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ICHTHYOSIS IN DOGS—CONGENITAL DERMATOLOGIC DISORDER

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ABSTRACT

The skin provides protective functions, such as thermoregulation, resorption, provision of immune responses, storage and sensory functions, which all play an important role in the internal stability of the organism. The skin has 3 major layers: the epidermis, the dermis and subcutis. The outermost protective layer of the epidermis, the stratum corneum, consists of 20 to 30 overlapping layers of anucleate cells, the corneocytes. Ichthyosis is an autosomal recessive congenital skin disease, in which the corneocytes form defects that appear like individual steps of the stratum corneum. Ichthyosis is characterized by excessive scaling over the entire body surface and is not curable; the symptoms can only be alleviated. Several genetic variants have been identified in specific dog breeds: *PNPLA1* in the Golden Retrievers, *SLC27A4* in the Great Danes, *NIPAL4* in the American Bulldogs, *TGM1* in the Jack Russel Terriers, *ASPRV1* in the German Shepherds, which cause different forms of nonepidermolytic ichthyosis and *KRT10* in the Norfolk Terriers, which causes epidermolytic ichthyosis. When classifying breeds of dogs predisposed to ichthyosis, it is necessary to determine the presence of defective genes in the genome of the individual animals involved in mating.

Key words: dog; gene; hereditary disease; keratin; skin

INTRODUCTION

Ichthyosis represents a group of rare congenital skin disorders characterized by excessive scaling caused by defective formation of the stratum corneum, which is the main skin barrier. It makes life very unpleasant for the suffering patients. The disease is caused by changes in the genes that encode a wide range of molecules, including enzymes, structural proteins and lipids, involved in the formation of the stratum corneum. Ichthyosiform dermatoses affect humans, dogs, cattle, rats, cats and pigs [4, 7, 9, 18, 26, 27].

The skin is the largest organ of the organism and forms an important outer barrier between the factors of the ex-

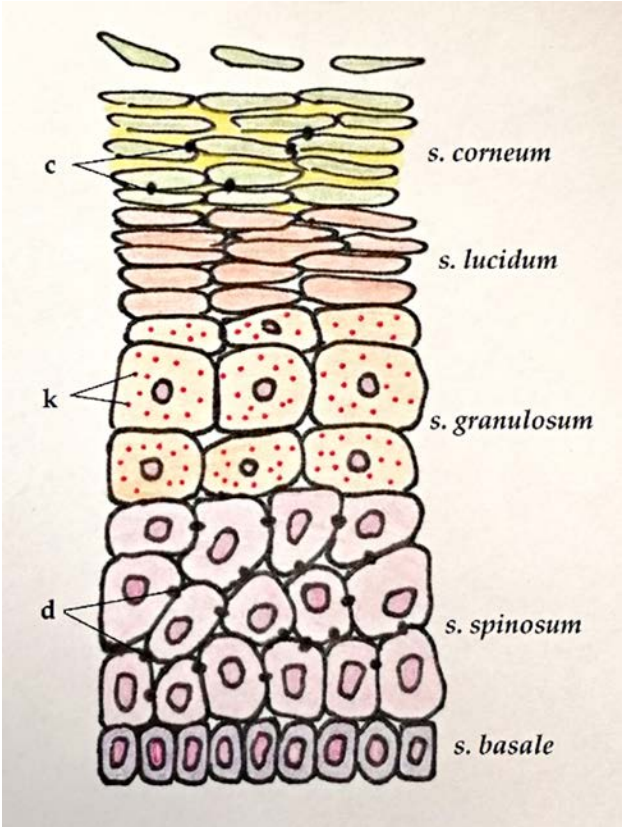

Fig. 1. The epidermis
c—corneodesmosomes; d—desmosomes; k—keratohyalin granules

ternal environment and the internal environment of the organism. In addition to providing a protective barrier against the different effects (physical, chemical, ultraviolet radiation, microbial, etc.) of the environment, the basic functions of the skin include thermoregulation, resorption, provision of immune responses, storage and sensory functions. If the skin is not in order, the whole internal stability of the organism may be disturbed [15, 34].

The skin

The skin has 3 major layers: the epidermis (outermost layer), the dermis (middle layer) and subcutis (innermost layer). The thickness of the skin is not the same over the entire body surface. Other important parts of the skin include: skin appendages (such as hair and claws) and subcutaneous muscles and fat [28, 35].

The outer layer of the skin, the epidermis (Fig. 1), is composed of several cell types, including keratinocytes, melanocytes, Langerhans cells and Merkel cells. In the process of the keratinization (cornification) new epidermal cells are created near the base of the epidermis and migrate upwards and differentiate from basal keratinocytes to the highly specialized corneocytes at the same time. The outermost protective layer of epidermis, stratum corneum, consists of 20 to 30 overlapping layers of polyhedral anucleate cells, the corneocytes. Corneodesmosomes play an important role, they contribute to the cohesiveness of the stratum corneum by connecting corneocytes to each other [35]. On the healthy skin, there is always a layer of dead skin cells, which are continuously removed and replaced by cells from the lower layers. The melanocytes are located mostly at the base of the epidermis and produce the skin and hair pigment called melanin. The Langerhans cells are representative of immune processes in the skin and provide phagocytosis and antigen presentation. Merkel cells are specialized cells associated with the sensory organs in the skin. Their role in animals is to provide the sensory information from whiskers and the deep skin areas called tylotrich pads [19, 29, 35].

There are no blood vessels in the epidermis and its nutrition is ensured through tissue fluid. Under the stratum corneum are other epidermal layers: stratum lucidum, stratum granulosum with keratohyalin granules, stratum spinosum and stratum basale. In the connection zone between the epidermis and the dermis is located the basement membrane, which can be damaged by skin diseases, including a number of autoimmune conditions [35].

The dermis is made up of connective tissue, and contains sebaceous and sweat glands, claws, blood vessels, nerves and hair. The blood vessels that supply the epidermis with nutrients are located in the dermis. Their role is also to regulate skin and body temperature. Sensory and motor nerves are present in the dermis and ensure the skin's response to the sensations of touch, pain, itch, heat and cold. A large amount of water is bound in the dermis, and in addition there are hyaluronic acid, elastic, collagen and reticular fibres.

The hair follicles in dogs are compound. The hair follicle has a central hair that is surrounded by 3 to 15 smaller secondary hairs, all exiting from one pore. The hair coat protects the skin from physical and ultraviolet light damage, and helps regulate the body temperature. The sebaceous glands secrete an oily substance (a mixture of fatty acids called sebum) into the hair follicles and onto the skin. These oil glands are present in large numbers near the paws, back of the neck, rump, chin, and tail area. Sebum is important for maintaining the skin soft, moist, and pliable.

The sweat glands in dogs are present only on the feet [28, 33, 35].

The innermost layer of skin is the subcutis (hypodermis) which is formed with the subcutaneous fat and muscles. The main functions of the subcutaneous fat are insulation, a reservoir for fluids, electrolytes and energy and a shock absorber [28].

Ichthyosis

Congenital malformation is a deviation that occurs during the intrauterine development of the fetus. It arises either on a hereditary basis or without a hereditary burden. A missing or altered chromosome or a missing and altered gene can cause the development of a birth defect. Congenital skin diseases in dogs are caused by the presence of a faulty gene [8, 24].

Ichthyoses belong to a heterogeneous group of genetically determined dermatoses characterized primarily by excessive skin scaling over the whole body surface. The name ichthyosis comes from the Greek word ichtys (fish), because the peeling skin resembles fish scales [8, 9]. The disease has been known for a long time, it occurs in several breeds of dogs, but it was not until 2012 that the genetic reason was confirmed [9]. In individual affected breeds, these are mostly mutations in different genes, which are transferred to the gene pool of the offspring. The mutations present in the genes cause defects in the formation of the stratum corneum in the epidermis. However, spontaneous mutations may occur in dogs of each breed or crossbreeds [24].

Although it does not seem so, the stratum corneum performs very important functions. It is the key layer that restricts water movement into and out of the skin. Even its slight damage results in increased transepidermal water loss [21, 32]. This was also confirmed by the increased water losses in dogs with atopic lesions [31]. The continuous desquamation largely ensures the barrier function of the skin and at the same time a certain resistance to microbial pathogens. In addition to the physical exclusion of pathogens, the stratum corneum also contains natural antimicrobial peptides such as defensins and cathelicidins. All abnormalities in the corneal layer may predispose the dog to bacterial and yeast infections [8]. The process of the stratum corneum formation is complex, with every single step being controlled by genes. If an erroneous entry of genetic information is present and one step in the process of forming this layer is disrupted, the formation of the original stratum corneum is impossible. The process of stratum corneum formation consists of several important steps: bundling of the keratin to establish the corneocyte core, replacement of the cell membrane with a thick cornified envelope, and formation of the lipid lamellar bilayers and desquamation. The final form of the stratum corneum is a tough hydrophobic but biochemically active layer of the corneocytes between lipid layers. When any step is changed, the stratum corneum barrier function is disrupted and an attempt is made to repair it. A state of lipid upregulation occurs to replenish lipids into the stratum corneum, causing the epidermis to become hyperplastic [8, 24].

In veterinary medicine, two forms of ichthyosis are described: non-epidermolytic and epidermolytic. The non-epidermolytic ichthyosis is characterized by hyperkeratosis and epidermal hyperplasia with hypergranulosis and the presence of vacuoles and lysis of the keratinocytes within the spinous and granular cell layers. defects arise in the formation step. It has been found in several purebred dog breeds, such as the Golden Retriever, Great Dane, American Bulldog, Jack Russell Terrier, German Shepherd and other breeds [1, 9, 13, 20, 22—25]. The epidermolytic ichthyosis was described in the Norfolk terrier and sporadically occurs in other dogs, e. g., Rhodesian Ridgeback or Labrador cross. The defects arise in the formation step of keratin formation (i.e. formation of the corneocyte core) [5, 11, 24].

Ichthyosis in Golden Retrievers

Ichthyosis as genodermatosis is best known in Golden Retrievers (Fig. 2), sometimes referred as lamellar ichthyosis (LI). In Golden Retrievers, ichthyosis is manifested by adherent scales of various size (from small to large) with a wide range of colorization; at the beginning with whitish scales, later from grey to brown and at the end with blackish scales are presented. The range of ichthyosis forms in this breed varies, ranging from mild, moderate to severe [12]. A mild form of ichthyosis is more common, it is often pronounced especially on the ventral trunk. The range of forms of ichthyosis in this breed varies, ranging from mild, moderate to severe associated hyperpigmentation. The glabrous skin is rough and looks like emery. The clinical signs of a fully manifested disease include lesions of exfoliation and hyperpigmentation that are generally not itchy. The lesions are located mainly in the axilla, thorax, flanks and

Fig. 2. Ichthyosis is typical for Golden Retriever breed

inguinal region with symmetrical mounting. The area of the paws, nose and ear canals are not usually affected. In dogs, it appears before the 1st year with moderate to severe degree, but it may not appear until adulthood. The formation of skin scales lasts for the whole life of the individual, but the disease may be manifested with a recurring exacerbation and/or remission. Secondary bacterial, mycotic or parasitic infections can be created and it may lead to pruritus [3, 10, 12, 22, 24].

On the histological examination, laminated or compact orthokeratotic hyperkeratosis and numerous persistent corneodesmosomes are usually recorded in the stratum corneum. The stratum granulosum is without significant involvement [12].

Golden Retrievers ichthyosis belongs to autosomal recessive inherited diseases. The disease has been known for a long time, but the exact cause was published in the year 2012; namely it is an insertion-deletion mutation in exon 8 of the gene *PNPLA1* (patatin-like phospholipase domain-containing protein 1), that leads to the formation of a premature stop-codon, with loss of 74 amino acids and is assumed to arise to a non-functional protein causing alterations in the keratinization process A mutant *PNPLA1* supposes to harbour potential causative mutations for human ichthyosis in European and North African populations and its discovery in Golden Retrievers has helped elucidate ichthyosis in humans [9]. A recessive simple Mendelian mode of inheritance applies to ichthyosis [25]. The disease occurs in individuals who inherit the faulty mutated gene from both parents, and in diagnostics are marked as positive/positive (homozygous). Heterozygous, individuals (positive/negative), who have one faulty gene present are clinically healthy but pass the gene on other offspring. When covering two heterozygotes (2 × positive/negative), there is a possibility that puppies with ichthyosis (positive/positive) of 25 % will be born [9]. Homozygous dogs will transmit the *PNPLA1* variant to 100 % of their lineage. The reliability of the *PNPLA1* mutation in predicting clinical signs of ichthyosis in dogs is unclear. It is not yet known whether *PNPLA1* is the only gene involved or whether other genes or environmental factors may play a role in the development of ichthyosis in Golden Retrievers [10]. In veterinary diagnostics, a genetic test by PCR using buccal swabs or whole blood is available to detect wild-type, heterozygous and homozygous dogs and helps to plan the right healthy breeding. Homozygous individuals must not be allowed to breed and each breeding dog should be examined for the *PNPLA1* presence. The homozygous puppies can exhibit clinical signs suggestive of ichthyosis prior to 1 year of age but in adulthood become subclinical or have moderate form of ichthyosis. The breeders often do not consider mild or moderate scales and hyperpigmentation as symptoms of hereditary disorder and they can unknowingly use these dogs in breeding and spread ichthyosis further [30]. Several studies have been performed to determine *PNPLA1* mutation in Golden Retriever individuals. In the year 2018, G r a z i a n o et al. [10] found that the prevalence of the *PNPLA1* gene variant in Italian breeding programs was high and that only 21 % of the sampled dogs represented the wild-type. A study in Germany reported the result in puppies: 19 % of wild type, 53 % of heterozygous and 28 % of homozygous and in adult dogs it was similarly: 18 % of wild type, 47 % of heterozygous and 35 % of homozygous [30].

In addition to the genetic test, the diagnosis is made by classical examination methods used in the veterinary practice. However, determining the correct diagnosis often

depends on the veterinarian's subjective view and experience and diagnostic possibilities. In a differential diagnosis, sebaceous adenitis, atopy, demodicosis and other parasitic skin disease, hormonal and metabolic disease, must be excluded. A skin biopsy is sometimes required to make a definitive diagnosis [24].

Ichthyosis cannot be cured. At the present, there is no effective treatment for ichthyosis; they can only supress the symptoms of the disease and maintain them to a certain acceptable extent. The proper treatment of an ichthyotic dog includes regular combing, bathing in special shampoos, applying emollient ointments to help maintain a skin barrier and prevent excessive water loss. A quality diet is essential; supplements of omega fatty acids are ideal [24].

Ichthyosis in Great Danes

Ichthyosis in Great Danes occurs with characteristic strong wrinkles in the head and legs area immediately since birth. The puppy's face looks like Shar Pei's. The skin on the head and legs, mostly around the nose and eyes has an oily appearance, and a yellow, greasy material gradually covers the skin in other areas of the body as well. Puppies may have trouble opening their eyes. Fine white to yellow dry flaking scales gradually begin to appear all over the body in the coat. The skin is dry, inelastic and lichenified. Glabrous skin in the axilla and inguinal area are very dry and has a leathery appearance. Ichthyotic changes with advancing age, may lead to secondary infections and inflammatory skin lesions, which occur mainly in-between wrinkles due to the increased exudative character of the skin. The prognosis is bad [14, 25].

The skin histopathological examination shows typical symptoms of lamellar ichthyosis: diffuse, orthokeratotic hyperkeratosis, follicular keratosis, focal keratin plugging, and acanthosis with vacuolization of keratinocytes without epidermolysis. The accumulation of an amorphous material within hair canals and sebocytes found with different staining patterns, which were observed in samples of ichthyotic Great Dane until electron microscopy, have not been reported in other breed suffering from ichthyosis [25].

In the genetic analysis of a Great Dane genome, a wide significant peak was detected on chromosome 9 at 57—58 Mb in the region of *SLC27A4*. The mutant transcript of *SLC27A4* showed an in-frame loss of 54 base pairs in exon 8, which resulted in the loss of 18 amino acids [14]. Defective *SLC27A4* was not found in genotyping 413 controls from 35 different breeds of dogs and seven wolves; it occurs only in Great Danes. In the analysis of skin biopsies in ichthyosis patients was found that mutant *SLC27A4* protein to induce an uneven distribution of lipids and disturb the formation of the skin barrier [17] and this was confirmed in the study of 15 cases of Great Dane puppies affected with ichthyosis [14].

Ichthyosis in American Bulldogs

The disease appears shortly after the birth of the puppies. The first symptom is a dishevelled pelage with generalized soft and white scales, which are recognizable in 1 to 2-week-old animals. Other symptoms are light brown and mildly erythematous skin of the abdomen and diffusely adherent light brown scales. These clinical signs persist into adulthood in a milder or more severe form. A diffuse and severe scaling with large white scales loosely adherent to the skin or in the hair on the dorsum and lateral thighs may be present. Adherent grey scales are present on the muzzle, around the eyes and on the pinna. Pruritus is present in the case of secondary infection, most often in Malassezia overgrowth [2, 4, 23].

A light microscopic examination records diffuse laminated to compact orthokeratotic hyperkeratosis with hypergranulosis and mild acanthosis. The epidermis has a prominent granular layer, and multifocal granular layer keratinocytes display, a perinuclear clear space and the stratum corneum contains randomly arranged layers of variably sized, often enlarged corneocytes. The keratin bars in the stratum corneum are closely apposed [23].

Ichthyosis in the American Bulldog is caused by a deleterious molecular defect in the *NIPAL4* gene encoding ichthyin. The ichthyin, a transmembrane protein is encoding by 6 exons that resides on canine chromosome 4, composed of 404 amino acids and expressed in the granular layer of the epidermis. It is thought to play a role in lipid metabolism during the epidermal development and works as a Mg^{2+} transporter. The inability to create the normal stratum corneum is caused by non-functional truncated ichthyin protein and leads to the specific symptoms of ichthyosis. 35.6 % of American Bulldogs are heterozygote (carriers) for the disease and 5.4 % are affected with ichthyosis [2, 4, 23].

Ichthyosis in Jack Russel Terriers

Nonepidermolytic ichthyosis in the Jack Russel Terrier is associated with insertion of a long-interspersed nucleotide element (LINE-1) in the transglutaminase 1 (*TGM1*) gene. This ichthyosis form is homologous with *TGM1*-deficient LI in humans *TGM1*. The symptoms are typical for ichthyosis and appeared as early as the puppy's age. The affected dogs have a generalized severe form of hyperkeratosis with large adherent scales. In histological examination, the laminated to compact hyperkeratosis without epidermolysis was observed and on transmission electron microscopy, the stratum corneum was thickened and intercorneocyte spaces were extremely narrow. The first three corneocyte layers contained tonofilaments that were irregular, coarse and wavy [6, 20].

Ichthyosis in German Shepherds and in other breeds

In German Shepherds a novel form of ichthyosis was described, which is caused by a de novo missense variant in the canine *ASPRV1* gene. *ASPRV1* encodes "aspartic peptidase, retroviral-like 1" also known as skin aspartic protease (SASPase), which is involved in profilaggrin-to-filaggrin processing [1, 16]. The novel variant had arisen by a de novo mutation event that must have occurred in either one of the parental germlines or during early embryonic development of this patient. The symptoms in the affected female include: severe scaling of the skin with mild pruritus, generalized hypotrichosis, allopathic lesions with severe exfoliation of greyish scales and mild erythema, comedones on the abdomen and in the perivulvar area. The symptoms developed immediately after birth [1].

In English Springer Spaniels, Labrador Retrievers and West Highland White Terriers the cases of ichthyosis were confirmed, but molecular identification has not been documented [24].

Epidermolytic ichthyosis in Norfolk Terrier Dogs

An autosomal recessive form of epidermolytic ichthyosis has been observed in Norfolk Terrier Dogs. This was caused due to a splice-site mutation in the gene encoding keratin 10 (*KRT10*). The mutation is associated with activation of at least three cryptic or alternative splice sites, which resulted in transcripts containing premature termination codons. The affected dogs displayed generalized and pigmented hyperkeratosis with epidermal fragility. In histologic examination, epidermolysis with hyperkeratosis, a decrease in tonofilaments and abnormal filament aggregations were found in the upper spinous and granular layer of keratinocytes [5].

CONCLUSIONS

Ichthyosis is an autosomal recessive inherited skin disease, which affects specific breeds of dogs e.g. Golden Retriever, Great Dane, American Bulldog, Jack Russel Terrier, German Shepherd and Norfolk Terrier. Ichthyosis is caused by the presence of defective genes, that affect the creation of corneocytes and individual steps in the process of stratum corneum formation. The main clinical sign of a fully manifested disease is abnormal skin scaling of the entire body surface. The disease is not treatable and makes life unpleasant for sick dogs and their owners. In veterinary practice, genetic tests are important in the diagnosis of ichthyosis. Tests are increasingly used not only in clinical practice, but also in dog breeding. The breeder creates new generations of dogs and should approach the health of their offspring responsibly. An important role here is played by a veterinarian, who should explain to the owners the importance of genetic tests and the possibilities of using their results. The veterinarian should also emphasize that the sick individual must not be used in breeding and that the carrier is a healthy dog, which can be used in breeding and have healthy offspring if the partner is carefully selected.

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