION

Amyloidosis is a group of organ or systemic diseases caused by the presence of extracellular or intracellular protein deposits of various origins, which are characterised by common physicochemical features. Abnormal proteins, called amyloid proteins, which build up in tissues or organs, cause this disease. As the amount of accumulated protein deposits in individual tissues and organs increases, their functions are disturbed, what in some cases may even lead to the death of the affected individual. Although amyloidosis is classified as a rare disease, its occurrence has been reported in humans and many other species of vertebrates [Benson et al. 2019]. Depending on the site of production and deposition of amyloid proteins, two main classes of amyloidosis are distinguished: localized and systemic [Murakami et al. 2014, Rising et al. 2017]. In localized or organ-limited amyloidosis amyloid fibrils are deposited in the same organs, where the precursors of these fibres are synthesized, such as brain, kidneys or liver. The much more common systemic amyloidosis are these, in which proteins circulate in blood and then accumulate throughout the body [Sipe et al. 2012].

Due to the complexity of this disease, it is not possible to fully discuss symptoms and transmission of all types of amyloidosis in one study. This article presents the mechanism of action of selected amyloid proteins and the occurrence of various types of amyloidosis in domestic, farm and wild animals.

AMYLOID PROTEINS

Amyloid proteins that turn into amyloid fibres and are deposited in various tissues and organs of the body trigger symptoms in all types of amyloidosis. So far, only 36 have been described in humans and 10 in various animal species (Table 1). Amyloidogenic (amyloid) proteins, due to changes in their spatial structure, cause the formation of specific, highly stable and insoluble fibres that form amyloid deposits [Benson et al. 2019]. All the sequences of amyloid proteins known so far are characterized by a significantly high content of asparagine and glutamine residues. Therefore, their primary structure allows to pre-

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Table 1. Amyloid fibril proteins and their precursors in animals [Benson et al. 2019, modified]

Tabela 1. Białka włókien amyloidowych u zwierząt i ich prekursorzy [Benson i in. 2019, zmodyfikowane]

Precursor protein Białko prekursorowe	Fibril protein Białko fibrylarne	Type of amyloidosis Rodzaj amyloidozy	Affected organs or syndrome Dotknięte narządy lub zespół
Immunoglobulin Light Chain Łańcuch lekki immunoglobuliny	AL.	systemic, localized ogólnoustrojowa, miejscowa	plasmacytoma plazmocytoma
(Apo) Serum Amyloid A (Apo) Surowiczy amyloid A	AA	systemic – ogólnoustrojowa	chronic inflammation or infections przewlekłe zapalenie lub infekcje
Apolipoprotein AI Apolipoproteina AI	AApoAI	systemic – ogólnoustrojowa	age-related związane z wiekiem
Apolipoprotein AII Apolipoproteina AII	AApoAII	systemic – ogólnoustrojowa	age-related związane z wiekiem
Transthyretin Transtyretyna	ATTR	systemic – ogólnoustrojowa	age-related związane z wiekiem
Fibrinogen Aα Fibrynogen Aα	AFib	systemic – ogólnoustrojowa	spleen, liver śledziona, wątroba
Aβ precursor protein Białko prekursorowe Aβ	Aβ	localized – miejscowa	age-related związane z wiekiem
Islet Amyloid Polypeptide Polipeptyd wysepki amyloidowej	AIAPP	localized – miejscowa	islets of Langerhans, insulinoma wysepki Langerhansa, insulinoma
Insulin Insulina	AIns	localized – miejscowa	islets of Langerhans wysepki Langerhansa
A-S2C casein Kaseina A-S2C	ACas	localized – miejscowa	mammary gland gruczoł mlekowy

dict infectious properties of a given protein; however, it is not the only one prognostic criterion. Amyloid proteins can be divided into localized and systemic amyloidosis proteins (Table 1) [Sipe et al. 2012, Benson et al. 2019]. All known forms of amyloidosis occurring in animals, except ACas amyloidosis, have also been found in humans [Benson et al. 2019].

Islet Amyloid Poly-Peptide (IAPP), also known as amylin, is a protein composed of 89 amino acids in humans (*Homo sapiens*), domestic dogs (*Canis lupus familiaris*), domestic cats (*Felis catus*), red foxes *(Vulpes vulpes*), cheetah (*Acinonyx jubatus*), 91 amino acids in domestic cattle (*Bos taurus*), 93 amino acids in domestic mice (*Mus musculus*), 119 amino acids in domestic pig (*Sus scrofa*) and as many as 135 in chicken (*Gallus gallus*). In humans, the gene coding for IAPP is located on chromosome 12 and encodes a precursor protein. Its N-terminus is the 22 amino acid sequence responsible for the transport of IAPP in endoplasmic reticulum. The precursor protein is matured by limited proteolysis which produces a mature 37 amino acid IAPP [Hoppener et al. 1994]. The main region of synthesis of this protein are pancreatic β-cells, but it can also be synthesized in other body regions [Christmanson 1993, Hou et al. 1999], such as gastric and duodenal mucosa cells as demonstrated in rabbits and mice [Azriel and Gazit 2001]. IAPP, like insulin and glucagon, is a pancreatic hormone involved in regulating glucose levels in the body. Contrary to insulin, amylin reduces the absorption of glucose from gastrointestinal tract, and also enhances hepatic glucogenesis [Karlsson 1999]. Moreover, it inhibits the synthesis of muscle glycogen [Kosowska et al. 2003]. The amyloidogenic role of IAPP relates to pancreatic β-cells. Under physiological conditions, homeostasis is maintained between the concentration of IAPP and the concentration of insulin, what in pathogenesis of type II diabetes it is permanently disturbed in favour of IAPP, which in about 90% of patients causes a gradual loss of the ability of pancreatic β-cells to synthesize insulin. Dysfunction of these cells occurs due to the excessive accumulation of IAPP in these cells in the form of amyloid fibres. This accumulation takes place primarily in the endoplasmic reticulum and the Golgi apparatus of pancreatic β-cells. The formation of amyloid fibres is associated with a change in the conformation of the IAPP protein, which consists in the conversion of some α-helical domains into β structures, without changing the primary structure of the protein. Conversion of soluble IAPP monomers into insoluble forms, fibrous and highly stable molecules capable of self-aggregation into oligomers that build amyloid fibres takes place when cell biochemistry is changed and that can happen due to the influence of many initiating factors [Karlsson 1999, Jaikaran and Clark 2001].

The apoptotic effects that precede the death of pancreatic β-cells are related to the rupture of cytoplasmic

membranes of these cells. Membrane fracture is initiated by small toxic molecules that are precursors to amyloid fibres, called ISTAPs (Intermediate-Sized Toxic Amyloid Particles) [Hiddinga and Eberhardt 1999]. The rupture of pancreatic β-cell membranes leads to the release of amyloid deposits into extracellular space. Their presence has been found not only in patients with type II diabetes, but also in patients with insulinoma [Westermark et al. 1999]. To date several studies have also shown different location of the IAPP amyloid fibre deposits in different species. In monkey and domestic cat amyloid fibres accumulate intracellularly, while in transgenic mice bearing human IAPP gene, these fibres accumulate both intra- and extracellularly with polymerisation beginning outside the cell [Westermark et al. 1999]. In humans, however, these fibres are formed and deposited primarily intracellularly [Westermark et al. 1999]. Research studies identified fragments within the mature amino acid sequence of the IAPP protein, which are necessary for initiation of amyloidogenesis of pancreatic β-cells [Jaikaran et al. 2001].

Insulin, one of the pancreatic hormones, may be associated with the formation of amyloid fibres in people with type II diabetes. Previous studies have shown that abnormal functioning of pancreatic β-cells may lead to production of insulin amyloid, which is toxic to these cells; it increases the volume of these cells and, as a result, damages their cytoplasmic membranes [Hiddinga and Eberhardt 1999]. In addition, the presence of insulin amyloid fibres have also been found in diabetics at the site of insulin injection [Kelly 1998].

Transthyretin (TTR) is a protein synthesized in the liver that plays an important role in thyroxine (T4) transport by binding this hormone to retinol, through indirect association with a retinol-binding protein. Analysis of different amyloidogenic mutations in the TTR gene showed that they all underwent main chain proteolysis at 48th amino acid residue. The resulting dimers then lost their ability to associate into natural final tetrameters and began to form amyloid fibres from the N-terminated truncates [Schormann and Murell 1998].

Amyloid β (Aβ) protein in its soluble form occurs in body fluids of healthy individuals and individuals with Alzheimer's disease. However, in affected sick individuals, this protein is transformed into a non-dissolving and fibrous form – the reason of this alteration currently remeins unknown. It is believed that gelsolin is an anti-amyloidogenic protein as it prevents formation of fibrous forms of the Aβ protein, preferring its soluble form. As a result of the mutation, gelsolin loses its anti-amyloidogenic properties [Kelly 1998]. Its functions are poorly understood, as are mutations in the gene that encodes it. So far, only a few mutations have been identified that cause the late form of systemic amyloidosis, known as the Finnish one [Levy et al. 1999]. The mutated forms of gelsolin undergo partial proteolysis, which initiates formation of proto-fibrils from the resulting fragments, and these polymerize to form amyloid fibres. As a result, systemic amyloidosis develops with symptoms of cranial neuropathy, bilateral reticular dystrophy of the cornea, skin lesions, and disturbances in homeostasis (changes in the shape of platelets), which causing blood clotting problems. Other known mutations are characterized by significant amyloid storage in rectum and skin, or only by reticulated corneal dystrophy in old age [Stewart and Parveen 2000].

Fibrinogen, i.e. clotting factor I, is a blood plasma protein produced in the liver, which is involved in the final stage of the clotting process and is converted into fibrinous protein – fibrin, which forms blood clot. This protein is a dimer that is formed on the breast of the connection of monomers by a disulphide bond [Hannidi et al. 1997]. In humans, 3 genes located on chromosome 4 are responsible for the synthesis of fibrinogen chains in hepatocytes, resulted in the amyloid storage and complete kidney breakdown after about 2 years [Hannidi et al. 1997]. Amyloid deposited in the transplanted kidneys was isolated. It consists of a hybrid protein that builds the A-chain of α-fibrinogen, composed of two different amino acid sequences: the correct (at the N-terminus) and the new 26-amino acid (at the C-terminus) [Hannidi et al. 1997].

Additionally, changes, including these associated with proteolysis of immunoglobulin light chains, can lead to amyloidosis. Its symptomps include frequent bleeding associated with deposition of amyloid in various organs, as well as the affinity of the amyloid protein for certain clotting factors. Moreover, various mutations in the genes encoding light chains can lead to the disease [Liepnieks et al. 1996, Stevens and Kisilevsky 2000].

Serum amyloid A (SAA) is a precursor protein for amyloid A, which is the major component of tissue amyloid deposits. SAA belongs to the acute phase proteins synthesized in the liver after stimulation with pro-inflammatory cytokines [Lis-Święty et al. 2012]. Previous studies have shown that increased concentration of this protein found in various chronic inflammatory and neoplastic diseases may lead to the development of amyloidosis [Van der Hilst 2011]. In this case insoluble amyloid fibres are accumulated in tissues, mainly in kidneys, liver or spleen, which in turn can lead to damage to these organs. These fibres, which are a reactive form of amyloid A (AA), are made of SAA fragments derived from the restricted proteolysis of C-terminus of this protein [Schultz and Arnold 1990]. Then the reactive form of A amyloid, after binding to proteoglycans and proteins, such as heparin sulphate or serum amyloid P (SAP) in the extracellular space becomes resistant to degradation (Schultz and Arnold 1990, Van der Hilst 2011]. Storage of the reactive form of amyloid A results

in AA amyloidosis, which is a systemic type of amyloidosis and occurs spontaneously in many mammalian and avian species, that experience chronic inflammation [Cowan 1968, Jakob 1971, Landman et al. 1998]. In humans, systemic AA amyloidosis occurs in patients with chronic inflammatory diseases, for example rheumatoid arthritis [Hazenberg and van Rijswijk 2000, Nakamura 2007]. This disease is very common in dogs. So far it has not been reported in the blue fox (*Alopex lagopus*), while in the grey fox (*Urocyon cinereoargenteus*) it was not reported until 2016 [Elisen et al. 2004, Gaffney et al. 2014, Gaffney et al. 2016, Rising et al. 2017].

Apolipoprotein AI (ApoAI) is a polypeptide belonging to the group of apoplipoprotein. It is the protein part of lipoproteins, especially high-density lipoproteins (HDL) and is synthesized in the liver and intestine, while in plasma circulates mainly in the form associated with high-density lipoproteins (90–95%). It is believed to be the main protein responsible for antiatherosclerotic activity of HDL [Kosowska et al. 2001, Wróblewska 2009].

AMYLOIDOSIS IN DIFFERENT ANIMAL SPECIES

The occurrence of various types of amyloidosis has been recorded in many animal species over the years (Table 2). The first reports of the occurrence of various types of this disease in animals date back to the 1960s and 1970s. Since then, there have been reports of identification of hitherto known types of amyloidosis in new species of animals and identification of new types of amyloidosis and amyloidogenic proteins. Studies have shown, that in animals the most common form is the so-called AA amyloidosis, associated with AA protein storage [Zschiesche and Jakob 1989, Rising et al. 2017], while the least common is amyloidosis resulting from a mutation in immunoglobulin light chains – AL amyloidosis [Kim et al. 2005]. In birds, amyloidosis most often occurs in waterfowl, in 1968 amyloidosis was identified in 304 birds belonging to 76 families of 22 orders that died at the Philadelphia Zoo [Cowan 1968, Gaweł et al. 2001].

In addition, prion amyloidosis has been observed in animals. So far 16 types of prion diseases have been described in humans and various species of mammals have been described (Table 2). Animal prion diseases include scrapie of sheep and goats, bovine spongiform encephalopathy (BSE) or mad cow disease, transmissible mink encephalopathy, feline spongiform encephalopathy, exotic ungulate spongiform encephalopathy, chronic wasting disease of cervids, and spongiform encephalopathy of primates [Imran and Mahmood 2011].

Symptoms of amyloidosis are extremely non-specific and difficult to recognize. Moreover, it also happens that one patient can be diagnosed with two types of amyloidosis that occur simultaneously [Sidigi et al. 2019]. When amyloidosis is suspected, first of all, it is necessary to conduct numerous laboratory tests, including: presence of light monoclonal chains in the urine or blood serum, protein concentration in urine, microscopic examination of tissues. Treatment of amyloidosis is aimed at improving functioning of organs affected and prognosis is usually poor because amyloidosis is an incurable disease and depends on its type and stage of organ advancement. By targeted treatment, one can only alleviate its symptoms and slow down its course. Modern methods of treatment are used in humans and they mainly include chemotherapy, often followed by an autologous transplant, which is a transplant of stem cells derived from the patient's blood. Alternatively, monoclonal antibodies, cytostatics, and immunosuppressants are also administered [Sidigi et al. 2019]. However, depending on the type of amyloidosis, its severity, and the organ in which amorphous amyloid proteins accumulate, prognosis varies [Sidigi et al. 2019]. In its primary form, when human amyloid is deposited in kidneys, heart, liver, spleen or nervous system, if patient is not properly treated, the average survival time is approx. 2 years (in case of a heart attack, only 6 months). However, in secondary amyloidosis, which accompanies many chronic diseases such as: Crohn's disease, juvenile idiopathic arthritis (JIA), bronchiectasis, tuberculosis, osteomyelitis, rheumatoid arthritis, the average survival time from diagnosis is approx. 10 years.

CONCLUSIONS

The cause of amyloidosis in a multi-system disease with a non-specific course is the accumulation of an abnormal protein in the tissues and organs-amyloid. The molecular causes of abnormal protein structure and deposition in organs are not yet fully understood. Extracellular deposition of this protein occurs most commonly in the kidneys, nervous system, liver, thyroid gland, spleen, and heart. It has been shown that the protein accumulated in large amounts oppresses the cells, which leads to the dysfunction of the organ and, as a consequence, the loss of its flesh and death of the affected individual. Depending on the causative factors of amyloidosis (genetic or autoimmune factors, chronic inflammations), there are several different types of this disease. The main goal of treating amyloidosis is to stop the progression of the disease and to support the function of the organs affected by the abnormal amyloid protein. Unfortunately, modern treatment methods, mostly because of their high cost, are only used when the patient is a human and not an animal. Currently, due to the high cost of treatments available for humans, they are not used for animals. The hope of reducing the incidence of this disease in animals is a better understanding of its molecular basis and thus the way of inheritance, which will allow to conduct a proper selection of individuals for reproduction.

Table 2. Occurrence of selected amyloidosis type in animals

Tabela 2. Występowanie wybranych typów amyloidozy u zwierząt

Species – Gatunek	References – Bibliografia
	AL amyloidosis – Amyldoiza AL
Domestic cat – Kot domowy	Farrow and Penny 1971, Drazner 1982, Mills et al. 1982, Hribernik et al. 1982, Hawkins et al. 1986, Carothers et al. 1989, Rowland and Linke 1994, Liepnieks et al. 1996, Burrough et al. 2012
Horse – Koń	Shaw et al. 1987, Van Andel et al. 1988, Linke et al. 1991, Niewold et al. 1996, Kim et al. 2005
Domestic dog – Pies domowy	Schwartzman 1984, Geisel et al. 1990, Rowland et al. 1991, Gross et al. 1992, Rowland and Linke 1994, Besancon et al. 2004, Labelle et al. 2004, Woldemeskel 2007
	AA amyloidosis – Amyldoiza AA
Domestic duck – Kaczka domowa	Guo and Aldrich 1996
Domestic cat – Kot domowy	Chew et al. 1982, Boyce et al. 1984, DiBartola et al. 1985, DiBartola and Tarr 1986, DiBartola et al. 1986, Johnson et al. 1989, Johnson et al. 1996, van der Linde-Sipman et al. 1997, Niewold et al. 1999
Domestic dog – Pies domowy	Cheville 1968, Osborne et al. 1968, Cheville et al. 1970, Slauson et al. 1970, Slauson and Gribble 1971, DiBartola and Meuten 1980, Hargis et al. 1981, Hol and Gruys 1984, Linke et al. 1984, Westermark et al. 1985, Benson et al. 1985, DiBartola and Tarr 1988, DiBartola et al. 1989, DiBartola et al. 1990, Bowles and Mosier 1992, Johnson et al. 1995, Johnson et al. 1996
Cattle – Bydło	Jakob 1971, Murray et al. 1972, Gruys 1975, Gruys 1977, Kim et al. 1981, Monaghan 1982, Burns et al. 1984, Johnson and Jamison 1984, Westermark et al. 1986, Husebekk et al. 1988, Benson et al. 1989, Rossevatn et al. 1992, Alsemgeest et al. 1995, Johnson et al. 1996, Seifi et al. 1997, Senturk and Ozyigit 2006, Yamada et al. 2006, Elitok et al. 2008
Birds – Ptaki	Cowan 1968, Landman et al. 1998
Pekin ducks – Kaczka pekińska	Rigdon 1961, Madej et al. 1995
Chicken – Kura domowa	Zekarias et al. 2000, Steentjes et al. 2002, Murakami et al. 2014, Murakami et al. 2015
Mouse – Mysz	Gorer 1940, Gelnner et al. 1971, Westermark et al. 1979
Cheetah – Hepard	Munson 1993, Papendick et al. 1997, Terio et al. 2008, Zhang et al. 2008
Horse – Koń	Hayden et al. 1988, Van Andel et al. 1988, Vanhooser et al. 1988, Johnson et al. 1996, Murakami et al. 2014
Domestic pig – Świnia domowa	Jakob 1971, Szuperski et al. 1980, Zschiesche and Jakob 1989,
Goat – Koza	Crawford et al. 1980, Farnsworth and Miller 1985, Tham and Bunn 1992, Ménsua et al. 2003
Bighorn sheep – Owca kanadyjska	Hadlow and Jellison 1962, Wolfe and Kradel 1973, Kingston et al. 1982
Red fox – Lis pospolity	Rising et al. 2017
Bottlenosed dolphin – Delfin butelkonosy	Cowan 1995
Bat – Nietoperz	Gruber and Linke 1996
Siberian tiger – Tygrys syberyjski	Schulze et al. 1998
Island gray fox – Urocjon wyspowy	Gaffney et al. 2016
Wild boar – Dzik	Segalés et al. 2005
Gazelle – Gazela	Linke et al. 1986, Rideout et al. 1989
Mink – Norka	Nieto et al. 1995
Lion – Lew	Williams et al. 2005
Sheep – Owca	Ménsua et al. 2003
	AApoAI amyloidosis – Amyldoiza AApoAI
Domestic dog – Pies domowy	Roertgen et al. 1995
	AApoAII amyloidosis – Amyldoiza AApoAII
Mouse – Mysz	Xing et al. 2001, Korenaga et al. 2006
	AIAPP amyloidosis – Amyldoiza AIAPP
Domestic dog – Pies domowy	Johnson et al. 1986, Johnson et al. 1989
Cynomolgus monkey – Makak krabożerny	Wagner et al. 1996
Domestic cat – Kot domowy	O'Brien et al. 1987, Jordan et al. 1990, O'Brien et al. 1990, Gruys 2004
	Aβ amyloidosis – Amyldoiza Aβ
Domestic dog – Pies domowy	Russell et al. 1996, Wisniewski et al. 1970, Shimada et al. 1992, Cummings et al. 1996, Russell et al. 1992, Yoshino et al. 1996
Sea lion – Lew morski	Takahashi et al. 2014
Domestic cat – Kot domowy	Nakamura et al. 1996

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BIAŁKA AMYLOIDOGENNE I WYSTĘPOWANIE RÓŻNYCH RODZAJÓW AMYLOIDOZY U RÓŻNYCH GATUNKÓW ZWIERZĄT

STRESZCZENIE

Amyloidoza to choroba wieloukładowa. Przyczyną jest pozakomórkowe odkładanie, najczęściej w nerkach, wątrobie, układzie nerwowym, tarczycy, śledzionie i sercu, różnych biologicznie nieaktywnych białek amyloidowych. W zależności do miejsca wytwarzania i miejsca odkładania białka wyróżnia się postać zlokalizowaną/ograniczoną lub uogólnioną amyloidozy. Zaburzenia funkcji poszczególnych organów następują wraz ze wzrostem ilości w nich nagromadzonych złogów białkowych, co w konsekwencji może prowadzić do śmierci chorego osobnika. Występowanie amyloidozy odnotowano w populacji ludzkiej. Wśród zwierząt najczęściej występującą formą jest amyloidoza AA, natomiast najrzadziej występuje amyloidoza AL. Objawy są zróżnicowane, przypominające dolegliwości występujące w przebiegu innych chorób, dlatego amyloidoza jest trudna do rozpoznania. Leczenie jest ukierunkowane na poprawę funkcjonowania narządów, których amyloidoza dotyczy.

Słowa kluczowe: białka amyloidogenne, postać zlokalizowana/ograniczona amyloidozy, postać uogólniona amyloidozy

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