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Systemic AA amyloidosis: a potential public health problem

Amiloidosis sistémica AA: un problema potencial de salud pública

Meléndez-Soto Rosa ID

Departamento de Ciencias Veterinarias, Centro de Ciencias Agropecuarias, Universidad Autónoma de Aguascalientes, Av. Universidad #940, Ciudad Universitaria, C. P. 20131. Aguascalientes, Aguascalientes, México. E-mail: rmelende@correo.uaa.mx

ABSTRACT

The objective of this review is to inform animal health professionals about systemic AA amyloidosis, a little known potential public health problem in Mexico, which can result from the consumption of animal products. It is difficult to diagnose, since clinical signs depend on the type and location of the amyloid; and its terminal phase corresponds to renal failure. It consists of the accumulation of an extracellular protein material that can originate from about 37 normal proteins in humans and more than 15 in other aquatic and terrestrial mammals and in birds. It has a peculiar fibrillar structure in a β-folded arrangement that confers great resistance to physicochemical agents, which makes difficult its elimination from food. Some amyloidosis, such as Alzheimer's disease in humans and cognitive dysfunction disorder in dogs, are localized, but AA amyloidosis is systemic and there is natural and experimental evidence that it can be transmitted intra- and interspecies when there is oral, intravenous or intraperitoneal entry of amyloid material in an individual with pre-existing chronic inflammatory disease or other risk factors, such as obesity, making it a potential public health problem.
Keywords: Public health, food safety, amyloidosis, chronic inflamation, renal insufficiency.

RESUMEN

El objetivo de esta revisión es informar a los profesionales en salud animal, sobre la amiloidosis sistémica AA, un problema potencial de salud pública poco conocido en México, que puede derivarse del consumo de productos animales. Es difícil de diagnosticar, pues los signos clínicos dependen del tipo y localización del amiloide; y su fase terminal corresponde con un cuadro de insuficiencia renal. Consiste en la acumulación de un material proteico extracelular que puede originarse a partir de alrededor de 37 proteínas normales en los humanos y más de 15 en otros mamíferos acuáticos y terrestres, y en aves. Posee una estructura fibrilar característica en disposición β plegada que le confiere gran resistencia a agentes fisicoquímicos, que hace difícil su eliminación de los alimentos. Algunas amiloidosis, como el Alzheimer en humanos y el trastorno de disfunción cognitiva en los perros, son localizadas, pero la amiloidosis AA es sistémica y existe evidencia natural y experimental de que puede transmitirse intra e inter-especie cuando hay ingreso por vía oral, intravenosa o intraperitoneal de material amiloide en un individuo con una enfermedad inflamatoria crónica pre-existente u otros factores de riesgo, como la obesidad, lo que la convierte en un potencial problema de salud pública.
Palabras clave: Salud pública, inocuidad alimentaria, amiloidosis, inflamación crónica, insuficiencia renal.

INTRODUCTION

Proteins, in addition to building tissues, are essential for cell metabolism and communication; their three-dimensional structure depends on how the amino acid sequence that constitutes their primary structure is folded. The structure governs the function and that is why some have certain flexibility that allows them to adjust to the required task; that makes it necessary to have mechanisms that ensure the production, folding and elimination (if applicable), of defective proteins (Jucker & Walker, 2013).

Several proteins that are soluble under physiological conditions may undergo changes or conformational changes towards a molecular structure in a β-folded arrangement and subsequently self-assemble into extremely insoluble fibers (Sipe *et al.,* 2012). There are many diseases that arise from protein misfolding. Amyloidosis is one of them and comprises a wide range of very different human and animal disorders that have in common the infiltration of one or several tissues with an extracellular protein, amorphous accumulation with a characteristic appearance under electron microscopy; a typical X-ray diffraction pattern, affinity for Congo red staining and the production of green or yellow birefringence, under polarized light (Jucker & Walker, 2013; Sipe *et al*., 2016; Benson *et al*., 2018); although "amyloid-like" proteins are now known to be associated with important biological functions ranging from long-term memory, formation of hormone secretion granules (Maji *et al*., 2009; Rubel *et al*., 2020), membrane changes in the egg and sperm that enable fertilization and others not only in mammals; but also in plants and prokaryotic cells (Rubel *et al*., 2020).

The word amyloid was coined by Rudolph Virchow in 1854, after he described it as a starch-like material (because it stains with iodine), which infiltrated the liver, kidney and heart and was often found in *post-mortem* examinations (Gruys, 2004). Subsequently, the protein nature of the infiltrate was discovered and electron microscopy revealed its fibrillar structure.

In 1984, Glenner and Wong found the same type of fibers in the plaques of human brains with Alzheimer's disease and of hamsters experimentally infected with Scrapie (Gruys, 2004).

To date, 37 amyloidogenic proteins have been associated with approximately 70 human diseases. The best known include Alzheimer's disease, Parkinson's disease, type 2 diabetes and spongiform encephalopathies (Rubel *et al*., 2020). Also with some forms of cancer, such as multiple myeloma and plasmacytoma, in both humans and animals (Andrei & Wang, 2019, Kadota *et al*., 2020, Tamura *et al*., 2020).

Clinical data indicate that the proteins that constitute amyloid are different, since the deposits have been found in very different pathological contexts and have therefore been classified according to two criteria, their distribution and the precursor protein (Rubel *et al*., 2020). Despite their diverse origins, all amyloid deposits have a common basic structure, which also shares many cofactors; such as the P component of serum amyloid, apolipoprotein E and heparan sulfate-type proteoglycans (Martin *et al*., 2010; Benson *et al*., 2018). This isomorphism in such a heterogeneous group of proteins and diseases is unprecedented and suggests a common pathogenesis (Martin *et al*., 2010).

When amyloid is confined to a particular area of the body, it is known as localized amyloidosis and when it is found in more than one tissue it is known as systemic amyloidosis (Sipe *et al*., 2016). In localized amyloidosis, amyloid fibrils are deposited in organs where the precursor protein is produced; for example: amyloid Aβ peptide and Tau protein in the brain (Alzheimer's) and islet of Langerhans amyloid polypeptide or amylin and in the pancreas (type 2 diabetes) (Westermark *et al*., 2011). In systemic amyloidoses, the precursors are serum proteins, such as portions of immunoglobulins (AL amyloidosis), transthyretin (familial amyloidotic polyneuropathy) and b2-microglobulin (dialysis-related amyloidosis), which circulate in blood and polymerize to form amyloid fibers that are deposited in various organs of the body, except the brain (Sipe *et al*., 2012; Westermark *et al*., 2018).

The term amyloidosis is currently used mainly for systemic forms of disease in which the aggregates are definitely pathogenic; some types of amyloidosis have known genetic components, such as: familial amyloidoses in Abyssinian and Siamese cats (van der Linde *et al*., 1997; Paltrineri *et al*., 2015), Shar pei dogs (Segev *et al*., 2012) and hereditary transthyretin amyloidosis in humans (Silva-Hernández *et al*., 2020). Also in chickens (*Gallus gallus domesticus*), there is some predisposition to lineage-associated amyloid arthropathy, occurring only in brown egg layers (Ovelgöne, 2001).

There are observational studies in captive wild animals, which have reported a high prevalence of amyloidosis: Rhesus monkey (Macaca mulatta) (Blanchard *et al*., 1986; Rice *et al*., 2013, Leung *et al*., 2019), cheetahs (*Acinonyx jubatus*) (Papendick *et al*., 1997; Zhang *et al*., 2008; Franklin *et al*., 2016), marmosets (*Callithrix jacchus*), pig-tailed macaques (*Macaca nemestrina*) (Rice *et al*., 2013; Hukkanen *et al*., 2006), hunting falcons (Hampel *et al*., 2009), pronghorn (*Antilocapra americana*) (Martínez *et al*., 2019), badgers (*Meles meles*) (Bianco *et al*., 2020), caracals caracales (*Caracal caracal*) (Greunz *et al*., 2020); Japanese tree sparrows (*Lonchura striata* var. domestica) (Nakano & Madarame, 2020) and treeshrew (*Tupaia belangeri*) (Klein *et al*., 2021).

The same has been observed in wildlife in species such as: island foxes (*Urocyon littoralis*) (Gaffney *et al*., 2016), red foxes (*Vulpes vulpes*) (Rising *et al.*, 2017), gulls (*Larus argentatus*) (Jansson *et al.,* 2018) and Stejneger's beaked whales (*Mesoplodon stejnegeri*) (Nakagun *et al*., 2019; Nakagun *et al*., 2020), among others.

Such observations, especially in captive animals, have suggested the possibility of disease transmission. Experimental studies (Sørby *et al*., 2008; Murakami *et al*., 2011; Murakami *et al*., 2013; Murakami *et al*., 2014; Murakami *et al*., 2015) have allowed gathering evidence that amyloidosis known as systemic, indeed can be contagious intra- and interspecies, and thus constitutes a public health risk.

Tojo *et al*., (2005), found a 5% incidence of renal amyloidosis (15/302) in cattle slaughtered at the slaughterhouse, with no history of disease; although it has been found rarely; systemic AA amyloidosis has also been reported in pigs (Niewold *et al*., 2005). In a country where viscera are widely consumed, the study of its presence in slaughter cattle becomes more important.

Amyloidosis classification

From the amyloidogenic proteins identified, in humans at least 14 are associated with systemic disease (Westermark *et al*., 2018) and 19 with localized forms (Benson *et al*., 2018). In animals 9 have been identified, under normal conditions; all of these proteins are soluble (Zhang *et al*., 2008).

The accepted nomenclature is AX. Fibrillar (amyloid) proteins are designated as A proteins, followed by a suffix abbreviating the name of the precursor protein (X) (Cooper *et al*., 2013); for example, in AL amyloidosis, L corresponds to immunoglobulin light chains (light chains), in Alzheimer's disease amyloidosis is ATau, because the precursor protein is named *Tau*, IAPP is the amyloidosis located in the pancreas of people with type 2 diabetes, as the precursor is islet amyloid polypeptide (Sipe *et al*., 2016). In the case of systemic AA amyloidosis, it is referred to as AA, because the generating protein is serum amyloid A, a protein of the acute phase of inflammation (Brunger *et al*., 2020).

The types of amyloidosis that have genetic components and were previously known as "familial" are now suggested to be called hereditary; an example of the former is hereditary transthyretin amyloidosis (hATTR). The precursor protein is thyroxine-retinol transporter prealbumin whose mutation causes a rare multisystem disease in humans, consisting of amyloid deposition mainly in the peripheral nervous system and heart, causing progressive autonomic and sensorimotor peripheral neuropathy and restrictive cardiomyopathy. The eyes, kidneys and central nervous system may also be affected (Silva-Hernández *et al*., 2020).

In pets, familial amyloidosis (FA) is a hereditary disease that affects Abyssinian cats, and mainly the kidney; the precursor protein is serum amyloid (Paltrinieri *et al*., 2015). Similarly familial Shar-pei fever (FSF), is a hereditary disorder occurring in up to 23% of animals of this breed; it is characterized by recurrent episodes of fever of unknown origin, concurring with swelling and pain of the hocks, muzzle, abdominal pain, diarrhea and anorexia. It has been proposed that FSF predisposes to secondary reactive amyloidosis, as in humans suffering from Familial Mediterranean fever (Segev *et al*., 2012). Analysis of 255 DNA samples from Shar pei dogs revealed on chromosomes 13 and 14, areas associated with both FSF and amyloidosis (Olsson *et al*., 2013).

FSF is similar to Familial Mediterranean fever, an inherited autoinflammatory disease relatively common in people originating from the Eastern Mediterranean Basin, whose most severe complication is AA amyloidosis (Wekell *et al*., 2016).

It is worth mentioning as a particular case, pharmacological amyloidosis, occasionally amyloidomas appear on the skin, around insulin injection sites in diabetics and in HIV patients, due to the administration of an antiretroviral peptide called enfurvitide (Mollee *et al*., 2013; D'Souza *et al*., 2014).

Composition, characteristics and pathogenesis

Regardless of the protein of origin, amyloid molecules have unbranched fibrillar structure, with secondary structure in a β-folded arrangement, linked by noncovalent bonds that form both *in vivo* and *in vitro*. In the amyloid fiber the repeating polypeptide chains are cross-linked by intercatenary hydrogen bridges; two or more identical ones interact through side chains to form the characteristic fibers of about 8 to 12 nm in diameter, which appear rigid and unbranched under the electron microscope (Martin *et al*., 2010; Benson *et al*., 2018).

In most amyloid deposits there are other elements, a glycoprotein called P-component and heparan sulfate-type proteoglycans; complement factors C1q and C3; in addition there may be several apolipoproteins, such as E9. (Martin *et al.*, 2010; Benson *et al*., 2018; Westermark *et al*., 2018).

It is important to emphasize that a protein is not a static structure. In a living organism or even *in vitro*, a protein bends, spins, and vibrates; it collides with many molecules every second, such that what is called protein structure is only the state in which the energetic interactions between amino acid groups are most stable. It is this molecular dance that gives rise to the conformation that can act as a "seed" or amyloid core, which when it interacts with the precursor proteins and attaches to them, forms a growing fiber (Martin *et al*., 2010).

Due to their structure, these proteins, besides being insoluble, become hydrophobic, non-functional and resistant to ionic detergents and some proteases; they also have affinity to stains, such as Congo red and thioflavin T (Rubel *et al*., 2020; Picken, 2020).

In general terms, a protein can change to its amyloid state when a segment exposes the amide-NH and C=O groups of its backbone, allowing them to dock through hydrogen bridges with other protein chains. Several conditions produce exposure of the skeleton of amide groups: denaturation of normally folded proteins, overexpression of a protein that overcomes protein repair mechanisms through chaperones and sends them to inclusion bodies, cleavage of a peptide (such as Aβ) from a folded protein, or overproduction of a disordered protein from its origin (such as Tau or IAPP) (Eisenberg & Jucker, 2012).

In vivo conditions that promote amyloid formation are:

a) An increase in precursor protein concentration. Nucleated polymerization and fibril formation are dependent on the concentration of the protein. The pathogenesis of some of the systemic amyloidoses (AA, AL, for example); involves an increase in the plasma concentration of the precursor protein (Westermark *et al*., 2018). In systemic AA amyloidosis, a pre-amyloid phase is required and is characterized by elevated serum amyloid a (SAA) levels, which can result from bacterial infection, viral, autoimmune, autoinflammatory disorders, and metastasis; i.e., inflammatory conditions (Gursky, 2020).
b) Mutations that destabilize the native forms of the protein and allow amyloidogenic segments to interact with each other. A large proportion of systemic amyloidoses are inherited usually depending on a point mutation resulting in an amino acid substitution. This may be sufficient to destabilize proteins and predispose their misfolding or, as in the case of transthyretin (TTR), make the quaternary structure less stable (Westermark *et al*., 2018).
c) Exposure and/or de *novo* generation of amyloidogenic segments through native protein cleavage or aberrant translation.
d) Thermodynamically destabilizing conditions, such as temperature or pH modifications. The formation of amyloidomas by insulin administration in diabetics seems to be related to the above two conditions; Amdursky et al., 2012 (Cited by D'Souza *et al*., 2014), showed that insulin can self-assemble to form a crystalline core, from which fibrils subsequently develop and that such process is accelerated by the acidic environment and high insulin concentration.
e) Deterioration of the quality control of the cellular proteome (proteostasis), which occurs with aging. Many cellular functions decline, including the regulation of protein synthesis, folding, assembly and degradation. It is well known that amyloid deposits are found after the age of 50 years and that abnormal

proteostasis is involved in chronic neuromuscular proteinopathies such as Alzheimer's disease and inclusion body myositis (Romani *et al*., 2021). Systemic amyloidoses ATTR and AAPoAIV and some localized forms (atrium and seminal vesicles) are associated with aging. ATTR is an underdiagnosed cause of heart failure in older adults. With age the TTR tetramer becomes less stable and this results in the release of misfolding intermediates that eventually form amyloid deposits mainly in the heart of men older than 75 years (Picken, 2020)..

It can be summarized that, in some proteopathies, such as Alzheimer's disease, amyloid arises from de *novo* misfolding and sustained modification of endogenous proteins; whereas prion diseases can be of infectious origin; although they can also be genetic or sporadic. An amyloid polymer can immobilize monomeric non-amyloid protein molecules of the same sequence and thus grow through a process of nucleic polymerization.

Similar to what occurs in prion diseases, AA amyloidosis is considered to be transmitted through a process of "seeding-nucleation" (Murakami *et al*., 2015). In these disorders, protein aggregates form characteristic lesions known generically as amyloid; the initial step for their formation is the aggregation of monomers into a "nest", "seed" or nucleus, which acts as the point of origin for fibrillar growth. This individual fiber grows as monomers are added to the free ends. When long fibers break, they produce a greater number of free ends. The formation of the core is the time-determining step in the process and can be shortened from weeks to days when minute amounts of preformed fibrils are added, referred to as amyloid enhancing factor (AEF) (Lundmark *et al*., 2013).

Infectivity involves the transfer of seeds (prions), from one organism to another; whereas genetic and idiopathic appear to be generated endogenously (Jucker & Walker, 2013).

With any of the above circumstances, the amyloid protein begins to accumulate extracellularly, either locally or systemically, in which case it is deposited in various organs, except the central nervous system; as they accumulate, they deteriorate organ function and clinical signs begin to appear according to their location.

The mechanisms of toxicity have not been completely understood, but it has been observed that in smooth myocytes they alter cell adhesion (Bobylev *et al*., 2021). In the case of neurodegenerative diseases such as Alzheimer's and Parkinson's, translocation of fibrils to cell membranes can generate mitochondrial damage and trigger apoptosis (Hashimoto *et al*., 2003). The latter has also been observed *in vitro* in cardiac myocytes in the case of AL amyloidosis (Shi et al., 2010; Cited by Blancas & Ramírez, 2013).

Systemic AA amyloidosis

Background

Systemic amyloidoses culminate in death about 6 months after diagnosis in up to 20% of patients and cause 1/1000 deaths in developed countries where they remain an unresolved medical problem (Scarpioni *et al.*, 2016). Fibrillar proteins are synthesized in their native form in a location such as the liver or bone marrow, released into the circulation and eventually deposited in various tissues (Rising *et al*., 2017).

In 1961, Benditt and Eriksen observed an "amyloid of unknown origin" protein from gel electrophoresis in cases of so-called "secondary amyloidosis" as being associated with chronic or recurrent inflammatory conditions. Antibodies prepared against these proteins identified a small serum protein of 104 amino acids that turned out to be the precursor of such amyloid deposits; being the first serum protein of a type other than immunoglobulins to be identified as an amyloid precursor, it was named serum amyloid A (SAA) (Sack *et al*., 2018).

Systemic AA amyloidosis, has worldwide distribution, mainly affects the kidneys and it is caused by the aggregation and deposition of AA protein, a product of the degradation of the N-terminus of serum amyloid (SAA); a protein of the acute phase of inflammation. The kidneys are the organs that are affected earliest, although clinical signs, including proteinuria, develop in very late stages of the disease (Blank *et al*., 2015).

This disorder affects less than 5% of patients with chronic inflammation (Gursky, 2020). In 90 % of them the kidney is affected and if the concomitant inflammatory process is not controlled, the damage progresses to renal failure. In a study by Lachmann *et al*., (2007) it was observed that this is more frequent when proteinuria per day is greater than 500 mg and serum creatinine concentrations greater than 1.5 mg/dL. In 20% of patients the gastrointestinal tract is involved and diarrhea and malabsorption occur. With access to hemodialysis and renal transplantation increasing life expectancy, patients with digestive disorders are more common. Amyloidotic gout, hepatomegaly, splenomegaly and polyneuropathies are less frequent clinical findings (Van der Hilst, 2011).

Causes and risk factors of systemic AA amyloidosis

The acute phase response of inflammation comprises a series of very important changes in serum protein levels, such as C-reactive protein and serum amyloid. Both are present in the blood of healthy individuals, although at very low levels (SAA: 20-50 µg/ml); however, these can increase as much as a thousandfold in 24 hours after the onset of the event, basically by their de *novo* hepatic synthesis.

SAA is normally secreted by the liver, although also by macrophages, endothelial and smooth muscle cells (Scarpioni *et al*., 2016). It circulates associated with high density lipoprotein, stimulates the release of proinflammatory cytokines such as TNF-α, IL-8 and IL-1b and in turn, its production is stimulated by IL-1, IL-5 and TNF; but also by glucocorticoids and LPS (Brunger *et al*., 2020).

SAA functions are not fully understood, but are associated with modulation of immune response, cholesterol homeostasis and cell signaling. It is considered to be important for its ability to mobilize cholesterol for cellular repair. It also interacts with a wide array of other diverse ligands: cholesterol, retinol, the proteoglycan heparan sulfate, metal ions, various proteins, etc. (Frame & Gursky, 2017).

In this type of amyloidosis, the existence of a pre-amyloid phase in which there is overproduction of serum amyloid is proposed; this may overcome the quality control of extracellular proteins and the degradation system (Blancas & Ramírez, 2013); however, more than elevated levels of SAA are required as a prerequisite to develop the disease.

Some of the risk factors observed are described below (Table 1); although idiopathic amyloidosis has also been observed when no underlying inflammatory disease is found and obesity and female gender have been associated.

Table 1. Underlying risk factors for systemic AA amyloidosis in humans

Risk factor		Association	Presence in Mexico	References
Genetics: 5 variants of SAA have been described: SAA 1 (in Caucasian patients) SAA 3 (in Japanese patients)		Up to 5 times higher risk of presentation with SAA 1 variants	Not determined. There is one study in which being of Mexican ancestry was a risk factor, but it was for ALEC2 renal amyloidosis. (Larsen *et al*., 2016)	Van der Hilst, 2011 Sikora *et al*., 2021
Age		Abnormal proteostasis after 50 years of age	12% of older adults (INEGI, 2000)	Romani *et al*., 2021
Obesity		Induces chronic inflammation	30% of pupulation (Flores *et al*., 2019)	Van der Heijden *et al*., 2015; Westermark *et al*., 2018
Underlying inflammatory diseases	Rheumatoid arthritis	67% of cases	0.8% of adult population (Galindo *et al*., 2013)	Brunger *et al*., (2020)
	Skin infections due to chronic abuse of narcotics		2.5 million drug users (ENCODAT, 2016)	Mendoza *et al*., 2013; Cooper *et al*., 2013; Brunger *et al*., 2020
	HIV		33 new infections/day (CONASIDA 2021)	Jung *et al*., 2012 Breillat *et a*l., 2021 CONASIDA, 2021
	Tuberculosis		16,913 cases in 2016 (Flores *et al*., 2019)	Real de Asúa *et al*., 2014; Khellaf *et al*.,2022
	Mediterranean Fever and other autoinflammatory diseases		No diagnosis	Brunger *et al*., 2020
Blood serum amyloid A levels (>155 mg/dL)		17.7 increased risk of death		Van der Hilst, 2011;Lachmann *et al*., 2007; Blank *et al*., 2015, Blank et al., 2018
Other markers:		Associated with chronic inflammatory processes and renal damage*.		Van der Hilst, 2011 Van der Heijden *et al*., 2015 Lachmann *et al*., 2007
Duration of elevated SAA levels				
Serum creatinine levels >1.5 mg/dL				
C-reactive protein				
Proteinuria >500 mg/day				
Consumption of animal products containing amyloid		5% in slaughter cattle (Japan), 1.03% (Swedish cattle) and 15.2% (Italian cattle, including muscle samples)	It has not been determined	Tojo *et al*.,(2005) Rising *et al*., (2021)

*Nephrotic syndrome is a terminal stage of the disease

Pathogenesis of systemic AA amyloidosis

It is considered a pre-amyloid phase in which there is an increase in serum amyloid (precursor protein), due to underlying inflammatory processes or other conditions (such as obesity) (Westermark *et al*., 2018). Experimentally, it has been observed that the time in which the disease develops, is dramatically shortened when animals are stimulated with injections of cells, homogeneous mixtures or extracts of any amyloid-containing tissue. The active components of these various preparations are called: amyloid facilitating factors (AEF) and it is known that they can function as "seeds" for fiber formation (Lundmark *et al*., 2005).

Some of the proteins naturally grow from one "seed" of another; in the case of SAA, apoprotein A-II in mice (Yan et al., 2007; Cited by Sack *et al*., 2018). Even preformed fibers can act as core for amyloid formation *in vitro* and AA amyloid and similar synthetic fibers; they can also serve for its formation *in vivo*. Lundmark *et al*., (2005) conducted a study in mice inoculated with three naturally fibrillar proteins: silk from *Bombyx mori*, Sup35 from *Saccharomyces cerevisiae* and curli from *Escherichia coli*. All proteins had the ability to accelerate the process of AA amyloidosis formation that is well studied in animal models in which $AgNO_3$ is repeatedly injected.

For SAA to be incorporated into an amyloid fiber, two processes are required: first, the C-terminal end must be cleaved from the molecule to adopt the β-folded configuration, and in the second process SAA undergoes clathrin-mediated endocytosis by macrophages and is transported to their lysosomes. Structural reorganization then occurs at pH 4.3 with or without proteolysis by cathepsin B. Under normal conditions, it would be completely degraded; however, in patients with amyloidosis this does not occur. After deposition of the accumulated intermediates in the extracellular space, several elements bind to the fibril and confer resistance: glycosaminoglycans, the plasma glycoprotein known as the P-component, which is a member of the pentraxin protein family (like C-reactive protein), and lipid components (Van der Hilst, 2011; Sack *et al*., 2018).

Macrophages are often detected in close association with amyloid and there is evidence that they are involved in both its formation and degradation, since they synthesize a wide range of proteases (Van der Hilst, 2011; Lundmark *et al*., 2013).

It has also been observed that destruction of macrophages (with an injection of clodronate, a biophosphonate); in murine models for AA amyloid formation via AEF and $AgNO_3$, delayed amyloid formation. The finding of intracellular amyloid in macrophages also suggests that the process of "seeding nucleation", indeed initiates there (Lundmark *et al*., 2013).

The fact that the onset of AA amyloidosis can be accelerated by fibers derived from unrelated proteins, which are normally non-pathogenic, indicates that environmental factors may be important risk factors. In addition to AEF, poor hygiene or stimuli to the immune system by repeated vaccinations could also be important (Murakami *et al*., 2013). As mentioned above, Westermark *et al*., (2018), observed similarities to prion transmission and emphasized the process of nucleus formation as central; such a mechanism could be the underlying factor for AA transmission among captive animals (Ranlov 1967; cited by Sack *et al*., 2018).

AA amyloidosis in animals and intra- and interspecies transmission

AA amyloidosis occurs spontaneously in many avian and mammalian species, but prevalence varies considerably even among subgroups of the same species (Rising *et al*., 2017). As with prions, transmission has been observed in cattle, birds, mice and cheetahs (Murakami *et al*., 2014).

One of the first studies suggesting the possibility of interspecies transmission was that of Papendick *et al*., (1997), who from necropsy data of 141 cheetahs from 38 different zoos, observed a prevalence of systemic amyloidosis AA of 20% in animals that died before 1990, which increased to 70% in 1995. Subsequently, Zhang *et al*. (2008) identified AA amyloid through immunohistochemistry in livers, and subsequently in feces through Western blotting. From these results, it was presumed that fecal proteins could be involved in the spread of amyloidosis; this was proven in mice inoculated with such material intravenously and it was also observed that fecal fibrils presented greater transmission capacity.

A high prevalence has been observed in many other species in captivity. Martínez *et al*. (2019), reported 77% in a population of pronghorn (*Antilocapra americana*) at the Columbus Zoo, from animals whose necropsies were performed between 1997 and 2016, and concluded that in this case the underlying inflammatory problems were haemonchosis and pneumonia.

In other species, such as badgers (*Meles meles*) (Bianco *et al*., 2020), due to its frequency, it has also been concluded that it should be included in the differential diagnoses of consumptive diseases.

In Europe, 9 cases were reviewed in caracals (*Caracal caracal*) (Greunz *et al*., 2020), all animals presented renal amyloidosis, although only one case of systemic AA amyloidosis was confirmed by immunohistochemistry. In the study they concluded that due to the kinship of the animals, the problem could be associated with genetics and that given the prevalence, it should be considered within the differential diagnosis of renal problems.

A relationship between disease and AA amyloidosis has been experimentally proven: with subcutaneous inflammation in mice and hamsters, hydatid alveolar disease in mice and infection by *Opisthorchis viverrini* and *Enterococcus faecalis* in chickens (Brunger *et al.,* 2020).

Some research has considered risk factors. At the Oregon National Primate Research Center, data were used retrospectively, from macaques (*Macaca mulatta*) that died within 5 years (n=3061), with the goal of identifying risk factors that would predict the development of amyloidosis AA prior to the onset of clinical signs, and exploring potential new markers of the disease for use on a large scale (Leung *et al*., 2019). It was found a prevalence of systemic amyloidosis of 9.2% and observed that chronic colitis, gastrointestinal adenocarcinoma, endometriosis, and osteoarthritis, entities characterized by chronic, systemic inflammation, were the main risk factors; trauma, number of pregnancies, and diarrhea not associated with colitis followed. Circulating levels of serum amyloid A, triglycerides and triglyceride:HDL ratio were also observed, as well as lower levels of HDL and lower LDL than in healthy controls. These results are consistent with findings in chronic inflammation of altered lipoprotein metabolism and SAA.

In wildlife animals, important data have also been found, the island fox (*Urocyon littoralis*), which is located in the Northern Archipelago, off the coast of California; free-living and captive animals coexist on these islands. A study was conducted using necropsy data from 321 animals that died between 1987 and 2010; the prevalence of amyloidosis was 34% (109/321). Evidence of chronic inflammation was found in 83.5% of amyloidosis cases. The most common macroscopic lesions were splenomegaly, macroglossia and pallor; as well as waxy appearance of the kidneys in the most severe cases. Twenty-nine percent of the animals died from renal amyloidosis.

Some risk factors could be studied and it was found that captive animals had a significantly higher prevalence (59 vs. 27%). A higher risk was also observed in female foxes and in certain subspecies. The latter could be a factor associated with the type of SAA, as in the case of other species (Gaffney *et al*., 2016).

In marine mammals, a study was conducted following stranded animals off the coast of Hokkaido, Japan between 2013 and 2018; in 2 of 3 Stegnejer's whales (*Mesoplodon stejnegeri*) systemic AA amyloidosis was diagnosed, associated with renal parasitosis by *Crassicauda* sp.; slight splenomegaly and hepatomegaly were also observed and the most important involvement in kidney and gastrointestinal tract. It is considered that these cetaceans, as has been observed in other species, may have some genetic predisposition to amyloidosis (Nakagun *et al*., 2019).

Animal models have been developed to produce systemic AA amyloidosis. Initially, it was observed that repeated exposure of mice to inflammatory stimuli, such as subcutaneous injections of silver nitrate, complete Freund's adjuvant, casein, or lipopolysaccharide, can induce the disease within several weeks; but this period can be shortened if an amyloid-enhancing factor (AEF) is administered. Amyloid AA fibrils, amyloid AL fibrils and Alzheimer's brain extract can function as AEF. The work of Murakami *et al*., (2011) in which systemic amyloidoisis AA was induced experimentally after observing that pododermatitis lesions in which a *Staphylococcus aureus* infection was frequently found, provides insight into part of the pathogenesis of the disease.

An intravenous solution of AA amyloid fibrillar material from Holstein friesian bovine kidneys with systemic amyloidosis was inoculated into rabbits previously induced with pododermatitis lesions; it was concluded that the presence of *S. aureus* was very efficient in the development of amyloidosis and that the presence of pododermatitis also favored it. Rabbits without lesions did not develop the disease. Similar findings have been found in waterfowl where a prevalence of amyloidosis of 78.4% was observed in swans (*Cygnus olor*) and a very high frequency (96.3%) of an inflammatory condition known as bumblefoot (Tanaka *et al*., 2008), which is a chronic inflammatory condition of the plantar metatarsal and/or digital patches of the birds' feet.

Diagnosis

Amyloidosis can present with puzzling clinical pictures, depending on the organs involved. In humans, localized amyloidosis usually presents periorbital, nasopharyngeal, pulmonary and/or bronchial, cutaneous, gastrointestinal and urinary; as well as in lymph nodes. Fatigue and thinning may also occur initially and later signs according to the organs involved. It has already been commented that in systemic amyloidosis, the final picture corresponds with nephrotic range proteinuria (Mollee *et al*., 2013).

In all cases, the patient's phenotype should be considered and the search for associated diseases or chronic inflammation should begin; however, association is not always evidence of causality. For the case of AA amyloidosis, since inflammation is usually present, SAA levels should ideally be measured; however, it is an assay that is not routinely available and C-reactive protein may be a suitable marker if used in serial measurements (Mollee *et al*., 2013).

Diagnosis of amyloidosis requires identification of amyloid deposits in tissue samples; in animals, it is usually a *post-mortem* diagnosis. In humans, to avoid highly invasive procedures, abdominal fat aspiration is used, although its sensitivity is limited (Mollee *et al*., 2013). Congo Red staining with polarized light microscopy is the first histological method used to confirm its presence, followed by subtype classification through immunohistochemistry of the main precursors; however, it is sometimes not as specific and can generate false positives; in addition, it is a semi-quantitative technique. More recently, laser microdissection, liquid chromatography, followed by mass spectrophotometry have been used. This method has high sensitivity and specificity, and minimal sample quantities are required.

There is already evidence that the sensitivity and specificity of laser microdissection, liquid chromatography and mass spectrophotometry is adequate to detect amyloidosis with very small amounts of tissue and not only amyloid precursors, but also associated proteins (Kadota *et al*., 2020).

Although this technique is becoming the method of choice for amyloid typing, the application of immunological methods remains clinically useful. Caution and experience are required, as well as knowledge of the limitations of each method to properly interpret the results (Picken, 2020) and classify the disease to know whether or not it is treatable, both in humans and animals.

D'Souza *et al*., (2014), used mass spectrophotometry to identify the components of amyloid deposits reported in 52 patients who had been administered insulin or efurvitide. Similarly, Ogawa *et al*., (2020), were able to identify 12 of 13 precursors, including serum amyloid, transthyretin and immunoglobulins, with that technique; these were quantified even though the results by immunohistochemistry were inconclusive.

In animals, laser microdissection has also been used for sample collection and processing by liquid chromatography and mass spectrophotometry to diagnose AL amyloidosis. In a case study of 15 dogs and 2 cats; in 11 the disease could not be diagnosed by immunohistochemistry, this occurs because antibodies of human origin are sometimes used. It has been observed that the use of a combination of antibodies can improve the sensitivity of the test.

In this study, 100% of the cases could be diagnosed by liquid chromatography-mass spectrophotometry (Kadota *et al*., 2020).

CONCLUSIONS

There are no reports in Mexico on systemic AA amyloidosis in wild or domestic animals. Since this disease is difficult to diagnose and has unspecific clinical signs, it is probably underdiagnosed. In the review performed, only one report on ALEC2 renal amyloidosis was found in the southwestern United States, in which 54% of the diagnoses were associated with race (Mexican-Americans). Other risk factors such as chronic inflammatory diseases, obesity and/or advanced age are present in the Mexican population. Given that in Mexico a large amount of animal products are consumed, including viscera, and that interspecies transmission of the disease has been proven, it is considered very important for public health to awaken interest in the study of systemic AA amyloidosis.

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Errata Erratum

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