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MUCOPOLYSACCHARIDOSES (MPS) IN DOMESTIC DOG (*CANIS LUPUS FAMILIARIS).* PART I. CHARACTERIZATION OF TYPES OF MUCOPOLYSACCHARIDOSES

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Abstract. Mucopolysaccharidosis (MPS) are a group of metabolic diseases (7 types in human and 5 types in domestic dog), which result from the accumulation of glycosaminoglycans in cells, tissue, organs, causing their abnormal functioning. They are the result of a deficiency or total inactivity of catabolic enzymes responsible for the break down of glycosaminoglycans. MPSs are characterized by a wide spectrum of clinical symptoms. Skeletal deformation, organomegaly, delayed growth and corneal opacities are typical symptoms of the disease. This is a group of rare, inherited metabolic diseases that affect the body's ability to break down mucopolysaccharides. The aim of the literature research was to present information on the mode of inheritance of mucopolysaccharidosis and the genetic basis of individual types, including the breeds of dogs in which a given type of disease was identified. Due to the complexity of symptoms, mucopolysaccharidoses are difficult to treat. The diagnosis of mucopolysaccharidoses uses clinical diagnostic methods based on screening methods and molecular diagnostics, which are characterized by accuracy and sensitivity similar to methods used in humans.

Key words: mucopolysaccharidosis, lysosomal storage diseases, glycosaminoglicans, animal model.

INTRODUCTION

Mucopolysaccharidoses are a heterogeneous group of lysosomal storage diseases (LSD), characterized by the progressive accumulation of glycosaminoglycans (GAGs) in lysosomes of various tissues as a result of deficiency or complete lack of activity of lysosomal enzymes (Kloska et al. 2011). The result of excessive accumulation of partially degraded glycosami-

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noglycans is abnormal functioning of cells, tissues and organs. Depending on which enzyme is deficient, glycosamines such as keratan sulphate, heparan sulphate, dermatan sulphate, chondroitin sulphate and hyaluronan are stored (Neufeld and Muenzer 2001).

Domestic dog mucopolysaccharidoses are divided into 5 types depending on the deficiency of lysosomal enzymes, i.e. MPS type I (Shull et al. 1982), II (Wilkerson et al. 1998), IIIA (Jolly et al. 2002), IIIB (Ellinwood et al. 2003), VI (Neer et al. 1995), VII (Silverstein-Dombrowski et al. 2004) (Table 1). Moreover, mucopolysaccharidosis type III has two subtypes: IIIA and IIIB. These subtypes are characterized by the accumulation of the same type of GAG (heparan sulphate) and the same clinical form, but they have a different genetic basis (defect of a certain lysosomal hydrolytic enzyme). Each type of MPS has a characteristic phenotype and urinary glycosaminoglycan excretion profile (Wang et al. 2005).

Most types of mucopolysaccharidoses are inherited in an autosomal recessive manner. It means that a dog will be healthy if it inherits two normal copies of the same gene. The disease will occur when the dog inherits two mutated copies of the gene. However, if he inherits one mutated copy and one normal copy, he will be a healthy carrier because the copies balance each other (Ruvinsky and Sampson 2001). The exception is Hunter syndrome (MPS II), which is inherited in a recessive manner linked to the X chromosome (Kloska et al. 2011). In males, having only one X chromosome, one mutated copy of the gene will cause the disease. For females, who have two X chromosomes, one altered copy of the gene will not cause the disease because the normal copy of the gene, located on the other X chromosome, can offset the presence of the mutated copy. Therefore, the female will be a healthy carrier, which means that she carries an altered copy of the gene, but is not diseased. There is a small probability that both changed copies of the gene will appear in females, therefore the frequency of mutations in males is much more frequent than in females. In sporadic cases, females experience mild symptoms of the disease.

The incidence of various types of mucopolysaccharidoses in both human and domestic dog populations is difficult to estimate because few population studies have been conducted. This disease is not easy to diagnose, and its treatment may be difficult. The diagnosis of mucopolysaccharidoses is mainly based on the examination of the activity of lysosomal enzymes, as well as the quantitative analysis of glycosaminoglycans excreted in urine (Kloska et al. 2011).

The aim of the literature research was to characterize the types of mucopolysaccharidosis in domestic dog and to analyze the factors determining its development.

CHARACTERISTICS OF MUCOPOLYSACCHARIDOSES

As mentioned earlier, all types of mucopolysaccharidoses, except MPS II, are inherited in an autosomal recessive manner. The basis for the division of mucopolysaccharides (MPS) are mutations in genes encoding various lysosomal enzymes necessary for the degradation of glycosaminoglycans. The summary and division of MPS is presented in Table 1. These diseases are progressive. Most symptoms are not visible immediately after birth. The lack of symptoms in the early stages of life is a typical feature of many metabolic diseases. Clinical symptoms include organomegaly (enlargement of the liver, spleen and tongue), changes in the skeletal system in the form of dysostosis multiplex caused by abnormal bone formation, and characteristic facial features (in humans, thickened facial features, prominent forehead). As a result of the disease, hearing and vision are damaged (corneal opacity, damage to the optic nerve). The respiratory and cardiovascular systems are also affected (heart valve

defects, cardiomegaly and cardiomyopathy), and as the disease progresses, joint mobility is limited and numerous contractures appear (Wang et al. 2005).

Table 1. Types of mucopolysaccharidosis in domestic dogs (own study based on literature data https://omia.org; Wang et al. 2005; Kloska et al. 2011)

MPS type	Gene	Chromosome number	Location	Inheritance mode	Amino-acids' number	Enzyme	GAG -storage	Breed
I	*IDUA*	3	NC_006585.3 (91517225..91534593)	AR	655	α-L-iduronidase	HS, DS	Rottweiler, Boston Terrier
II	*IDS*	X	No information	XR	No information	Iduronian 2-sulphatase	HS, DS	Labrador Retriever
IIIA	*SGSH*	9	NM_001003114.1	AR	415	sulphohydrolase N-sulphoglukosamine	HS	Wirehaired Dachshund, New Zealand Huntaway
IIIB	*NAGLU*	9	NC_006591.3 (20414094..20407296)	AR	747	N-α-acetylogluko-\-soaminidase	HS	Schipperke
VI	*ARSB*	3	NC_006585.3 (27870111..28034906)	AR	535	arylosulphatase B	DS	NZ Huntaway, Toy Poodle, Pinscher, Schnauzer, Pembroke Welsh Corgi
VII	*GUSB*	6	NC_006588.3 (743916..730345)	AR	651	β-glucouronidase	HS, DS, CS	German Shepherd, Brazilian Terrier, crossbreeds

MPS – mucopolisacharidose, AR – autosomal recessive, XR – X-linked recessive, HS – heparan sulphate, DS – dermatan sulphate, CS – chondroitine sulphate.

Mucopolysaccharidosis type I (Hurler syndrome)

Mucopolysaccharidosis type I is caused by deficiency of α-L-iduronidase activity, resulting from a mutation in intron 1 of the *IDUA* gene (in the domestic dog), responsible for its production (Haskins and Giger 1992). The absence or deficit of the α-L-iduronidase enzyme leads to the accumulation of heparan sulphate and dermatan sulphate in lysosomes (Clarke 2016). The accumulation of GAGs increases the size of lysosomes, which results in the enlargement of tissues and organs. This type of disease is most similar to MPS I, which occurs in humans. It covers a wide spectrum of clinical phenotypes, from the most severe (Hurler syndrome – MPS I-H) to the mildest (Scheie syndrome – MPS I-S). Moreover, between these two extreme forms, an intermediate form called Hurler-Scheie syndrome (MPS I-H/S) is diagnosed (Kuiper et al. 2018). In humans, MPS I symptoms include facial dysmorphia, kyphoscoliosis, stiff joints and hip dysplasia with subluxation, which causes a waddling gait (Kloska et al. 2011). In a domestic dog with MPS I, the symptoms are related to abnormalities in the structure of the spine, especially in the cervical vertebrae. Radiological findings include collapsed intervertebral spaces, vertebral disc herniation, spinal ankylosis, osteopenia, vertebral dysplasia, focal joint strains, degenerative joint disease, and joint effusions (Chiaro et al. 2013). However, growth inhibition is observed in both humans and animals. No

changes are noted in puppies with MPS I after birth. The first symptoms appear at the age of 4–6 months. Mucopolysaccharidosis type I occurs in Rottweiler and Boston Terrier dogs (Wang et al. 2005). The gene encoding α-L-iduronidase (*IDUA*) consists of 14 exons and is approximately 19 kb (thousands of base pairs) long. The gene is located on chromosome 4, at position p16.3. The two most common mutant alleles, W402X and Q70X, and the less common allele, P533R, account for more than half of all alleles underlying mucopolysaccharidosis type I in the Caucasian human population. The product of these alleles is the non-functional enzyme α-L-iduronidase, and their presence in the homozygous or heterozygous form translates into the development of a severe form of MPS IH (Herati et al. 2008). Provoost et al. (2020) demonstrated the possibility of using appropriate tests to assess the cognitive abilities of dogs suffering from mucopolysaccharidosis type I.

Mucopolysaccharidosis type II (Hunter syndrome)

Hunter syndrome, unlike other types of MPS, is a recessive, lysosomal storage disease linked to the X chromosome. Mucopolysaccharidosis type II results from the accumulation of dermatan sulphate and heparan sulphate in tissues, as a result of deficiency or lack of activity of iduronate 2-sulfatase (IDS; EC 3.1.6.13), the enzyme responsible for the hydrolysis of these glycosaminoglycans (Pytrus et al. 2006).

MPS II is a rare disease. The first symptoms appear between 2 and 3 years of age. The first case of an animal model of MPS II was described by Wilkerson et al. (1998) approximately 20 years ago in a 3-year-old Labrador Retriever dog. The dog's symptoms included corneal opacity, sharp facial features, enlarged tongue, ataxia, paresis of all limbs, osteopenia, and an enlarged spleen and liver. Clinical progression was slow, resulting in longer survival. However, due to the progressive nature of the disease, the animal was euthanized 18 months (at the age of 5) after diagnosis.

In humans, the incidence of mucopolysaccharidosis type II is estimated to be 1 in 162,000 live births, with the majority of cases reported in the literature occurring in men. Data published by the MPS II Association show that in Poland Hunter syndrome accounts for 30% of all cases of mucopolysaccharidosis (Pytrus et al. 2006). Based on the clinical symptoms in humans, there are two types of the disease: A (severe) and B (mild). The severe form occurs in children and causes skeletal deformities and mental retardation. The mild form occurs in adults and is characterized by a slower and less devastating course. Mental retardation is not present or is just moderate (Pytrus et al. 2006).

Mucopolysaccharidosis type III (Sanfilippo syndrome)

Mucopolysaccharidosis type III (A, B, C and D), also known in humans as Sanfilippo syndrome, is the result of heparan sulphate storage, caused by deficiency of the activity of one of 4 different enzymes – N-sulphoglucosaminesulphohydrolase (SGSH in MPS IIIA; EC 3.10.1.1), N-α-acetylglucosaminidases (NAGLU in MPS IIIB; EC 3.2.1.50), N-acetyltransferases, heparan-α-glucosaminide (HGSNAT in MPS IIIC; EC 2.3.1.3) or N-acetylglucosamine 6-sulfatase (GNS in MPS IIID; EC 3.1.6.14), responsible for the degradation of the previously mentioned glycosaminoglycan (Hopwood and Morris 1990). All MPS III subtypes are characterized by similar clinical symptoms related to progressive damage to the central nervous system. According to histological studies, these changes are found in the spinal cord, brain stem, and especially in neuronal degeneration of the cerebellum. This organ is responsible for balance. Therefore, a sharp decline in muscle control and coordination is observed in humans and animals suffering from MPS III (Fischer 1998). MPS III occurs

in humans, domestic dogs, domestic cats and domestic mice. There are two subtypes of MPS III in dogs – A and B. MPS-IIIA is the result of a mutation in the *SGSH* gene, responsible for coding the enzyme N-sulphoglucosaminesulphohydrolase, while MPS-IIIB involves N-α-acetylglucosaminidase deficiency, caused by damage to the *NAGLU* gene (encoding N-α-acetylgluconamidase) (Yogalingam and Hopwood 2001).

Mucopolysaccharidosis IIIA occurs in Dachshunds (long-haired, short-haired, wire-haired, miniature), although it was also diagnosed in the New Zealand Huntaway dog (Yogalingam et al. 2002). Mucopolysaccharidosis type IIIB has been observed in the Schipperke breed (Ellinwood et al. 2003).

The first symptoms of MPS III in domestic dogs are recognized by owners when the animal is 3 years old. These include ataxia of the pelvic limb, which is characterized by hypermetria, dysmetria, problems with walking, and frequent trips and falls. Additionally, corneal opacity and thickened facial features are observed. Initial balance problems worsen to the point where the dog is unable to walk, eat or stand. However, no changes in behaviour were noticed. Moreover, affected animals are fertile and can have offspring. However, affected dogs are euthanized within a few years of diagnosis due to its progressive nature (Jolly et al. 2001).

The results of studies using the domestic dog as an animal model of mucopolysaccharidosis type IIIB have become the basis for future assessment of therapeutic effectiveness not only in humans, but also in this model of the disease in large animals (Egeland et al. 2020).

Mucopolysaccharidosis VI (Maroteaux–Lamy syndrome)

Mucopolysaccharidosis type VI, also known in humans as Maroteaux–Lamy syndrome, is the least common type of MPS. MPS VI is a progressive and multi-organ disease caused by mutations in the gene encoding arylsulphatase B, called *ARSB*. The gene damage results in a deficiency of arylsulphatase B, which is involved in the catabolism of chondroitin sulphate and dermatan sulphate. MPS VI has been described in humans, the domestic dog, the domestic cat, the guinea pig, and knockout mice (Pérez et al. 2015).

Affected animals usually differ in terms of phenotype and dynamics of disease progression. The central nervous system is not affected, and the main symptoms concern the circulatory and skeletal systems. The severity of clinical symptoms is variable and includes: inhibited growth and development, facial dysmorphia, skeletal disorders – degeneration of intervertebral discs, collapse of disc spaces, osteopenia and spondylosis, as well as umbilical hernia, corneal opacity, hearing loss, cardiomyopathy, heart valve damage (leading to heart failure caused by the accumulation of GAG in heart valves and arteries), damage to the cardiovascular system (progressive narrowing of the airways, leading to right ventricular failure) and hepatomegaly (Jolly et al. 2012). Another common symptom is loosening of the joints caused by abnormalities in the ligaments and tendons. Due to the progressive nature of the disease, dogs are euthanized at the age of 2–3 years. The disorder has been found in dogs of the following breeds: Huntaway, Toy Poodle, Miniature Pinscher, Miniature Schnauzer, and Pembroke Welsh Corgi (Haskins and Giger 2008).

Mucopolysaccharidosis VII (Sly syndrome)

Mucopolysaccharidosis VII (Sly syndrome) results from the accumulation of chondroitin sulphate, heparan sulphate and dermatan sulphate in various tissues. The accumulation of GAGs is the result of deficiency of β-glucuronidase (GUSB) activity. The phenotype of animals with this disease is similar to that of Hurler disease (MPS I-H). Typical symptoms of most MPS are skeletal abnormalities, referred to as *dysostosis multiplex*, and mainly

include abnormalities in the vertebrae, intervertebral discs (or other sections of the spine), bone dysplasia, degenerative joint disease (steep acetabular roof, valgus hips), hypoplastic bones, widened and deformed shafts of long bones and bone cysts (Opoka-Winiarska et al. 2012). Hypoplasia may occur in the cervical spine, resulting in neck instability. However, abnormal development in the ossification of the anterior part of the vertebrae results in the formation of biconvex oval vertebral bodies with a wedge-shaped narrowed anterior part (*platyspondylia*) in the lower part of the thoracic spine and in the upper part of the lumbar spine. These abnormalities may be associated with deformities such as kyphosis (or gibbus) and scoliosis. However, the degradation of intervertebral discs leads to compression of the nerve root or spinal cord. Intense compaction of dural ligaments and bony structures may also contribute to spinal cord compression (Peck et al. 2016). Analysis of studies conducted as part of the impact of neonatal gene therapy on lumbar spine disease in animals with MPS VII showed that canine lumbar vertebrae had purulent lesions in the form of decreased calcium content and increased GAG content in the ventral and dorsal regions, suggesting a lack of cartilage-to-bone conversion during development. This phenomenon resulted in decreased stiffness and increased range of motion in the lumbar spine in dogs with MPS VII (Smith et al. 2012). At the age of 3–6 months, affected dogs are unable to stand on their own. However, after about a year, animals often become lethargic and lose interest in their surroundings. In addition to the skeletal system, the circulatory system is also affected. Symptoms include cardiomyopathy, thickening of the mitral and aortic valves, and dilatation of the aortic floor, and may cause death in the early months of life or may be consistent with a normal life expectancy. Heart disease is the leading cause of death in MPS VII, caused by the accumulation of GAG in cells of the cardiovascular system (Slepper et al. 2004). Mucopolysaccharidosis type VII has been observed in German Shepherds, Brazilian Terriers, and crossbreeds (Silverstein-Dombrowski et al. 2004).

Currently, at least 55 mutations in the *GUSB* gene have been found to cause mucopolysaccharidosis type VII. Most of these mutations are changes in the gene sequence of a single nucleotide. This heterogeneity of *GUSB* gene mutations contributes to the extensive clinical variability among MPS VII patients. Moreover, research shows that the mutated *GUSB* gene contributes to a post-transcriptional defect and the production of an unstable protein (Ray et al. 1999). A dog with MPS VII has mutations in the R166H allele. The affected dog had many of the musculoskeletal symptoms seen in humans (Tomatsu et al. 2009).

CONCLUSIONS

Mucopolysaccharidoses are difficult diseases to treat. The diagnosis of mucopolysaccharidoses uses clinical diagnostic methods that are based on screening and molecular diagnostic methods that are similar in accuracy and sensitivity to those used in humans. Continuous research in animal models is of great importance in understanding the molecular, pathological and physiological consequences of lysosomal storage diseases, as well as in evaluating the efficacy and safety of the therapy used. Despite significant advances in the fields of molecular biology, genetics, biochemistry and biotechnology, it has not been possible to develop a therapy with spectacular results in the treatment of the disease. The treatment methods known to date (bone marrow transplantation, enzyme replacement therapy, gene therapy) are the most advanced therapeutic procedures currently being tested in clinical trials. They are based on direct enzyme replacement, by removing the defective gene product, and are limited to symptom relief only. Recent studies have shown that in order to attempt to devel-

op an effective therapy, it is necessary to understand not only the mechanisms involved in the degradation of GAGs in the body, but also the mechanisms involved in their synthesis (substrate reduction therapy) and to combine several therapies to effectively alleviate some or most of the clinical symptoms.

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MUCOPOLISACHARYDOZY U PSA DOMOWEGO. CZĘŚĆ 1: CHARAKTERYSTYKA RODZAJÓW MUCOPOLISACHARYDOZ

Streszczenie. Mukopolisacharydozy (MPS) to grupa rzadkich dziedzicznych chorób metabolicznych, które wpływają na zdolność organizmu do rozkładania mukopolisacharydów. Występuje 7 typów u człowieka i 5 u psa domowego. Wskutek niedoboru lub całkowitego braku aktywności enzymów katabolicznych następuje kumulacja glikozaminoglikanów w komórkach, tkankach oraz narządach, co powoduje ich nieprawidłowe funkcjonowanie. MPS charakteryzują się szerokim spektrum objawów klinicznych, do których należą m.in. deformacje szkieletu, organomegalia, spowolniony wzrost czy zmętnienie rogówki. Celem pracy było przedstawienie informacji dotyczących sposobu dziedziczenia mukopolisacharydozy oraz podłoża genetycznego poszczególnych typów z uwzględnieniem ras psów, u których zidentyfikowano dany typ choroby. Ze względu na złożoność objawów mukopolisacharydozy są chorobami trudnymi do leczenia. W diagnostyce mukopolisacharydoz wykorzystuje się kliniczne metody diagnostyczne oparte na metodach przesiewowych i diagnostyce molekularnej, które charakteryzują się dokładnością i czułością zbliżoną do metod stosowanych u ludzi.

Słowa kluczowe: mukopolisacharydozy, lizosomalne choroby spichrzeniowe, glikozaminoglikany, model zwierzęcy.