Computed tomographic grading of middle ear disease in domestic rabbits (Oryctolagus cuniculi)

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Abstract

Ear disease, involving the middle and external ear, is commonly reported in pet rabbits, with lop-eared breeds predisposed. CT is the most reliable imaging modality for identifying otitis media (OM) in rabbits. This study aimed to develop a CT-based grading scale to classify the severity of CT changes in rabbits with presumed OM. Three observers independently reviewed CT images of 36 rabbits with OM. For both OM and material within the external ear canal, a grade of I to IV was used, (I=mild, IV=severe disease) and the level of agreement between reviewers was statistically evaluated. The study demonstrated that grades from the three reviewers showed a strong level of interobserver agreement. Comparisons between clinical signs and CT grade were also evaluated. Rabbits with grade IV OM had a high grade of material in the external ear canal. A high proportion of rabbits (83 per cent) underwent CT scanning conscious, demonstrating that diagnostic quality CT images are achievable without the need for anaesthetic intervention, minimising patient risk. This novel CT-based grading scale provides a methodology to correlate grade of disease with clinical signs, ear canal cytology, predisposing factors, treatment options and outcomes for rabbits with ear disease.

Introduction

Ear disease, involving the middle ear and external ear canal, is a common problem in domestic rabbits. Although it can occur in any rabbit, lop-eared breeds appear predisposed.1–3 In the UK, lop-eared rabbits are popular, with nine recognised breeds, varying in size from the mini lop to the English lop.4 Altered ear anatomy, with folding of the pinna and stenosis of the distal external ear canal, predisposes to ceruminous accumulations. Initially asymptomatic, disease can progress to otitis externa (OE) with headshaking, ear scratching and head shy behaviour.1 5 Clinical findings may include the presence of bacteria and inflammatory cells, inflammation of the mucosal wall, lateral pouching to the distal external ear canal and bulging or rupture of the tympanum. Material from the external ear canal may enter the tympanic bulla, when rupture of the tympanum occurs, causing secondary otitis media (OM).2 Chronic OM can lead to loss of hearing, which has been reported in geriatric rabbits.5 OM can also occur via ascending infection from the Eustachian tubes, secondary to respiratory disease.7 8

OM is commonly asymptomatic in rabbits, therefore diagnosis by conventional methods can be challenging.9 Even severe OM with bone lysis can be overlooked during physical examination, as integrity of the lateral tympanic bulla wall is difficult to evaluate by palpation, due to the position of the mandible.10 Severe, progressive disease however, has been associated with clinical signs of ipsilateral facial contracture, soft tissue swelling and abscessation lateral to the tympanic bulla.1 11 12 In some cases, this can progress to otitis interna with nystagmus, head tilt and other associated neurological signs.13–16 Prompt diagnosis and treatment of ear disease is therefore of critical importance.

CT scanning is the most accurate diagnostic method for determining the presence of fluid in the tympanic bulla of rabbits; ultrasonography and radiography are less accurate for diagnosing early to intermediate disease.11 17–21 However, there is no well-validated clinical scale which allows the severity of CT changes
seen in rabbits with OM to be objectively defined. This limits the ability of clinicians to objectively investigate the factors which influence disease severity. In addition, it is difficult for the efficacy of novel treatments to be meaningfully assessed if the grade of underlying disease process cannot be quantitatively evaluated.

A secondary issue is the use of anaesthesia to facilitate CT investigation. Rabbits are a prey species that can be skilled at masking clinical signs of disease. Subtle changes, indicative of disease, are often overlooked by owners. It is commonplace for a rabbit to present for veterinary assessment once significantly debilitated. Diagnostic procedures in sick patients, involving anaesthesia, should be carefully considered as rabbits have an increased risk of anaesthetic-related death. Consequently, the avoidance of chemical restraint in clinically unwell patients is therefore advantageous.

The primary aim of this study was to evaluate the degree of agreement between reviewers in assessing CT changes associated with OM cases, with the aid of a grading scale for determining the severity of middle ear disease in the domestic rabbit. The secondary aim was to evaluate the feasibility of conscious CT scanning in the identification of ear disease. The authors hypothesise that a simplified assessment of CT-diagnosed middle ear disease can be achieved with a grading system that has a high level of interobserver agreement. The authors also hypothesise that the CT grading of OM would correlate well with the clinical signs of the patient.

Materials and methods
A retrospective analytical study was conducted. CT records from January 2014 to January 2017 in the database of the Royal (Dick) School of Veterinary Studies, University of Edinburgh, Hospital for Small Animals, were retrospectively reviewed for the presence of OM in pet rabbits. For each patient, medical records were analysed identifying the age, breed, sex, neuter status, ear conformation, presenting complaint, CT restraint method and presence or absence of ear disease based on physical examination findings. Rabbits included in the study were diagnosed with OM during CT scanning performed as part of their diagnostic investigation for a clinical complaint. Due to the potentially asymptomatic nature of OM, all clinical complaints were included. All CT images over a three-year time period were included in the study, with the exclusion of repeated scans from individual patients to prevent duplication of data. A helical multidetector 4-slice CT (Somatom Volume Zoom, Siemens, Germany) was used from January 2014 to July 2016, with another helical multidetector 64-slice CT unit (Somatom Definition AS, Siemens, Germany) from October 2016. A standard whole body CT protocol was used for all patients, with scan settings of a pitch of 1.5, tube potential of 120 kVp, reference tube current of 160 mA, slice thickness of 1.5 mm, matrix 512×512 and reconstruction with low and high frequency algorithms. Scan tube current was modulated by an automatic exposure control system (Care Dose 4D, Siemens Medical Solutions, International). The total time taken for completion of all scans was less than five minutes.

Conscious restraint was facilitated using a VetMouseTrap plexiglass tube, (Universal Medical Systems, Solon, Ohio, USA), with the patient in sternal recumbency. Tube dimensions were 40 cm length with 18 cm diameter. Flow-by oxygen was provided throughout the procedure. Visual stimulation was reduced with the reduction of light levels and placement of a blanket over the restraint device. Environmental noise was also minimised. A towel was provided within

Figure 1 Rabbits were positioned on a towel in sternal recumbency in a plexiglass tube device, with a rolled towel in a U-shape around them (A). The device was secured for patient safety (B), and a blanket was used to reduce visual stimulation while the device was secured to the CT table (C). The front of the tube remained uncovered, allowing provision of supplementary oxygen and observation of the patient from the CT control room (D).
the device to improve comfort and reduce movement (figure 1, figure 2).

In the small number of cases patients were sedated, protocols used were dependent on clinician preference. These included either fentanyl/fluanisone (Hypnorm, VetaPharma, UK) at 0.3 ml/kg subcutaneously or midazolam (Hynovel 10 mg/2 ml, Roche, UK) at 0.5 mg/kg and buprenorphine (Buprecare 0.3 mg/ml, Animalcare, UK) at 0.03 mg/kg both administered subcutaneously. Three rabbits underwent a general anaesthetic for CT scanning. The protocols used for all three cases were premedication of midazolam at 0.5 mg/kg and buprenorphine at 0.03 mg/kg administered subcutaneously. The patients were induced with alfaxalone (Alfaxan 10 mg/ml, Jurox, UK) at 1–2 mg/kg given intravenously, before intubation with an appropriate sized, uncuffed endotracheal tube. General anaesthesia was maintained with inhalation isoflurane (Isoflurane-Vet 100% w/w Inhalation vapour, liquid), using a range of 2 per cent–3 per cent.

Following discussions between three observers, all highly experienced in rabbit CT interpretation, a grading scale was produced to evaluate the CT appearance of ear disease. For both OM and the quantity of material within the external ear canal, a grade of I to IV was used (I=mild, IV=severe disease). CT images for all rabbits diagnosed with OM (n=36) within the study period were retrieved and blindly evaluated independently by three observers. High-resolution CT images of the middle and external ear were analysed in transverse plane using bone and soft tissue algorithms. Both ears in each animal were assessed using a blinded method. A CT diagnosis of the presence or absence of OM and the quantity of material in the external ear canal was determined, along with the grade of severity of the findings in all 72 ears. To avoid clustering of data, the authors considered each rabbit as a single unit for statistical analysis. Comparative data analysis was performed on the results using an online statistics program,25 26 with the OR calculated using a case-control study for 2×2 table and the P value obtained using a Fisher’s exact test (two-tailed). For all analyses, a P value of <0.05 was considered to be statistically significant. The data were analysed for agreement between observers using concordance statistics.27–29 Intraclass correlation (ICC) was used to assess the rating reliability of the three observers, by comparing the variability of disease grade awarded, after evaluation of the same CT images. The ICC was estimated using a two-way random effects, of a single rater, assessing the level of absolute agreement between observers30 31 (figure 3, figure 4).

**Results**

One hundred and ninety-nine rabbit CT scans were performed between January 2014 and January 2017. Of these, 161 rabbits underwent their first CT scan. The remaining 38 scans included second or third CT scans performed on the same animal at a subsequent time point within the three-year study period and were therefore excluded from this study. CT scans were analysed to determine the presence or absence of ear disease of which 36 of the 161 rabbits were diagnosed with OM from CT examination. In this cohort, two-thirds (24/36) of rabbits with OM had lop ear conformation, with upright ears in one-third (12/36) of rabbits. The total study population had an equal distribution

| Table 1 | Material within the external ear canal CT grading scale: descriptive reference |
|---------|--------------------------------------------------------------------------------|
| Grade I | ► Material filling the external ear canal from the tympanum to the proximal aspect of the acoustic meatus cartilage.  
  ► No deviation of the tympanum. |
| Grade II | ► Material filling the external ear canal from the tympanum to the proximal aspect of the acoustic meatus cartilage.  
  ► No deviation of the tympanum.  
  ► Lateral pouching of the external ear canal. |
| Grade III | ► Material filling the external ear canal from the tympanum to the proximal aspect of the acoustic meatus cartilage.  
  ► Ventral deviation or obliteration of the tympanum. |
| Grade IV | ► Material filling the external ear canal from the tympanum to the proximal aspect of the acoustic meatus cartilage.  
  ► Ventral deviation or obliteration of the tympanum.  
  ► Lateral pouching of the external ear canal. |

| Table 2 | Otitis media CT grading scale—descriptive reference |
|---------|---------------------------------------------------|
| Grade I | ► Incomplete fill of material in the tympanic cavity.  
  ► No tympanic bulla involvement, with normal anatomical shape and wall thickness. |
| Grade II | ► Complete fill of material in the middle ear.  
  ► No tympanic bulla involvement, with normal anatomical shape and wall thickness. |
| Grade III | ► Material (either complete or incomplete fill) in the tympanic cavity.  
  ► Tympanic bulla involvement without alteration to bulla shape, but areas of bone lysis and/or wall thickening. |
| Grade IV | ► Tympanic bulla derangement with alteration to bulla shape and areas of bone lysis or expansile anatomical distortion. |
between lop (n=80) and upright (n=81) eared rabbits. In the cohort of 161 rabbits, lop-eared breeds were significantly more likely to have OM (P=0.02), with OR of 2.46 (95 per cent CI 1.13 to 5.36), than those rabbits with upright ears.

In the external ear canal, the presence of heterogeneous fluid/soft tissue dense ill-defined material within the external ear canal lumen was assessed on CT. Of the 36 rabbits with OM, concurrent similar material was present in the external ear canal in 32/36 rabbit and was graded by CT appearance (figure 3), per individual ear, as grade I (n=14), grade II (n=8), grade III (n=11), grade IV (n=29), respectively. In 83.3 per cent (30/36) of rabbits, the material was present in both external ear canals. In the rest of the patients the same material within the external ear canal was visible, unilaterally in 5.6 per cent (2/36) of cases and absent bilaterally in 11.1 per cent of rabbits (4/36).

Of the 36 rabbits with OM, 72 individual ears were evaluated. The grades awarded per ear were grade I (n=20), grade II (n=8), grade III (n=3), grade IV (n=17). Bilateral disease was present in one-third (12/36) of rabbits, with unilateral OM in two-thirds (24/36) of cases. In unilateral cases, disease was absent in one side (n=24).

Within the OM cohort, 21/36 were referral cases, with 15/36 first opinion cases. Only 14 of the rabbits were presented specifically for ear disease investigation. Undetected middle ear disease (either by owner or referring veterinary surgeon) was diagnosed in 22/36 rabbits that presented for other clinical complaints (table 3).

Of the 17 cases with grade IV OM, no disease was present in (n=7) the contralateral ear. The remaining 10 rabbits had unilateral disease with concurrent OM at grade I (n=1), grade II (n=2), grade III (n=1) and grade IV (n=3). There was no obvious correlation between severity of OM grade between the right and left ear (table 4).

Clinical signs evaluated from the retrieved 36 patient records included: head shaking (n=4), ear scratching (n=3), presence of palpable ear base swellings (n=12), material visible to the naked eye in the external ear canal (n=28), odour from the ear (n=1), altered ear position (n=2), mass in the external ear canal (n=2), facial contracture (n=4), altered balance (n=2), head tilt (n=3), perceived deafness (n=1) and absence of clinical signs (n=1).

OE was confirmed by cytological evaluation of external ear canal contents in twelve cases. Of the 36 rabbits, the majority had more than one clinical sign associated with ear disease. Rabbits had one clinical sign (n=8), two clinical signs (n=10), three clinical signs (n=4) and four clinical signs (n=11). In three cases there were no clinical signs detected.

There appeared to be a strong correlation between grade IV OM and the volume of material in the external ear canal. Of the seventeen cases with grade IV OM, fifteen had grade IV of material within the external ear canal, with the remaining two having grade III (table 5).
Of the 12 cases with palpable ear base swellings, OM was confirmed as grade IV (n=9), grade III (n=1), grade II (n=1) and absence of OM (n=1).

Three out of four rabbits with facial contracture had grade IV OM, with one having grade I disease.

An excellent ICC inter-rater agreement was noted between the three observers during the grading of both middle ear disease and material within the external ear canal. The ICC of material within the external ear canal was 0.89 (95 per cent CI 0.83 to 0.94), for the right ear and 0.85 (95 per cent CI 0.76 to 0.92), for the left ear. Collectively between the three observers the ICC for material within the external ear canal was 0.87 (95 per cent CI 0.82 to 0.91).

For OM the ICC for the right ear was 0.98 (95 per cent CI 0.96 to 0.99) and 0.96 (95 per cent CI 0.94 to 0.98) for the left. There was a higher collective ICC for OM, between the three observers, at 0.97 (95 per cent CI 0.96 to 0.98).

Eighty-three per cent (134/161) of the total study population underwent conscious CT scanning, using the VetMouseTrap plexiglass restraint method. Fifteen per cent (24/161) of rabbits were sedated, with two per cent (3/161) of rabbits requiring general anaesthetic. CT scanning was performed conscious in 94.4 per cent (34/36) of the rabbits diagnosed with OM.

**Discussion**

In this study, a significantly greater number of rabbits with lop-eared conformation were diagnosed with OM, compared with rabbits with upright ears. Due to the popularity of lop breeds as pets, the incidence of ear disease in the pet rabbit population is likely to remain prevalent. As OM is often asymptomatic, knowledge of when to use CT examination is key in disease identification. CT interpretation of the rabbit head is well documented in the literature. A CT grading system for ear pathology however, has not been previously described in domestic rabbits. With some cases that see a worsening of otitis over time, the ability to categorise disease severity is clinically useful, both in serving as a prognostic indicator and for aiding in selection of appropriate treatment.

All the observers were highly experienced in interpreting CT images of rabbits. The level of agreement in use of the grading scale with the ICC of OM was high, performing better than the ICC of classification of material within the external ear canal, which was moderately high (0.97 and 0.87, respectively). This provides evidence that the grading system is effective at providing an easy-to-interpret scale, for disease quantification. The disparity between the two results accounts for the difference in bone versus soft tissue involved with the two ear regions. Alterations to the tympanic bulla, with presence of material in tympanic cavity, were readily identifiable by CT. The tympanic membrane had increased definition when material from the external ear canal was pressing against the tympanum, highlighting the distorted alignment, and when there was thickening of the tympanum, presumed secondary to the effects of OM.

With material within the external ear canal, ear position during the CT scan (ie, lateral to the face vs resting on the dorsum) affected the certainty of the presence of subtle ear base swellings in a small number of cases. To gain the most reliable results from the material within the external ear canal CT grading system, the rabbit’s ears should rest on the dorsum. This prevents misinterpretation caused by artificial ‘folding’ and pouching of the ear due to patient position within the restraint box. The use of an intravenous contrast agent during CT evaluation would also provide further clarity as to the presence or absence of ear base swellings. While all rabbit CT scans from 2017 onwards were performed with intravenous contrast administration, it was not used for the majority of patients in this study. Further research assessing the safety, efficacy and advantages of intravenous contrast agent are indicated. It is expected that ear canal mucosal enhancement, periauricular soft tissue swelling, myositis and abscessation of the tympanic bulla would be readily identified.

The variation in distribution of grades seen in both OM and material within the external ear canal confirm the usefulness of a grading system, allowing more accurate quantification of the level of suspected disease present. Further studies evaluating the correlation between CT diagnosed OM and material within the external ear canal and associations between disease severity, region of ear involved (middle vs external) and the presence of unilateral or bilateral disease could be investigated, with predisposing factors reviewed. The preliminary results from the current study support the hypothesis that higher OM grade is correlated with presence of material obliterating the external ear canal, with grade IV OM being over-represented in the sample size of 36 cases. However, the small sample size with retrievable clinical findings limits the validity of these findings.

Throughout the study, material within the external ear canal was not referred to as OE. OE is a complex
OM is defined as inflammation of the middle ear. A normal tympanic cavity is gas filled, with the tympanic bulla wall thinnest ventrally and thickest laterally. Although not pathognomonic for OM, fluid/material in the tympanic cavity may be the only abnormality observed in acute cases, before secondary involvement of the tympanic bulla that can develop as the condition becomes more chronic. The findings of this study support those of a previous study concluding that OM is often clinically subtle or asymptomatic. Twenty-two of the rabbits with OM were not presented for a problem relating to the ear. Of these, 5 rabbits had advanced disease at grade IV OM and 11 had early OM with grade I.

As well as CT diagnosis, the presence of OM could be confirmed at surgery or by endoscopic-guided meringotomy for cytological analysis. Further studies are recommended assessing long-term outcomes of patients diagnosed with OM, evaluating how disease severity affects treatment options and clinical prognosis. This could be particularly relevant for those rabbits diagnosed with OM grade I and II, to monitor progression of disease.

The main limitation of this paper is that classification of OM is based on CT images. Further prospective studies are advised correlating cytological, histopathological or surgical findings with the grade of CT diagnosed ear disease. Monitoring of disease progression, treatments undertaken and clinical outcomes would be beneficial in understanding the complexities of ear disease in rabbits.

The study sample size could also be seen as a limitation, with 36 cases of OM, diagnosed from the 161 rabbits, included in the study. This limits the statistical significance of the clinical signs of ear disease where rabbit numbers were low, or example, facial contracture (n=4) and ear base swellings (n=12). The data obtained does appear to show a correlation between the severity of OM and (1) the presence of material in the external ear canal, (2) the presence of ear base swellings and (3) the likelihood of facial contracture resulting from OM. Additional cases obtained from a prospective study would improve cohort number. Furthermore, collaborations between referral institutes would further promote sample size and population diversity.

A considered limitation of the study was the type of CT machine, as only the second scanner (used from October 2016) had automatic modulating exposure control system. All CT examinations however included high-resolution reconstruction of the head which provided a high level of detail of the middle and external ear. Overall therefore, it was felt the quality of the images readily allowed severity of ear disease to be graded.

Eighty-three per cent of rabbits (134/161) underwent conscious CT scanning using the VetMouseTrap, with 94.4 per cent (34/36) of the rabbits diagnosed with OM conscious for their scan. Visual monitoring of the patient in the transparent plexiglass tube was possible throughout the scanning procedure. Patient size however, was a limiting factor due to the dimensions of the plexiglass tube, the largest rabbit to undergo conscious imaging was a three-year-old, neutered female, New Zealand white rabbit weighing 3.6 kg, with body condition score 3/5 (BCS: 1=emaciated, 5=obese). VetMouseTraps, of the same design, of varying sizes would be helpful to accommodate a variety of rabbit breeds.

The authors do not dispute that rabbits may incur stress undergoing conscious scanning, however the procedure appears readily tolerated by patients. The experience can be likened to transportation in a travel box, with no lasting effects noted. Supplementary oxygen was provided throughout, reducing risk of respiratory compromise. A rolled towel positioned in a U-shape around the patient was found to significantly reduce movement artefact, such that motion artefact was negligible. The scanning procedure typically lasted less than five minutes with patients returned to their ward enclosure postprocedure. The scanning was not deemed to negatively influence the overall welfare of the patient, with rabbits promptly resuming prescan behaviours. Fifteen per cent (24/161) of the total study population were sedated to facilitate CT scanning, of which two had OM. The use of sedation was influenced by the initial hospital protocol in 2014, and was unrelated to patient compliance. Two per cent (3/161) of the total population of rabbits were scanned under general anaesthetic, for the purpose of radiation therapy planning. None of these animals were diagnosed with OM.

Studies have shown that rabbits are at a higher anaesthetic-related mortality risk than other companion
animals.23 Furthermore, the parenteral administration of anaesthetic agents (eg, intramuscular injections) can cause discomfort, while also requiring physical restraint to facilitate safe administration. Recovery from sedation or anaesthesia can be disorientating, with negative effects on gastrointestinal motility and appetite.42 The avoidance of chemical restraint, while achieving diagnostic quality scan images, is therefore advantageous and is particularly prudent in debilitated patients.

Conclusion

In this study, the use of a CT Ear Disease Grading System was found to be reproducible between different observers. Using the grading scale, ear pathology in the domestic rabbit can be quantified and should be considered as an adjunct to clinical findings. Further studies are recommended to investigate the relationship between the severity of CT graded ear disease with prognosis, treatments, clinical outcomes and findings in the contralateral ear. In this study, OM was found to be most prevalent in lop-eared rabbits and grade IV of OM appeared to correlate with grade IV of material within the external ear canal.

Due to the popularity of lop breeds as pets, awareness of ear disease and knowledge of likely disease sequelae is clinically important for small animal practitioners.

The authors’ believe avoidance of chemical restraint in rabbits, where a viable conscious option is available, is preferable. This study demonstrated that CT diagnosis of OM and performance of ear disease grading of OM and possibly OE can be readily achieved using conscious scanning in rabbit patients.

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Competing interests

None declared.

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