THESIS

Elsa Similowski

2023

UNIVERSITY OF VETERINARY MEDICINE BUDAPEST
DEPARTMENT OF PATHOLOGY

Classification of main diseases in pet rats

Elsa Similowski

Supervisors:
Dr. Szilasi Anna, Senior lecturer
Pr. Mandóki Míra, Professor and head of department
Department of Pathology

2023

Table of content

List of abbreviations

A: adenoma

AFRMA: American Fancy Rat and Mouse Association

BMGT: benign mammary gland tumor

C: canine

CA: cystadenoma

CPN: chronic progressine nephrosis

CRD: chronic respiratory disease

CT: computed tomography

FA: fibroadenoma

FS: fibrosarcoma

I: incisor

M: molar

MG: mammary gland

MGF: mammary gland fibroma

MGT: mammary gland tumor

MMGT: malignant mammary gland tumor

MRI: magnetic resonance imaging

MRM: murine respiratory mycoplasmosis

Neuro: neurological

NFRS: National Fancy Rat Society

NMGT: non-mammary gland tumor

PCR: polymerase chain reaction

PGT: pituitary gland tumor

PM: premolar

PODO: pododermatitis

SD: standard deviation

SDAV: sialodacryoadenitis virus

Spp.: species

UTI: urinary tract infection

UV: ultraviolet

UVMB: University of Veterinary Medicine Budapest

WL: weight loss

ZGT: Zymbal's gland tumor

1. Introduction and aims

Fancy rats (*Rattus norvegicus domestica*) are more and more frequent patients of veterinary practices in Europe. Indeed, their calm and gentle nature make them easy to handle, hence very good pets. Intelligent and playful, they can be trained to perform tasks and easily live in large groups, as they are very social [1, 2].

While rats have been domesticated since the eighteenth century, their breeding and promotion significantly grew from the late twentieth century. In the United Kingdom, the National Fancy Rat Society (NFRS, created in 1976), and in the United States of America, the American Fancy Rat and Mouse Association (AFRMA, created in 1983) promote rats as pets and help breeders expose their work [2–4]. Currently, seven varieties are recognized, and a wide variety of coat colors is available, offering a large choice to new owners. The use of rats in research increased exponentially from the early twentieth century. They are nowadays the model of choice in toxicology and psychology research. In certain cases, some rats may be adopted as pets after studies are completed [2]. A growing importance of rat rescues further increases the number of potential rat patients for veterinarians.

As rats have been used in laboratories for decades, a fair knowledge of their diseases has been documented. Nevertheless, fancy rat strains differ greatly from laboratory ones. Lab rats are highly selected while fancy rat genetic pool is more diverse, even more because of the increasing number of rescued rats with unknown origin. Furthermore, rats kept in laboratories are exposed to a very controlled environment with strict hygiene standards that highly differ from pet stores, fancy rat hobbyist breeding facilities and owner's homes.

Currently, the scientific literature on pet rats' diseases is scarce and often based on laboratory books. In Europe, while veterinarians who specialized in exotic animals medicine have basic knowledge about rat clinical examination, little is taught about their specific pathologies. Thus, enriching the knowledge about the most common diseases of pet rats seems necessary. On the other hand, pet rats often hide their illness, making it very difficult for the owners to detect them in good time. Therefore, more knowledge about pet rats' most common illnesses would help educate the owners to recognize diseases at an early stage.

This study aims to offer a classification of pet rats' main diseases for both the use of veterinarians and owners.

Additionally, an ancillary study aims to enrich data about rat mammary gland tumors (MGT), one of the main pathologies in geriatric rats [1, 5]. Histopathology on excised tumors being very seldomly performed in pet rats, the goal of this side study is to establish how the histologically determined tumor type and the veterinarian diagnosis match.

2. Literature review

2.1. Rat domestication and uses

The domestication of rats started in the 1800s, with the sport of "rat baiting", particularly popular in England and France [6]. Modern domesticated rats are derived from the Norway rat (*Rattus norvegicus*) and are used in laboratories, as working animals, as feeder animals, and they also make excellent pets [2].

2.1.1. Rats in research

Rats, along with mice, have been one of the most commonly used laboratory species since the late 1940s. They have been the first mammalian species specifically bred for biological experimentation. Their relative large size for rodents allows researchers to perform many procedures that are more difficult in mice [6]. The use of rats in research, and in particular albino rats, has been increasing since the beginning of the 20th century [2]. Currently, three main strains are used in laboratories: Wistar, Fisher344 and Sprague-Dawley, and many strains exist to study specific diseases. They are the model of choice in oncology, toxicology and immunology studies, and their use continue to increase with specific genetic engineering technologies research.

2.1.2. Rats as working animals

Because of their highly sensitive and discriminatory olfactory system, rats may be useful in narcotics or explosives detection. Otto *et al.* (2002) describe them as good alternatives for working dogs, as their small size allow them to infiltrate areas that dogs cannot reach. They are also less disturbed by presence of humans, reducing the dependency to the handler, and making them able to maintain performance longer during repetitive work. Furthermore, they are inexpensive and easy to train with computer-based methods [7]. Giant pouched Gambian rats (*Cricetomys gambianis*), while belonging to a different genus from *Rattus norvegicus*, are used for explosives and human tuberculosis detection [2, 8, 9].

2.1.3. Rats as feeder animals

Rats can be bred in massive scale (tens of thousands) for feeding captive reptiles, birds and small carnivores. In those breeding facilities, less attention is paid to environmental hygiene and general care management. Hence, disease spreading and mortality rate are higher than accepted for laboratory and fancy rats breeding [2].

2.1.4. Rats as pets

In the early 1840s, the spreading of wild rat population in England led to the new profession of rat catcher. Jack Black was the royal rat catcher of Elisabeth I and can be credited for the

first true pet rats. During the course of his work, he kept and bred rats presenting an unusual colour coat and started selling the very first fancy rats in London [10].

Fancy rats are very intelligent and playful animals, making them trainable and very enjoyable pets. Their relatively large size for rodents makes them easy to handle. They are very gentle and calm, thus safe to keep around children. They are also easy to maintain [2]. After decades of domestication, the fancy rat is still a quite atypical pet, but is becoming more and more popular. Nowadays, they come from pet shops, local fancy rat hobbyists, rescue facilities, and even laboratories. This diversity of sources and housing methods must be considered by owners, keepers and veterinarians [1, 2].

2.2. Important biological features

Rats present several physiological particularities that need to be addressed to better understand them as pets and as patients.

2.2.1. Life-span

Rats have a short-life span of 24 to 36 months, with an average of 24 months [1]. Thus, they become geriatric patients quite early. There is no current consensus on rat “old age”. In the literature, they can be referred as geriatric from the age of 12, 24 or 30 months [5, 11–13].

2.2.2. Behavioral considerations

Rats are social and communal animals. They need to be kept at least by pairs, and isolated rats exhibit depressive and stereotypical behavior, as well as reduced immunity [14]. They are nocturnal and playful animals, which must be taken into consideration by the owners.

2.2.3. Integument and thermoregulation

Rats don’t have sweat glands, and thermoregulation occurs through the ears and the tail. Their normal body temperature is 37.7°C. Special attention should be paid to naked rats, especially susceptible to hypothermia [1].

2.2.4. Gastrointestinal system

2.2.4.1. Teeth and dental health

Rats have a total of 16 teeth (dental formula I 1/1, C 0/0, PM 0/0, M 3/3), with an orange-to-yellow enamel. While their cheek teeth are *brachydont* and stop growing after eruption (*anelodont*), their incisors are *hypsodont* and grow continuously throughout their life (*elodont*). Rats exert bruxism, grinding their incisors together by lateral movements of the jaw, filing them down. During this process, physiological ocular bulging might happen. Abnormal incisor growth can lead to malocclusion and malnutrition, which makes a regular oral cavity examination essential by the owners, keepers and veterinarians [1, 15].

2.2.4.2. Stomach and nutrition

Rats are monogastric and omnivorous animals. Adults eat 20% of their body weight daily [16]. Their stomach presents a non-glandular part separated from the glandular stomach by a *margo plicatus*. Their stomach is empty after six hours without food, and in underfed rats, hyperkeratosis and bacterial overgrowth can occur on the non-glandular area [15]. Proper diet, regular to *ad libitum* feeding and *ad libitum* water access should be applied.

Because of their strong oesophageal cardiac sphincter, reduced diaphragmatic muscularity, and absence of emetic centres in the brainstem, rats are unable to vomit [1, 2, 15]. Particular attention should be paid to ingestion of foreign material.

In rats, coprophagy is physiological, but can also be the first sign of fibres deficiency [16].

2.2.5. Urogenital and reproductive systems

Rats are weaned at 21 days of age and reach puberty around day 50 ($\pm$10). Individuals should be separated by sex to avoid unwanted litters. Sex determination can be challenging in young rats. The anogenital distance method, greater in males than in females, should be applied [1]. Male rats present a penile bone (*baculum*) and can retract their testicles into their abdomen during fights. Because of their tendency to fight more than females for hierarchy, male rats should be checked regularly for fight wounds by the owners.

In females, the urinary and reproductive tracts terminate in separate external urethral and vaginal orifices, which can easily be checked with visual examination. Female rats have a duplex uterus and exert four-to-five-day-long estrus cycles [17]. Prolonged estrus cycles and high estrogen levels in aging intact female rats increase the risk of uterine tumors and mammary gland tumors (MGT) [5, 15, 18]. Uterine tumors can manifest by bloody vaginal discharge, making a regular checking of intact female's genital area particularly relevant.

Rats present an extensive mammary tissue, with 6 pairs of mammary glands (MG) (3 thoracic, 1 abdominal, 2 inguinal). Hence, MGT can develop from the neck to the perianal region [1, 5]. Regular extensive palpation of the mammary tissue is thus recommended.

2.2.6. Sensory organs

2.2.6.1. Eyes and Harderian glands

Rats' eyes are naturally exophthalmic, which increases the risk of injuries or drying out. Rats' vision is binocular and dichromatic, and their eyesight is relatively poor [1, 15, 17]. Thus, they rely more on facial vibrissae and smell for sensory input. To adjust their depth perception, they may exert lateral horizontal movements of the head [19]. Nocturnal and burrowing animals, rats tend to prefer low-light environments and like to hide. Red-eyed rats

are particularly sensitive to light (phototoxicity) [6, 17], but all rats should be provided with hiding areas in their cage and not be exposed to bright light.

Rats have Harderian glands, located in the caudomedial aspect of their orbit. They secrete a porphyrin-containing substance, often referred as “read tears” or chromodacryorrhea, that helps with corneal lubrication [1, 15, 17]. It also contains lipids that act as pheromones [15]. It can be differentiated from blood as it is fluorescent if exposed to ultraviolet (UV) light. It is usually noticed by the owners during illness or stress, during which the secreted amount increases [1, 15, 17].

2.2.6.2. Olfactory organs

Rats have a very well developed sense of smell, on which they rely heavily for sensory input [1, 6, 17]. Their olfactory system is highly sensitive, and rats are sometimes used for their discriminative smell (see 2.1.2). Rats have a well-developed vomeronasal (Jacobson’s) organ, critical for many pheromone responses [6, 17]. Rats recognize the social status of other rats, estrus in females, and kinship by olfaction [6].

2.2.6.3. Facial vibrissae

Rats rely heavily on touch for sensory input. Their whiskers are highly sensitive (trigeminal innervation) and involved in navigation and balance [17].

2.2.6.4. Hearing and Zymbal’s glands

Rats hearing range from 25Hz to 80kHz at 70dB [6, 17, 19]. They can hear, vocalize and communicate with ultrasounds (> 20kHz) [6, 19]. Studies show that such vocalizations can be triggered by tickling them, which enhances welfare of laboratory rats [20, 21]. Those ultrasonic vocalizations may also indicate negative affect, and have different meanings at different frequencies [19]. Rats can recognize human voices and pet rats can respond to verbal commands [19].

Rats have unique auditory modified sebaceous (holocrine) glands called Zymbal’s glands. They are located within the epithelium of the external ear canal, ventrolaterally [1, 15, 17] and secrete the human-equivalent of cerumen. Those glands are susceptible for tumors [22], making them a great interest of toxicologists in research. In pet rats, Zymbal’s gland tumors (ZGT) should be included in the differential diagnosis when owners report a swelling at the base of the ear, often accompanied with a head tilt.

2.2.7. Respiratory system

Rats are obligatory nasal breathers, with a respiratory rate between 70 and 150 breaths per minute for an adult rat [1]. Their lungs are immature at birth and remodeling occurs around 4–7 days of age, making them particularly sensitive to respiratory insult, even at young age.

The left lung has one lobe, while the right is divided into four lobes (cranial, middle, accessory, caudal). Rats pulmonary veins are thicker and wider than in most species, increasing the risk for infectious agents to spread from the heart to the lungs [17].

Particular attention should be spent on dust and ammonia levels of the cage. Rats tend to mark their territory with urine, quickly increasing the ammonia level of their environment. Owners can be advised to use dust-free litters, regularly clean their cage with non-irritant products and ensure a good ventilation of the room where the rats are kept.

2.2.8. Cardiovascular system

Heart rate in rats is very high (250–450 beats per minute) and usually can't be counted. Because of their small size, blood collection can be risky. Blood sampling can be performed from the lateral saphenous, femoral, jugular, lateral tail veins, cranial vena cava, and tail arteries (dorsal and ventral), usually under general anesthesia. Orbital plexus collection is performed in laboratory rats but not recommended in pet rats [1]. Mean flow rate differs from contralateral arteries, which should be taken into consideration when assessing femoral pulse in rats [17].

2.2.9. Skeletal system

Rat bone maturation is slower than in most mammals, with an incomplete ossification of long bones until 12 months of age, which is already half of their average lifespan. Bone mineral density is higher in twelve-month-old rats than in six- and twenty-month-old rats [17]. These considerations are important in examining rats for traumatic injuries and potential joint diseases.

Rats' vertebral column includes 7 cervical, 13 thoracic, 6 lumbar and 4 sacral vertebrae, and a particularly long tail (27–30 caudal vertebrae) helping them to balance themselves while climbing [17, 23]. Rats should not be picked up by the tail but grabbed gently around the thorax [24]. Grabbing them by the tip of their tail can induce degloving injuries and hanging them using the base of the tail is particularly stressful and potentially painful [17, 24]. Traumatic injuries assessment should include a particular attention to the tail in rats.

2.3. Current literature on rat diseases

As rats have been the model of choice in research for decades (see 2.1.1), a good variety of laboratory and pathology books provide detailed information on the anatomy, histology and main diseases of laboratory rats (mainly Sprague-Dawley, Fisher 344 and Wistar strains).

For instance, Sharp and Villano (2012) and Otto *et al.* (2015) offer a detailed list of the pathogens affecting laboratory rats, as well as non-infectious diseases, neoplasms, and other miscellaneous conditions. Suttie (2015) provides a very detailed approach to the rat

pathology and Maynard and Downes (2019) recently published a complete and well-illustrated book on rat anatomy and histology. Other excellent books are available.

When it comes to veterinary clinical books for pet rats, literature is more scarce, and rarely focused on rats. Among pet small mammals, rabbits, guinea pigs, ferrets and hamsters are more common, and more literature is available for those species.

Among veterinary books covering companion rats, Mayer and Donnelli (2013) and Frohlich (2020) dedicate a section to rat diseases [1, 15]. Turner *et al.* (2018) also offers a section on pet rat pathology [2]. Those books also refer greatly to laboratory rat literature, even though pet rats differ from laboratory rats both through breeding but also through husbandry conditions. Minh *et al*. (2019) offer a very useful guide of the most frequent cases for small mammal pets, including for pet rats, based on clinical experience.

Based on those books, it seems relevant to approach pet rat ailments by systems and neoplastic diseases.

2.3.1. Ocular conditions

Rats' Harderian glands, located caudally from their eyes, produce a porphyrin-containing secretion, helping with the corneal lubrication (see 2.2.6.1). When this secretion is increased, it results in "red tears" or chromodacryorrhea. In their books, Mayer and Donelly (2013) and Frohlich (2020) dedicate a section to chromodacryorrhea in rats, which is a common presentation in rat patients. The owners often describe "bleeding" or red-to-brown staining around the eyes and nostrils, possibly with lethargy and decreased appetite. Red tears can be the sign of Harderian gland inflammation (dacroadenitis) caused by the sialodacryoadenitis virus (SDAV), a coronavirus of rats [15], but are most often a manifestation of chronic stress and/or a chronic underlying disease [1, 15]. Affected rats should be thoroughly examined by the treating veterinarian. Note that red tears are fluorescent if exposed to UV light and hence can be easily differentiated from blood with Wood's lamp examination. Therapeutic goal in case of chromodacryorrhea is to identify and treat the underlying disease, support the immune system, while insureing a proper husbandry [15].

2.3.2. Orodontal diseases

Rats have ever-growing (*elodont*) incisors and regularly fill them down through bruxism (see 2.2.4.1). Incisor overgrowth and malocclusion is described as the main and most common oral abnormalities of rats by Frohlich (2020) and Turner *et al.* (2017). It is more common in older rats, in which the incisors are becoming thicker. Treatment involves regular trimming by the veterinarian, using a dental drill under sedation or anesthesia to minimize

stress and prevent patient injury. Trimming using nail clippers (as in mice) is not recommended for rats, as their incisors are thicker and more susceptible to fractures [1].
Occasional incisor and mandibular fractures following trauma and cheek teeth periapical abscesses are described by Turner *et al.* (2017). Orodontal tumors are very rare in rats [2].

2.3.3. Auricular diseases

In rats, auricular diseases mostly include *otitis media* caused by *Mycoplasma* species (*spp*.), *otitis externa* due to ear mites (*Notoedres muris*) and Zymbal's gland tumors [2, 25].
Rats with *otitis media* usually present with a head tilt and purulent odorous discharge from the ear. Many pathogens can lead to otitis in rats, but *Mycoplasma* is most often suspected [25]. Treatment includes meloxicam, coupled to an antibiotic indicated against *Mycoplasma spp*., such as doxycycline or enrofloxacin. If left untreated, *otitis media* can lead to a peripheral vestibular syndrome (dizziness, disorientation).
Notoedres muris, a burrowing mite, usually causes head tilt, head shaking and ear pinnae injury, due to the frequent and intensive scratching. Application of local anti-parasitic agents in rats should be done with caution as the epithelium of the ear canal is very thin [25].
Zymbal gland's tumors should be considered in case of facial swelling (see 2.3.9.3).
In patients presenting with a head tilt with or without vestibular syndrome, special attention should be given to the ears' examination, including smelling and palpation of the area. Evaluation of the ear canal can be performed under sedation or anesthesia. Note that vestibular syndrome can also be the manifestation of pituitary gland tumors (PGT) (see 2.3.9.2), that should be considered in the differential diagnosis.

2.3.4. Respiratory diseases

Respiratory diseases caused by infectious agents are presented as the most common health problem in laboratory rats by Graham and Schoeb (2011), Fouriez-Lablée *et al.* (2017) and Frohlich (2020). *Mycoplasma pulmonis, Streptoccocus pneumoniae* and *Corynebacterium kutscheri* are the major respiratory pathogens in rats. Other organisms such as Sendai virus (paramyxovirus), *Pneumocystis carinii* (a fungus), cilia-associated bacillus, and *Haemophilus spp*. are minor respiratory pathogens of rats that usually cause clinical disease synergistically as copathogens. Those pathogens cause two main major clinical syndromes: bacterial pneumonia and chronic respiratory disease (CRD).

2.3.4.1. Acute respiratory tract disease – bacterial pneumonia

Acute bacterial pneumonia in rats is mostly caused by *Streptococcus pneumoniae* and/or *Corynebacterium kutscheri* [18, 25–28]. Rats with bacterial pneumonia eventually display dyspnea [18, 26, 29], which is the most common emergency presentation for rats [29].

After stabilization (involving oxygen therapy, saline nebulization, fluid therapy and eventual sedation), thoracic radiographs most often reveal pulmonary nodules and alveolar pattern due to abscesses [26, 29]. Due to the small patient size, assessment of the pulmonary lesions' severity is particularly challenging in rats. Three-view thoracic radiographs (two latero-lateral and one dorsoventral view) are recommended to better determine the location and extend of the lesions [26]. Young rats are more severely affected than older ones, and they might suffer sudden death [1].

Treatment of bacterial pneumonia in rats involves antibiotics such as doxycycline, enrofloxacin or azithromycin [1, 18, 29], bronchodilators and nebulization (0.9% saline) if tolerated by the patient. Note that enrofloxacin and doxycycline have been widely used in exotic medicine in Europe, and bacterial resistance should be considered. Performing a bacterial culture with antibiotic resistance test should be recommended to the owners.

2.3.4.2. Chronic respiratory tract disease - CRD

Chronic respiratory disease (CRD) is described as the best-understood multifactorial respiratory infection in rats by Frohlich (2020). CRD is primarily caused by *Mycoplasma pulmonis* and the disease is also referred as murine respiratory mycoplasmosis (MRM). Most rats are thought to be carrier of the pathogen [26, 30], which, in association with concurrent infections (cilia-associated respiratory bacillus, Sendai virus), causes chronic bronchitis and bronchiectasis [2, 15]. Immunodepression, stress, elevated ammonia levels, vitamin A or E deficiency, and obesity are the main predisposing factors for CRD in rats [31]. Owners report red tears (see 2.3.1), sneezing, nasal discharge in the early stages of the disease. Later on, the affected rats exert labored breathing, lethargy, weight loss, sometimes with a head tilt. As *Mycoplasma* species culture is difficult, PCR is recommended to confirm mycoplasmosis. Assessing the severity of the lesions is even more challenging in CRD than bacterial pneumonia through thoracic radiographs. In those patients, computed tomography (CT) would be the best diagnostic imaging method [1, 31]. The prevalence and severity of clinical signs increase with the age of the patient [1, 31]. Rats with CRD can hide their symptoms for months and live with the disease for years [1]. Correlation between the extension of the pulmonary lesions and the severity of the clinical signs in rats with CRD has not yet been studied to the best of our knowledge.

CRD treatment includes systemic antibiotics (such as doxycycline or azithromycin), immunostimulants and regular nebulization (0.9% or 7% saline), with bronchodilators and glucocorticoids (dexamethasone) if needed [1, 31]. Note that glucocorticoids should only be used locally through inhalation to avoid immunosuppression in those patients. Prognosis is

very variable and depends on many factors, but clinical signs can be significantly improved with the proper antibiotic and supportive care [31].

2.3.5. Gastrointestinal diseases

Sialodacryoadenitis virus (SDAV, coronavirus) is causing rhinitis followed by inflammation of the cervical salivary glands and lacrimal glands [1, 2]. Owners might refer at their rats having mumps, due to the enlarged salivary glands. Because of the lacrimal dysfunction, ocular lesions such as conjunctivitis, keratitis, corneal ulcers are also observable [1]. There is currently no treatment for this disease.

Rats are susceptible for pinworm infections such as *Syphacia muris*, *Syphacia obvelata* and *Aspiculuris tetrapetra.* Affected rats are mostly asymptomatic, but may exert tail base mutilation due to perianal pruritus [1, 31]. Treatment consists of deworming (with ivermectin, fenbendazole or levamisole) and decontamination of the environment [1].

2.3.6. Urinary diseases

Chronic progressive nephrosis (CPN) is one of the most common cause of death in older laboratory rats [12, 32]. CPN occurs earlier and with greater severity in males than females. High-protein diet results in earlier onset of more severe disease. Signs include polyuria/polydipsia, lethargy, weight loss, proteinuria, and azotemia. Kidneys of affected rats are enlarged, pale, with mottled surface and pinpoint cysts [1, 31, 32]. Supportive care, caloric restriction, low-protein diet (10–14%) and anabolic steroids help managing the disease [1, 12].

Nephrocalcinosis is occasionally observed in laboratory rats. The disease is more common in females and can occur very early (from 7 weeks of age). Kidney's lesions mostly include calcium-phosphate deposits at the corticomedullary junction. Diet imbalance (high calcium or phosphorus, low magnesium) seems to be the primary cause, but estrogen levels may also play a role in the pathogenesis. In females, early ovariectomy seems to prevent the disease.

Pyelonephritis is also described in laboratory rats. It is caused by various Gram-negative bacteria (e.g *Pseudomonas spp., Escherichia coli, Proteus mirabilis*), which usually ascend from the lower urinary tract.

Urolithiasis and renolithiasis are relatively rare in rats, especially compared to guinea pigs, rabbits and chinchillas.

2.3.7. Musculoskeletal and peripheral nervous system diseases

Disturbances in motor function, hindlimb paresis and paralysis, loss of tail control are common presentations of old rats [1]. Differential diagnosis includes age-related nervous system changes, neurogenic muscular atrophy, and primary muscle changes. Distinction

between the three is very difficult. Ideally, ultrasonography, electromyography and blood work should be performed for a definite diagnosis.

Hind limb paresis, also called (poly)radiculoneuropathy or degenerative myelopathy is usually caused by spinal nerve root degeneration at the level of the lumbosacral plexus, accompanied with neurogenic muscular atrophy [1, 12]. The incidence in rats over 24 months old may be as high as 75% to 90%. Treatment with B complex (B1, B6, B12) and meloxicam appears to decrease the symptoms [12]. Physiotherapy might be recommended and consists of gentle mobilization of the hip and stifle joints with massage of the distal limbs and spinal muscles. Rats with hind limb paresis usually maintain a good quality of life for months.

2.3.8. Integument conditions

Skin and tail diseases in rats are quite common and include self-traumatic injuries due to ectoparasites, bacterial (ulcerative) dermatitis, abscesses and ringtail [1, 31].

Ectoparasitic infestation is more common in rats than mice and is mostly caused by the rat fur mite (*Radforida ensifera*), the tropical rat mite (*Ornithonyssus bacoti*), the rat ear mite (*Notoedres muris*, see 2.3.3) and blood sucking lice (*Polyplax serrata, P. spinolosa*). Occasionally, rats can get infested with sarcoptic mites (e.g *Sarcoptes scabei, S. ananthos* and *Trixacarus diversus*), and rarely with demodectic mites (*Demodex ratti, D. norvegicus, D. ratticola*). All ectoparasitic infections can lead to self-mutilation and secondary bacterial infections, and severe infestation can lead to anemia and death in rodents [1, 31]. Ivermectin or selamectin are indicated to treat the affected rats [1], and supportive care with vitamin B12 injection might be indicated in case of anemia.

Ulcerative dermatitis caused by *Staphylococcus aureus* is usually secondary to self-trauma due to pruritus from mites, pain from SDAV infection (see 2.3.5), or fight wounds. Treatment consists of clipping the toenails, cleaning the skin and applying an antibiotic ointment [1]. In case of fight wounds, it might be recommended to isolate the injured patient from the cage mates until resolution of the skin lesions. Isolated patients shoud be monitored for stereotypical behavior and signs of depression (see 2.2.2).

Abscesses are quite common in rats, especially after fight and bite wounds. Causative agents include *Staphylococcus spp*., *Streptococcus spp*., *Pasteurella pneumotropica* and *Actinomyces bovis* [31]. Opening and flushing the abscess capsule with secondary intention healing is usually enough for abscess management. Rats' healing capacity is quite remarkable and open wounds usually close in a few days if kept clean.

Ringtail is a condition occurring in preweaned rats (2 to 19 days old), characterized by dry skin and formation of annular constrictions on the tail. Relative low humidity seems to be the primary cause. In severe cases, distal blood vessels constriction leads to thrombosis, pain, necrosis and sometimes autoamputation. It is rarely seen in pet rats, but if diagnosed, it can be managed by unsaturated fatty acids supplementation to the diet and topical application of lanolin. If necrosis occurs, amputation proximal to the lesion should be performed [1, 31].
Tail degloving in rats can occur in case of improper handling, holding adult rats by the tail.
Dermatophytosis, or ringworm, caused by *Microsporum spp*. and *Trichophyton mentagrophytes* is not commonly seen in pet rats. Subclinical infection can occur and the condition manifests with immunosuppression or stress [2]. If dermatophytosis is diagnosed by clinicians, owners should be warned that this disease is zoonotic.

2.3.9. Neoplastic diseases

Rats are prone to tumors and have been used as models in oncology research for decades (see 2.1.1). In laboratory rats, most non-induced tumors are reported in rats older than 18 months of age. The most frequent tumors in laboratory rats are mammary gland tumors and pituitary gland tumors.

2.3.9.1. Mammary gland tumors

Mammary gland tumors (MGT) are the most common spontaneous subcutaneous tumors of rats [1, 5, 31], with an incidence as high as 67% in female Sprague-Dawley rats [5, 6, 33]. They are more common in females than males. Because of their extensive mammary tissue, rats can develop MGT from the cervical to the perianal region (see 2.2.5) and can significantly impair the patient's locomotion. They can become very large and ulcerate, predisposing to secondary bacterial infection [33]. The large majority of MGT in rats are benign fibroadenoma, but adenocarcinomas can occur. Females tend to develop benign forms, while malignant MGT are more frequent in males [2]. In laboratory rats, benign fibroadenoma represent 90% of MGT of females [33]. For that reason, not all veterinarians recommend histopathological analysis of subcutaneous masses after removal. Nevertheless, in a retrospective study on 100 companion rats, Vergneau-Grosset *et al.* (2016) identified, that 25% of subcutaneous masses in rats were malignant. Thus, histology of excised masses should be systematically offered to the owner.
After surgical excision, MGT reoccurrence is frequent within a few months [5]. Ovariohysterectomy concurrent with MGT excision in mature rats is suggested in literature, but the beneficial effects related to decreased estrogen levels late in the rat's life are

unknown [34]. However, it should be performed in case of suspicion of uterine lesions. Deslorelin implant post-MGT removal does not influence the recurrence rate of MGT [35]. Prevention of MGT is the current recommendation. In early ovariectomized rats (90 days old), MGT incidence is significantly decreased [5, 12, 36]. However, sterilization is recommended around 120 days old to decrease the risk of osteoporosis, as rats' bone maturation is slower than that of most mammals (see 2.2.9). Deslorelin implant to prevent MGT has not yet been studied.

Concurrent incidence of MGT and prolactin-secreting pituitary gland tumors suggests a possible link between the two tumor types, but no correlation has yet been established [33].

2.3.9.2. Pituitary gland tumors

Pituitary gland tumors (PGT) are common in rats [2, 18, 31, 33]. Most of PGT in rats are prolactin-secreting chromophobic adenomas and their incidence seems to be lower in ovariectomized rats [18, 33, 36]. Obesity, high-protein and high-fat diet are contributing factors to PGT development. Clinical signs include behavioral changes and central vestibular syndrome manifesting with a head tilt, ataxia, proprioception deficit, wide-based stance and abnormal gait [18, 33, 37]. MRI or computed tomography (CT) may identify pituitary enlargement. However, CT is preferred as the process is faster, reducing the anesthesia time. Treatment of PGT with a dopamine agonist such as cabergoline is suggested to reduce the symptoms [18, 36].

2.3.9.3. Zymbal's gland tumors

Rats possess modified sebaceous glands located in their external ear canal called Zymbal's glands (see 2.2.6.4). Zymbal's gland tumors (ZGT) are unique to rats and well described in the current literature. ZGT appear as firm subcutaneous masses ventrally from the ear and may be ulcerated. Affected rats usually present with a head tilt, head shaking and occasionally bleeding from the ear [1, 2]. Most ZGT are adenocarcinomas locally invasive, but slow to metastasize [1, 2, 23]. Because of their location and their malignant nature, they are almost impossible to excise safely and the prognosis is quite poor [1].

3. Materials and methods

3.1. Main study – Major chief complaints and diseases in rat patients

3.1.1. Database

The database used for this study was built from 1017 rat patient files, provided by Dr. Quinton, head of the Department of Exotic Medicine of the French Veterinary Hospital and Reference Clinic *Advetia*. The clientele and patient pool were mostly from Paris and its agglomeration. Data were collected following owner's name alphabetical order, allowing a random distribution of the patients between 2006 and 2021.

3.1.2. Variables

From the individual files, the patient name, age in months, sex, castration status, as well as the date of consultation, chief complaint, and final diagnosis were recorded into an excel file. As the age in months was often approximated by the owner or the veterinarian, age categories were created specifically for this study. As no consensus exists in the current literature on the definition of an old rat (see 2.2.1), categories were defined using different publications on aging-rats [1]. "Junior" rats were under 6 months old (<6) [11, 39, 40]. "Adult" rats were between 6 and 11 months old (6–11) [11, 13, 38]. "Senior" rats were between 12 and 23 months old (12–23) [12, 13, 41]. "Geriatric" rats were between 24 and 29 months old (24–29) [5, 39, 40]. "Geriatric+" rats were 30 months old and older (30+) [11, 38, 40]. Later on, junior and adult rats were regrouped into "young" rats, and geriatric and geriatric+ into "geriatric" rats.

3.1.3. Statistical analyses

3.1.3.1. Descriptive analysis

Descriptive analysis on the patient population was performed using Rstudio and Excel. Data were analyzed using the tables of the raw results and box-plots displaying the median (vertical line through the box), upper and lower quartiles (box borders), and the maximum and minimum (whiskers extremities). A violin-plot was also used to assess the frequency of each age group in the population (width of the curve at a given point).

3.1.3.2. Classification tree

A classification tree (conditional interference tree) was created using the function "*ctree*" from the "*partykit"* package of Rstudio. This method predicts an output or response variable using one or more dependent input variables or covariates [42]. In our study, the goal was to predict the variable "chief complaint" (output or response) using "sex" and "age category" of the patient (inputs or covariates).

In this way, by using the patient basic data (sex and age category), the veterinarian and the owner could know which main health problems (chief complaints) to expect.

Using permutation tests and the values of correlations, the program resampled the population using the sex and the age category, to explain the chief complaint in the best way possible. To do so, it selected the covariates with the strongest association to the chief complaint (lowest p-value) and split this covariate, creating a node seperating groups that were significantly different from each other at a threshold p-value below 0.001 (purposely set very low to optimize the separation). The process was repeated until no more split was necessary ($p \geq 0.001$). At the terminal nodes, the program displayed the chief complaint distribution in each group, using bar charts. This method allowed us to create patient groups characterized by their sex and age category and that had significantly different chief complaint profiles.

3.1.3.3. Double-level pie charts

In each group established with the classification tree based on the chief complaint (see 3.1.3.2), a disease profile was assessed using the disease diagnosed by the treating veterinarian. Those profiles were represented through double-level pie charts, displaying the distribution of the diseases (2nd level) in the main chief complaints (1st level).

3.2. Ancillary study – Histopathological analysis of mammary gland tumors

3.2.1. Tumor collection

Suspected mammary gland tumors surgically excised in rat patients from the French *Exotic Clinic* were collected by Dr. Bulliot. A total of 36 tumors coming from 20 pet rats were then fixated in 10% neutral-buffered formalin solution at room temperature for 24h, before being transported to Hungary. For each suspected tumor, the mass location, sex, castration status, age at surgery were recorded. The mass location included cervical, axillary, thoracic, ventral, laterodorsal and inguinal (Figure 1).

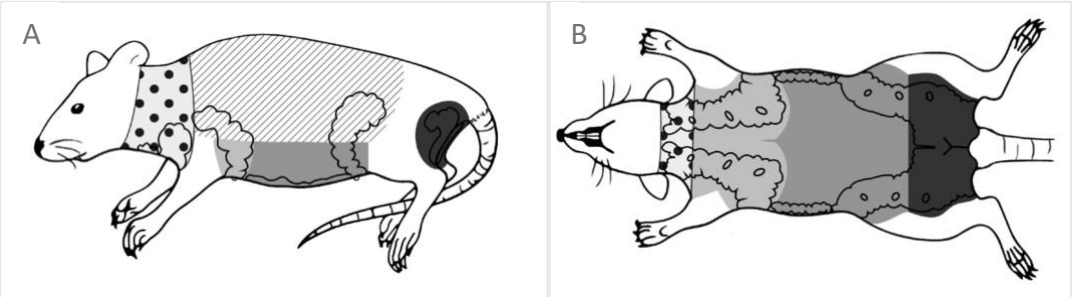

Figure 1 - Lateral (A) and ventral (B) distribution of rat mammary gland tissue
The different regions are marked as follow: Cervical (caudal to the mandible and cranial to the shoulder) with polka dots, axillary (caudal or medial to the elbow joint and cranial to the xiphoidal process) in light grey, laterodorsal (dorsal to the elbow and stifle joints with stripes, ventral (ventral portions of the thorax and abdomen not included in the axillary and inguinal location) in medium gray], and inguinal (caudal to the pelvis and cranial to the tail) in dark grey. (Copyright 2015 by Delphine Grosset. Reprinted with permission, [5])

3.2.2. Histopathology

Histopathological analysis was performed by the Department of Pathology of the University of Veterinary Medicine Budapest (UVMB). Excised tumors were embedded into a paraffin block and sections of 3–4 µm were performed using a microtome. Sections were then stained with hematoxylin and eosin (H&E). The slides were scanned, and representative images were taken (Pannoramic Midi II slide scanner; Case-Viewer software; 3DHistech, Budapest, Hungary). Tumor type evaluation and description were performed with the help of Dr. Szilasi, senior lecturer at UVMB.

4. Results

4.1. Main study – Major chief complaints and diseases in rat patients

4.1.1. Descriptive analysis

4.1.1.1. Yearly patient number

Between 2006 and 2021, a total of 1017 patients from Paris and its agglomeration were recorded in our database. The annual patient amount is displayed in Figure 2.

After 2007, a remarkable increase in rat patients' number could be associated with an increased popularity of pet rats after the release of the Disney animated movie "*Ratatouille*". Indeed, French pet stores reported a significant increase in pet rat sales that year, and pet rat sales doubled in the United Kingdom after the movie was released. [43, 44]

After 2015, the annual number of rat patients increased again, one year after the amusement park Disneyland Paris released the "*Remy's Ratatouille adventure*", an attraction offering the opportunity to experience how the rats view the world, through a 3D adventure [45].

During the past 3 years, with an average of 80 patients per year, exotic veterinarians from this clinic received around 6 rats per months, making rats relatively frequent patients.

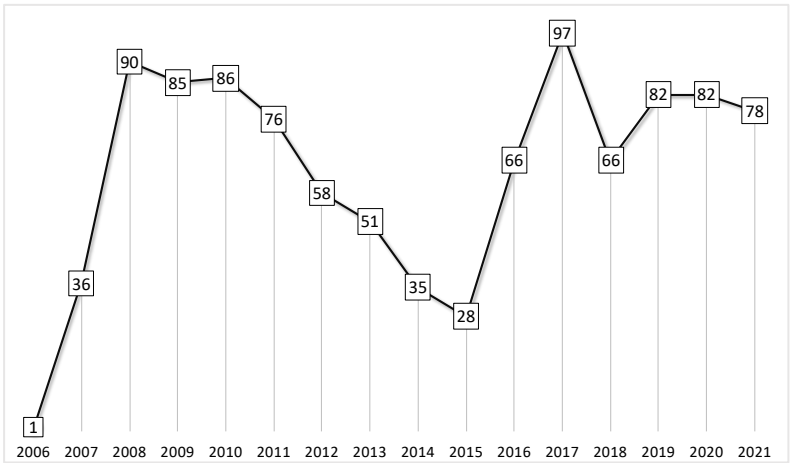

Figure 2 - Annual amount of recorded patients of the reference clinic for this study. At each point, the number displayed correspond to the annual patient amount for the given year.

4.1.1.2. Age distribution in the population

In the total population (n=1017), age ranged from 1 to 43 months old. The median age was 20 months and 50% of the population was between 13 and 25 months old (interquartile range 13–25) (Table 1, Figure 3A, 3B). Out of the 1017 patients, 93 were junior (9%), 102 were adult (10%), 442 were senior (43%), 251 were geriatric (25%), and 129 were geriatric+ (13%). Overall, 19% of the population were young patients (junior and adult), 43% were senior, and 38% were geriatric patients (geriatric and geriatric+).

Junior rats had a median age of 3 months (standard deviation (SD) 1.2), adults of 8 months (SD 1.7), senior of 18 months (SD 3.4), geriatric of 25 months (SD 1.7) and geriatric+ of 35 months (SD 2.9) (Table 1, Figure 3C).

Table 1 - Descriptive statistics of the total population per age category.
The range of each category is given in months.

	Junior (<6)	*Adult (6-11)*	*Senior (12-23)*	*Geriatric (24-29)*	*Geriatric+ (30+)*	*Grand Total*
n	93	102	442	251	129	1017
% total	9.1%	10.0%	43.5%	24.7%	12.7%	100%
Q1 (25% percentile)	2	7	15	24	32	13
Median	3	8	18	25	35	20
Q3 (75% percentile)	4	10	21	27	36	25
Minimum	1	6	12	24	30	1
Maximum	5	11	23	29	43	43
Range	4	5	11	5	13	42
Mean	2.8	8.1	17.8	25.7	34.5	19.5
Std. Deviation (SD)	1.2	1.7	3.4	1.7	2.9	9.2

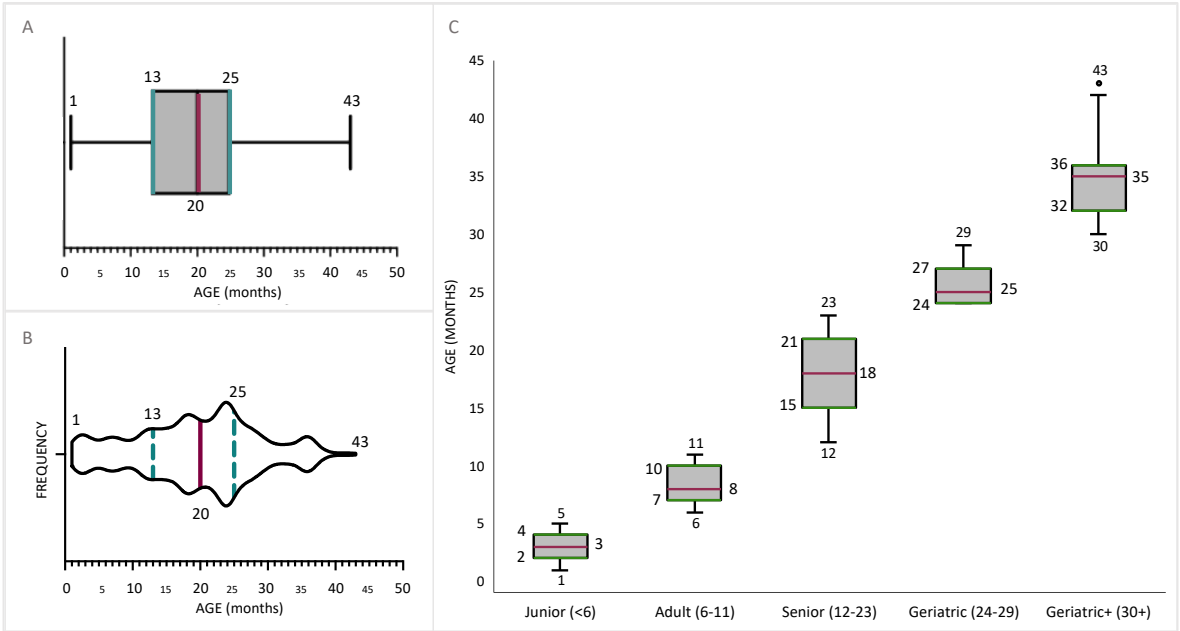

Figure 3 - Age distribution in the population (A, B) and in each age category (C).
The median is represented as a red line, the quartiles in green and the whiskers extremities correspond to the maximum and minimum. In figure 2B, the width of the curves is proportional to the frequency at each point.

4.1.1.3. Sex-ratio

The sex-ratio in the total population was of 0.9 with 46% of males for 54% of females.

In the different age categories, this sex-ratio was approximately maintained with 0.9 in the junior group, 0.8 in senior, geriatric and geriatric+ groups, except for the adult group that contained more males (60%) than females (40%) with a sex-ratio of 1.5 (Table 2, Figure 4).

Table 2 - Sex distribution and sex ratio in the population.
For each age category (months) and for the all population, the number (n) and percentage (%) of females (F) and males (M) is displayed. The sex-ratio was calculated dividing the number of males by the number of females (M:F).

	F		***M***		***Sex ratio***
Age category (months)	n	%	n	%	(M:F)
Junior (<6)	48	(51.6%)	45	(48.4%)	**0.9**
Adult (6-11)	41	(40.2%)	61	(59.8%)	**1.5**
Senior (12-23)	246	(55.7%)	196	(44.3%)	**0.8**
Geriatric (24-29)	143	(57.0%)	108	(43.0%)	**0.8**
Geriatric+ (30+)	71	(55.0%)	58	(45.0%)	**0.8**
Grand Total	**549**	**(54.0%)**	**468**	**(46.0%)**	**0.9**

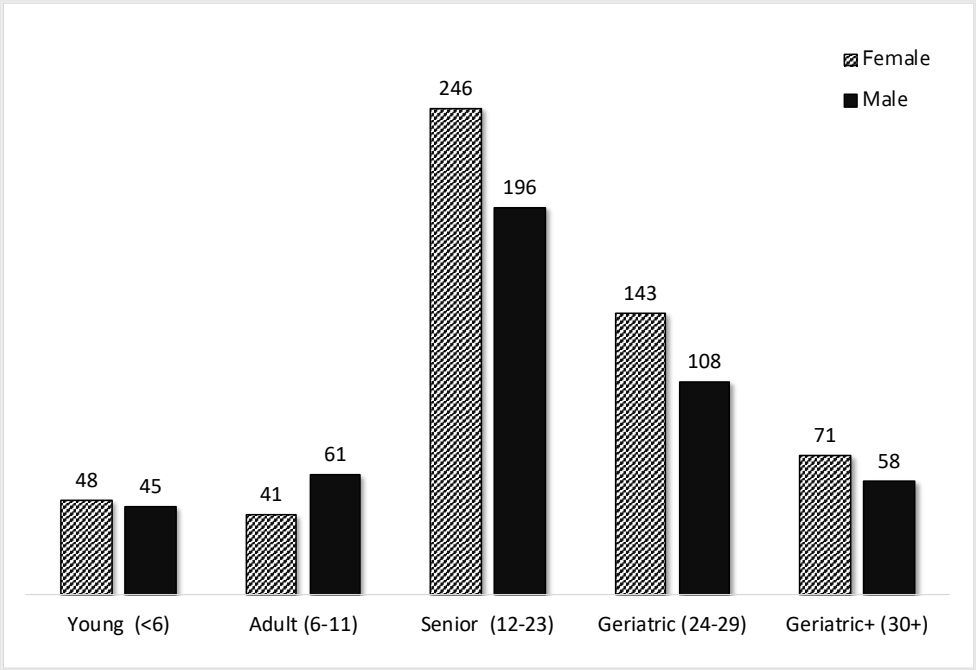

Figure 4 - Sex distribution in the different age categories.
The range of each age category is indicated in months. On top of each bar, the number of females and males in the given group is displayed.

4.1.1.4. Chief complaint distribution

Patients were categorized according to the chief complaint of the owner. Ten major chief complaints lead to a veterinary consultation in our population. Respiratory signs (Respiratory, 35.4%), masses (Mass, 21.0%), neurological signs (Neuro, 13.5%), and lameness (Lameness, 9.0%) were the main four chief complaints, with Respiratory and Mass representing more than 50% (56.4%) of consultations.

Other chief complaints included ophthalmological issues (Ophthalmo, 4.1%), skin and/or fur abnormalities (Skin-fur, 3.5%), urogenital issues (Urogenital, 3.4%), decreased activity (Apathy, 3.3%), appetite loss and/or weight loss (Anorexia-weight loss, 3.3%), and wounds (Wound, 3.2%) (Table 3, Figure 5).

Table 3 - Chief complaint distribution in the population and the different age categories. Each cell represent the number (n) and proportion (%) of patients belonging to a given age category (row) and presenting a given chief complaint (column). (WL: weight loss)

	Respiratory		Mass		Neuro		Lameness		Ophthalmo		Skin-fur		Urogenital		Anorexia-WL		Apathy		Wound	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Young (n=195)	**98**	**(27.2%)**	**20**	**(9.3%)**	**17**	**(12.4%)**	**13**	**(14.1%)**	**10**	**(23.8%)**	**11**	**(30.6%)**	**3**	**(8.6%)**	**2**	**(5.9%)**	**7**	**(20.6%)**	**14**	**(42.4%)**
Junior (n=93)	54	(15.0%)	6	(2.8%)	9	(6.6%)	7	(7.6%)	4	(9.5%)	2	(5.6%)	1	(2.9%)	2	(5.9%)	3	(8.8%)	5	(15.2%)
Adult (n=102)	44	(12.2%)	14	(6.5%)	8	(5.8%)	6	(6.5%)	6	(14.3%)	9	(25.0%)	2	(5.7%)			4	(11.8%)	9	(27.3%)
Senior (n=442)	**153**	**(42.5%)**	**100**	**(46.7%)**	**68**	**(49.6%)**	**28**	**(30.4%)**	**16**	**(38.1%)**	**17**	**(47.2%)**	**18**	**(51.4%)**	**7**	**(20.6%)**	**21**	**(61.8%)**	**14**	**(42.4%)**
Geriatric (n=380)	**109**	**(30.3%)**	**94**	**(43.9%)**	**52**	**(38.0%)**	**51**	**(55.4%)**	**16**	**(38.1%)**	**8**	**(22.2%)**	**14**	**(40.0%)**	**25**	**(73.5%)**	**6**	**(17.6%)**	**5**	**(15.2%)**
Geriatric (n=251)	74	(20.6%)	66	(30.8%)	38	(27.7%)	26	(28.3%)	10	(23.8%)	4	(11.1%)	9	(25.7%)	15	(44.1%)	5	(14.7%)	4	(12.1%)
Geriatric+ (n=129)	35	(9.7%)	28	(13.1%)	14	(10.2%)	25	(27.2%)	6	(14.3%)	4	(11.1%)	5	(14.3%)	10	(29.4%)	1	(2.9%)	1	(3.0%)
Total (n=1017)	**360**	**(35.4%)**	**214**	**(21.0%)**	**137**	**(13.5%)**	**92**	**(9.0%)**	**42**	**(4.1%)**	**36**	**(3.5%)**	**35**	**(3.4%)**	**34**	**(3.3%)**	**34**	**(3.3%)**	**33**	**(3.2%)**

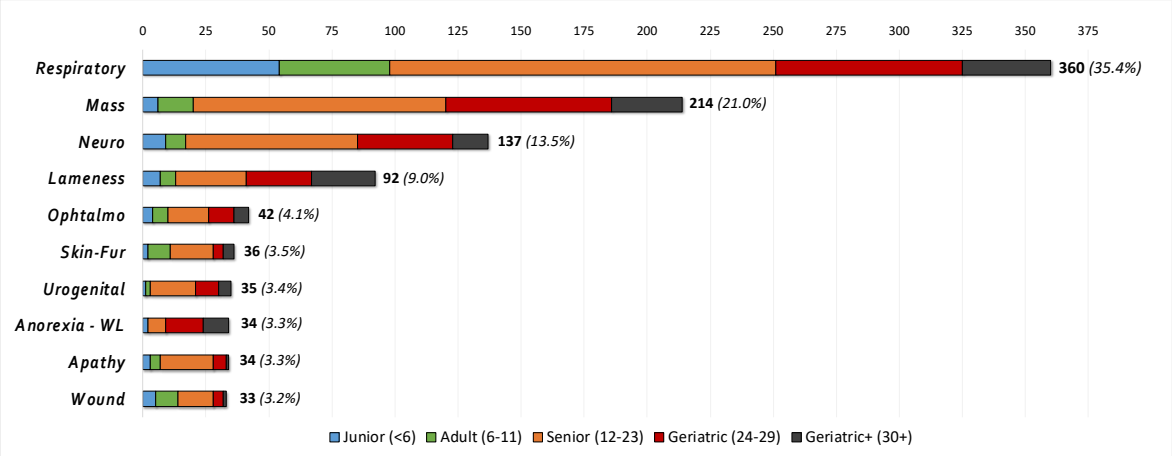

Figure 5 - Chief complaint distribution in the population. For each chief complaint the age category distribution is displayed. The range of each age category is given in months. At the end of each bar, the number (n) and proportion (%) of patients appear. (WL: weight loss)

Among patients with respiratory signs, 42.5% were senior, 30.3% were geriatric patients (geriatric and geriatric+), and a non-negligeable portion (27.2%) were young patients (junior and adults), with junior patients representing 15% by themselves, making a respiratory complaint likely, even at an very early age. Similarly, ophthalmological abnormalities arose at any age, touching 38.1% of senior, 38.1% of geriatric and 23.8% of young patients.

Masses, neurological signs, lameness, urogenital issues, and anorexia-weight loss were mostly problems of older patients (senior and geriatric). In particular, anorexia and/or weight loss (73.5%) and lameness (55.4%) were overrepresented among geriatric patients. Skin and fur abnormalities and wounds were mostly in young and senior patients (Table 3, Figure 5).

4.1.2. Classification tree based on the chief complaint

From the sex and the age category of the patients, a decision tree was built to predict the chief complaint (see 3.1.3.2). The sex of the patient was most strongly associated with the chief complaint (p=0.98E-12, Table 4), as females had overall significantly different chief complaints from males (p<0.001, Figure 6). Among females and among males, the age category (p=1.3E-12, Table 4) was then used to create groups of similar chief complaint profiles (p<0.001, Figure 6).

Table 4 - Outcome values of the decision tree "Chief complaint = Sex + Age Category"
The table displays the statistical value as well as the p-value for the permutation tests at each node of the classification tree. If the p-value was considered significant (p<0.001), a split was created.

Node	Node description	Covariates			
		SEX			
		Statistic	p value	p<0.001	Comment
Node 1	Root	77.58	9.75E-13	***	split
		AGE CATEGORY			
		Statistic	p-value (p)	p<0.001	Comment
Node 1	Root	97.44	1.30E-12	***	split
Node 2	Females	73.38	1.20E-08	***	split
Node 3	Senior, Geriatric, Geriatric+	28.94	6.63E-04	***	split
Node 4	Geriatric, Geriatric+ (n=214)	NULL			final node
Node 5	Senior (n=246)	NULL			final node
Node 6	Junior (n=89)	NULL			final node
Node 7	Males	45.54	3.46E-04	***	split
Node 8	Junior, Adult, Senior (302)	14.19	0.11577	No	final node
Node 9	Geriatric, Geriatric+ (n=166)	NULL			final node

Among females, junior and adult females had similar chief complaint profiles and were grouped together, as well as geriatric and geriatric+ females. Hence, three groups of females presented significantly different chief complaint profiles (p<0.001): young rats under 12 months old (<12) (junior and adult, n=89), senior rats between 12 and 23 months old (12–23) (senior, n=246) and geriatric rats being 24 months old and older (24+) (geriatric and geriatric+, n=214).

Among males, junior, adult and senior rats had similar profiles, as well as geriatric and geriatric+ males. Thus, two groups of males had significantly different chief complaint profiles (p<0.001): rats under 24 months old (<24) (junior, adult and senior, n=302), and rats over 24 months old (24+) (geriatric and geriatric+, n=166) (Table 5, Figure 6).

According to the chief complaint profiles, it seems relevant to consider three age categories instead of five for the rest of the study: young (<12 months old), senior (12–23 months old) and geriatric (24+ months old) rats (Table 5, Figure 6).

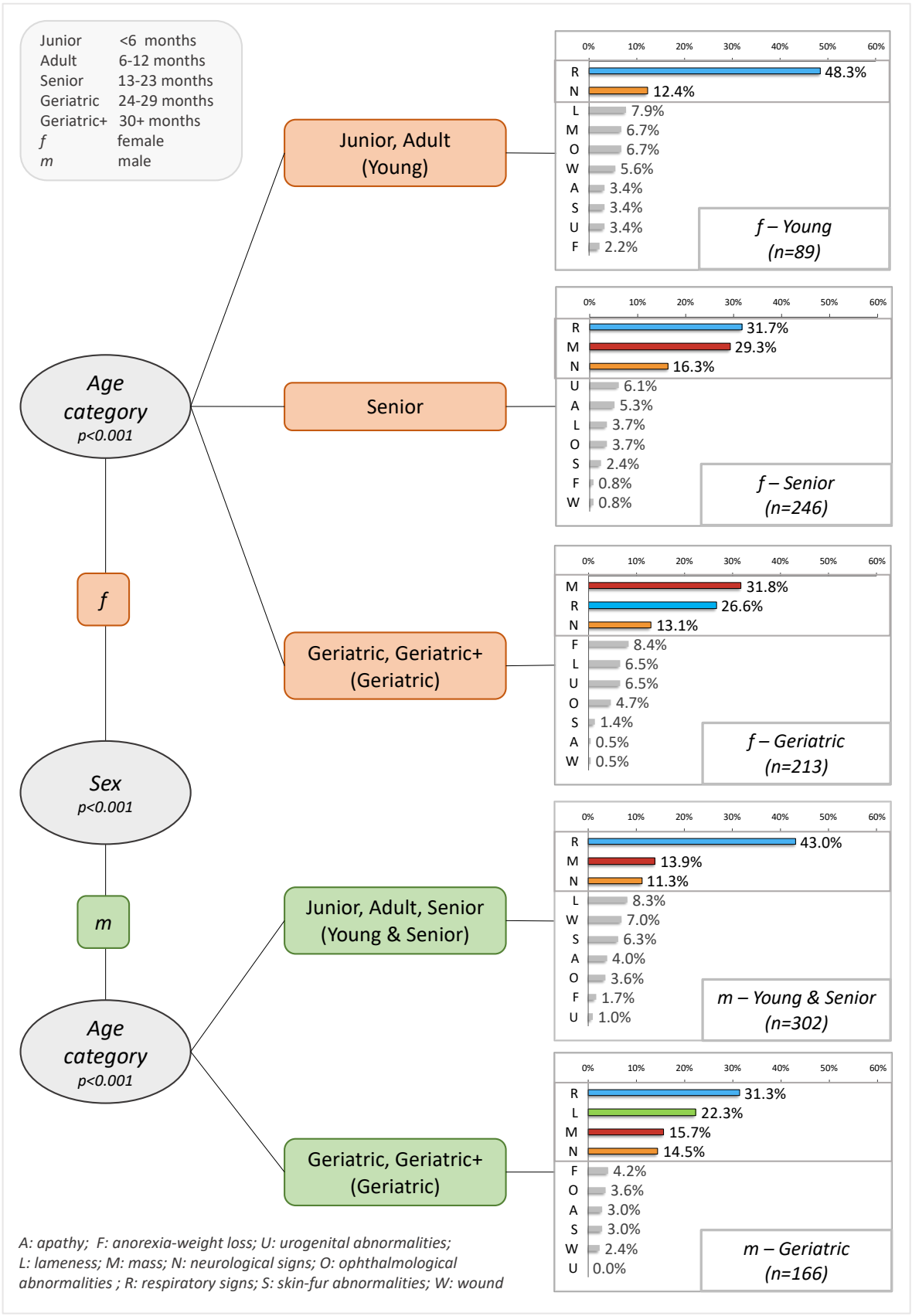

Figure 6 - Classification tree predicting the chief complaint from the sex and age category of the patient. From the patient basic data (Sex and Age category), the tree was set to display the most likely chief complaint profile as a bar chart.

Table 5 - Chief complaint and diagnosis distribution in the different age categories.
Each cell displays the number (n) and proportion (%) of patients in each age category (column), presenting with a given chief complaint (bold row), and a given diagnosis (italic row).
(UTI: urinary tract infection; Neuro: neurological)

	Females						***Males***			
	Young *(<12)*		***Senior*** *(12-23)*		***Geriatric*** *(24+)*		***Young & Senior*** *(<24)*		***Geriatric*** *(24+)*	
	n	%	n	%	n	%	n	%	n	%
Respiratory	**43**	**(48.3%)**	**78**	**(31.7%)**	**57**	**(26.6%)**	**130**	**(43.0%)**	**52**	**(31.3%)**
Acute	*8*	*(9.0%)*	*15*	*(6.1%)*	*15*	*(7.0%)*	*25*	*(8.3%)*	*16*	*(9.6%)*
Subacute	*6*	*(6.7%)*	*5*	*(2.0%)*			*15*	*(5.0%)*	*2*	*(1.2%)*
Chronic (CRD)	*27*	*(30.3%)*	*56*	*(22.8%)*	*38*	*(17.8%)*	*87*	*(28.8%)*	*31*	*(18.7%)*
Other	*2*	*(2.2%)*	*2*	*(0.8%)*	*4*	*(1.9%)*	*3*	*(1.0%)*	*3*	*(1.8%)*
Mass	**6**	**(6.7%)**	**72**	**(29.3%)**	**68**	**(31.8%)**	**42**	**(13.9%)**	**26**	**(15.7%)**
Tumor	*1*	*(1.1%)*	*48*	*(19.5%)*	*52*	*(24.3%)*	*4*	*(1.3%)*	*5*	*(3.0%)*
Mammary gland tumor	*1*	*(1.1%)*	*47*	*(19.1%)*	*51*	*(23.8%)*	*2*	*(0.7%)*	*4*	*(2.4%)*
Other tumors			*1*	*(0.4%)*	*1*	*(0.5%)*	*2*	*(0.7%)*	*1*	*(0.6%)*
Abscess	*4*	*(4.5%)*	*14*	*(5.7%)*	*8*	*(3.7%)*	*29*	*(9.6%)*	*14*	*(8.4%)*
Unidentified	*1*	*(1.1%)*	*8*	*(3.3%)*	*8*	*(3.7%)*	*5*	*(1.7%)*	*2*	*(1.2%)*
Other			*2*	*(0.8%)*			*2*	*(0.7%)*	*1*	*(0.6%)*
Neuro	**11**	**(12.4%)**	**40**	**(16.3%)**	**28**	**(13.1%)**	**34**	**(11.3%)**	**24**	**(14.5%)**
Vestibular	*10*	*(11.2%)*	*25*	*(10.2%)*	*18*	*(8.4%)*	*19*	*(6.3%)*	*12*	*(7.2%)*
Vestibular syndrome	*6*	*(6.7%)*	*17*	*(6.9%)*	*13*	*(6.1%)*	*8*	*(2.6%)*	*6*	*(3.6%)*
Otitis	*4*	*(4.5%)*	*6*	*(2.4%)*	*4*	*(1.9%)*	*8*	*(2.6%)*	*5*	*(3.0%)*
Ear polype					*1*	*(0.5%)*	*2*	*(0.7%)*	*1*	*(0.6%)*
Zymbal gland tumor			*2*	*(0.8%)*			*1*	*(0.3%)*		
Pituitary tumor	*1*	*(1.1%)*	*9*	*(3.7%)*	*4*	*(1.9%)*	*9*	*(3.0%)*	*7*	*(4.2%)*
Seizure			*4*	*(1.6%)*	*1*	*(0.5%)*	*1*	*(0.3%)*	*3*	*(1.8%)*
Other			*2*	*(0.8%)*	*5*	*(2.3%)*	*5*	*(1.7%)*	*2*	*(1.2%)*
Lameness	**7**	**(7.9%)**	**9**	**(3.7%)**	**14**	**(6.5%)**	**25**	**(8.3%)**	**37**	**(22.3%)**
Neuro (Hindlimb paresia)	*1*	*(1.1%)*	*3*	*(1.2%)*	*10*	*(4.7%)*	*4*	*(1.3%)*	*22*	*(13.3%)*
Trauma	*3*	*(3.4%)*	*3*	*(1.2%)*	*1*	*(0.5%)*	*7*	*(2.3%)*	*7*	*(4.2%)*
Tumor			*2*	*(0.8%)*	*3*	*(1.4%)*	*1*	*(0.3%)*	*1*	*(0.6%)*
Pododermatitis			*1*	*(0.4%)*			*4*	*(1.3%)*	*5*	*(3.0%)*
Idiopathic	*3*	*(3.4%)*					*9*	*(3.0%)*	*2*	*(1.2%)*
Ophthalmo	**6**	**(6.7%)**	**9**	**(3.7%)**	**10**	**(4.7%)**	**11**	**(3.6%)**	**6**	**(3.6%)**
Exophthalmia	*3*	*(3.4%)*	*2*	*(0.8%)*	*4*	*(1.9%)*	*4*	*(1.3%)*	*3*	*(1.8%)*
Eye wound	*1*	*(1.1%)*	*4*	*(1.6%)*	*2*	*(0.9%)*	*3*	*(1.0%)*		
Other	*2*	*(2.3%)*	*3*	*(1.1%)*	*4*	*(1.9%)*	*4*	*(1.3%)*	*3*	*(1.8%)*
Skin-fur	**3**	**(3.4%)**	**6**	**(2.4%)**	**3**	**(1.4%)**	**19**	**(6.3%)**	**5**	**(3.0%)**
Dermatological	*1*	*(1.1%)*	*2*	*(0.8%)*			*7*	*(2.3%)*	*3*	*(1.8%)*
Ectoparasite	*2*	*(2.2%)*	*4*	*(1.6%)*	*3*	*(1.4%)*	*12*	*(4.0%)*	*2*	*(1.2%)*
Urogenital	**3**	**(3.4%)**	**15**	**(6.1%)**	**14**	**(6.5%)**	**3**	**(1.0%)**		
Uterine tumor	*3*	*(3.4%)*	*13*	*(5.3%)*	*13*	*(6.1%)*				
UTI							*2*	*(0.7%)*		
Urolithiasis							*1*	*(0.3%)*		
Other			*2*	*(0.8%)*	*1*	*(0.5%)*				
Anorexia - Weight loss	**2**	**(2.2%)**	**2**	**(0.8%)**	**18**	**(8.4%)**	**5**	**(1.7%)**	**7**	**(4.2%)**
Orodental	*2*	*(2.2%)*	*2*	*(0.8%)*	*12*	*(5.6%)*	*2*	*(0.7%)*	*6*	*(3.6%)*
Idiopathic					*4*	*(1.9%)*	*3*	*(1.0%)*	*1*	*(0.6%)*
Other					*2*	*(0.9%)*				
Apathy	**3**	**(3.4%)**	**13**	**(5.3%)**	**1**	**(0.5%)**	**12**	**(4.0%)**	**5**	**(3.0%)**
Digestive	*2*	*(2.2%)*	*4*	*(1.6%)*	*1*	*(0.5%)*	*5*	*(1.7%)*		
Idiopathic	*1*	*(1.1%)*	*7*	*(2.8%)*			*5*	*(1.7%)*	*5*	*(3.0%)*
Other			*2*	*(0.8%)*			*2*	*(0.7%)*		
Wound	**5**	**(5.6%)**	**2**	**(0.8%)**	**1**	**(0.5%)**	**21**	**(7.0%)**	**4**	**(2.4%)**
Fight wound	*2*	*(2.2%)*					*15*	*(5.0%)*	*2*	*(1.2%)*
Other	*3*	*(3.4%)*			*1*	*(50.0%)*	*6*	*(2.0%)*	*2*	*(1.2%)*
Grand total	**89**		**246**		**214**		**302**		**166**	

4.1.3. Detailed group profiles

Using the chief complaint of the owner and the diagnosis of the veterinarian, a detailed profile was built for each group established in the classification tree (see 3.1.3.3).

Among young females (n=89), 43/89 (48.3%) presented with respiratory signs most of them with a duration of more than 8 weeks (chronic respiratory disease or CRD, 27/43 or 62.8% of young female with respiratory signs). Eleven out of 89 (12.4%) of young females presented neurological signs, that were mostly diagnosed as vestibular syndrome (10/11 or 90.9% of neurological signs of young females) (Table 5, Figure 6, Figure 7).

Other chief complaints in young females included lameness (7.9%), masses (6.7%) with majority of abscesses (4/6 or 66% of young females masses), ophthalmological abnormalities (6.7%), wounds (5.6%), skin and/or fur abnormalities (3.4%), urogenital issues (3.4%) being exclusively suspected uterine tumors, apathy (3.4%) mostly associated with digestive problems, and anorexia and/or weight loss (0.8%) exclusively due to orodontal problems (Table 5, Figure 6, Figure 7).

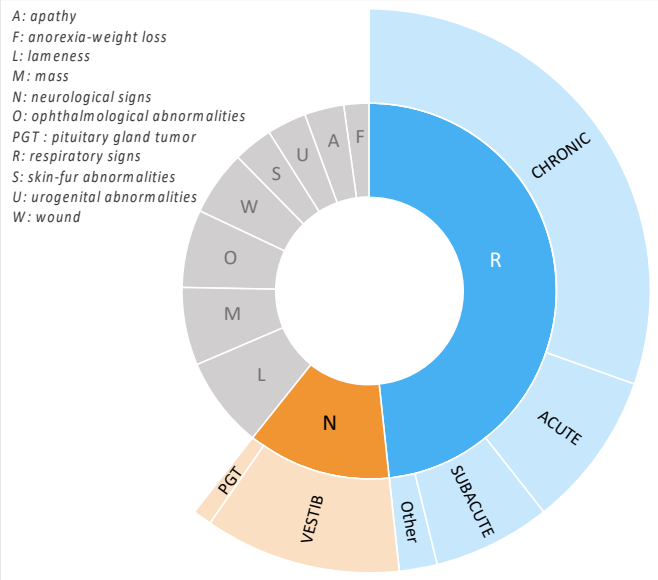

Figure 7 - Detailed chief complaint profile of young females (n=89).
The first level (inner circle) of the double-level pie chart displays the chief complaint, and the second level (outer circle) displays the diagnosis given by the veterinarian.

Senior females (n=246) profile presented similarities with the young and senior males (n=302) profile. In both groups, respiratory signs were the dominant chief complaint, with 78/246 (31.7%) females and 130/302 males (43%). Those respiratory signs were mostly chronic (CRD) in both groups (56/78 or 71.8% of females, and 87/130 or 66.9% of males with respiratory signs). Fifteen out of 78 or 19.2% of females and 25/130 or 19.2% of males presented with acute respiratory signs (Table 5, Figure 6, Figure 8).

Senior females and young and senior males are most likely to present to the veterinarian with respiratory signs, mostly of chronic duration (CRD) but possibly with acute onset.

Masses were the second most important chief complaint in senior females and young and senior males, with a significant larger number of masses in females (72/246 or 29.3%) than in males (42/302 or 13.1%). Among senior females with masses, 48/72 presented tumors, almost exclusively suspected to be mammary gland tumors (47/48 or 97.9%). Among young and senior males with masses, 29/42 (69%) were diagnosed with one or more abscesses (Table 5, Figure 6, Figure 8). Hence, masses in senior females were mostly tumoral, while masses in young and senior males were mostly abscesses.

Neurological signs were the third chief complaint in those groups, with 40/246 senior females (16.3%) and 34/302 young and senior males (11.3%) affected. In both groups, vestibular signs were the most frequent manifestation of those neurological signs (respectively 25/40 or 62.5% and 19/34 or 55.9%). While some rats were anecdotally diagnosed with precise diseases such as *otitis externa*, suspected pituitary gland tumor or Zymbal's gland tumor, vestibular syndrome was the most frequent conclusion of the veterinarian for rats presenting with neurological signs (17/25 or 68% of senior females and 8/19 or 42.1% of young and senior males) (Table 5, Figure 6, Figure 8).

Other chief complaints in senior females included urogenital issues (15/246 or 6.1%) being mostly uterine tumors (13/15 or 86.7%), apathy (13/246 or 5.3%) of mostly idiopathic nature (7/13 or 53.8%), ophthalmological abnormalities (3.7%), lameness (3.7%), skin and/or fur abnormalities (2.4%), wounds (0.8%) and anorexia and/or weight loss (0.8%) (Table 5, Figure 6, Figure 8A).

In young and senior males, lameness (8.3%) and wounds (7.0%) were more represented than in senior females (respectively 8.3% *vs* 3.7% and 7.0% *vs* 0.8%). Other chief complaints included skin and/or fur abnormalities (19/302 or 6.3%) mostly secondary to ectoparasites (12/19 or 63.2%) but with a significant amount of primary dermatological issues (7/19 or 37%), apathy (4%), ophthalmological abnormalities (3.6%), anorexia and/or weight loss (1.7%) and urogenital issues (3/302 or 1%), being exclusively linked to the urinary system (2/3 or 66.6% due to suspected urinary tract infection (UTI) and 1/3 33.3% due to urolithiasis) (Table 5, Figure 6, Figure 8A).

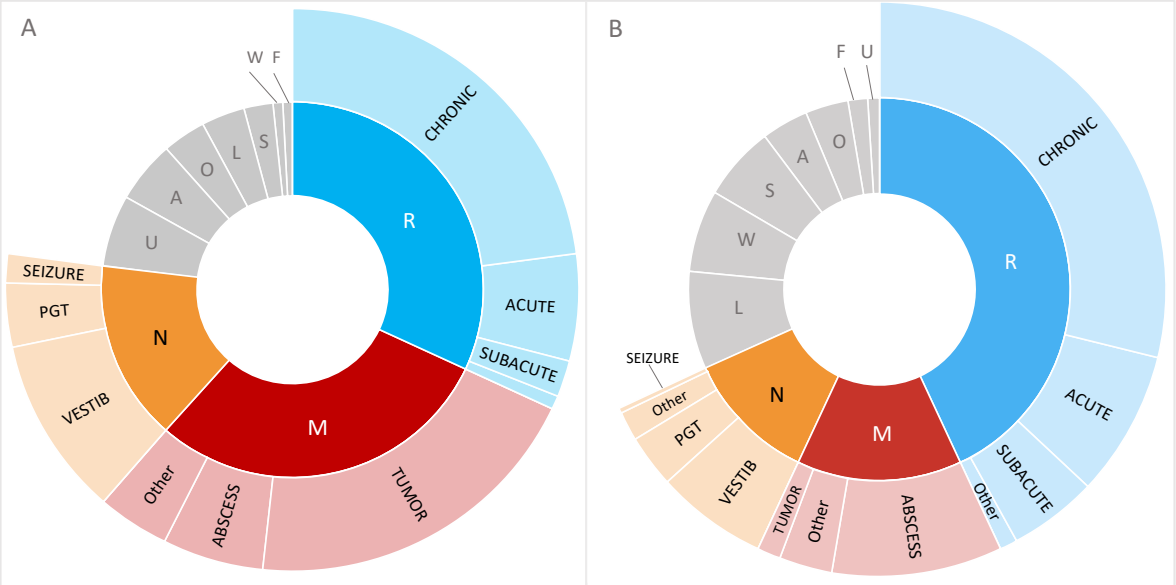

Figure 8 - Detailed chief complaint profiles. A: Senior females (n=246). B: Young and senior males (n=302). The first level (inner circle) of the double-level pie chart displays the chief complaint, and the second level (outer circle) displays the diagnosis given by the veterinarian.

Geriatric females (n=213) and geriatric males (n=166) had different chief complaint profiles. While geriatric females presented mostly with masses (78/213 or 31.8%), respiratory signs (57/2013 or 26.6%) or neurological signs (28/213 or 13.1%), majority of geriatric males presented with either respiratory signs (52/166 or 31.3%), lameness (37/166 or 22.3%), masses (26/166 or 15.7%) or neurological signs (24/166 or 14.5%).

In both groups, respiratory issues were of mostly chronic nature (CRD, 38/57 or 67% of females and 31/52 or 68% of males with respiratory signs) (Table 5, Figure 9).

Masses types were significantly different between geriatric females and geriatric males. Geriatric females presented mostly mammary gland tumors (52/68 or 76.4%), while geriatric males with masses presented mostly with abscesses (14/26 or 53.8%).

In geriatric males, lameness (37/166 or 22.3%) was overrepresented compared to females (14/213 or 6.5%). Lameness in both groups were mostly attributed to hindlimb paresis or polyradiculoneuropathy (10/14 or 71% for females and 22/37 or 59% for males) (Table 5, Figure 6, Figure 9).

Other chief complaints in geriatric females included anorexia and/or weight loss (8.4%), urogenital problems (14/213 or 6.1%) mostly attributed to uterine tumors (13/14 or 92.9%), lameness (6.5%), ophthalmological issues (4.7%), skin and/or fur abnormalities (1.4%), wounds (0.5%), and apathy (0.5%) (Table 5, Figure 6, Figure 9).

In geriatric males, other chief complaints included anorexia and/or weight loss (4.2%), ophthalmological abnormalities (3.6%), skin and/or fur abnormalities (3%), apathy (3%) and wounds (2.4%) (Table 5, Figure 6, Figure 9B).

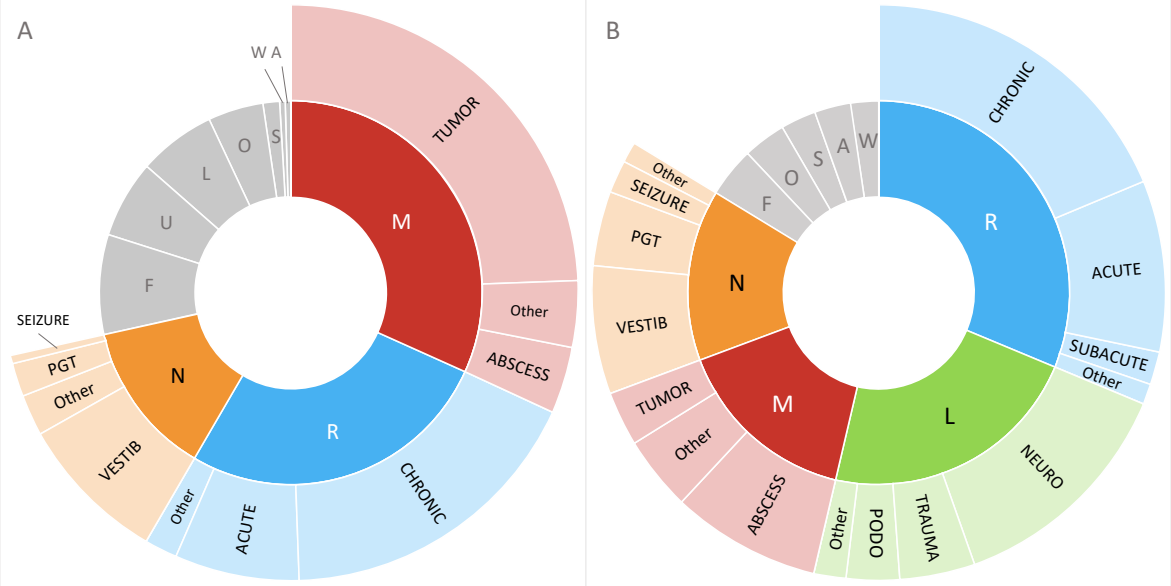

Figure 9 - Detailed chief complaint profiles. A: Geriatric females (n=213). B: Geriatric males (n=166). The first level (inner circle) of the double-level pie chart displays the chief complaint, and the second level (outer circle) displays the diagnosis given by the veterinarian.

4.2. Ancillary study – Histopathological analysis of mammary gland tumors

In total, 36 masses from 20 female rats were analyzed for histological diagnosis. The excised masses were expected to be mammary gland tumors (MGT) by the veterinarians. Out of the 36 masses, 29 were benign mammary gland tumors (81%), 6 were malignant mammary gland tumors (17%) and 1 was a malignant non-mammary gland tumor (3%) (Table 6, Figure 10). The most common identified tumor type was mammary gland fibroadenoma (MGF) (n=27, 75%), followed by mammary gland adenocarcinoma (n=6, 17%).

Table 6 - Frequency distribution of the histological diagnoses of 36 excised masses from 20 rat patients. For each histological type (bold), the exact diagnosis was displayed (italic). The corresponding amount (n) and proportion (%) of masses is displayed.

	n	%
Benign mammary gland tumors	**29**	**(81%)**
Fibroadenoma	*27*	*(75%)*
Fibroadenoma + Cystadenoma	*1*	*(3%)*
Adenoma	*1*	*(3%)*
Malignant mammary gland tumors	**6**	**(17%)**
Adenocarcinoma	*6*	*(17%)*
Malignant non-mammary gland tumors	**1**	**(3%)**
Fibrosarcoma	*1*	*(3%)*
Grand total	**36**	

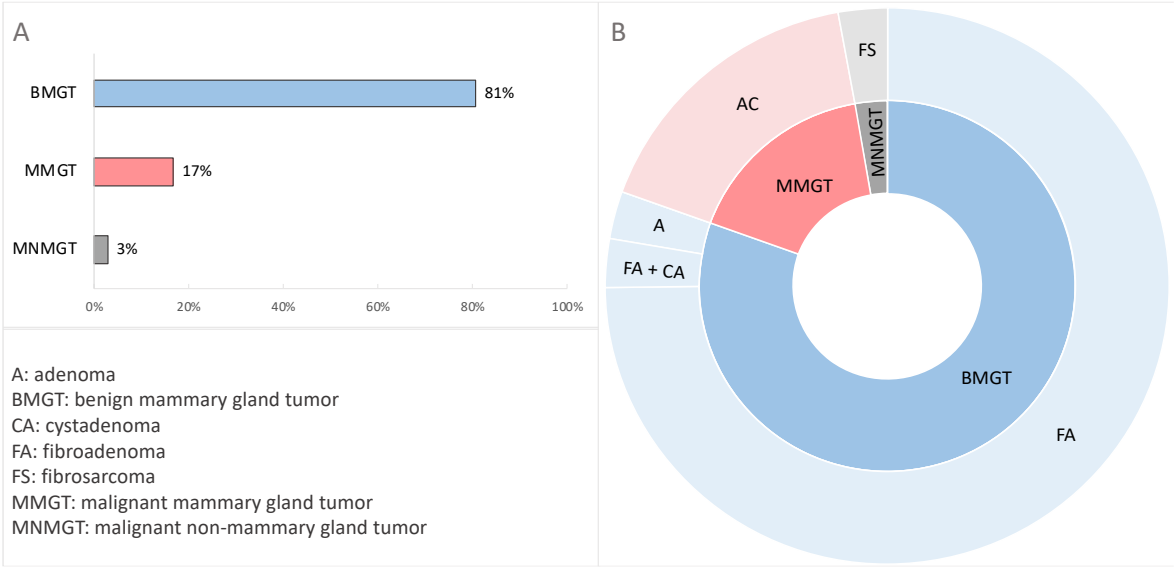

Figure 10 - Distribution of the histological diagnoses in 36 excised masses from 20 rats. A: Distribution of the histological types. B: Distribution of the exact diagnoses for each histological type.

The age at diagnosis ranged from 8 to 27 months and the median age was 24 months. Half of the rats were between 18 and 26 months old (interquartile range 18–26), making this population mostly composed of senior (12–23 months old) and geriatric (24–29 months old) rats (see 3.1.2) (Figure 11).

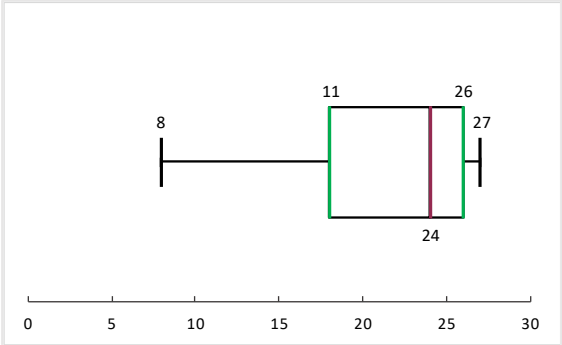

Figure 11 - Age distribution in 20 rat patients with masses analyzed for histopathological diagnosis. The median is represented as a red line, the quartiles in green and the whiskers extremities correspond to the maximum and minimum.

Masses were mostly located in the inguinal and axillary regions. Indeed, 18/36 (50%) of all tumors were in the inguinal region and 8/36 (22%) in the axillary region. In particular, mammary gland fibroadenoma (MGF), the most frequently identified tumor type in our population, was mostly located in the inguinal region (15/27, 56% of MGF), followed by the axillary region (8/27, 30% of MGF) (Table 7).

Overall, tumors were mostly from intact females (29/36, 81% of all masses). Twenty two of the 27 (85%) MGF and 4 of the 6 (66%) MMGT were from intact females (Table 7).

Table 7 - Distribution of mass location and sex by histological type for the 36 masses identified in Table 6. Each cell displays the number of tumors of a given histological type (column) at a certain mass location or for a given sex (row).

	Fibroadenoma	Other benign MGT	Malignant MGT	Malignant NMGT
Mass location				
Axillary	8	0	0	0
Cervical	0	0	1	0
Inguinal	15	1	1	1
Laterodorsal	2	1	2	0
Thoracic	1	0	2	0
Sex				
Intact female	22	2	4	1
Spayed female	5	0	2	0
Total	**27**	**2**	**6**	**1**

5. Discussion

When considering pet rats, it is necessary to take into account their short life-span, making them old patients quite early. To the best of our knowledge, no studies has yet been conducted on aging of pet rats, and our study offers a definition of the "old rat patient". According to our results, it seems relevant to consider pet rats as young until they reach 12 months of age, senior from 12 months old, and geriatric from 24 months old. This definition is based on the chief complaint profiles of those age groups, with young rats presenting significantly different health issues than senior rats, themselves having different affects than geriatric rats. Based on the age category and the sex of the patients in our data pool, it was possible to build a decision tree displaying the most likely chief complaints from the owners. This tree is hoped to be useful for veterinarians who are less familiar with rats and for rat owners to better understand their pet's potential health issues.

Over 75% of our patient pool were senior (over 12 months old) and geriatric patients (over 24 months old). Veterinarians can expect most of their rat patients to be over 12 months old and thus mostly be dealing with older rats' ailments. According to our study, these mostly include CRD, neurological disorders and masses in senior males and senior and geriatric females, but also lameness caused by hindlimb paresis in geriatric male rats. Masses in older females are mostly mammary gland tumors while they are mostly abscesses in older males. Other conditions such as incisor malocclusion and kidney diseases, while not appearing as major chief complaints in our study, are widely described in the literature and should not be overlooked in aging rats. It is to be noted that a non-negligeable proportion (almost 20%) of our pool were young rats (under 12 months old). Those mostly presented with respiratory signs, making respiratory disease likely even at an early age in pet rats.

Overall, veterinarians preparing a rat consultation should expect respiratory signs, masses, neurological signs and lameness as the more frequent chief complaints from the owners.

Respiratory signs are very frequent in pet rats and include increased respiratory noises (wheezing), sneezing, nasal discharge, and can worsen to respiratory distress with or without open mouth breathing. More often, rats presented with chronic signs (more than 8 weeks duration), indicative of chronic respiratory disease (CRD) or murine respiratory mycoplasmosis (MRM). On the other hand, a large proportion of the patients were brought to the clinic for respiratory distress, most likely due to bacterial pneumonia. However, it is important to consider that rats are prey animals and tend to hide their symptoms. Thus, owners might notice respiratory difficulties only late in the course of the disease. For that

reason, it would be relevant to conduct a study evaluating the correlation between the severity of the clinical signs and the severity of the pulmonary lesions in pet rats with respiratory disease. This could be achieved using diagnostic imaging such as CT scan [26]. Owners should also be taught to recognize early signs of respiratory disease in their pets (sneezing, increased respiratory effort and rate, red discharge around the eyes and nose, weight loss, lethargy, increased time hiding). If a rat is brought in with respiratory signs, after eventual stabilization, a bacterial culture and antibiotic resistance test should be offered to the owner. While not always conclusive, those analyses can help choosing the best treatment, as antibiotic resistance is getting more and more frequent. Unfortunately, in our patient files, those analyses were rarely performed, most likely declined by owners for financial reasons. Rats with either CRD or bacterial pneumonia can also benefit from daily saline nebulization that can contain bronchodilators, mucolytics and glucocorticoids if necessary (see 2.3.4). Nevertheless, when considering respiratory disease in pet rats, prevention remains the best option. Owner education on adapted diet, cage hygiene, proper ventilation, and enrichment to minimize stress is essential. In older rats, oral immune booster can be given to prevent immunodepression, which is the main risk factor of respiratory disease in rats. It is to be emphasized that rats kept as pets should be provided with a healthy environment, including during the first weeks of their life. In our data pool, numerous young rats presenting respiratory signs were coming from pet shops. According to a study conducted in the United Kingdom [46], it is the second most common source of pet rats, after breeders. A comparative study comparing respiratory health between pet shops rats and breeders' rats could help bringing more data and better inform about the risk of buying pets from pet stores.

Masses, in particular mammary gland tumors and abscesses, are the second most frequent chief complaint of pet rat owners. While adult and older males presented abscesses, senior and geriatric females mostly presented mammary gland tumors, which correspond with the literature [5, 46]. Mammary gland tumors are the most frequent tumor type of laboratory rats, and according to our results also in pet rats. MGT mostly occurred in females, and were overrepresented in senior and geriatric females, which corresponds to the current literature (see 2.3.9.1). Although, it is important to highlight that an important amount of masses in females of our patient pool were only "suspected MGT". Indeed, histopathology of the excised tumors is still rarely performed, whether for financial reason or because of the benign nature of most MGT in rats. In our ancillary study, most of the excised tumors were indeed benign fibroadenoma (75%). However, mammary gland adenocarcinoma represented

almost 20% of the tumors. Those results correspond with the current literature [5]. While survival time between MG fibroadenoma and MG adenocarcinoma does not differ greatly [5], knowledge of malignancy could help breeder reducing or stopping breeding of the affected rats line. Hence, histopathological analysis of excised masses in pet rats should systematically be offered to the owner. Rats are particularly prone to tumors, especially MGT. Currently, spaying at an early age (from 4 to 8 months old) is considered the best way to prevent MGT. However, neutering in pet rats is still uncommon, either for financial reasons or because of the presumed anesthesiological risk. Preventive deslorelin implants in young females rats, while already used by some veterinarians, have not yet been studied but could offer an interesting alternative to spaying. Spontaneous dwarf rats, naturally deficient in growth hormones, have been studied for their resistance to tumors and increased lifespan [47, 48] and some breeders are already introducing them to owners. In males rats, abscesses are more frequent than in females. In particular, adult male rats were overrepresented in our patient pool (sex ratio 1.5) and presented more often with wounds, abscesses as well as skin and fur abnormalities. Male rats tend to fight more to establish hierarchy than females which lead them to get injured more. Castration of male rats at an early age (from 4 months old) could help reducing the aggressivity in those individuals. Abscesses in rats should be opened and flushed by the veterinarian and the wound kept clean by the owner. Rats healing capacity is quite remarkable, and usually only painkiller (meloxicam) and eventually a local ointment are recommended.

Neurological signs are the third most common presentation in our patient population. Those were presented by young and older male rats, but mostly by senior and older females rats. Most of those neurological signs were described as “vestibular syndrome”, rarely with a precise etiology. Pituitary gland tumors (PGT), otitis and Zymbal’s gland tumors (ZGT) were occasionally diagnosed. PGT were often suspected in older rats (24+ months old) with neurological symptoms but rarely confirmed. Pituitary adenoma should indeed be considered in senior to older rats (from 18 months old) presenting with proprioception deficit and head tilt [18, 37]. To confirm the presence of PGT, advanced imaging is needed. While MRI is theoretically the best method, CT is more adequate for rats, as it a much quicker process with a shorter anesthesia and can be even performed under sedation. However, such imaging methods are often declined by the owners because of their important cost. The few confirmed PGT of our data pool were suspected based on clinical presentation and diagnosed *ex juvantibus*, after cabergoline treatment. Cost of advanced imaging methods but also the overall poor prognosis could explain the lack of final etiology in our neurological patients.

It is interesting to mention that while Sinclair (2021) characterizes PGT as more common in females than males, our results did not suggest any sex predisposition. However, this could be due to the lack of definite diagnosis due to the previously mentioned limitations. On the other hand, ZGT were less frequent that expected. Indeed, ZGT are a very rat-specific disease and well described in the current veterinary literature. However, they were very rarely suspected nor diagnosed in our patient pool.

Lameness was the fourth most common complaint leading to a veterinary consultation in our patient pool. Polyradiculoneuropathy or hindlimb paresis is a well described cause of lameness in aging rats and was indeed the most suspected etiology in our lame patients. It is remarkable that lameness was overrepresented in geriatric male rats. This suggests that male rats are more prone to develop polyradiculoneuropathy in old age than females. This corresponds to the current literature [29]. NSAIDs, vitamin B complex and physiotherapy can me offered to the owners to maintain their rat quality of life.

In the less frequent complaints, it is relevant to mention that urinary diseases were extremely rarely suspected nor diagnosed (3 cases only) compared to suggested in the literature [1, 15]. This could be due to the difficulty of blood sampling in rats, limitation of ultrasonography due to rat size, or cost limitation.

Overall, this study offers a classification of main diseases in pet rats, using the chief complaint and the veterinary diagnosis of more than 1000 patient files. In some files, imprecise or lack of definite etiology due to the cost of diagnostic methods (advanced imaging, histopathology, bacterial culture, and antibiotic resistant tests) or practical difficulties (blood sampling) represent a limitation to our results. However, based on the chief complaint, the provided decision tree is hoped to be a useful pedagogic tool for both veterinarians and pet rat owners. It could be completed by additional informative material on main diseases affecting rats such as CRD, mammary gland tumors and abscesses, PGT and otitis, and hindlimb paresis.

6. Summary / Összefoglaló

Fancy rats (*Rattus norvegicus domestica*) are becoming increasingly frequent patients of veterinarians in Europe. Indeed, because of their gentle and intelligent nature, they make very good pets. Rats have been used in research for decades and literature provides a large choice of publications about the main laboratory rat strains. However, due to the highly selective breeding and unique husbandry conditions, their genetic background and their environment differ greatly from those of pet rats. Thus, it seems relevant to suppose that pet rats' ailments might differ from those of laboratory rats. Currently, veterinary literature on pet rats is still scarce, with exotic small mammals medicine books focusing more on rabbits, guinea pigs, ferrets, and hamsters.

Hence, this study aimed to provide a classification of the main diseases in pet rats in France. For this purpose, a retrospective study of more than 1000 rat patients was performed. Medical records of companion rats examined at a French Hospital and Reference Clinic between 2006 and 2021 were reviewed. Information regarding the age, sex, chief complaint of the owner and diagnosis of the veterinarian was extracted from each file and analyzed.

Major chief complaints in our total population included respiratory signs (35%), masses (21%), neurological signs (13%), and lameness (9%). Using the age and sex of the patients, chief complaint profiles could be established. Those profiles were displayed as a classification tree, allowing veterinarians to easily visualize the most likely chief complaints for a given age group and sex. Each profile was also further detailed and displayed as double level-pie charts using the most frequent veterinary diagnosis for each chief complaint. Through this process, three statistically relevant age groups emerged, offering a definition of aging in pet rats, not yet described to the best of the author's knowledge. Pet rats can be considered young until 12 months old, senior until 24 months, and geriatric over 24 months. In our population, respiratory signs were most often a manifestation of chronic respiratory disease (CRD) in all groups (over 60%). Masses were most often mammary gland tumors in senior and geriatric females (over 65%, 75% fibroadenoma) and abscesses in males (over 50%). Neurological signs were often under-investigated and mostly diagnosed as vestibular syndrome (over 55% in all groups). Pituitary gland tumors in senior and older rats were mostly suspected (14 to 65%). Lameness was overrepresented in geriatric male rats (22% *vs* 8% in geriatric females) and was mostly associated with polyradiculoneuropathy (59%).

The provided material is intended to be a useful pedagogic tool for both veterinarians and pet rat owners, which could be further complimented by providing illustrated clinical brochures of pet rats' major diseases.

Európa állatorvosi rendelőiben egyre gyakoribb páciens a háziasított patkány (*Rattus norvegicus domestica)*. Mivel igen szelíd és intelligens a természetük, így nagyon kedveltek mint társállatok. Emellett évtizedek óta használják őket kutatásokban mint modell állatok, és széleskörű irodalom áll rendelkezésre a főbb laboratóriumi törzsekről. Sajnos a tartási körülmények és az állatok genetikája igencsak különbözik a kedvencként tartott patkányokétól, mivel szelektíven tenyésztik őket, és specális körülmények között tartják. Így feltételezhetjük, hogy a társállatok megbetegedései is más karakterűek, mint a laborállatoké. Jelenleg még igen kevés irodalmi adat áll rendelkezésre a társállatként tartott patkányokról, mivel az egzotikus állatokkal foglalkozó szakkönyvek inkább a nyúlra, tengerimalacra, görényre és hörcsögre koncentrálnak. Jelen tanulmány a patkányok főbb betegségeinek csoportosítását tűzte ki célul franciaországi adatok alapján. Retrospektív kutatásunk során több, mint 1000 páciens adatait tekintettük át egy francia állatkórház és referencia klinikai adatbázisából 2006 és 2021 között. A patkányok életkorát, ivarát, főbb panaszát és a diagnózist gyűjtöttük ki és elemeztük. A teljes vizsgált populációban a főbb panaszok a légúti tünetek (35%), szövetszaporulatok (21%), neurológiai tünetek (13%) és sántaság (9%) voltak. A profilokat az életkor és ivar függvényében állítottuk fel – ezeket osztályoztuk, és egy fát alakítottunk ki, ami alapján könnyen láthatók a főbb panaszok adott életkor és ivar tekintetében. Ezeket a profilokat további részletekkel gazdagítottuk, így egy dupla kördiagramon tudtuk ábrázolni a főbb tünetekhez tartozó állatorvosi diagnózist. Az elemzés során három, statisztikailag releváns korcsoport alakult ki, ami így segít behatárolni az idősödő patkány fogalmát. A kedvencállatként tartott patkányt fiatalnak tekinthetjük 12 hónapos kor alatt, idősödőnek 24 hónapos korig és öregnek 24 hónapos kor felett. A vizsgált populációban a légúti tüneteket leggyakrabban idült légúti betegség (chronic respiratory disease, CRD) okozta minden korcsoportban (60% felett). A szövetszaporulatok emlőtumorok voltak az idősödő és öreg nőstény állatok körében (65% felett, ebből 75% fibroadenoma), és tályogok a hím állatokban (50% felett). Az idegrendszeri tünetek oki hátterét ritkán derítették ki, leggyakrabban a vestibularis szindróma diagnózisát állították fel (55% felett minden korcsoportban). Az agyalapi mirigy daganat diagnózisát is leggyakrabban gyanú alapján hozták az idősödő és öreg patkányok körében (14–65%). A sántaság felülreprezentált diagnózis volt az öreg hím állatok csoportjában (22% a nőstény állatokban látott 8%-kal szemben), és főképp polyradiculoneuropathiával hozták kapcsolatba (59%). A vizsgálat során nyert adatok hasznosak lehetnek mind az állatorvosoknak, mind a patkányok gazdáinak, továbbá alapul szolgálhatnak későbbi ismertető anyagok létrehozásához.

7. References

1. Frohlich J (2020) Diseases of rats. In: Ferrets, Rabbits, and Rodents Clinical Medicine and Surgery, 4th Edition. Elsevier Inc., Missouri, pp 361–365

2. Turner PV, Brash ML, Smith DA (2017) Rats. In: Pathology of Small Mammal Pets. John Wiley & Sons, Inc., Hoboken, pp 225–276

3. AFRMA Fancy Rat Standards. https://www.afrma.org/fancyrm.htm. Accessed 18 Dec 2021

4. National Fancy Rat Society - NFRS. https://www.nfrs.org/breeding_varieties.html. Accessed 18 Dec 2021

5. Vergneau-Grosset C, Keel MK, Goldsmith D, Kass PH, Paul-Murphy J, Hawkins MG (2016) Description of the prevalence, histologic characteristics, concomitant abnormalities, and outcomes of mammary gland tumors in companion rats (Rattus norvegicus): 100 cases (1990–2015). Journal of the American Veterinary Medical Association 249:1170–1179. https://doi.org/10.2460/javma.249.10.1170

6. Otto GM, Franklin CL, Clifford CB (2015) Biology and Disease of Rats. In: Laboratory Animal Medicine, 3rd Edition. Academic Press, Elsevier, London, pp 151–207

7. Otto J, Brown MF, Long W (2002) Training rats to search and alert on contraband odors. Applied Animal Behaviour Science 77:217–232. https://doi.org/10.1016/S0168-1591(02)00052-7

8. Poling A, Weetjens BJ, Cox C, Beyene NW, Sully A (2010) Using Giant African Pouched Rats (*Cricetomys Gambianus*) to Detect Landmines. Psychol Rec 60:715–728. https://doi.org/10.1007/BF03395741

9. Poling A, Weetjens B, Cox C, Beyene N, Durgin A, Mahoney A (2011) Tuberculosis detection by giant African pouched rats. BEHAV ANALYST 34:47–54. https://doi.org/10.1007/BF03392234

10. AFRMA - The History of Fancy Rats. https://www.afrma.org/historyrat.htm. Accessed 11 Apr 2022

11. Burek JD (1978) Pathology of aging rats: a morphological and experimental study of the age-associated lesions in aging BN/Bi, WAG/Rij, and (WAG x BN)F_1 rats. CRC Press, West Palm Beach, Fla

12. Dutton M (2020) Selected Veterinary Concerns of Geriatric Rats, Mice, Hamsters, and Gerbils. Veterinary Clinics of North America: Exotic Animal Practice 23:525–548. https://doi.org/10.1016/j.cvex.2020.04.001

13. Planas-Silva MD, Rutherford TM, Stone MC (2008) Prevention of age-related spontaneous mammary tumors in outbred rats by late ovariectomy. Cancer Detection and Prevention 32:65–71. https://doi.org/10.1016/j.cdp.2008.01.004

14. Krügel U, Fischer J, Bauer K, Sack U, Himmerich H (2014) The impact of social isolation on immunological parameters in rats. Arch Toxicol. https://doi.org/10.1007/s00204-014-1203-0

15. Mayer J, Donnelly TM (2013) Small Mammals : Rats. In: Veterinary Clinical Advisor Birds and Exotic Pets. Saunders, Elsevier Inc., London, pp 242–252

16. National Research Council. (1995) Nutrient Requirements of Laboratory Animals. National Academies Press, Washington

17. Sharp P, Villano JS (2012) The Laboratory Rat, 2nd Edition. CRC Press, Boca Raton

18. Mayer J, Sato A, Kiupel M, DeCubellis J, Donnelly T (2011) Extralabel use of cabergoline in the treatment of a pituitary adenoma in a rat. American Veterinary Medical Association 239:. https://doi.org/10.2460/javma.239.5.656

19. Burn CC (2008) What is it like to be a rat? Rat sensory perception and its implications for experimental design and rat welfare. Applied Animal Behaviour Science 112:1–32. https://doi.org/10.1016/j.applanim.2008.02.007

20. LaFollette MR, O'Haire ME, Cloutier S, Blankenberger WB, Gaskill BN (2017) Rat tickling: A systematic review of applications, outcomes, and moderators. PLoS ONE 12:e0175320. https://doi.org/10.1371/journal.pone.0175320

21. Popik P, Potasiewicz A, Pluta H, Zieniewicz A (2012) High-frequency ultrasonic vocalizations in rats in response to tickling: The effects of restraint stress. Behavioural Brain Research 234:223–227. https://doi.org/10.1016/j.bbr.2012.06.028

22. Pucheu-Haston CM, Brandao J, Krista LJ, Seals SL, Tully Jr TN, Nevarez JG, Evans D (2016) Zymbal Gland (Auditory Sebaceous Gland) Carcinoma Presenting as Otitis Externa in a Pet Rat (Rattus norvegicus). Journal of Exotic Pet Medicine 25:133–138

23. Maynard RL, Downes N (2019) Anatomy and Histology of the Laboratory Rat in Toxicology and Biomedical Research. Elsevier, Academic Press, London

24. Deacon RMJ (2006) Housing, husbandry and handling of rodents for behavioral experiments. Nat Protoc 1:936–946. https://doi.org/10.1038/nprot.2006.120

25. Huynh M (2019) Rat. In: Les 60 consultations les plus fréquentes des petits mammifères, Med'Com. Paris, pp 136–145

26. Fouriez-Lablee V, Vergneau-Grosset C, Kass PH, Zwingenberger AL (2017) Comparision between Thoraric Radiographic Findings and Postmortem Diagnosis of Thoracic Diseases in Dyspneic Companion Rats (Rattus Norvegicus). Vet Radiol Ultrasound 58:133–143. https://doi.org/doi:10.1111/vru.12459

27. Schoeb TR (2000) Respiratory Diseases of Rodents. The Veterinary Clinics of North America Exotic Animal Practice 3:481–496. https://doi.org/10.1016/s1094-9194(17)30083-x

28. Goodman G (2009) Rodents : respiratory and cardiovascular system disease. In: BSAVA Manual of Rodents and Ferrets. BSAVA, Gloucester, pp 142–149

29. Sinclair KM (2021) Rats and Mice. In: Exotic Animal Emergency and Critical Care Medicine. John Wiley & Sons, Inc., pp 330–348

30. Graham JE, Schoeb TR (2011) Mycoplasma pulmonis in Rats. Journal of Exotic Pet Medicine 20:270-276. https://doi.org/10.1053/j.jepm.2011.07.004

31. Mayer J, Donnelly TM (2013) Veterinary Clinical Advisor Birds and Exotic Pets. Saunders, Elsevier Inc.

32. Fisher PG (2006) Exotic Mammal Renal Disease: Causes and Clinical Presentation. Vet Clin North Ame Exotic anim Pract 9:33–67. https://doi.org/10.1016/j.cvex.2005.10.004

33. Hocker SE, Eshar D, Wouda RM (2017) Rodent Oncology. Veterinary Clinics of North America: Exotic Animal Practice 20:111–134. https://doi.org/10.1016/j.cvex.2016.07.006

34. Capello V (2011) Common Surgical Procedures in Pet Rodents. Journal of Exotic Pet Medicine 20:294–307. https://doi.org/10.1053/j.jepm.2011.07.002

35. Vergneau-Grosset C, Peña L, Cluzel C, Hawkins MG, Maccolini E, Sinclair K, Graham J, Sadar MJ, Guzman DS-M, Lair S, Langlois I, Paul-Murphy J (2019) Evaluation of deslorelin implant on subsequent mammary tumors of rats (Rattus norvegicus). Journal of Exotic Pet Medicine 31:108–116. https://doi.org/10.1053/j.jepm.2019.08.001

36. Hotchkiss CE (1995) Effect of surgical removal of subcutaneous tumors on survival of rats. Vet Med Assoc 206:1575–9

37. Vannevel JY (2006) Clinical Presentation of Pituitary Adenomas in Rats. Veterinary Clinics of North America: Exotic Animal Practice 9:673–676. https://doi.org/10.1016/j.cvex.2006.05.017

38. Inukai T (1928) On the loss of Purkinje cells, with advancing age, from the cerebellar cortex of the albino rat. J Comp Neurol 45:1–31. https://doi.org/10.1002/cne.900450102

39. Mota C, Taipa R, das Neves SP, Monteiro-Martins S, Monteiro S, Palha JA, Sousa N, Sousa JC, Cerqueira JJ (2019) Structural and molecular correlates of cognitive aging in the rat. Sci Rep 9:2005. https://doi.org/10.1038/s41598-019-39645-w

40. Altun M, Bergman E, Edström E, Johnson H, Ulfhake B (2007) Behavioral impairments of the aging rat. Physiology & Behavior 92:911–923. https://doi.org/10.1016/j.physbeh.2007.06.017

41. Malhotra S, Kritchevsky D (1975) Cholesterol exchange between the red blood cells and plasma of young and old rats. Mechanisms of Ageing and Development 4:137–145. https://doi.org/10.1016/0047-6374(75)90015-9

42. Hothorn T, Hornik K, Zeileis A (2006) Unbiased Recursive Partitioning: A Conditional Inference Framework. Journal of Computational and Graphical Statistics 15:651–674. https://doi.org/10.1198/106186006X133933

43. Chantry C (2007) C'est la ruée sur les rats. Le Parisien

44. Taylor J (2007) "Ratatouille" inspires a run on rats at British pet shops. The Independent

45. MacDonald B (2013) Disneyland Paris pulls back the veil on Ratatouille dark ride. Los Angeles Times

46. Neville V, Mounty J, Benato L, Hunter K, Mendl M, Paul ES (2021) Pet rat welfare in the United Kingdom: The good, the bad and the ugly. Veterinary Record 189:. https://doi.org/10.1002/vetr.559

47. Kuramoto K, Tahara S, Sasaki T, Matsumoto S, Kaneko T, Kondo H, Yanabe M, Takagi S, Shinkai T (2010) Spontaneous dwarf rat: A novel model for aging research. Geriatrics & Gerontology International 10:94–101. https://doi.org/10.1111/j.1447-0594.2009.00559.x

48. Swanson SM, Unterman TG (2002) The growth hormone-deficient Spontaneous Dwarf rat is resistant to chemically induced mammary carcinogenesis. Carcinogenesis 23:977–982. https://doi.org/10.1093/carcin/23.6.977

Acknowledgments

Firstly, I would like to acknowledge and thank my thesis supervisor, Dr. Szilasi, senior lecturer at the Department of Pathology of the UVMB, for her guidance. As a teacher she made me interested in pathology, oncology and histology. Our shared interest for exotic pets led to a great collaboration and research experience.

For granting me access to his patients records, I would like to thank Dr. Quinton, head of the Exotic Medicine Department of the French Hospital and Reference Clinic Advetia (92, France). The histological ancillary study of this thesis was made possible by Dr. Bulliot from the Exotic clinic (71, France), who kindly collected tumors from his rat patients, and whom I thank greatly. I also thank Pr. Bakony, assistant professor at the Department of Biostatistic of the UVMB, for helping me with coding in Rstudio. I am also deeply grateful to Dr. Vergneau-Grosset, assistant professor in Zoological medicine at the University of Montreal, for her professional input on my work and for sharing her precious knowledge about pet rats.

I would also like to thank my dear friends, Clara G, Clara M, Mathilde and Antoine, as well as my partner and future colleague, Björn, for supporting me and never doubting me.

I could not have written this thesis without my family's support. They encouraged me to pursue my dream of becoming a veterinarian and supported my choice to start my veterinary studies after another diploma, and for that I am deeply grateful. To my mother Kathy, my father Thomas, my siblings Laura, Paul and Clara, my grand-parents Gérald, Huguette, Jackie and Odette, my sister-in-law Noëlle and brother-in-law Romain, "Merci".

Last but not least, I dedicated this thesis to my amazing pet rats who inspired my work and whom I miss deeply.

Thesis progress report for veterinary students

Name of student: **Similowski Elsa**

Neptun code of the student: **GWRDLJ**

Name and title of the supervisor: **Pr. Míra Mándoki, Professor and head of department**

Department: **Department of Pathology**

Thesis title: **Classification of main diseases in pet rats**

Consultation – 1st semester

Timing				Topic / Remarks of the supervisor	Signature of the supervisor
	year	month	day		
1.	2021	09	22	Thesis writing plan	
2.	2021	09	24	Delivery of mammary gland tumors for ancillary study	
3.	2021	10	19	Review of introduction	
4.	2021	11	08	Statistical analysis plan	
5.	2022	12	18	Review of material and method Literature review plan	

Grade achieved at the end of the first semester: 5

Consultation – 2nd semester

Timing				Topic / Remarks of the supervisor	Signature of the supervisor
	year	month	day		
1.	2022	03	01	Correction of literature review	
2.	2022	04	25	Discussion of histopathology results	
3.	2022	05	16	Review of main study results	
4.	2022	05	22	Review of thesis discussion	
5.	2022	06	07	Finalization of thesis paper, translation of summary	

Grade achieved at the end of the second semester: 5

The thesis meets the requirements of the Study and Examination Rules of the University and the Guide to Thesis Writing.

I accept the thesis and found suitable to defence,

.....
signature of the supervisor

Signature of the student: .....

Signature of the secretary of the department: .....

Date of handing the thesis in: 2022/10/03

DECLARATION

I hereby declare that the thesis entitled "**Classification of main diseases in pet rats**" is identical in terms of content and formal requirements to the TDK research paper submitted in 2022.

Budapest, 2023. October 16th

……..

Elsa Similowski