Otitis media/interna and encephalitozoonosis are the most common causes of head tilt in pet rabbits in the UK: 73 cases (2009-2020).

Otitis media/interna and encephalitozoonosis most common causes of head tilt in pet rabbits in the UK: 73 cases (2009-2020)

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ABSTRACT

Background: There are limited studies identifying diseases associated with head tilt in pet rabbits.

Methods: This was an observational, retrospective, single-centre study of 73 rabbits with head tilt from 2009-2020. Descriptive statistics were performed for all cases. Univariate and multivariate analysis was performed for the 36 cases with a final diagnosis.

Results: Seventy-three rabbits met the inclusion criteria. The final diagnosis included *Encephalitozoon cuniculi* meningoencephalomyelitis (EC) (15/36; 41.7%), otitis media/interna

(OMI) (8/36; 22.2%) or concurrent EC and OMI (13/38; 36.1%). Subacute-to-chronic onset was more common in rabbits with OMI than EC (p=0.018). Previous middle ear surgery (p=0.046) and a diagnosis of otitis externa (p=0.004) significantly increased the risk of OMI. Use of meloxicam was associated with improvement (p=0.007). Upright ears (p=0.013), recumbency (p=0.037), and impaired mentation (p=0.001) were associated with higher risk of death/euthanasia. Proportions of residual head tilt (66.7%) and relapse of vestibular signs (42.1%) were high.

Limitations: This was a retrospective study with variable investigation (often client finance dependent) and conclusive final diagnoses.

Conclusion: Concurrent EC and OMI, sole OMI and sole EC are the most common aetiologies of head tilt in pet rabbits in the UK. Meloxicam might be associated with a favourable outcome. Paired EC serology and head CT scan should be the baseline investigation for head tilt in rabbits.

INTRODUCTION

Head tilt (lateral torticollis or laterocollis) is one of the clinical signs suggesting vestibular disease in many animal species (de Lahunta 2021) and is the most prevalent manifestation of neurological disease in rabbits (Figure 1).[1]

Vestibular disease is divided into peripheral and central depending on whether there is involvement of the peripheral (inner ear and vestibulocochlear nerve) or the central component (brainstem and cerebellum) of the vestibular system.[2] In peripheral vestibular disease, clinical signs include head tilt, vestibular ataxia, nystagmus (horizontal or rotatory), positional strabismus, kinetosis, Horner's syndrome, and facial paresis or paralysis. Proprioception abnormalities, cranial nerve (CN) deficits other than CN VII, or changes in mentation may be

more closely associated with central vestibular disease.[2,3] In dogs, neurological examination is useful in differentiating central from peripheral disease,[2] but this can be more challenging in rabbits.[3]

The pet rabbit population in the UK is estimated at 1.1 million, with rabbits as the third most common companion animal species.[4] Unlike cats and dogs, rabbits are a prey species and may not exhibit typical signs of pain or illness. As a result, they may only present to veterinary clinics with advanced disease or when severely debilitated.[5]

The most common diseases associated with peripheral and central vestibular syndrome in rabbits are OMI and EC, respectively.[6-12] However, vestibular syndrome has also associated with other conditions. Peripheral vestibular syndrome has been associated with otitis media/interna (OMI), [6,7,11,12] and middle/inner ear neoplasia.[13] Central vestibular syndrome has been associated with meningoencephalitis of fungal (encephalitozoonosis caused by *Encephalitozoon cuniculi* [EC]),[6,8-10] bacterial (*Pasteurella multocida*, *Staphylococcus* sp.),[1,14] viral (Rabies lyssavirus, herpes simplex virus),[15-18] protozoal (toxoplasmosis)[19] or helminthic (*Baylisascaris procyonis*)[20] origin, aberrant *Cuterebra* intracranial migration,[21] lead intoxication,[22] congenital meningoencephalocele,[23] and brainstem cerebrovascular accident.[24] Paradoxical vestibular syndrome has been described secondary to cerebellar ischaemic cerebrovascular accident.[25] Listeriosis, head trauma, degenerative changes, and neoplasia have also been reported to cause head tilt in rabbits.[1,26-28]

The aims of this study were to investigate the diseases are associated with head tilt in pet rabbits, to describe their clinical features, and to assess which clinical findings can be used to predict the final diagnosis and/or outcome.

MATERIALS AND METHODS

This observational, retrospective, single-centre, study was conducted in a veterinary teaching hospital in the UK. Ethical approval was granted by the institution's veterinary Ethical review committee (VERC 32/21).

Pet rabbits with head tilts and complete medical records between 1 January 2009 and 31 December 2020 were included in the study. For statistical analysis, only rabbits with computed tomography (CT) of the head and single/paired serology for *E. cuniculi* IgM and IgG, and/or post-mortem histopathological examination were included.

Cases were recruited from the institutional medical databases (Tristan©, Tristan Veterinary Software and Provet Cloud©, Nordhealth). Search words included "rabbit" and "head" and "tilt". Data collected included signalment, ear conformation (upright/lop), clinical history (including previous history of otitis or EC infection), onset of clinical signs, neurological examination findings, clinicopathological findings (including phosphate and creatine kinase/CK), EC serology results, CT findings, treatment, outcome, and follow-up. Follow-up information was recorded at clinical or telephone re-examinations at the time. The onset of clinical signs was grouped according to the following criteria: hyperacute – less than 24 hours; acute – 24 hours to 7 days; subacute – 8 to 14 days; chronic – over 14 days.

For CT evaluation, a 4-slice helical CT scanner (Volume Zoom®, Siemens, Erlangen, Germany) was used from 2009 to October 2016 and a 64-slice helical CT scanner (Somatom Definition AS®, Siemens, Erlangen, Germany) from November 2016. A standard whole body CT protocol was performed with all patients conscious using a VetMouseTrap plexiglass tube (40 x 18cm; Universal Medical Systems, Solon, Ohio, USA). The patient was positioned in sternal recumbency on a comfortable bed on folded towels, with flow-by oxygen, reduction of light levels and a blanket over the restraint device.[29] The total duration of each scan was less than five minutes. The main objective was to identify intracranial abnormalities and investigate middle/inner ear health status. CT is the most reliable modality for identifying otitis media

97 (OM) in rabbits.[30] However, OM alone does not cause vestibular signs.[31] Therefore, middle ear
98 effusion with concurrent vestibular signs was considered OMI.

99 *E. cuniculi* serology was based on an ELISA for IgG and IgM antibodies.[32] Positive
100 titres (>1:80 for IgM or IgG) on single serology with concurrent vestibular signs were
101 considered consistent with EC infection.[33] Nevertheless, false positive results due to previous
102 exposure or false negative results in recently infected could not be ruled out.[33] In cases without
103 EC serology, the diagnosis of EC was based on post-mortem histopathological findings.[32]

104 Improvement of clinical signs was considered complete when the rabbit returned to
105 normal and partial when the rabbit had a subjective improvement of one or more of its
106 neurological signs.

107 Descriptive statistics were performed for all 73 cases; univariable and multivariable
108 analysis was performed on cases for which all the required data were available. Statistical
109 analysis was performed in TIBCO Statistica 13.3 (TIBCO Software Inc., Palo Alto, CA). Due
110 to significant deviation from normality (normal probability Q-Q plots and Shapiro-Wilk test),
111 numerical variables were presented as the median, interquartile range (IQR) and range, and
112 compared between groups using the Mann-Whitney U test (two groups) or Kruskal-Wallis H
113 test (>2 groups). Categorical variables were described as counts and percentages, and compared
114 between groups using the maximum likelihood G test or Fisher's exact test (if the expected
115 count in any cell of the contingency table <5). The 95% confidence intervals (CI 95%) for
116 percentages were calculated using the Wilson score method. The relationship between
117 demographic and clinical characteristics of the rabbits and the outcome was analysed by
118 multivariable logistic regression performed according to the backward stepwise procedure and
119 expressed as the odds ratio (OR). Only variables whose p-value was <0.1 in the univariable
120 analyses were entered into the multivariable models. A significance level (α) was set at 0.05
121 and all statistical tests were two-tailed.

RESULTS

Seventy-three rabbits met the inclusion criteria. For the statistical analysis, 40 rabbits had CT of the head and a single/paired EC serology or post-mortem diagnosis of EC. However, four were excluded as a definitive diagnosis was not reached and therefore 36 rabbits were included in the statistical analysis.

A. ALL RABBITS WITH A HEAD TILT

The signalment, previous medical history, presenting complaints, clinical, ophthalmological, dermatological, and neurological findings of all the rabbits are described in Table 1. A definitive diagnosis was made in 36/73 rabbits (49.3%).

B. RABBITS WITH A DEFINITIVE DIAGNOSIS

Neurological findings

The history, signalment, onset of clinical signs, clinical, dermatological and neurological findings are available for each diagnosis in Table 2.

Clinicopathological findings

Complete blood counts were performed in 27/36 (75%) rabbits with abnormalities found in 9/27 (33.3%); most of these were non-specific other than a stress leukogram (7/27; 25.9%) and thrombocytosis (4/27; 14.8%). Serum biochemistry was performed in 28/36 (77.8%) rabbits with abnormalities found in 27/28 (96.4%). The most common findings were increased CK (24/28; 85.7%), increased LDH (19/28; 67.9%), and hypophosphataemia (11/28; 39.3%). Urinalysis was performed in 1/36 (3%) rabbits, where it was unremarkable.

Serology

E. cuniculi serology was performed in 34/36 (94.4%) rabbits on single (24/34; 70.6%) or paired (10/34; 29.4%) serum samples. At least one IgM or IgG seropositive result was found in 25/34 (74.5%) (Table 3). The remaining two cases without serology were suspected to have EC based on post-mortem examination findings.

Computed tomography findings

The main findings included evidence of otitis externa (OE, 23/36; 63.9%), middle ear effusion and OM (22/36; 61.1%), and suspected cholesteatoma (3/36; 8.3%).

Definitive diagnoses

A definitive diagnosis was reached in 36/73 (49.3%) rabbits, including EC (15/36; 41.7%; CI 95%: 27.1%-57.8%), OMI (8/36; 22.2%; CI 95%: 11.7%-38.1%), and concurrent EC/OMI (CON) (13/36; 36.1%; 22.5%-52.4%). Of the remaining cases excluded from the statistical analysis, 2 rabbits exhibited head tilt following trauma (jumped with head against a pole and a fight with a cat), one had a periodontal abscessation extending into the brain, and one, a 1.4 month old dwarf lop rabbit, had suspected congenital encephalopathy.

Treatment and Outcome

Treatment included myringotomy (8/36; 22.2%), ear surgery (partial ear canal ablation-lateral bulla osteotomy [PECA-LBO]) (4/36; 11.1%) and medical treatment (36/36; 100%). This included intravenous fluid treatment (28/36; 77.8%), antibiotics (28/36; 77.8%), fenbendazole (25/36; 69.4%), analgesia (22/36; 61.1% – 19 with meloxicam), gastroprotectants (19/36; 52.8%), antiemetics (15/36; 41.79%), prokinetics (14/36; 38.9%), glucocorticoids (5/36; 13.9%), and a marbofloxacin/dexamethasone ear solution (5/36; 13.9%).

Outcome data were available for 33/36 (91.7%) rabbits. An improvement was seen in 22/33 rabbits (66.7%; CI 95%: 49.6%-80.2%); this was complete in 8/33 (24.2%) and partial

in 14/33 (42.4%). 6/33 rabbits (18.2%) remained static, 2/33 (6.1%) deteriorated and 3/33 (9.1%) were euthanised. Head tilt outcome was available for 27/36 (75.0%) rabbits, with residual head tilt in 18/27 (66.7%). Follow-up data were available for 19/36 (52.8%) rabbits; relapse of vestibular signs occurred in 8/19 (42.1%; CI 95%: 23.1%-63.7%).

Post-mortem examinations

Post-mortem examination was performed in 5 rabbits. Two rabbits, neither of which had serology performed, were diagnosed with EC on the basis of chronic bilateral renal infarcts (n=2), subcapsular cataract (n=1), diffuse heterophilic enteritis (n=1), hepatopathy (n=1), pleural and peritoneal effusion (n=1), and/or chronic inflammation of lumbar spinal cord and femoral nerve (n=1). Two rabbits were diagnosed with OMI. One had diffuse bronchopneumonia and abscessation of the right sublingual muscle with chronic suppurative right-sided OMI positive for *Pasteurella multocida*. The other had bilateral OMI with expansion of the infection to the left zygomatic arch (osteomyelitis) and brain (pyogranulomatous meningoencephalitis). One rabbit with CON had lymphoplasmatic meningoencephalitis and multifocal lymphoplasmatic interstitial nephritis supportive of EC with chronic suppurative neutrophilic right-sided OMI.

Statistical analysis

Lop rabbits were more likely to have OE (OR = 2.6, CI 95%: 1.0–6.6; p=0.046), but not OM (p=0.864). Previous OM was only present in the history of rabbits with current OM (either sole OMI or CON cases) (p=0.006). Subacute or chronic progressive onset of neurological signs was more often observed in rabbits with OMI (either sole OMI or CON cases) than in rabbits with EC without OM (p=0.018). Evidence of OE in CT was found significantly more often in rabbits with OMI (either sole or CON) than in rabbits with EC without OMI (p=0.005). A clinical diagnosis of OE was significantly more common in rabbits

with OMI (either sole or CON) than in rabbits with EC without OMI (p=0.015) (supplementary material**).** Univariable analysis revealed that previous ear surgery (p=0.046), evidence of OE in CT (p=0.002) and diagnosis of OE (p=0.004) significantly increased the risk of OMI. The only factor that remained significantly linked to a diagnosis of OMI in the multivariate analysis was the presence of evidence of OE in CT (OR 8.7; CI 95%: 2.0–38.4; p=0.004).

For OMI cases, no treatment was significantly associated with improvement. However, in EC cases, NSAIDs were significantly associated with higher chances of improvement (p=0.026). Upright ears (p=0.013), recumbency (p=0.037), and impaired mentation (p=0.001) were associated with significantly higher risk of death/euthanasia in the univariable analysis. Both death (p=0.931) and improvement (p=0.951) were similarly frequent in EC, OMI, and CON. Although complete recovery occurred less often in rabbits with OMI (3/13; 23.1%) compared to rabbits without OMI (5/9; 55.6%) this difference was not significant (p=0.187). The frequency of residual head tilt (p=0.853) and relapse (p=0.173) did not differ significantly between the definitive diagnoses. Although relapse of vestibular signs was more common in rabbits with OM (sole or CON – 6/10; 60%) than in rabbits with EC only (2/9; 22%), this was not significant (p=0.170).

DISCUSSION

This is the first retrospective study to investigate the diseases associated with head tilt in pet rabbits, to describe their clinical features and investigate risk factors that can be used to predict the definitive diagnosis and/or outcome.

The most common cause of head tilt in pet rabbits in the UK was CON followed by OMI and EC. This is in agreement with previous studies that have shown that EC and OMI are the two most common neurological diseases in rabbits.[1]

Reaching a definitive diagnosis can be challenging due to the need for advanced imaging (CT) and/or difficulty in interpreting EC serology results due to lack of paired samples. Based on our study, there is high incidence of single EC seropositivity and/or middle ear effusion in CT of rabbits presented with head tilt. Therefore, we propose that paired EC serology and head CT scan should be the baseline investigation for head tilt in rabbits.

None of the clinical variables were significantly associated with a definitive diagnosis of EC or CON. This might have been a result of low numbers of rabbits with these definitive diagnoses.

Uncommon causes of head tilt in rabbit were also found. Three cases diagnosed with OMI were suspected to have cholesteatomas. Only experimentally induced cholesteatoma has been previously reported in rabbits.[34] The changes compatible with this diagnosis were severe bone changes/lysis at the contour of the tympanic bulla, expansion of the tympanic cavity, and sclerosis or osteoproliferation of the ipsilateral temporomandibular joint and paracondylar process.[35] It is possible that the cholesteatomas developed from chronic OE with herniation and rupture of the TM and/or chronic inflammatory/infectious OM. In four cases, a definitive diagnosis was not reached, and they were treated for EC. Differential diagnosis for those cases could include otitis interna without OM, idiopathic (geriatric) peripheral vestibular disease (although this has not been reported in rabbits), viral encephalitis, or seronegative EC due to titre variation. Two cases presented with suspected vestibular disease following head trauma and one case with had suspected congenital vestibular disease. Even though these are described in reviews there are no clinical reports in the veterinary literature.[27]

This study revealed useful information about the clinical presentation of head tilt and vestibular disease. Subacute to chronic progressive onset of head tilt, previous ear surgery, previous OM or concurrent OE were more common in rabbits with OMI. In contrast, EC cases

had a hyperacute to acute progressive onset of head tilt and neurological signs. A detailed clinical history may therefore guide clinicians towards the most appropriate diagnostic tests or treatment.

Although ear disease is known to be common in lop eared rabbits, in this study, lop-eared rabbits had a higher prevalence of OE than previously described.[36] In contrast, while OE was common these rabbits did not commonly present with OM, which differs from previous studies.[11,30] The presence of concurrent OE (defined as excessive wax/serum material in the external ear canal and confirmed with cytology or aural otoscopy) on CT scans was significantly more likely in rabbits with OMI. In a previous study this was strongly suspected but not proved.[30]

Interestingly, there were findings from the history (e.g. complaints related to renal dysfunction) associated with a final diagnosis of EC. In contrast, previous ear surgery, previous OM or concurrent OE were associated with presence of OMI. Gut stasis was present in 32% rabbits regardless of the final diagnosis. Any neurological disease, and in particular vestibular disease, can cause hyporexia, stress and nausea predisposing to gut stasis.[37] Ear base swelling, ear scratching or head shaking have been associated with OMI,[27] although are more often attributed to OE. Urine staining and scalding, due to myelopathy-associated urinary incontinence, has been reported in rabbits with EC.[38] These findings could not be associated with a specific diagnosis, but this could be due to the small number of cases in each group with a final diagnosis. Ophthalmological examination revealed cataracts in only 1 rabbit with EC, whereas no EC case with phacoclastic uveitis was found. However, rabbits with EC-related ocular lesions may not exhibit other clinical findings.[10] The ocular discharge could be a result of neuroparalytic keratitis or exposure keratitis. Neuroparalytic keratitis can be observed in rabbits with facial neuropathy accompanying the vestibular disease in OMI cases. Keratitis can

be seen in rabbits with head tilt as a result of the mechanical irritation of the ground-sided eye and potential exposure keratitis on the top facing one.

Neurological examination could help differentiate central and peripheral vestibular disease. However, central vestibular disease related to EC can mimic the clinical signs of peripheral disease.[8,10,39] In this study, a more specific neuroanatomical localisation to peripheral or central vestibular system was not possible as mentation and postural reactions were not consistently recorded for all rabbits. This could be due to inconsistent medical records, difficulty in performing postural reactions especially with severe ataxia, and/or unreliability of postural reactions in rabbits due to behaviour and stress.[3] Head tilt can therefore be the main presenting complaint in rabbits with vestibular syndrome.

Facial paralysis and Horner's syndrome might be associated with peripheral vestibular syndrome in rabbits,[27] and therefore accompany OMI rather EC. In our population, 8/73 rabbits (11%) had ipsilateral facial neuropathy. However, only 5 cases had a definitive diagnosis: three rabbits were diagnosed with CON and one with OMI. As CON includes both EC and OMI, a clear association between final diagnosis and facial paralysis could not be made. Horner's syndrome was seen in two rabbits with final diagnoses, one diagnosed with CON and one diagnosed with EC. Hence, Horner's syndrome might have been a result of the peripheral vestibular component (OMI) or a first order neuron dysfunction. The low number of rabbits with Horner's syndrome and a final diagnosis is a limitation. Therefore, although facial paralysis and Horner's syndrome have been associated with peripheral vestibular disease in dogs and cats,[2] this study failed to provide strong evidence of this in rabbits.

An interesting clinical sign in 6 rabbits was 'head nystagmus', which describes the fast and slow phase movement of the head in phase with ocular nystagmus.[40] We hypothesise that head nystagmus might have been underreported within the clinical records due to lack of a

knowledge and recognition. This sign is more common in birds, rabbits, and guinea pigs, less common in dogs and cats, and rare in humans.[40] It's possible that this is related to differences in the visual pathway and influence of the visual system on vestibular function between these animals.[41]

Hemifacial tetanus was present in 6 rabbits: three with CON, one with OM and PECA/LBO, and 2 with open diagnoses. Hemifacial tetanus is a known sign of OM (Figure 2),[30] and a post-operative complication after PECA-LBO in rabbits.[42] Hemifacial tetanus (previously misnamed as spasm) is a sustained contracture of the muscles innervated by facial nerve as a result of chronic irritation of the facial nerve (e.g. chronic facial neuropathy in OM).[31] This study could not associate hemifacial tetanus with a particular definitive diagnosis, but we believe that hemifacial tetanus, as a clinical sign of unilateral facial nerve dysfunction,[31] indicates peripheral neuroanatomical localisation and therefore should be associated with peripheral (e.g. OMI) rather than central (e.g. EC) vestibular disease.

No clinicopathological findings were associated with specific diagnoses in rabbits with head tilts. Increased LDH and CK were commonly seen but can be explained by muscle damage due to struggling, falling or rolling.[43] Although paired serology for EC was negative in one rabbit, its post-mortem findings were consistent with EC. There is marked individual variation in antibody production against EC between rabbits.[43] Therefore (and especially in seronegative cases), post-mortem examination of the brain and kidneys is considered the gold standard for diagnosis.[32]

Meloxicam was associated with a favourable outcome in rabbits with EC. Historically, glucocorticosteroids have been administered to rabbits with EC.[10] However, glucocorticosteroids are not routinely recommended in rabbits as a study did not support the use of dexamethasone in rabbits with neurologic EC.[44] We suspect that NSAIDs decrease the

311 inflammatory response of the central nervous system against EC and may improve recovery.
312 Fenbendazole was used in 9/13 rabbits. However, while fenbendazole is widely used in the
313 treatment of EC, there is no controlled study confirming its clinical efficacy in chronic cases
314 involving the central nervous system.[33] Nevertheless, two controlled studies suggest using
315 fenbendazole for EC prevention.[44,45]

316 Upright ears, recumbency, rolling and impaired mentation were associated with higher
317 risk of death or euthanasia. However, a clear association between ear conformation and risk of
318 death was not found, and over-representation of upright ear rabbits was suspected. A precise
319 estimation of the population of lop *versus* upright ear rabbits in the UK does not exist, but the
320 majority of the available breeds are upright. Therefore, the over-representation of upright ear
321 rabbits in this study might reflect population trends. Recumbency has been previously
322 associated with a poorer outcome in rabbits with EC.[8] Our study shows that recumbency, along
323 with impaired mentation, regardless of a diagnosis of EC or OMI, should be considered as
324 negative prognostic factors.

325 The main limitations of this study include its retrospective nature, the low number of
326 cases with a final diagnosis, inconsistent diagnostic procedures (especially cytology),
327 inconsistent diagnostic criteria and presumptive diagnoses, a lack of consistency in reporting
328 clinical and neurological finings, considering EC seropositivity as active disease although it
329 could be due to exposure, and consideration of middle ear effusion in CT as OMI although
330 primary secretory OM cannot be ruled out.

331 **Conclusions**

332 In conclusion, CON followed by OMI and EC were the most common causes of head
333 tilt in pet rabbits in the UK. The specific details of the onset of the clinical signs and history
334 might support a diagnosis of OMI. Baseline investigations in rabbits with head tilt should

include paired EC serology and head CT scan. Meloxicam was associated with a favourable outcome in EC. Recumbency and impaired mentation were associated with euthanasia or death, whilst rolling decreased the odds of improvement. Regardless of reaching a final diagnosis or not, the rates of residual head tilt (67%) and relapse of vestibular signs (42%) were high. It is therefore necessary that this information is communicated to the owners.

AUTHOR CONTRIBUTIONS

Conceptualisation, methodology, investigation, analysis and writing—original draft and review and editing: Theofanis Liatis, Nikoleta Makri, Anna Suñol. Methodology, analysis, review, editing and supervision: Michał Czopowicz, Jenna Richardson, Tim Nuttall, Anna Suñol

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474

475 **FIGURE LEGENDS**

476 **Figure 1.** Right-sided head tilt in a rabbit.

477 **Figure 2.** Left-sided hemifacial tetanus (contracture) of the muscles of the facial expression.