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Ocular Surface Disease in Rodents (Guinea Pigs, Mice, Rats, Chinchillas)

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KEYWORDS
- Cornea
- Chromodacryorrhea
- Dystrophy
- Conjunctivitis
- Scurvy
- Keratoconjunctivitis sicca

KEY POINTS
- The small size of rodent eyes makes examination and individualized treatment challenging.
- As with all exotic species, improper husbandry plays a disproportionate role in the development of many rodent corneal diseases.
- Although rodent eyes have their own unique anatomy, they remain susceptible to many of the same diseases that affect dogs and cats. Emphasis has been placed on conditions unique to the species discussed herein.
- Mice and rats frequently present with varying forms of corneal opacification and deposits that may not be of clinical significance.
- Rodents are hypsodonts, with enamel extending past the gum line and a continuous growth of their teeth, making them highly susceptible to uneven wear and overgrowth that can be reflected in secondary ocular disease.

INTRODUCTION
Rodents are mammals of the order Rodentia, and constitute up to 40% of all known mammal species. Rodents are defined by their hypsodont dentition, with continuously growing incisors of the upper and lower jaw. The species discussed herein are domesticated from their wild counterparts for laboratory, farm, and pet purposes. The presence of inbred strains, most notably in mice and rats, must be considered when examining pet rodents, as many originate from laboratory strains. These genetic ocular defects are occasionally sought as models for human disease, but they can also be unwelcome byproducts linked to the desired trait. As social species that naturally live in colonies, herd management and individual welfare may be presented to the

The author has nothing to disclose.
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Vet Clin Exot Anim 22 (2019) 15–26
https://doi.org/10.1016/j.cvex.2018.08.001
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attending veterinarian. Mice, rats, and chinchillas are thought to be predominantly nocturnal to crepuscular, while guinea pigs are diurnal. Their eye anatomy reflects their origins. All rodents have a cornea divided into stratified epithelium, a Bowman layer (epithelial basement membrane), stroma, Descemet membrane, and the endothelium.

**GUINEA PIG (CAVIA PORCELLUS)**

Guinea pigs are the largest of the rodents covered in this section. They live an average of 4 to 5 years, but can live as long as 8 years. They are not found in the wild, but are a domesticated relative of other species of cavi. Once used frequently for research studies, they are now primarily a household pet.

**Normal Anatomy**

Fine superficial corneal neovascularization (usually extending from limbus axially to the first or second third of the cornea) has been reported as a normal finding in fetal, newborn, and adult guinea pigs. However, a later confocal microscopy study did not confirm this.

Small palpebral conjunctival outpouchings were noted in the upper and lower fornixes in almost all examined animals according to Dwyer and colleagues (1983), and were determined via histology to be masses of lymphoid tissue. Their prevalence across individuals resulted in researchers concluding these foci to be a normal finding.

Guinea pigs have a remarkably low corneal sensitivity (or a high pressure threshold is needed to elicit a blink), replicated in 3 studies. In these studies, the guinea pig was observed to have limited to no reflex tearing, which may be a component of the lack of corneal sensitivity (Fig. 1, Table 1). This plays an important clinical role.

*Staphylococcus epidermidis*, *α*-hemolytic *Streptococcus*, and *Corynebacterium* were the top 3 aerobic commensal isolates from normal healthy guinea pigs.

**Adnexa-Related Corneal Disease**

Trichiasis, or hair from the skin contacting the cornea, occurs in a wire-haired breed of guinea pigs, Texel cai; 0.8% of surveyed animals had this congenital abnormality. After birth the wiry hair can curl inwards into the eye, causing corneal ulcers and epiphora. Lubricating the eyes and hair around frequently immediately after birth until the hair grows in a more controlled manner can help.

Fig. 1. Guinea pig undergoing Schirmer tear test. Guinea pigs have been shown to have a remarkably insensitive cornea relative to other domesticated species, and little to no reflex tearing. (Courtesy of Dr Stacy Andrew.)
Entropion, either primary or cicatrical after an eyelid trauma, is reported in guinea pigs. Entropion is typically treated via a variety of blepharoplasties. To the author’s knowledge, blepharoplasty in a guinea pig has not been reported. Because of their small adnexal structures, they may be more suited to a hyaluronate injection that can evert the lids semipermanently or to frequent lubrication of the cornea to mitigate pathology.

**Primary Corneal Disease**

To the author’s knowledge, guinea pigs are the only species discussed in this article formally reported to exhibit periocular dermoids. Large corneal dermoids can compromise vision by their opacification of the visual axis. Haired dermoids may contaminate the conjunctival sac by harboring foreign material and debris. The treatment of choice for dermoids is surgical removal via keratectomy, but given the thinness of the guinea pig cornea (Table 2), this treatment should be undertaken with great care.

| Corneal parameter | STT 1 (mm/min) | PRRT (mm/15 s) | CTT (g/mm²) |
|-------------------|----------------|----------------|-------------|
| Guinea pig        | 3 mm⁴          | 21.2 ± 4.2⁴    | 6.64⁴       |
|                   | 0.36 ± 1.1 (Duncan Hartley cavies)⁵ | 16.0 ± 4.7⁵ | 3.7⁵       |
|                   | 9.65 ± 3.5 (used a 3 x 35 mm strip instead of traditional 5 x 40 mm)³ |                 | 7.75¹       |
| Mouse & Rat       | 6 – 8⁶         | ~0.96 (6 cm)⁷  | ~12.8 (0.8 ± 0.9 mm, sedated rats, author noted result was unusually high)⁹ |
| Chinchilla        | 1.07 ± 0.54⁹   | 14.6 ± 3.5¹⁰   | ~10.84 (1.24 ± 0.46 cm)⁹ |

Selected selected tear film parameters in rodents. Mean ± standard deviation is included when available. Corneal sensitivity is reported in g/mm². When applicable, a standard conversion table for Cochet-Bonnet aesthesiometer was used to convert from cm to g/mm². Range: 6.0-0.5 cm = 0.96-17.68 g/mm².

Ocular Surface Disease in Rodents

To the author’s knowledge, guinea pigs are the only species discussed in this article formally reported to exhibit periocular dermoids. Large corneal dermoids can compromise vision by their opacification of the visual axis. Haired dermoids may contaminate the conjunctival sac by harboring foreign material and debris. The treatment of choice for dermoids is surgical removal via keratectomy, but given the thinness of the guinea pig cornea (Table 2), this treatment should be undertaken with great care.

| Table 2 | Selected corneal parameters in rodents and their respective method of measurement. Mean ± standard deviation is included when available |
|---------|---------------------------------------------------------------------------------------------------------------|
|         | **Central Corneal Thickness (µm)** | **Endothelial Cell Count (Peak, Cells/mm²)** | **Mechanism of Measurement (Respectively)** |
| Guinea pig | 227.85 ± 14.09⁹ | 2352 ± 49³ | Pachymetry Confocal |
| Mouse | 108.0 ± 5.1¹³ | 1587 ± 74¹⁵ | Optical coherence tomography Optical low coherence reflectometer Confocal |
| Rat | 159.08 ± 14.99 (Winstar)¹⁴ | 1951 ± 67¹⁵ | Optical low coherence reflectometer Confocal Histology |
| Chinchilla | 340 ± 30⁹ | 3423¹⁷ | Pachymetry Contact specular microscope |
Corneal lipidosis (bilateral stromal lipid dystrophy) is also reported.\textsuperscript{11} This has been described as a bilateral paracentral lipid deposition with varying degrees of density and coverage. This appears to be less common than the corneal dystrophy reported in mice and rats.

**Corneal Foreign Bodies**

As previously discussed, guinea pigs have been found to have a low corneal sensitivity and a negligible ability to produce reflex tears, thereby placing them at an unusual risk for ocular foreign bodies. They have also been noted to have an unusually low blink rate.\textsuperscript{2,5} This is compounded by their typical housing, in a bedded enclosure with straw and hay at eye level. In a survey of 1000 guinea pigs, 4.7\% had conjunctivitis, which was frequently secondary to a traumatic injury from a foreign body.\textsuperscript{11} This had also been seen in a previous survey of guinea pigs.\textsuperscript{1} It has been theorized that the corneal vessels and lymphoid tissue unique to guinea pigs eyes were an evolved strategy over increased blinking and discomfort seen in other animals. That being said, foreign bodies should still be taken seriously and treated promptly. Per Williams and Sullivan (2010), these foreign bodies, along with congenital trichiasis, seemed to be the most irritating for the animals.

**Treatment Considerations**

Guinea pigs have lost their ability to endogenously form ascorbic acid, like people and capybaras, and are therefore at greater risk for scurvy relative to other species of rodent. Scurvy often starts with mucous membrane disease including petechiation and ulceration. Dry eye has also been reported as a sequela. Vitamin C is used in other species as an anticollagenase.\textsuperscript{18} Therefore, supplementation during times of ulceration, especially a melting ulcer (Fig. 2), is likely to be beneficial regardless of nutritional status. Many foods are rich in vitamin C, and there are also nutritional supplements available.

Because guinea pigs are the largest of the species discussed here, topical treatment is more feasible in terms of administration. Systemic absorption is still a risk, and so prolonged treatment, especially with topical steroids and nonsteroidal anti-inflammatory drugs, should be approached cautiously. Guinea pigs are typically docile and amenable to handling. Given their common place as a household pet, individualized treatment including frequent topical medication is more achievable.

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**Fig. 2.** Infected corneal ulcer in a guinea pig. This is a disease process in which guinea pigs would benefit from additional supplementation of vitamin C for normal physiology and also for its anticollagenolytic properties. (Courtesy of Dr Stacy Andrew.)
MICE (MUS)

Mice are the smallest rodent discussed in this section. They are one of the most successful mammals on Earth today and are viewed as pets, research subjects, vermin, and vectors. They are the most common experimental laboratory animal in recent decades because of their homology with people, small size, and rapid reproduction. Breeding onset is about 50 days, and the life span is typically 1 to 2 years when kept as pet.

Normal Anatomy

A detailed comparative study was performed using confocal microscopy of normal 4-month-old Swiss mice. Bowman layer was observed between basal epithelial cells and the anterior stroma. Similar to rats, the anterior and posterior stroma had numerous anuclear reflective stellate structures. Endothelial cell density was also determined (see Table 2).

Just like guinea pigs, corneal vascularization has been reported to be a normal finding in 2 mouse strains – athymic and euthymic nude mice.

Schirmer tear test with traditional Whatman filter paper is not possible in the species based on size, but normal tear volume can be assessed via phenol red thread testing (see Table 1).

Mice in Research

No article on mice would be complete without touching on their significance as a research model.

Mice are models for certain ocular surface diseases, most notably Sjögren syndrome (SS), a common autoimmune dry eye syndrome in people. Mice exhibiting SS-like characteristics have a mononuclear cell infiltration into exocrine glands, loss of acinar tissue, and secretory dysfunction. Corneal pathology includes corneal vascularization, keratinization, and the propensity for bacterial corneal ulcers (Fig. 3). Numerous murine strains have been used for their SS-like disease manifestations,
and an excellent review article summarizing the various models has been published.\textsuperscript{20} Initially these characteristics were spontaneously arising, but later the alterations were associated with gene knockout, resulting in transgenic mice that model aspects of the disease.

Mice have helped make a breakthrough in the link between primary open-angle glaucoma and the thickness of the central cornea. Mice were recently used to identify a transcription factor, POU6F2, that is associated with central corneal thickness and susceptibility of retinal ganglion cells to injury.\textsuperscript{21}

**Primary Corneal Disease**

Corneal deposits are a common finding in laboratory mice (Fig. 4). Deposition of calcium in Bowman layer with or without accompanying vascularization has been reported in both normal and SS-model mice (MRL/Mp strain).\textsuperscript{22} It is speculated that these deposits are genetically linked, but excess ammonia in cage bedding may also contribute.\textsuperscript{23} After investigating husbandry, treatment of the deposits is not performed.

Peter anomaly, a form of anterior segment dysgenesis, has been documented spontaneously mice and is being used as a model for the disease.\textsuperscript{24,25} The keratolenticular adhesion results in the presence of a leukoma (corneal opacity) of varying size. Corneal transplant is the treatment in people, but even then overall visual prognosis is poor.\textsuperscript{26} This treatment has not been reported in veterinary patients. Additionally, intraocular pressure should be assessed, as aggressive glaucoma often accompanies these changes.\textsuperscript{24}

Fig. 4. Severe example of corneal dystrophy in a laboratory mouse. This individual was considered comfortable (no blepharospasm) and clinically acceptable as a research subject.
**Treatment Considerations**

The primary limiting factor in treatment of mice is their small size. Corneal transplants have been performed successfully, but the success rate of these surgeries has not been published, as most studies focus on graft rejection, excluding those leaking or infected grafts from statistical analysis.²⁷,²⁸ In veterinary medicine, conjunctival grafts are more commonly performed relative to clear corneal transplants, but to the author’s knowledge, this surgical technique has not been reported in any the species covered in this article.

The small size of the mouse also means many topical treatments have the potential for significant systemic absorption. Even the application of a topical sodium channel blocker to facilitate examination should be applied with judiciousness given its potential for systemic toxicity.²⁹

**RATS (RATTUS)**

Rats and mice are closely related and only differentiated by their size, not specific taxonomic criteria. This section focuses on the most common rat species, *Rattus norvegicus* (brown rat and laboratory rat), *Rattus rattus* (black rat), and fancy rat (*Rattus norvegicus*). Life span is typically 2 years when kept as a pet, but they can live up to 3 years.

**Normal Anatomy**

Rats and mice have 3 tear-producing glands, the intraorbital, the extraorbital, and the Harderian. The Harderian is a well-studied exocrine gland associated with the third eyelid. This is what produces the porphyrin and lipid-laden tears in rats and is of clinical significance because of the vivid, visible tears it produces in several diseases.³⁰

**Adnexa-Related Corneal Disease**

Tear staining or chromodacryorrhea refers to a dark stain below the inner corner of the eye, caused by porphyrin-pigmented secretion from the Harderian gland. It indicates stress in rats but can have other indirect causes. Chromodacryorrhea was produced within 15 minutes in young rats following intravenous injection of acetylcholine or acute stress induced by limb restraint.³¹ By a similar mechanism, the presence of chromodacryorrhea was even identified as a welfare indicator on commercial pig farms.³² This finding may gain more attention in the laboratory animal sphere, where welfare is paramount. The presence of chromodacryorrhea should not be ignored, as it is not a normal finding. As discussed, it may be caused by environmental stress, physical illness, or underlying disease. Furthermore, even when not hypersecreted, porphyrins are labile until photic energy. Exposure to high-intensity light induced necrosis of the glandular cells in a study on a research population of Wistar rats.³³ The injury appeared to be caused by the creation of free radicals within glandular cells, probably as a result of photodynamic action on the porphyrins in the gland. Proper husbandry with a day-night cycle is essential for rat health and welfare.

**Primary Corneal Disease**

Certain strains of rat are reported to have a high rate of subepithelial mineralization (corneal dystrophy), just like mice. Clinically, these opacities are subepithelial (associated with abnormal epithelial basement membrane, Bowman layer). They vary from a few punctate opacities only visible with a slit lamp to marked dense opacities covering a majority of the corneal surface (*Fig. 5*). A thorough ophthalmologic and histopathological study was performed on Fischer-344 (F344) rats that demonstrated a high incidence of corneal basement membrane dystrophy.³⁴ In the most severely affected
strains, this correlated to a systemic basement membrane disorder. It was speculated that these opacities are relatively under-reported for several reasons, and in this study anywhere from 50% to 100% of rats examined from various breeders had corneal dystrophy. Thankfully, these opacifications did not appear to cause the animals discomfort or have an adverse effect on normal physiologic function. However, in people, epithelial basement membrane dystrophy is associated with recurrent corneal erosions.\textsuperscript{35}

F344 rat strains are also unusually prone to intraocular tumor, which may manifest as a pigmented opacity in the cornea. Orbital malignant schwannomas and amelanotic melanoma are reported.\textsuperscript{36}

**Infectious Corneal Disease**

Sialodacryoadenitis (SDA) is a highly contagious common viral infection in rats. SDA is caused by rat coronavirus and can spread rapidly, especially through laboratory colonies. Anorexia occurs during these viral infections. The virus has a tropism for epithelial cells and can infect the Harderian and extraorbital glands, causing ocular disease.\textsuperscript{37} Often, lacrimal gland involvement leads to reduced tear production. Young rats are especially susceptible to SDA, and the infection can occur in the lower respiratory tract, resulting in pneumonia. Thankfully, the primary disease is usually self-limiting and resolves within a week; however, secondary signs may take up to a month to fully resolve. Diagnosis is confirmed by detecting coronavirus antigen with reverse transcriptase polymerase chain reaction (RT-PCR)\textsuperscript{38} or serologic testing.\textsuperscript{39}
Treatment Considerations

Treatment limitations are similar between rats and mice. Their small size and colony habitat often preclude topical treatment.

CHINCHILLA (DOMESTICATED FROM CHINCHILLA LANIGERA)

Of the species covered, chinchillas are the most recently domesticated and the least studied. They are also the longest lived in this group of rodents, living on average 10 years in captivity, although chinchillas living into their 20s have been reported.10 Chinchillas were originally bred for fur but since have become pets and are used in scientific research. Of the species discussed here, chinchillas have the most recent literature regarding presentation as a pet for ocular examination, and less research-based publications relating to their ocular biology. In a recent retrospective study over the course of 10 years, 7.8% of chinchillas presenting to a tertiary clinic had primary ophthalmic complaints.10

Normal Anatomy

Chinchillas are characterized as having a shallow orbit, and proptosis can easily be induced with pressure on the eyelids; therefore, care must be taken when examining them.40 Chinchilla endothelial cell density has been determined via specular microscopy (see Table 2).17 Like in other species, cell density decreases and pleomorphism increases with age.

Adnexa-Related Corneal Disease

Of the available publications and consensus among zoo veterinarians, ocular discharge appears to be the most common condition. The discharge/epiphora is suspected to be secondary to dental disease, as in all rodents, chinchillas are hypsodonts with continually growing teeth. This continual growth is compounded by their longevity and potential for inappropriate husbandry.41 Root extension into the nasolacrimal duct and subsequent epiphora is the most common clinical sign. Chinchillas with only clear epiphora are typically considered primary dental disease patients.10

Infectious Corneal Disease

Bacteria normally populate the conjunctival fornix. In chinchillas,9 Lima and colleagues (2010) found that Streptococcus species (27.45%) was most commonly isolated, followed by Staphylococcus aureus (23.52%), and finally coagulase-negative Staphylococcus (19.60%). This is in comparison to42 Ozawa and colleagues (2017), who studied chinchillas affected by bacterial conjunctivitis. In diseased individuals, 61.5% yielded a gram-negative isolate (50% being Pseudomonas aeruginosa). The remainder yielded gram-positive isolates, Staphylococcus species being most common (26.9%). Chinchillas with acute conjunctivitis (1–3 days) were much more commonly affected by gram-negative organisms, and most cases were unilateral; 36.7% had concurrent dental disease.

Treatment Considerations

As chinchillas often experience conjunctivitis secondary to other disease, a thorough dental examination addressing the underlying cause is essential. However, despite this clinical paradigm, most chinchillas with bacterial conjunctivitis are reported to fully resolved with topical with or without oral antimicrobial therapy within 3 weeks.42 Being larger in size than rats and mice and more typically housed in a pet environment, chinchillas may be more amenable to topical medication, similar to guinea pigs.
SUMMARY

Most diseases specific to rodents are either congenital or related to husbandry. Unfortunately, their small size limits many of the typical surgical treatments routinely performed in other veterinary species. Once husbandry is addressed, treatment may be limited to mitigation of the disease process but not complete resolution.

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