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Genetics of Endocrine Diseases in Miniature Schnauzer

(Review of literature)

DIPLOMA WORK

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1. Introduction

"The Miniature Schnauzer breed is like a big dog in a small dog's body", this is what I was told when I was looking for my first dog. I now own my third Miniature Schnauzer. I am very pleased with the breed, and I am not alone feeling that way. The miniature Schnauzer is a breed with increasing popularity, and a frequent guest at the small animal clinics. They are extremely active and sporty, always ready for action, great watch- and lapdogs, as well excellent ratting dogs. However, as with all breeds there are some health issues.
A list of inherited disorders is made public on "Online Mendelian Inheritance in Animals". Authored by Professor Frank of the University of Sidney, Australia. It is a catalogue/compendium of inherited disorders, other (single-locus) traits, and genes in 215 animal species. The catalogue reports disorders of congenital and hereditary origin, found in purebred dogs as well as common conditions thought to have a genetic background because they occur more often than expected in certain breeds. Disorders listed for Miniature Schnauzers include cardiovascular-, endocrine-, gastrointestinal-, immune-, integument-, musculoskeletal-, nervous-, respiratory- and urogenital disorders.
http://sydney.edu.au/vetscience/lida/dogs/search/breed
I would like to find out more about the endocrine disorders of the Miniature Schnauzer. I find endocrinology interesting and endocrine disorders concern a large population of dogs in general.

Genetic disorders of the endocrine system
Organs and structures of the endocrine system produce hormones that exert specific effects on other organs or parts of the body. Only a few endocrine conditions are believed to have an inherited component, these are:
Diabetes mellitus
Hypothyroidism
Hyperadrenocorticism (Cushing's syndrome)
Hypoadrenocorticism (Addison's disease)
Growth-hormone responsive dermatosis
Adrenal sex-hormone dermatoses
Primary hyperparathyroidism
Pituitary dwarfism (hypopituitarism)

I have discussed diabetes mellitus, hypothyroidism and Hyperadrenocorticism in details, as those are the endocrine disorders with a genetic background, frequently presented in the Miniature Schnauzer. I have also discussed hyperlipidaemia, as that is a disorder with a genetic component affecting a high number of Miniature Schnauzer, and could be regarded an endocrine disorder because of the leptin hormone.
I have also mentioned the remaining endocrine disorders with a genetic component in other breeds.

Canine genomic data

Good dog health and disease-free life is important to all pet owners. Dog health problems are either hereditary/congenital or acquired through injury or environmental conditions. Breeding genetically clear animals appears to be the most important factor in prevention of hereditary disease and to assure good health of our dog population.
Sequencing of the dog (Canis familiaris) genome began in June 2003 (Broad Institute of MIT and Harvard, Cambridge, Mass., and Agencourt Bioscience Corp., Beverly, NHGRI's Large-Scale Sequencing Research Network). The breed of dog sequenced was the boxer, which was chosen after analyses of 60 dog breeds found it was one of the breeds with the least amount of variation in its genome and therefore likely to provide the most reliable reference genome sequence. The Canine Genome Sequencing Project produced a high-quality draft sequence of a female boxer named Tasha (2004) the most inbred dog in the world.
The dog genome is similar in size to the genomes of humans and other mammals, containing approximately 2.5 billion DNA base pairs. The dog's DNA represents 39 chromosome pairs. The dog genome encodes for more than 19.000 genes. Up to now more than 1000 inherited diseases have been described in dogs representing the major challenge of breeding purebred dogs in the 21st century. Among them nearly 100 disorders (gene mutations) were either directly or indirectly associated with conformation. Molecular selection methods currently allow an efficient genetic management for purebred dogs, using direct or indirect – linkage DNA-tests. However, it is true only for a minor part; at present approximately for 70 of the known genetic defects in dogs. Nowadays, reputable breeders screen their breeding stock, primarily their sires for common inherited diseases.

2. Material and methods

For me the greater part of the work creating this thesis was collecting appropriate articles.
The Miniature Schnauzer breed is all over a healthy breed, free from many genetic diseases. In addition to this, not much research has been done directly towards to the Miniature Schnauzer, compared to research done on many other breeds.
The larger part of the articles I have used are articles from surveys and experiments done in veterinary universities all over the world, often regarding several breeds.
In my thesis, I have chosen to use the book "The miniature Schnauzer" written by Phyllis Degiola and Wayne Hunthausen DVM (12) as a source of information on the history of the Miniature Schnauzer. I have also used the webpage of the English kennel club for a detailed description of the breed.
I used Pubmed and google scholar for information about genetic disorders in the Miniature Schnauzer and genetics in general. For information about endocrine disorders, I have used the book: "Small Animal Internal Medicine", written by Richard W. Nelson and C. Guillermo Couth. (9)

In addition, I have analysed several research articles that will also be referred to when they become relevant.

3. Result of literature review

3.1. The miniature schnauzer

3.1.1. History of the breed

The schnauzers have been a popular breed for the last 600 years. There are three different variations of the breed. Originally, there was only the Standard Schnauzer, which gave rise to the Miniature and the Giant Schnauzer. The Miniature Schnauzer being the most popular. The Schnauzer was bred with Affenpinschers and small, black Poodles creating the smaller Miniature Schnauzers.

German history

In Germany, the Miniature Schnauzer is called "Zwergschnauzer", meaning dwarf Schnauzer. The Schnauzer is found in artwork from the 15th century. In the 1600s even Rambrandt used a Schnauzer in his work.

Picture 1. Painting by Rambrandt, year 1600.

http://www.happy-case.ru/general.html

The Germans saw how effective the British terriers were at getting rid of rodents and still be a affectionate family dog. Because of this, the Germans wanted to create a similar dog, the perfect farm dog. A smart, hardworking dog, who enjoyed pleasing people, and had a rough

hair coat for protection in hard weather. The three variants of the Schnauzer have always been considered working dogs in Germany.
A dog with the name Schnauzer, won in 1879, the Wire-Haired Pinscher class at an international dog show in Germany. This is the dog giving rise to the breed name, Schnauzer. The first breed club was formed in Cologne, in 1895. It was called "The Pinscher Club", and included both the smooth-haired and the wired-haired dogs. Three years later, in 1898, a Pinscher-Schnauzer club emerged, this club has continued until this day.
In their studbook, Jocco Fulda Liliput, was registered as the first miniature Schnauzer. One year later, the miniature Schnauzer, was formally shown for the first time. (3)

American history

The first Miniature Schnauzer went to The United States in 1920, sadly he died shortly after arrival. In 1923, W. D. Goff from Massachusetts started to import Miniature Schnauzers. In 1925, the first litter was born in America. The Wired-Haired Pinscher Club of America was created the same year. In 1926, this club became the Schnauzer Club of America. The miniature Schnauzer became a separate breed, with its own standards. They were in the terrier group, while the Standard and Giant Schnauzers were categorized in the working group. (3)

British history

The Miniature Schnauzer arrived in England in the late 1920s. The Miniature schnauzer was recognized in 1935 as an independent breed from the bigger Schnauzers.

The breed today

The Miniature Schnauzer is bred throughout the world, despite its origin in one country. The breed is still good in ratting and general farm work, but is mostly seen as a companion and family dog. The Schnauzers job is no longer primarily the eradication of vermin, although they love it. They excel as an alert watchdog, and always ready to play and have fun.
Unlike some terriers, they are very vocal, but not aggressive. They prefer being with their people compared to being with other dogs.
"A Schnauzers appeal is in his intelligence, affection, sense of humour, outgoing disposition, size, and sheer personality, which is much larger than the dog itself." (3)

3.1.2. English Kennel club Breed standards

"A Breed Standard is the guideline which describes the ideal characteristics, temperament and appearance of a breed and ensures that the breed is fit for function. Absolute soundness is essential.

General Appearance Sturdily built, robust, sinewy, nearly square, (length of body equal to height at shoulders). Expression keen and attitude alert. Correct conformation is of more importance than colour or other purely 'beauty' points.

Characteristics Well-balanced, smart, stylish and adaptable.

Temperament Alert, reliable and intelligent. Primarily a companion dog.

Head and Skull Head strong and of good length, narrowing from ears to eyes and then gradually forward toward end of nose. Upper part of the head (occiput to the base of forehead) moderately broad between ears. Flat, creaseless forehead; well muscled but not too strongly developed cheeks. Medium stop to accentuate prominent eyebrows. Powerful muzzle ending in a moderately blunt line, with bristly, stubby moustache and chin whiskers. Ridge of nose straight and running almost parallel to extension of forehead. Nose black with wide nostrils. Lips tight but not overlapping.

Eyes Medium-sized, dark, oval, set forward, with arched bushy eyebrows.

Ears Neat, V-shaped, set high and dropping forward to temple.

Mouth Jaws strong with perfect, regular and complete scissor bite, i.e. upper teeth closely overlapping lower teeth and set square to the jaws

Neck Moderately long, strong and slightly arched; skin close to throat; neck set cleanly on shoulders.

Forequarters Shoulders flat and well laid. Forelegs straight viewed from any angle. Muscles smooth and lithe rather than prominent; bone strong, straight and carried well down to feet; elbows close to body and pointing directly backwards.

Body Chest moderately broad, deep with visible strong breastbone reaching at least to height of elbow rising slightly backward to loins. Back strong and straight, slightly higher at shoulder than at hindquarters, with short, well developed loins. Ribs well sprung. Length of body equal to height from top of withers to ground.

Hindquarters Thighs slanting and flat but strongly muscled. Hindlegs (upper and lower thighs) at first vertical to the stifle; from stifle to hock, in line with the extension of the upper neck line; from hock, vertical to ground.

Feet Short, round, cat-like, compact with closely arched toes, dark nails, firm black pads, feet pointing forward.

Tail Previously customarily docked.

Docked: Set on and carried high, customarily docked to three joints.

Undocked: Set on and carried high, of moderate length to give general balance to the dog. Thick at root and tapering towards the tip, as straight as possible, carried jauntily.

Gait/Movement Free, balanced, vigorous, with good reach in forequarters, and good driving power in hindquarters.

Coat Harsh, wiry and short enough for smartness, dense undercoat. Clean on neck and shoulders, ears and skull. Harsh hair on legs. Furnishings fairly thick but not silky.

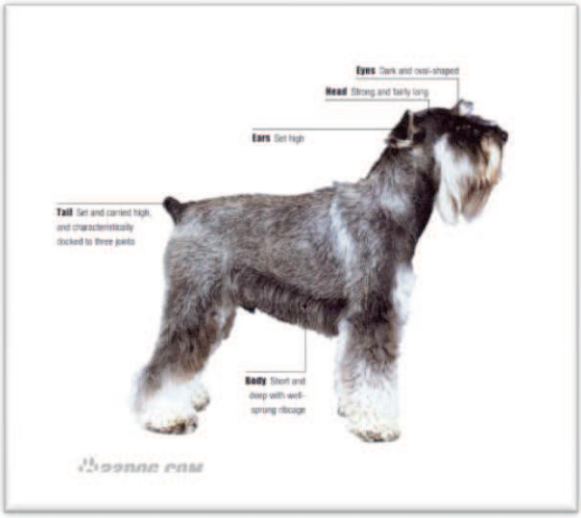
Colour All pepper and salt colours in even proportions, or pure black, or white, or black and silver. That is, solid black with silver markings on eyebrow, muzzle, chest and brisket and on the forelegs below the point of elbow, on inside of hindlegs below the stifle joint, on vent and under tail.

Size Ideal height: dogs: 36 cms (14 ins); bitches: 33 cms (13 ins). Too small, toyish appearing dogs are not typical and undesirable.

Faults Any departure from the foregoing points should be considered a fault and the seriousness with which the fault should be regarded should be in exact proportion to its degree and its effect upon the health and welfare of the dog.

Note Male animals should have two apparently normal testicles fully descended into the scrotum.” (12)

Picture 2. Miniature Schnauzer according to the breed standard



http://www.22dog.com/breeds/Miniature-Schnauzer.html

3.2 List of endocrine disorders

3.2.1 Diabetes mellitus

"Almost all dogs with diabetes has insulin dependent diabetes mellitus (IDDM). Characteristics for dogs with IDDM is hypoinsulinemia, essentially no increase of endogenously produced insulin after administration of an insulin secretagogue (e.g. glucose), failure to establish glycaemic control in response to diet or treatment with oral hypoglycaemic drugs, and an absolute need for exogenous insulin to maintain glycaemic control". (9)
Diabetes mellitus is a multifactorial disease in dogs. A genetic predisposition, infection, insulin antagonistic disease and drugs, obesity, immune mediated, insulitis, and pancreatitis have been found to be trigging factors. The result is loss of beta-cell function, which leads to hypoinsulinemia. The decreased amount of insulin, the transport of glucose into the cells will be impaired. Increased hepatic gluconeogenesis and glycogenolysis will be consequences. The dog will become hyperglycaemic; have glycosuria, polyuria, polydipsia, polyphagia and weight loss. Because of the decreased amount glucose transported into the cells, ketone body production will increase and lead to ketoacidosis. Loss of beta-cell function is irreversible in dogs with IDDM, and they will be dependent on lifelong insulin treatment. (9)

Clinical features
Most dogs are 4-14 years old when diagnosed with diabetes mellitus, with a peak at age 7-9 years. Juvenile diabetes is not common and occurs in dogs less than 1 year. Female dogs are affected twice as often as males. The dog's history is often polyuria and polydipsia, polyphagia and weight loss. Occasionally, sudden blindness might be the first clinical sign the owner recognize. As cataract is a secondary problem to diabetes.

Diagnosis
The diagnosis of diabetes mellitus is based on three elements: clinical signs (polydipsia, polyuria, polyphagia, weight loss and cataracts), fasting persistent hyperglycaemia and glycosuria. To give an early confirmation of diabetes mellitus, measurement of blood glucose should be done, and by testing the presence of glycosuria using urine reagent test strips.

It is important to document both persistent hyperglycaemia and glycosuria, because hyperglycaemia differentiates diabetes mellitus from primary renal glycosuria and glycosuria differentiates diabetes mellitus from other causes of hyperglycaemia. Some dogs might be stressed in the clinic and will because of that have a higher glucose blood level.
A thorough evaluation of the dog is important, to rule out any other causes. As a minimum a complete blood count and serum biochemistry, measurement of serum pancreatic lipase and a urine analysis with bacteriology should be done. In intact females, a progesterone measurement could be useful as well. (9)

Treatment

The most important regarding the treatment of diabetes mellitus is to eliminate the observed clinical signs. Persistence of those signs and development of chronic form are directly correlated with the duration and grade of hyperglycaemia.
To control hyperglycaemia is of course very important. It is done by administer insulin, diet, and exercise. It is also very important to prevent hypoglycaemia, which might be deadly. It occur most often by overdosing insulin. To balance the insulin/ glucose levels are the most important task of the veterinarian. (9)

Classification of diabetes in dogs

Diabetes is a heterogeneous disease, with many pathological mechanisms, which can lead to hyperglycaemia. There are no international classification systems for diabetes in dogs, as there is in human medicine. A suggestion made is that canine diabetes can be subdivided into insulin dependent or insulin non-dependent diabetes mellitus. However, this is not of very much help, because almost all diabetic dogs require insulin therapy. There is little evidence that dogs suffer from a type II diabetes, unlike in humans and cats. Despite the fact that obesity is a large problem in dogs as well.
The authors of "Canine diabetes mellitus: From phenotype to genotype" use a classification system based on the cause of hyperglycaemia:
"1) Insulin deficiency diabetes (IDD) – absolute insulin deficiency.
Primary IDD in dogs is characterised by a progressive loss of pancreatic beta cells.
The aetiology of beta cell deficiency/destruction in diabetic dogs is currently unknown, but a number of disease processes are thought to be involved:
- Congenital beta cell hypoplasia/abiotrophy

- Beta cell loss associated with exocrine pancreatic disease (for example, pancreatitis)
- Immune-mediated beta cell destruction
- Idiopathic process

2) Insulin resistance diabetes (IRD) – relative insulin deficiency*

Primary IRD usually results from antagonism of insulin function by other hormones.
These include the following:

-Dioestrus/gestational diabetes
- Secondary to other endocrinopathies
- Hyperadrenocorticism
- Acromegaly
- Iatrogenic
- Synthetic glucocorticoids
- Synthetic progestagens

*Dogs can progress from IRD to secondary IDD as a consequence of beta cell loss associated with uncontrolled hyperglycaemia". (2)

Dogs between 5-12 years of age are usually affected by IDD, this type seems to be the most common one. This is opposite to the human type, where type I most often has a juvenile onset. Juvenile onset of diabetes has occasionally been seen in Labradors, with diabetes starting at 3-6 months of age. This type is thought to be caused by an inherited defect of beta cell development, leading to beta cell aplasia, rather than an autoimmune process.
In most cases of canine diabetes, the cause of insulin deficiency is not known. However, it is believed to be the result of beta cell damage caused by pancreatitis or/ and an immune-mediated beta cell destruction.
Based on the findings of autoantibodies in a proportion of diabetic dogs, an autoimmune background has been proposed. In one study of newly diagnosed dogs, anti-islet cells antibodies were detected in 50%. Indications that canine diabetes mellitus is more comparable to the latent autoimmune diabetes of adults than the classical juvenile type I diabetes, are the age of onset and presence of autoantibodies. (2)

Genetics of diabetes mellitus

Breeds recognized to have high and low risk of developing diabetes mellitus based on analysis of the Veterinary Medical database (VMDB) from 1970-1993.

Examples:

Breeds with high risk	**Odds ratio**	**Breeds with low risk**	**Odds ratio**
Australian terrier	9,39	German shepherd	0,18
Standard schnauzer	5,85	Collie	0,21
Miniature schnauzer	5,10	Golden retriever	0,28
Samoyed	2,42	Shetland sheepdog	0,21

(Nelson, Richard W. - Guillermo Couto - Grauer – Hawkins – Johnson - Scott-Moncrieff – Taylor – Ware – Watson -Willard: Small animal internal medicine book. 2009, 4th edition, p764-771)

"Mixed breed dogs were used as the reference group. The VMDB comprises medical records of 24 veterinary schools in the United States and Canada. The records analysed included those from first hospital visits of 6078 dogs with IDDM and 5922 random selected dogs with first hospital visits for any other diagnosis, seen at the same veterinary schools in the same year". (9)

Certain breeds of dogs appears to be predisposed to developing diabetes mellitus. The miniature schnauzer is ranged as number 3 in a database containing medical records of more than 6000 diabetic cases from the veterinary school in North America. In contrast, other breeds, for instance the German shepherd dog and golden retriever has a much smaller tendency to develop diabetes mellitus. This breed differences in disease susceptibility may indicate that there is a genetic background in diabetes in dogs, there might be differences in genetic risk factors that are breed specific. (2)

Canine diabetes mellitus is a complex genetic disorder; with a high difference in breed susceptibility. A number of immune response genes, which have been seen in connection with human diabetes type 1 (TID), have also been seen in canine diabetes mellitus. This gives the pathogenesis an immune mediated component. Most important genes are the ones encoding canine MHC class II antigen, called the DLA (Dog Leucocyte Antigen) and the CTLA4 (Cytotoxic T-Lymphocyte Antigen 4). (11)

Dog Leucocyte Antigen-gene

The Kennel Club Charitable Trust and Petsavers, have investigated the DLA genetics of canine diabetes trying to explain the difference in breed-susceptibility to the disease. 530 diabetic dogs and more than 1000 control dogs were DLA genotyped and analysed. "The DLA-DRB1*009/DQA1*001/DQB1*008 haplotype was confirmed as being associated with diabetes in a large number of patients. In addition, two other haplotypes were found, they showed a significant increased prevalence in the diabetic population: DLA-DRB1*015/ DQA1*006/DQB1*023 and DLA-DRB1* 002/DQA1*009/DQB1*001. In contrast, one DLA-DQ haplotype, DLA-DQA1* 004/DQB1*013, had significantly reduced prevalence in diabetic cases compared with controls, meaning this could be a protective haplotype, similar to that seen with HLA-DR2 in human diabetes". (2).

As there are a high interbreed, but not that much intrabreed, a variability on DLA haplotype is often seen, this can make it hard to discriminate between haplotypes associated with disease and those associated with the breed profile of the sample groups used for analysis. There was not enough samples to do individual breed case-control analysis, so other groups were made. These groups were made based on their risk of having diabetes, in an attempt to determine whether particular DLA haplotypes segregated with susceptibility or resistance to the disease. In the high risk group (Australian terrier, standard and miniature schnauzer and Samoyed) similar genotypes were seen. These diabetes-prone breeds had similar DLA alleles, despite the fact that they originate from different gene pools. Of the 44 diabetic dogs in this group, 33 dogs expressed two high-risk haplotypes. Which in contrast was not at all present in the low-risk group of control dogs.

The result of the genetic analysis suggest that DLA gene is included in the susceptibility to canine diabetes. However, diabetes is a complex genetic disorder and there might be many other genes involved. (2)

The MHC gene associations are not necessarily specific for diabetes mellitus and similar DLA genotypes have proven to be connected with susceptibility to other canine endocrinopathies, including hypothyroidism. This means that the DLA gene can be considered a general risk factor for several immune mediated disease. (1)

CTLA4 and other immune response genes

The CTLA4 gene is another gene that has to be taken into consideration in association with diabetes mellitus in dogs. A. D. Short et al. did a study on this gene in 2009. Because of the

proven involvement of CTLA4 in human diabetes, they proposed that the canine CTLA4 would play a role in the development of canine diabetes mellitus too.
Diabetic dogs were selected from the UK Canine diabetes Database (Royal Veterinary College, University of London). The diagnosis was based on clinical signs and documented hyperglycaemia with glycosuria. Dogs that was suffering from an obvious non- immune mediated cause of the disease were eliminated. For example dogs with neonatal diabetes mellitus, hyperadrenocorticism or intact females.
Dogs representing six breeds were chosen. The breeds were Labrador retriever (n=70), West Highland white terrier (n=48), Miniature Schnauzer (n=10), Border terrier (n=10), Samoyed (n=20) and crossbreeds (n=54). Control non-diabetic dog samples were taken from a large collection of DNA samples (UK Companion animal DNA Archive, University of Manchester). Control dogs were breed matched to the diabetic cases, Labrador retriever (n=108), West Highland White (n=44), Miniature Schnauzer (n=19), Border terrier (n=14), Samoyed (n=9) and crossbreed (n=54). (11)
"Sequencing of the canine CTLA4 gene showed a large amount of variation within the promoter region. 15 SNP's (single-nucleotide polymorphism) and 2 deletions were found. The deletion did not occur in the Samoyed group, but was seen in the other five breeds. The number of samples with deletion was not high enough to be statistically important.
SNP15 was found to be monomorphic in all of the five breeds. An interesting observation was that the minor allele status could be between the breeds. As an example, in the Miniature Schnauzer the SNP 12 had a different minor allele in the case and control group. For the control population, "G" was the minor allele but the in the cases "T" was the minor allele." (11)

There was a connection observed between Canine CTLA4 promoter polymorphism and diabetes mellitus in the Samoyed, West Highland White, Miniature Schnauzer, Border terrier and Labrador.
Other canine immune response genes have also been analysed and have shown breed differences in allele frequencies. IL6 SNPs has been associated with diabetes mellitus in Yorkshire Terriers and Miniature Poodles, while IL4 SNPs is in strong connection with diabetes mellitus in Miniature Schnauzers. In contrast, in the Samoyed, none of the cytokine gene polymorphism examined show any association to diabetes mellitus. (1)

3.2.2. Hypothyroidism

Hypothyroidism is a deficiency in production or a decrease in secretion of thyroid hormones; it is caused by structural or functional abnormalities of the thyroid gland. It might have origin in the hypothalamus, pituitary gland or thyroid gland itself.
Primary hypothyroidism is the form most frequently seen. The most common histological findings are lymphocytic thyroiditis and idiopathic atrophy of the thyroid gland. Lymphocytic thyroiditis has increased risk in some breeds and lines with in a breed, genetics seems to play a role here as well as in diabetes mellitus, but its aetiology is not completely understood. It has an immune mediated origin and it is characterized by a diffuse infiltration of lymphocytes, plasma cells and macrophages into the thyroid gland. A characteristic of idiopathic atrophy is loss of parenchyma. Inflammation is not seen and the cause is not known. It might be a primary degenerative disorder, or it might be the end stage of an autoimmune lymphocytic thyroiditis.
The destruction of the thyroid gland is an ongoing process; more than 75 % of the gland might be destroyed before clinical signs are appear. Decreased serum hormone and clinical signs might not be seen before 1-3 years after onset of the disease, proving that it is a slow process.
Secondary hypothyroidism is the result of problems of the pituitary gland, caused by developmental failure, or a dysfunction of the pituitary thyrotrophic cells causing impaired secretion of thyroid- stimulating hormone.
Tertiary hypothyroidism is a deficiency of thyrotropin-releasing hormone by the hypothalamus. (9)

Clinical features
Clinical signs tends to appear at middle age, they usually develop earlier in breeds at increased risk. The signs are very variable and are dependent on the age of the dog. No sex related predilection have been seen. Clinical signs may also vary between breeds, from only thinning of the fur coat to complete truncal alopecia in other. Changes in the dog's mental status and activity. Most dogs shows dullness, lethargy, exercise intolerance, weight gain without increased appetite and dermatological signs, as alopecia, seborrhoea and pyoderma. (9)

Diagnosis

The diagnosis is based on clinical signs, physical examination, complete blood count, serum biochemistry and tests of thyroid gland function.

Baseline serum T4 concentration is often used as the first test for thyroid gland function. It is important to know there are many reasons for a supressed T4. Therefore, T4 measurement should be a confirmation of normal thyroid gland function, not to diagnose hypothyroidism. Evaluation of a thyroid panel including T4, fT4, TSH and Tg antibodies, provides a much more informative analysis of the pituitary-thyroid axis and thyroid gland function. (9)

Treatment

Synthetic levothyroxine is the treatment of choice for hypothyroidism. It is administered orally and should result in normal serum concentration of T4, T3 and THS.

Therapeutic monitoring is important, and include evaluation of clinical response to the treatment, measurement of T4 and TSH concentration before or after levothyroxine administration, or both. This should be done 4 weeks after initial therapy, if signs of toxicosis or if no response is seen. (9)

Genetics of hypothyroidism

Canine lymphocytic thyroiditis is an immune mediated condition and are likely to have a genetic component to the aetiology, the fact that many such diseases display an increased breed predilection or resistance support this. Doberman Pincher, Golden Retriever, Giant and Miniature Schnauzer, Pomeranians, Poodles and Boxers are breeds with a high breed predilection.

Recently an association between canine thyroiditis and the presence of a rare DLA (dog leucocyte antigen) class II haplotype was reported for Doberman Pinchers. This is because genes in the major histocompatibility complex (MHC) are important for the regulation of the immune response. Many immune-mediated conditions are associated with MHC polymorphism and haplotypes. For example Hashimoto's thyroiditis in humans.

In dogs, the MHC is referred to as the DLA system, which contains class I, II and III genes. These appear to be highly polymorphic. (6)

In 2006 L. J. Kennedy et al. extended this study on canine hypothyroidism to include other dog breeds as well, in order to examine whether the risk of developing canine immune mediated hypothyroidism is connected with the same specific canine MHC gene polymorphisms.

DNA samples from 173 dogs with hypothyroidism were collected. Of these, a subset of 85 dogs had full clinical data and could for sure be diagnosed with primary hypothyroidism. The other 88 dogs had incomplete clinical data and they represented a more heterogeneous group. The phenotypic and clinical data collected included sex, age and full hypothyroid panel test results (when possible) (TGAA%, TT4, TT3, FT4, FT3, autoT4, autoT3 and CTSH). The cases were compared with several different groups of control dogs.

Table 1 shows the distribution of breeds in 173 affected dogs, the subset of 85 putative primary hypothyroid dogs and a set of 27 breed-matched control dogs. The set of 80 controls is an exact match with 80 of the definitive cases. The affected dogs include only 42 different breeds, but their set of 873 controls contains dogs from more than 70 different breeds. (6)

Table 1. **Breed distribution of 173 hypothyroid dogs, 85 selected dogs with hypothyroidism and 267 control dogs.**

Breed	**Hypothyroid dogs**	**Subset**	**Controls**	**Breed**	**Hypo-tyroid dogs**	**Subset**	**Controls**
Basset hound	6		9	***Retriever, golden***	***2***		***16***
Beagle	***1***	***1***	***9***	Rhodesian ridgeback	26	20	15
Bernese mountain dog	1		4	Rottweiler	1	1	5
Boxer	***12***	***5***	*22*	German Schnauzer	**1**		
Collie, bearded	2	1	2	***Mini Schnauzer***	***1***		***4***
Collie, border	1		2	English setter, blue	1		
Collie, rough	1	1	2	***English setter***	*17*	***1***	***44***
Dalmatian	1		3	Gordon setter	2		
Doberman pincher	***32***	***30***	***21***	***Irish Setter***	***2***	***1***	***5***
German shepherd dog	3		14	***Old English sheepdog***	***1***		***4***
Great Dane	***1***		***4***	***Shetland sheepdog***	***2***	***1***	***2***
Hovawart	4		3	American cocker spaniel	1		2
Japanese Akita	***1***	***1***	***2***	Clumber spaniel	1		
Labrador	4	3	14	***Cocker spaniel***	***3***	***1***	***4***
Labrador, chocolate	2		2	English springer spaniel	2	1	4
Labrador retriever	3	2	3	Springer spaniel	3	1	6
Lagotto Romagnola	1	1		Welsh springer spaniel	1		1
Leonburger	1	1	1	Dandie dinmont terrier	1		
Lhaso Apso	1	1	3	Staffordshire bullterrier	2	1	6
Petit Basset Griffon Vendeen	***1***	***1***		West highland white terrier	1	1	3
Pointer	1	1		Cross breed	6	3	12
Pyrenean mountaindog	1		4	Unknown	14		9
Retriever, flatcoat	1		1	Totals	173		267

(Kennedy L.J. - et al.: Association of canine hypothyroidism with a common major histocompatibility complex DLA class II allele. Tissue antigens 2006)

Breeds that have been reported as being predisposed to hypothyroidism.

Boxers, Doberman, Rhodesian ridgeback and English setter are breeds with a high percentage of hypothyroid dogs, while other breeds as Siberian husky and Yorkshire terries does not have any. They compared The DLA allele frequencies of the patient group to those of the control group. In all the comparisons, the same allele, DLA-DQA1*00101, was shown to be connected with the presence of hypothyroidism.

Table 2. Association of DLA-DQA1*00101 with hypothyroidism.

Patient group		Control group		Odd ratio	p-value
All affected dogs	105/173 (60.7 %)	All controls	355/873 (40.7%)	2,25	<0.000002
All affected dogs	105/173 (60.7 %)	Breed-matched control	122/267 (45.7%)	1,84	<0,003
Selected subset	57/85 (67.1%)	Breed-matched control	122/276 (45.7%)	1,97	0.001
80 cases	52/80 (65%)	80 breed matched control	35/80 (43.75 %)	2,57	0.006

(Kennedy L.J. - et al.: Association of canine hypothyroidism with a common major histocompatibility complex DLA class II allele. Tissue antigens 2006)

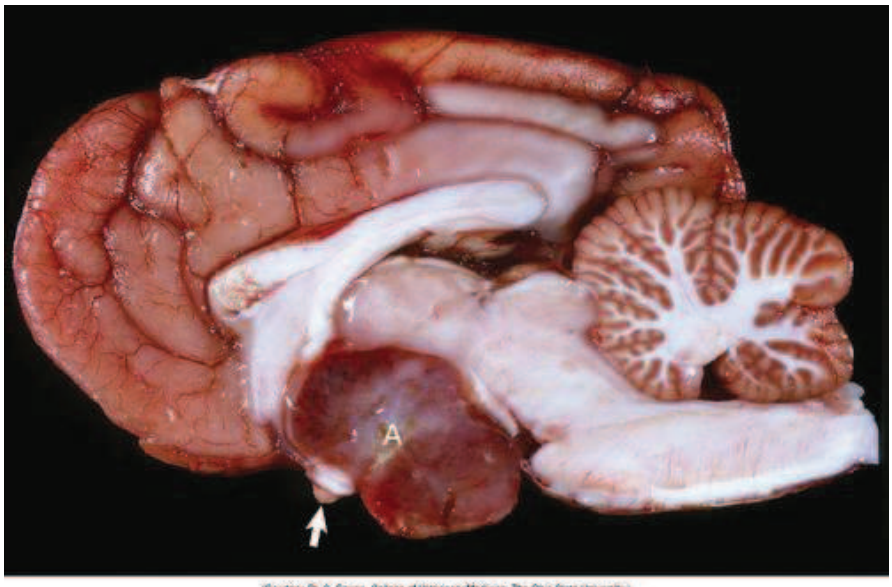
“The strongest comparison of 80 dogs with definitely diagnosed immune-mediated hypothyroidism with 80 breed matched controls gave an odds ratio of 2.57 and a *p*-value of <0,006. The study shows that there is a strong association of this allele with the disease in the total patient group. “These data suggest that some breeds may have MHC associations with thyroiditis that are different from MCH association in other breeds and that some may even lack a strong MHC association.” (6)

3.2.3. Hyperadrenocorticism

Hyperadrenocorticism (Cushing's syndrome) is classified into pituitary dependent, adrenocortical dependent and iatrogenic hyperadrenocorticism.

1) The most common is the pituitary dependent type (PDH); 80-85% of dogs has this type. The most frequent finding is adenoma of the distal part of the pituitary. Excessive secretion of ACTH causes a bilateral adrenocortical hyperplasia, leading to an excessive cortisol secretion from the adrenal cortex. Because of the missing feedback inhibition of ACTH secretion by cortisol, excessive secretion persist despite increased adrenocortical secretion of cortisol. (9)

Picture 3. Picture of Pituitary gland adenoma.



(Courtesy Dr. C. Capen, College of Veterinary Medicine, The Ohio State University.)
Zachary and McGavin: Pathologic Basis of Veterinary Disease, 5th edition.
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2) Adrenocortical dependent Cushing's syndrome is caused by adrenocortical tumours. As a consequence of the tumour, random secretion of excessive amounts of cortisol is secreted, independent of the pituitary. These tumours seem to keep the ACTH receptors and respond to exogenous ACTH. Adrenocortical tumours does not respond to manipulation of the hypothalamic-pituitary axis with glucocorticoids.

3) Iatrogenic Cushing's is a caused by an excessive administration of glucocorticoids to treat patients with allergic or immune-mediated disorders. Because the hypothalamic-pituitary-adrenocortical axis is normal, the prolonged excessive administration of glucocorticoids supresses plasma ACTH, causing a bilateral adrenocortical atrophy. (9)

Clinical features

Hyperadrenocorticism disease usually occur in dogs at the age of 6 years or older, but it has been documented in dogs as young as 1 year. There is no apparent sex-predisposition. Pituitary dependent hyperadrenocorticism is more often found in smaller dogs. 75% of dogs with PDH weigh less than 20kg.

The most common signs are polydipsia, polyuria, polyphagia, panting, abdominal enlargement, alopecia, mild muscular weakness and lethargy. Most dogs show many, but not all, of these clinical signs. Sometimes dogs are taken to the clinic only because of polyuria and polydipsia, bilateral symmetric endocrine alopecia, or panting. There may be no other historic or physical examination findings connected to hyperadrenocorticism. The diagnosis of hyperadrenocorticism is not readily apparent in these dogs. Fortunately, hyperadrenocorticism is a differential diagnosis for polyuria and polydipsia, endocrine alopecia, and panting and will most likely be identified as the veterinarian works through the differentials for these problems. (9)

Diagnosis

Many different screening test for hyperadrenocorticism syndrome is on the market, including systemic arterial blood pressure and urine protein: creatinine ratio. A normal urinary cortisol: creatinine is presumptive sign that the dog does not have hyperadrenocorticism. Final confirmation is usually proved by a low-dose dexamethasone suppression test or ACTH stimulation test. The low-dose dexamethasone suppression test can help distinguish dogs with pituitary tumour from those with adrenal tumours, unless no adrenal suppression is present. In that case, differentiating pituitary adrenal forms is made on the basis of high-dose dexamethasone testing, endogenous ACTH testing or adrenal ultrasonography. (7)

Treatment

There are several medical options for the treatment of hyperadrenocorticism, the most used being trilostane and mitotane. Both indicated for pituitary dependent hyperadrenocorticism and adrenal tumour hyperadrenocorticism. Other modes of treatment are surgical removal of the adrenal gland and radiation therapy. (9)

Genetics

The genetics of the hyperadrenocorticism are not fully understood yet, but because of the breed predisposition, it is thought to be of a genetic origin. It is therefore a good idea to avoid breeding from affected individuals, or from those with any close relatives (parents, siblings, grandparents or the siblings of parents and grandparents) affected by Hyperadrenocorticism. The problem with that is that many dogs are diagnosed at a relatively high age and breeding has already occurred.

There are currently no organised breeding schemes concerning the incidence of hyperadrenocorticism in the Miniature schnauzer breed. This is because the genes involved have not been determined yet. Breeding selectively from Miniature schnauzers who has relatives free of the disease (and which have good breeding values) is likely to be effective in decreasing the number of affected dogs. Breeding values consider genetic information and the presence or absence of diseases in both the dog that are planned to be breed and the dog's relatives. Progress in decreasing the prevalence of Hyperadrenocorticism is likely to be facilitated by a greater knowledge of the genetics that underlie the disease. (7)

3.2.4. Hyperlipidemia

The term hyperlipidaemia refers to a higher than normal value of lipids (triglycerides, cholesterol or both) in the blood. An increase in blood concentration of triglycerides is called hypertriglyceridemia, while an increase in blood concentration of cholesterol is termed hypercholesterolemia. The term hyperlipoproteinaemia refers to increased blood concentration of lipoproteins, but is often used interchangeably with hyperlipidaemia.

Canine hyperlipidaemia is classified into primary and secondary hyperlipidaemia. Primary hyperlipidaemia is of idiopathic origin and it is the form most often seen in Miniature Schnauzers. It is characterized by severe hypertriglyceridemia resulting from excessive VLDL (very low-density lipoprotein) particles and by mild hypercholesterolemia. The exact mechanism is not fully understood yet.

Secondary hyperlipidaemia is the result of an endocrine disorder, rather than an endocrine disorder itself. Secondary hyperlipidaemia is as well an increase of concentration of triglycerides, cholesterol or both in the blood. It has been related to hypothyroidism, diabetes mellitus, and hyperadrenocorticism. Increases in both serum triglyceride and cholesterol concentrations have been reported in dogs with hypothyroidism. In one study,

hypertriglyceridemia and hypercholesterolemia were found in 88% and 78% of hypothyroid dogs. Usually, lipid abnormalities disappears after treatment of hypothyroidism. In dogs with diabetes mellitus, hyperlipidaemia is most commonly associated with hypertriglyceridemia but hypercholesterolemia might also be present. Similarly, hypertriglyceridemia usually disappears after successful treatment of diabetes, but hypercholesterolemia might be persistent despite therapy. Finally, both naturally occurring and iatrogenic hyperadrenocorticism have been associated with hyperlipidaemia in dogs. (13)

Clinical features

Waxing and waning vomiting, diarrhoea, and abdominal discomfort are the most common clinical presentations associated with hyperlipidaemia. Severe hyperlipidaemia has been associated with pancreatitis, lipemia retinalis, seizures, cutaneous xanthomas, peripheral nerve paralysis, and behavioural changes.

In additional to clinical manifestations, hyperlipidaemia is known to interfere with the results of several routine biochemical tests. Such as total bilirubin, conjugated bilirubin, phosphorus, alkaline phosphatase, glucose, total protein, lipase, alanine amino transferase.

Hyperlipidaemia may in some cases cause haemolysis, which in turn can interfere with some biochemical tests. These possible alterations in biochemical data must be considered when interpreting results in animals with hyperlipidaemia. (9)

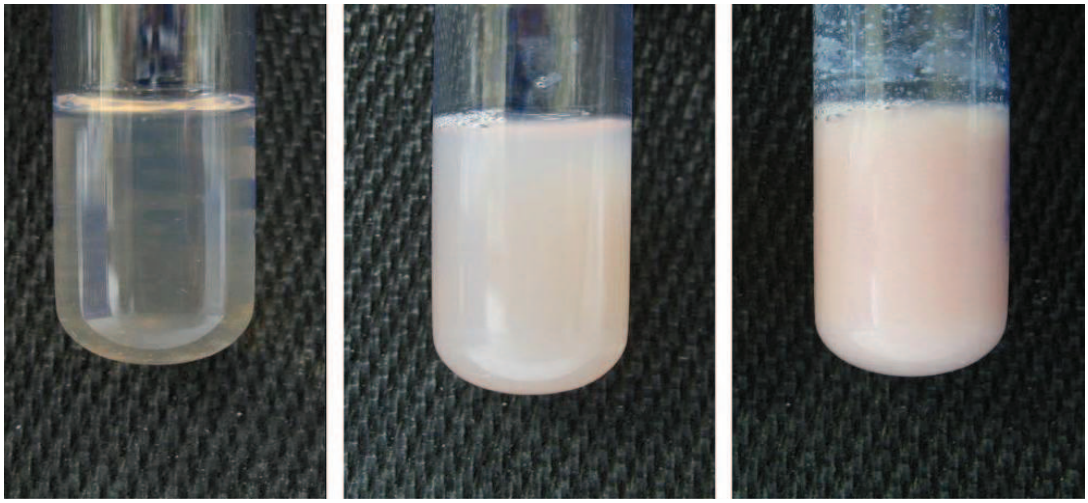
Diagnosis

The presence of opaque, milk like appearance (called lactescence) is an indicator of hyperlipidaemia. Animals that has lactescence serum typically have triglyceride concentrations that exceed 1000mg/dl. However, animals that are only hypercholesterolemic do not have lactescence. The reason for this is that the cholesterol rich LDL and HDL particles are too small to refract the light.

A blood test should be done after fasting at least 12 hours.

Quantitative measurement of total cholesterol and triglyceride concentrations in serum or plasma is usually done by the use of spectrophotometric or enzymatic methods. Other methods (e.g., lipoprotein electrophoresis, ultracentrifugation) are possibilities as well, but those methods are not a routine in clinical evaluation of hyperlipidaemia dogs. (9)

Picture 4. Serum samples with normal triglyceride concentrations are clear (left tube). As the serum triglyceride concentration increases, serum becomes turbid (middle tube) and ultimately lactescent (right tube).



(Xenoulis, P.G – Steiner J. M: lipid metabolism and hyperlipidaemia in dogs, Journal 2010,183, p 12-21)

Treatment

Hyperlipidaemia secondary to an underlying disorder will most likely resolve or improve by treating the primary cause. A low fat diet should be given dogs with primary hyperlipidaemia throughout their lives. The recommendation is a diet that contain less than 20 grams of fat per 1000 kcal. Many commercially available diets are good for dogs with primary hyperlipidaemia. Treats and human foods should be avoided, unless they are low in fat. (13) Pharmacological agents can be considered for the management of seriously affected animals. Such as bile acid sequestrates, HMG-CoA reductase inhibitors and probucol. (9)

Genetics

Primary hyperlipidaemia in Miniature Schnauzers was the first breed-related primary lipid disorder described in dogs. This condition was for the first time reported in the Miniature Schnauzer in the United States than more than 30 years ago.

A recent study has shown that primary hypertriglyceridemia is quite common in healthy Miniature Schnauzers. In 32.8% of 192 healthy Miniature Schnauzers, investigated fasting hypertriglyceridemia was seen. However, hypertriglyceridemia was much more common in older dogs; more than 75% of healthy Miniature Schnauzers above 9 years of age had hypertriglyceridemia. The severity of hypertriglyceridemia increased with age; more than 80% of Miniature Schnauzers with moderate to severe hypertriglyceridemia were 6 years or

older. There was no difference between male and female Miniature Schnauzer regarding the prevalence to hypertriglyceridemia. The cause of hypertriglyceridemia is still not revealed in Miniature Schnauzers. However, the fact that hypertriglyceridemia is prevalent within a single breed indicate a possible hereditary background.
Because lipoprotein lipase is the major enzyme involved in the clearance of triglycerides, deficiency of this enzyme has been considered to be a possible cause of hypertriglyceridemia in Miniature Schnauzer. However, a study in this breed with hypertriglyceridemia failed to identify any mutations of the lipoprotein lipase gene, this means that inherited lipoprotein lipase dysfunction is not the cause of hypertriglyceridemia in Miniature Schnauzers. (13)

“In a more recent study, the gene encoding apo C-II (which is an activator of lipoprotein lipase) was evaluated for the presence of possible mutations in Miniature Schnauzers with primary hypertriglyceridemia. They were not able to identify mutations that co-segregated with hypertriglyceridemia. Further studies are needed to identify the genetic basis of primary hypertriglyceridemia in Miniature Schnauzers”. (13)

3.2.5. Hypoadrenocorticism (Addison's disease)

Addison’s disease (primary adrenocortical insufficiency) is an autoimmune disorder. It is characterized by destruction of the adrenal cortex, which lead to the inability to produce cortisone when stimulated with adrenocorticotrophic hormone (ACTH). The disease occurs in many breeds, with frequencies ranging from 1.5% to as high as 9% for Standard Poodles and Bearded Collies. The most common clinical manifestations are connected to alterations in the gastrointestinal tract and mental statues and include clinical signs as lethargy, anorexia, vomiting and weigh loss. Additional physical examination may include dehydration, bradycardia, weak femoral pulse and abdominal pain. (9)

An inherited susceptibility has been proposed for more than 30 dog breeds. Even though canine Addison's is well documented to be common in certain families, the mode of inheritance is unclear. One breed, the Standard Poodle, exhibits the presence of a single major autosomal locus affecting expression, while another breed, the Bearded Collie, has a less definitive mode of inheritance for Addison's. (10)

3.2.6. Pituitary dwarfism (hypopituitarism)

Pituitary dwarfism is a result of congenital deficiency in growth hormone. Studies in German Shepherd Dog dwarfs suggest that congenital GH deficiency is because a primary failure of the differentiation of craniopharyngeal ectoderm into normal tropic hormone- secreting pituitary cells. Pituitary cyst are often seen with diagnostic imaging and may get larger as the dwarf grows older. Pituitary dwarfism occurs primary in German Shepherd Dogs, but might be seen in other breeds as well. (4)

Picture 5. Dogs from the same litter, one with proportional dwarfism.

http://openi.nlm.nih.gov/detailedresult.php?img=3223203_pone.0027940.g001&req=4

Most common clinical manifestations in dogs that lack growth hormone are endocrine alopecia and hyperpigmentation of the skin. Affected animals are usually normal in size during the 2-4 months of life, but after that the growth decrease. Dwarfs with only GH deficiency typically maintain a normal body shape and body proportion compared to dwarfs with combined deficiencies (mostly TSH) may acquire a square or chunky body shape, which are typically associated with congenital hypothyroidism. The most common dermatological sign is retention of secondary hairs. As a result, their hair coat is soft and wool like. After a while symmetrical alopecia develops. The skin is normal from the start, but as they grow older it becomes hyperpigmented, thin, wrinkled and scaly. Comedones, papules and secondary pyoderma is frequently seen in the adult dwarf.

The therapy for pituitary dwarfism is administration of GH. Unfortunately, there is no effective GH therapy available for dogs at the moment. The long-term prognosis for animals with pituitary dwarfism is poor; and they usually die before the age of five despite therapy. (4)

“Pituitary dwarfism is encountered most often as a simple, autosomal recessive inherited abnormality in the German Shepherd Dog. Inherited pituitary dwarfism may be due to isolated GH deficiency or may be part of a combined pituitary hormone deficiency. Concurrent deficiency thyroid stimulating hormone and prolactin are most commonly identified. The hypothesis is that the disorder is caused by a mutation in a developmental transcription factor that precludes effective expansion of a pituitary stem cell after differentiation of the corticotropic cells that produce ACTH.” (4)

3.2.7. Growth-hormone responsive dermatosis

Growth Hormone-Responsive Dermatosis is a poorly understood skin disease of adult dogs. It may represent an initially mild but progressive form of congenital hyposomatotropism. However, it is not severe enough to cause dwarfism, but over time, the result will be a dermatological manifestation in the young adult dog. In some cases, it may occur after normal growth has finished. The cause is not known yet. Clinical manifestation of GH-responsive dermatosis are due to hyposomatotropism, all the other tropic cells of the pituitary are normal. In the mature dog the hair growth and skin pigmentation, are affected. The clinical signs usually appears after 1-3 years of age. Characteristics are bilaterally symmetrical alopecia of the trunk, neck, pinnae, tail and caudomedially on the thighs. Hyperpigmentation usually occur in the areas of alopecia. In chronic cases, the skin becomes thin and hypotonic. Otherwise the dog is normal.
Although GH-responsive dermatosis may occur in any dog, there seems to be a breed predilection for it in the Chow Chow, Pomeranian, Keeshond and Samoyed. Still much remain unknown and it is recommended to exclude affected families from breeding programs. (4)

3.2.8. Adrenal sex-hormone dermatoses

This endocrine disease has dermatological manifestations including endocrine alopecia that starts at the perianal, genital and ventral abdominal areas and spread cranially. The hair is dull, dry, easily plucked and the hair does not grow back after clipping. There might also be seborrhoea and hyperpigmentation present. Additional clinical signs of hyperestrogenism may be seen in some cases.
There are no pathognomonic histologic changes for sex hormone- induced dermatoses. The increased plasma oestrogen concentration would indicate a functional Sertoli cell tumour in the male and hyperestrogenism in the bitch. An ultrasound might reveal ovarian cyst or neoplasia in the female with hyperestrogenism. Surgical removal of the ovaries or testicles will resolve the hyperestrogenism and alopecia. An abnormal increase in serum progesterone may also be found, this is the result of a neoplasia or a functional ovarian luteal cysts. Clinical features of progesterone secreting adrenocortical tumours are similar to hyperadrenocorticism. Adrenal sex-hormone dermatoses has been reported to be a predisposed dermatoses in Chow Chow, Keeshond, Pomeranian, Poodle and Samoyed. The condition is thought to have become more common as breeders selected for animals that grow a thick hair coat. Until the genetics of the condition is better understood in the different breeds affected, all affected animals should be excluded from breeding programs. (7)

3.2.9. Primary (juvenile) hyperparathyroidism

It is a rare cause of primary hyperplasia of the parathyroid gland. In German Shepherd Dogs it is inherited as an autosomal recessive trait, and leads to stunted growth, muscle weakness, polyuria and polydipsia. Most cases of adult onset primary hyperparathyroidism are seen in dogs older than 4 years of age. The breeds most affected are Keeshond, Golden Retriever and Dachshunds. In the Keeshond it is transmitted as a dominant trait.
Affected dogs should be excluded from breeding, and the parents are considered obligate carriers of the trait. A genetic test is on the marked, but only for the Keeshond. This test could help to eliminate hyperparathyroidism from breeding animals. (7)

4. Discussion and conclusion

In the earliest days of domestication, dogs were selected for breeding based on the ability to interact with humans. Many of the traits seen today were traits bred for a function; athletic dogs were bred for hunting, short, thick legs were preferred for dogs working in caves, powerful jaws for fighting dogs and so on. Most of the traits subjected to selection had a direct utility and functionality. Many of the traits that initially were bred for functionality is now incorporated into the breeds standards.

Now a day it seems that there are more breeding for the looks than functionality. We want Pugs with the flat faces and the curly tails, the Basset hound with the shortest legs and most skin or the King Charles Cavalier with the smallest head. Breeding for desired traits are done by line breeding. It involves mating related individuals who have the desired traits, with the aim of fixing that wanted trait. However, this technique fixes unwanted traits as well. There is a discussion still going on where to draw the line between in- and linebreeding.

Inbreeding coefficient

In the 1920s, Sewell Wright developed the "inbreeding coefficient". This gives the probability that both copies of a given gene are derived from the same ancestor. A total outcross would have an inbreeding coefficient of zero.

An inbreeding coefficient of 100% is rare, and would be the result if there were only real siblings mating over several generations. A mating between a brother and sister from unrelated parents would result in an inbreeding coefficient of 50%. A mother/son or father/daughter mating would result in a breeding coefficient of 25% assuming that there were no other related mating in the preceding generations. A cousin-to-cousin mating actually gives a relatively low percentage. (8)

"Because deleterious genes are maintained by natural selection at a low frequency the incidence of any particular defect is usually so low as to go without notice. However, the mating of relatives (inbreeding) change this drastically. Inbreeding does not, on average, change the frequency of the deleterious gene, but it does dramatically change the frequency of genotypes. In particular, it increases the frequency homozygotes, which have the effect of bringing those deleterious recessive genes out in the open, where their effect can be seen." (8)

Based on these facts breeders should avoid mating of close relatives. This is a real problem in many breeds, because the genetic pool has become so small it is almost impossible to find individuals without common ancestors. "Their gene pools are so small that they have, in

effect, no room to move; there is no choice but to mate close relatives, and hence to increase substantially the level of inbreeding, thereby increasing the prevalence of inherited disorders due to recessive genes." (Professor I. A. Watson, Sidney University).

As mentioned before, up to now more than a 1000 inherited diseases have been described in dogs. Among them nearly a 100 disorders (gene mutations) were either directly or indirectly associated with conformation. Molecular selection methods currently allow an efficient genetic management for purebred dogs, using direct or indirect – linkage DNA-tests. However, it is true only for a minor part, at present approximately for 70 of the known genetic defects in dogs. Nowadays, reputable breeders screen their breeding stock, primarily their sires for common inherited diseases.

DNA-tests for endocrine disorders

The only DNA-tests available for endocrine disorders at this stage are tests for:

-Congenital Hypothyroidism with Goiter (CHG): In Rat Terrier and Toy Fox Terrier (it is a direct DNA-test, Michigan State, U. Fyfe Lab, PennGen, HealthGene).

-Primary Hyperparathyroidism: In Keeshond, (it is a direct DNA-test, Cornell U – Goldstein Lab.)

As there are no DNA tests available for the endocrine disorders in the Miniature Schnauzer, other protocols should be used to prevent further deleterious breeding.

Keeping the inbreeding coefficient as low as possible is one possibility; meaning one should only breed animals that is no closer related than cousins are.

Another is to constantly move away from families known for possessing deleterious genes.

5. Summary

I have studied general endocrinology in several textbooks, read scientific papers and studies done on genetics on its own and in connection with endocrinology, I have also looked at books, and the English kennel club webpage to learn more about the Miniature Schnauzer as a breed.
Here I have listed the nine endocrine disorders that are believed to have a genetic background. The first four on the list have a high frequency in the Miniature Schnauzer.

Diabetes mellitus is the most prevalent endocrine disorder in the Miniature Schnauzer. The disease usually occur at the age of 4-14 years. The high prevalence indicate a genetic background.
Two immune response genes, the genes coding for the "Dog Leucocyte Antigen" and the "Cytotoxic T-Lymphocyte antigen 4" has been connected to diabetes mellitus, suggesting there is a genetic origin of diabetes mellitus. There are no DNA-test available.

Hypothyroidism does also show a high prevalence in the Miniature Schnauzer, this disease is likely to be immune mediated as well. According the investigation done by L. J. Kennedy in 2006, there is a connection between the "dog Leucocyte Antigen" and hypothyroidism as well as in diabetes mellitus and DLA, indicating there is a genetic background. DNA-tests are only available for Rat terriers and Toy fox terriers.

Hyperadrenocorticism (Cushing's syndrome), there is a clear predisposition in the Miniature Schnauzer although there has not been done any genetic studies, and further there are no DNA-tests available. Breeding of affected animals should be prevented, but it is not easy as the animals usually are diagnosed at a high age.

Hyperlipidaemia is a primary lipid disorder with high incidence the Miniature schnauzers. Research has been done to reveal the gene causing this disorder, but all research has failed this far, consequently there are no DNA-test available.

Hypoadrenocorticism (Addison's disease) is predisposed in more than 30 different breeds, including the Miniature Schnauzer. The disease is well documented, but the mode of inheritance is unclear.

Growth-hormone responsive dermatosis and **Adrenal sex-hormone dermatoses** are both endocrine disorders frequently seen in particular breeds, for example chow Chows, Pomeranian and Keeshonds. However, there are not done any genetic investigation.

Primary hyperparathyroidism is seen in several breeds. In the Keeshond it is transmitted as a dominant trait. There is DNA-tests available for this disease in Keeshonds.

Pituitary dwarfism (hypopituitarism) is a simple, autosomal recessive inherited anomaly in the German Shepherd Dog. The disease is usually seen before sexual maturity and the related individuals should not be bred. There are no DNA-test available yet.

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