Received: 10 November 2023 | Accepted: 3 May 2024

DOI: 10.1002/vetr.4267

Vet Record

ORIGINAL RESEARCH

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

Theofanis Liatis[1,2] | **Nikoleta Makri**[1] | **Michał Czopowicz**[3] | **Jenna Richardson**[1] | **Tim Nuttall**[1] | **Anna Suñol**[1,4]

[1]Hospital for Small Animals, Royal (Dick) School of Veterinary Studies, University of Edinburgh, Midlothian, UK

[2]Queen Mother Hospital for Animals, Royal Veterinary College, Hatfield, UK

[3]Division of Veterinary Epidemiology and Economics, Institute of Veterinary Medicine, Warsaw University of Life Sciences—SGGW, Warsaw, Poland

[4]Hospital Veterinaria del Mar, Barcelona, Spain

Correspondence
Theofanis Liatis, Queen Mother Hospital for Animals, Royal Veterinary College, Hatfield, UK.
Email: theofanis.liatis@gmail.com

Abstract

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

Methods: This was an observational, retrospective, single-centre study of rabbits with head tilt presented between 2009 and 2020. Descriptive statistics were performed for all cases, whereas univariate and multivariate analyses were only performed for the 36 cases with a final diagnosis.

Results: Seventy-three rabbits met the inclusion criteria. The final diagnoses included *Encephalitozoon cuniculi* meningoencephalomyelitis (EC) (15/36; 41.7%), otitis media/interna (OMI) (8/36; 22.2%) and concurrent EC and OMI (13/38; 36.1%). Subacute-to-chronic onset was more common in rabbits with OMI than in those with 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. Meloxicam was associated with improvement of clinical signs ($p = 0.007$). Upright ears ($p = 0.013$), recumbency ($p = 0.037$) and impaired mentation ($p = 0.001$) were associated with a higher risk of death/euthanasia. The proportions of residual head tilt (66.7%) and relapse of vestibular signs (42.1%) were high.

Limitations: This was a retrospective study with cases varying in their investigation and conclusive final diagnoses.

Conclusion: OMI and EC were the most common aetiologies of head tilt in pet rabbits in the UK. Meloxicam might be associated with a favourable outcome in affected rabbits. Paired EC serology and a CT scan of the head 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,[1] and is the most prevalent manifestation of neurological disease in rabbits (Figure 1).[2]

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, changes in mentation or cranial nerve (CN) deficits other than CN VII may be more closely associated with central vestibular disease.[3,4] In dogs, neurological examination is useful in differentiating central from peripheral disease,[3] but this can be more challenging in rabbits.[4]

The pet rabbit population in the UK is estimated to be 1.1 million, with rabbits being the third most common companion animal species.[5] 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.[6]

FIGURE 1 Right-sided head tilt in a rabbit

The most common diseases associated with peripheral and central vestibular syndrome in rabbits are otitis media/interna (OMI) and encephalitozoonosis (EC), respectively.[7–13] However, vestibular syndrome has also been described in other diseases. Peripheral vestibular syndrome has been associated with OMI[7,8,12,13] and middle/inner ear neoplasia.[14] Central vestibular syndrome has been associated with meningoencephalitis of fungal (EC caused by *Encephalitozoon cuniculi*),[7,9–11] bacterial (*Pasteurella multocida* and *Staphylococcus* sp.),[2,15] viral (rabies lyssavirus and herpes simplex virus),[16–19] protozoal (toxoplasmosis)[20] or helminthic (*Baylisascaris procyonis*)[21] origin, aberrant *Cuterebra* intracranial migration,[22] lead intoxication,[23] congenital meningoencephalocele[24] and brainstem cerebrovascular infarction.[25] Paradoxical vestibular syndrome has been described secondary to cerebellar ischaemic cerebrovascular infarction.[26] Listeriosis, head trauma, degenerative changes and neoplasia have also been reported to cause head tilt in rabbits.[2,27–29]

The aims of this study were to investigate the diseases 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 complete medical records that presented with head tilt 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* immunoglobulin M (IgM) and immunoglobulin G (IgG) and/or postmortem histopathological examination were included.

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

For CT evaluation, a four-slice helical CT scanner (Volume Zoom, Siemens) was used from 2009 to October 2016 and a 64-slice helical CT scanner (Somatom Definition AS, Siemens) was used from November 2016. A standard whole-body CT protocol was performed with all patients conscious, using a VetMouseTrap plexiglass tube (40 × 18 cm; Universal Medical Systems). 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.[30] The total duration of each scan was less than 5 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 (OM) in rabbits.[31] However, OM alone does not cause vestibular signs.[1] Therefore, middle ear effusion with concurrent vestibular signs was considered to be OMI.

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

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

Descriptive statistics were performed for all 73 cases; univariable and multivariable analyses were performed on cases for whom all the required data were available. Statistical analysis was performed

in TIBCO Statistica 13.3 (TIBCO Software). Due to significant deviation from normality (normal probability Q–Q plots and Shapiro–Wilk test), numerical variables are presented as the median, interquartile range and range, and compared between groups using the Mann–Whitney *U*-test (two groups) or Kruskal–Wallis *H*-test (>2 groups). Categorical variables are described as counts and percentages, and compared between groups using the maximum likelihood *G*-test or Fisher's exact test (if the expected count in any cell of the contingency table was less than 5). The 95% confidence intervals (95% CIs) for percentages were calculated using the Wilson score method. The relationships between the demographic and clinical characteristics of the rabbits and the outcomes were analysed by multivariable logistic regression performed according to the backward stepwise procedure and are expressed as the odds ratio (OR). Only variables whose *p*-value was less than 0.1 in the univariable analyses were entered into the multivariable models. The significance level (α) was set at 0.05 and all the statistical tests were two-tailed.

RESULTS

Seventy-three rabbits met the inclusion criteria. Forty rabbits had CT of the head and a single/paired EC serology or postmortem diagnosis of EC. However, four rabbits were excluded because a final diagnosis was not reached; therefore, 36 rabbits were included in the statistical analysis.

All rabbits with a head tilt

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

Rabbits with a final diagnosis

Neurological findings

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

Clinicopathological findings

Complete blood counts were performed in 27 of 36 (75%) rabbits, with abnormalities found in nine of 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 of 36 (77.8%) rabbits, with abnormalities found in 27 of 28 (96.4%). The most common findings were increased CK (24/28; 85.7%), increased lactate dehydrogenase (LDH) (19/28; 67.9%) and hypophosphataemia (11/28; 39.3%). Urinalysis was performed in one of 36 (3%) rabbits and the result was unremarkable.

Serology

E. cuniculi serology was performed in 34 of 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 of 34 (74.5%) rabbits (Table 3). The remaining two cases without serology were suspected to have EC based on postmortem 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%).

Final diagnoses

A final diagnosis was reached for 36 of 73 (49.3%) rabbits: EC in 15 rabbits (41.7%; 95% CI: 27.1%−57.8%), OMI in eight rabbits (22.2%; 95% CI: 11.7%−38.1%) and concurrent OMI and EC (CON) in 13 rabbits (36.1%; 95% CI: 22.5%−52.4%). Of the remaining cases excluded from the statistical analysis, two rabbits exhibited head tilt following trauma (jumped with head against a pole and a fight with a cat), one had 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%). Medical treatment 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 of 36 (91.7%) rabbits. An improvement was seen in 22 of 33 rabbits (66.7%; 95% CI: 49.6%−80.2%), which was complete in eight (of 33; 24.2%) and partial in 14 (of 33; 42.4%). Out of 33 rabbits, six (18.2%) remained static, two (6.1%) deteriorated and three (9.1%) were euthanased. Head tilt outcome was available for 27 of 36 (75.0%) rab-

TABLE 1 Signalment, previous medical history, presenting complaints, clinical findings and outcomes of the study population of rabbits with head tilt

Variables[a]	Results
Signalment	
Sex	
Male	38/72 (52.8%)
Neutered	27/38 (71.1%)
Female	34/72 (47.2%)
Spayed	29/34 (85.3%)
Age at presentation	Median: 4.3 years (interquartile range: 2.5–6.0 years; range: 1.44 months–11.3 years)
Breeds	
Purebred	45/73 (61.6%); 31/45 (68.9%) standard and 14/45 (31.1%) miniature size
Crossbreed	28/73 (38.4%)
Bodyweight at presentation[b] (data available only for 69 rabbits)	2.3 kg, 1.7–2.7 kg (0.6–4.4 kg)
Ear conformation	
Upright ear	37/73 (50.7%)
Lop ear	36/73 (49.3%)
Previous medical history	
Otitis	20/73 (27.4%)
OE	8/20 (40.0%)
OM	1/20 (5.0%)
OME	11/20 (55.0%)
Previous partial ear canal ablation and lateral bulla osteotomy	9/73 (12.3%)
Recent treatment with ear drops or an ear flush prior to referral	4/73 (5.5%)
Previous *Encephalitozoon cuniculi* infection	12/73 (16.4%)
Presumptive	7/12 (58.3%)
Attributed to household seropositivity	3/12 (25.0%)
Positive based on in-clinic serology	2/12 (16.7%)
Previous vestibular episode that was not investigated	3/73 (4.1%)
History of recent trauma	2/73 (2.7%)
Common presenting complaints	
Head tilt	73/73 (100%)
Hyporexia	31/73 (42.5%)
Ataxia	25/73 (34.2%), of which 10/25 included falling
Nystagmus	17/73 (23.3%)
Common general physical examination findings	
Abnormal findings	57/73 (78.1%)
Gut stasis signs (decreased intestinal sounds, distended abdominal wall)	23/73 (31.5%)
Urine scalding	5/73 (6.8%)
Head shaking/ear scratching	3/73 (4.1%)
Upper respiratory sounds	3/73 (4.1%)
Common ophthalmological findings	
Ocular discharge	11/73 (15.1%)
Corneal ulcers	3/73 (4.1%)
Cataract	2/73 (2.7%)
Common dermatological findings	
OE signs (ear discharge, external ear canal stenosis, erythema, ulceration or oedema)	25/73 (34.2%)
Pododermatitis	17/73 (23.3%)
Ear base swelling	9/73 (12.3%)

(Continues)

TABLE 1 (Continued)

Variables[a]	Results
Common neurological findings	
Head tilt	73/73 (100%)
Right sided	46/73 (63.0%)
Left sided	24/73 (32.9%)
Side not recorded	3/73 (4.1%)
Vestibular ataxia	45/73 (61.6%)
Nystagmus	28/73 (38.4%)
Urinary incontinence	9/73 (12.3%)
Ipsilateral facial neuropathy	8/73 (11%); 6/8 manifested as hemifacial tetanus
Head nystagmus	6/73 (8.2%)
Horner's syndrome	3/73 (4.1%)
Deterioration of neurological signs after stress, being carried or head shaking	7/73 (9.5%)
Outcome	
Improvement	43/67 (64.2%)
Complete	18/43 (41.9%)
Partial	25/43 (58.1%)
No change	10/67 (14.9%)
Deterioration	2/67 (3.0%)
Death	12/67 (17.9%)
Euthanasia	10/12 (83.3%)
Natural death	2/12 (16.7%)
Definitive diagnosis	
Known	36/73 (49.3%)
EC	15 (41.7%)
OMI	8 (22.2%)
CON	13 (36.1%)
Undetermined	37/73 (50.7%)

Abbreviations: CON, concurrent EC and OMI; EC, encephalitozoonosis; OE, otitis externa; OM, otitis media; OME, otitis media/externa; OMI, otitis media/interna.
[a]Presented as the count and percentage in the group unless stated otherwise.
[b]Presented as the median, interquartile range and range.

bits, with residual head tilt in 18 of 27 (66.7%) rabbits. Follow-up data were available for 19 of 36 (52.8%) rabbits, and relapse of vestibular signs occurred in eight of 19 rabbits (42.1%; 95% CI: 23.1%–63.7%).

Postmortem examinations

Postmortem examination was performed on five 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 of these rabbits had diffuse bronchopneumonia and abscessation of the right sublingual muscle with chronic suppurative right-sided OMI positive for *P. multocida*. The other rabbit 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-eared rabbits were more likely to have OE (OR = 2.6, 95% CI: 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 on CT images 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

TABLE 2 History, signalment, onset of signs and clinical, dermatological and neurological findings of rabbits with head tilt and a definite diagnosis

	Diagnosis		
Variables[a]	**EC (*n* = 15), *n* (%)**	**OMI (*n* = 8), *n* (%)**	**CON (*n* = 13), *n* (%)**
Signalment			
Males	9 (60.0)	6 (75.0)	6 (46.2)
Neutered	11 (73.3)	7 (87.5)	11 (84.6)
Pedigree	11 (73.3)	5 (62.5)	6 (46.2)
Miniature	5 (33.3)	0	3 (23.1)
Upright ear type	7 (46.7)	3 (37.5)	6 (46.2)
Age (years)[b]	6, 3–8 (1–10)	4, 3–5 (2–9)	4, 2–5 (1–8)
Bodyweight (kg)[b]	1.9, 1.6–2.7 (1.0–4.4)	2.3, 1.7–2.6 (1.7–3.2)	2.3, 2.0–2.6 (1.6–3.7)
History			
Previous otitis externa	3 (20.0)	4 (50.0)	4 (30.8)
Previous otitis media	0	3 (37.5)	5 (38.5)
Previous ear surgery	1 (6.7)	3 (37.5)	3 (23.1)
Previous EC	3 (20.0)	1 (12.5)	2 (15.4)
Ear drops/flush prior to referral	1 (6.7)	0	2 (15.4)
Onset of clinical signs			
Hyperacute/acute	15 (100)	7 (87.5)	8 (61.5)
Subacute/chronic	0	1 (12.5)	5 (38.5)
General examination findings			
Gut stasis signs	7 (46.7)	3 (37.5)	5 (38.5)
Ocular discharge	2 (13.3)	1 (12.5)	5 (38.5)
Corneal ulcer	0	0	2 (15.4)
Conjunctivitis	0	0	1 (7.7)
Cataract	1 (6.7)	0	0
Dental abnormalities	3 (20.0)	0	1 (7.7)
Nasal discharge	2 (13.3)	0	3 (23.1)
Dermatological findings			
Signs of otitis externa	6 (40.0)	3 (37.5)	5 (38.5)
Pododermatitis	3 (20.0)	2 (25.0)	7 (53.9)
Ear base swelling	1 (6.7)	2 (25.0)	2 (15.4)
Neurological findings			
Head tilt side			
Left	4 (26.7)	1 (12.5)	5 (38.5)
Right	11 (73.3)	7 (87.5)	8 (61.5)
Ataxia	12 (80.0)	6 (75.0)	10 (76.9)
Circling	3 (20.0)	3 (37.5)	2 (15.4)
Falling	2 (13.3)	0	2 (15.4)
Rolling	1 (6.7)	1 (12.5)	2 (15.4)
Leaning	1 (6.7)	1 (12.5)	1 (7.7)
Nystagmus	8 (53.3)	1 (12.5)	5 (38.5)
Side			
Binocular	6	1	4
Monocular	2	0	1
Direction			
Horizontal	8	0	5
Vertical	0	1	0

(Continues)

TABLE 2 (Continued)

Variables[a]	Diagnosis		
	EC ($n = 15$), n (%)	OMI ($n = 8$), n (%)	CON ($n = 13$), n (%)
Head nystagmus	2 (13.3)	0	0
Suspected urinary incontinence	2 (13.3)	0	0
Ipsilateral facial neuropathy	1 (6.7)	1 (12.5)	3 (23.1)
Ipsilateral Horner's syndrome	1 (6.7)	0	1 (7.7)

Abbreviations: CON, concurrent EC and OMI; EC, encephalitozoonosis; OMI, otitis media/interna.
[a]Presented as the count and percentage in the group unless otherwise stated.
[b]Presented as the median, interquartile range and range.

TABLE 3 Number of rabbits with different combinations of *Encephalitozoon cuniculi* serological test results

E. cuniculi serological test results		Number (%) from 43 serologically tested rabbits	
IgG	IgM	First test	Second test
–	–	15 (34.9%)	2 (16.7%)
–	+	0	0
+	–	26 (60.5%)	8 (66.7%)
+	+	2 (4.6%)	2 (16.7%)

Abbreviations: IgG, immunoglobulin G; IgM, immunoglobulin M.

EC without OMI ($p = 0.015$) (Table S1). Univariable analysis revealed that previous ear surgery ($p = 0.046$), evidence of OE on CT ($p = 0.002$) and diagnosis of OE ($p = 0.004$) significantly increased the risk of OMI (Table S2). The only factor that remained significantly linked to a diagnosis of OMI in the multivariate analysis was the presence of evidence of OE on CT (OR 8.7; 95% CI: 2.0–38.4; $p = 0.004$) (Table S3). No risk factor was found to be statistically significant for diagnoses of EC (Table S4).

For OMI cases, no treatment was significantly associated with improvement. However, in EC cases, nonsteroidal anti-inflammatory drugs (NSAIDs) were significantly associated with higher chances of improvement ($p = 0.026$) (Tables S5–S8). Upright ears ($p = 0.013$), recumbency ($p = 0.037$) and impaired mentation ($p = 0.001$) were associated with a significantly higher risk of death/euthanasia in the univariate analysis (Table S9). 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%) than in 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 final 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 difference was not significant ($p = 0.170$).

DISCUSSION

To the authors' knowledge, this is the first retrospective study to investigate the diseases associated with head tilt in pet rabbits, to describe their clinical features and to investigate risk factors that can be used to predict the final 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 finding is in agreement with previous studies that have shown that EC and OMI are the two most common neurological diseases in rabbits.[2]

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

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

Uncommon causes of head tilt in rabbits 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 tympanic membrane and/or chronic inflammatory/infectious OM. In four cases, a final diagnosis was not reached, and they were treated for EC. Differential diagnoses 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 suspected congenital vestibular disease. Although these are described in reviews, there are no clinical reports in the veterinary literature.[28]

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 treatments.

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.[12,31] 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 proven.[31]

Interestingly, there were findings from the history (e.g., complaints related to renal dysfunction) associated with a final diagnosis of EC. Meanwhile, previous ear surgery, previous OM and concurrent OE were associated with the presence of OMI. Gut stasis was present in 32% of the rabbits regardless of the final diagnosis. Any neurological disease, particularly vestibular disease, can cause hyporexia, stress and nausea, predisposing to gut stasis.[37] Ear base swelling, ear scratching and head shaking have been associated with OMI,[28] although they 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 one rabbit with EC, and no EC case with phacoclastic uveitis was found. However, rabbits with EC-related ocular lesions may not exhibit other clinical findings.[11] The ocular discharge could be a result of neuroparalytic keratitis or exposure keratitis. Neuroparalytic keratitis can be observed in rabbits with facial neuropathy accompanied by 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.[9,11,39] In this study, a more specific neuroanatomical localisation to the 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.[4] 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,[28] and therefore accompany OMI rather than EC. In our population, eight of 73 rabbits (11%) had ipsilateral facial neuropathy. However, only five cases had a final diagnosis: three rabbits were diagnosed with CON and one was diagnosed 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 are limitations. Therefore, although facial paralysis and Horner's syndrome have been associated with peripheral vestibular disease in dogs and cats,[3] this study failed to provide strong evidence of this in rabbits.

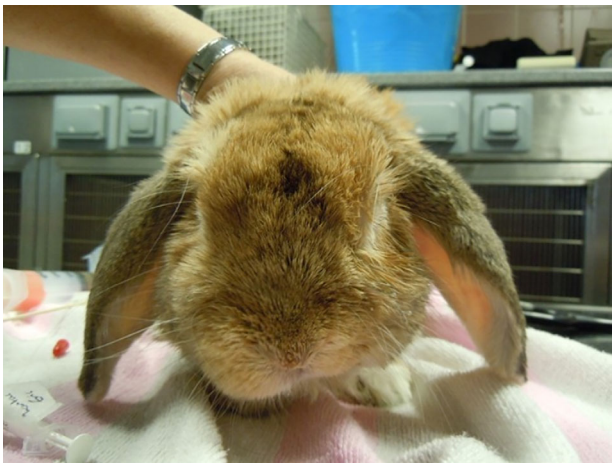

FIGURE 2 Left-sided hemifacial tetanus in a rabbit

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

Hemifacial tetanus was present in six rabbits: three with CON, one with OM and PECA-LBO and two with open diagnoses. Hemifacial tetanus is a known sign of OM (Figure 2)[31] and a postoperative complication after PECA–LBO in rabbits.[42] Hemifacial tetanus (previously misnamed as spasm) is a sustained contracture of the muscles innervated by the facial nerve as a result of chronic irritation of the facial nerve (e.g., chronic facial neuropathy in OM).[1] This study could not associate hemifacial tetanus with a particular final diagnosis, but we believe that hemifacial tetanus, as a clinical sign of unilateral facial nerve dysfunction,[1] 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, the postmortem findings were consistent with EC. There is marked individual variation in EC-specific antibody production between rabbits.[43] Therefore (and especially in seronegative cases), postmortem examination of the brain and kidneys is considered the gold standard for diagnosis.[32]

The administration of meloxicam was associated with a favourable outcome in rabbits with EC. Historically, glucocorticosteroids have been administered to rabbits with EC.[11] However, glucocorticosteroids are not routinely recommended for rabbits, as a study did not support the use of dexamethasone in rabbits with neurologic EC.[44] We suspected that NSAIDs decrease the inflammatory response of the central nervous system against EC and may improve recovery. Fenbendazole was used in nine of 13 rabbits. However, while fenbendazole is widely used in the treatment of EC, there is no controlled study confirming its clinical efficacy in chronic cases involving the central nervous system.[33] Nevertheless, two controlled studies suggested the use of fenbendazole for EC prevention.[44,45]

Upright ears, recumbency, rolling and impaired mentation were associated with a higher risk of death or euthanasia. However, a clear association between ear conformation and risk of death was not found, and overrepresentation of upright-eared rabbits was suspected. A precise estimation of the population of lop- versus upright-eared rabbits in the UK does not exist, but the majority of the available breeds are upright eared. Therefore, the overrepresentation of upright-eared rabbits in this study might reflect population trends. Recumbency has been previously associated with a poorer outcome in rabbits with EC.[9] Our study revealed that recumbency, along with impaired mentation, regardless of a diagnosis of EC or OMI, should be considered as negative prognostic factors.

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

CONCLUSIONS

In conclusion, OMI and EC were the most common causes of head tilt in this population of UK pet rabbits. The specific details of the onset of the clinical signs and history might support a diagnosis of OMI. Baseline investigations in rabbits with head tilt should include paired EC serology and a CT scan of the head. The administration of meloxicam was associated with a favourable outcome in EC. Recumbency and impaired mentation were associated with euthanasia or death, while rolling decreased the odds of improvement. Regardless of whether a final diagnosis was reached, the rates of residual head tilt and relapse of vestibular signs were high. This information should be communicated to the owners of affected animals to help guide their decision making.

AUTHOR CONTRIBUTIONS

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

CONFLICT OF INTEREST STATEMENT

The authors declare no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

FUNDING INFORMATION

The authors received no financial support for the research, authorship and/or publication of this article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Ethical approval was granted by the University of Edinburgh's veterinary ethical review committee (VERC 32/21).

ORCID

Theofanis Liatis https://orcid.org/0000-0003-2815-2527
Nikoleta Makri https://orcid.org/0000-0002-2331-1341
Michał Czopowicz https://orcid.org/0000-0002-4238-8360
Jenna Richardson https://orcid.org/0009-0005-2686-6499
Tim Nuttall https://orcid.org/0000-0002-7412-9398
Anna Suñol https://orcid.org/0000-0003-0985-6959

REFERENCES

1. De Lahunta A, Glass E, Kent M. Vestibular system: special proprioception. In: A De Lahunta, E Glass, M Kent, editors. De Lahunta's veterinary neuroanatomy and clinical neurology. 5th ed. Elsevier; 2021. p. 345–73.
2. Gruber A, Pakozdy A, Weissenbock H, Csokai J, Künzel F. A retrospective study of neurological disease in 118 rabbits. J Comp Pathol. 2009;14:31–37.
3. Bongartz U, Nessler J, Maiolini A, Stein VM, Tipold A, Bathen-Nöthen A. Vestibular disease in dogs: association between neurological examination, MRI lesion localisation and outcome. J Small Anim Pract. 2020;61:57–63.

4. Mancinelli E. Neurologic examination and diagnostic testing in rabbits, ferrets, and rodents. J Exot Pet Med. 2015;24:52–64.
5. PDSA. The PAW Report 2022. Available from: https://www.pdsa.org.uk/what-we-do/pdsa-animal-wellbeing-report/paw-report-2022. Accessed 25 July 2023.
6. Barter LS. Rabbit analgesia. Vet Clin North Am Exot Anim Pract. 2011;14:93–104.
7. Kunstýr I, Naumann S. Head tilt in rabbits caused by pasteurellosis and encephalitozoonosis. Lab Anim. 1985;19:208–13.
8. Keeble E. Common neurological and musculoskeletal problems in rabbits. In Pract. 2006;28:212–18.
9. Künzel F, Gruber A, Tichy A, Edelhofer R, Nell B, Hassan J, et al. Clinical symptoms and diagnosis of encephalitozoonosis in pet rabbits. Vet Parasitol. 2008;151:115–24.
10. Shin J, Kim S, Kim S, Song K. Head tilt associated with encephalitozoonosis in four pet rabbits. J Vet Clin. 2015;32:212–14.
11. Künzel F, Fisher PG. Clinical signs, diagnosis, and treatment of *Encephalitozoon cuniculi* infection in rabbits. Vet Clin North Am Exot Anim Pract. 2018;21:69–82.
12. de Matos R, Ruby J, Van Hatten RA, Thompson M. Computed tomographic features of clinical and subclinical middle ear disease in domestic rabbits (*Oryctolagus cuniculus*): 88 cases (2007–2014). J Am Vet Med Assoc. 2015;246:336–43.
13. Fisher PG, Künzel F, Rylander H. Neurologic and musculoskeletal diseases. In: KE Quesenberry, CJ Orcutt, C Mans, JW Carpenter, editors. Ferrets rabbits and rodents: clinical medicine and surgery. 4th ed. Elsevier; 2020. p. 233–49.
14. Bercier M, Guzman D, Stockman J, Zwingenberger A, Vapniarsky N, Lowenstine L et al. Salivary gland adenocarcinoma in a domestic rabbit (*Oryctolagus cuniculus*). J Exot Pet Med. 2013;22:218–24.
15. Murray KA, Hobbs BA, Griffith JW. Acute meningoencephalomyelitis in a rabbit infected with *Pasteurella multocida*. Lab Anim Sci. 1985;35:169–71.
16. Karp BE, Ball NE, Scott CR, Walcoff JB. Rabies in two privately owned domestic rabbits. J Am Vet Med Assoc. 1999;215:1824–27.
17. Grest P, Albicker P, Hoelzle L, Wild P, Pospischil A. Herpes simplex encephalitis in a domestic rabbit (*Oryctolagus cuniculus*). J Comp Pathol. 2002;126:308–11.
18. Müller K, Fuchs W, Heblinski N, Teifke JP, Brunnberg L, Gruber AD, et al. Encephalitis in a rabbit caused by human herpesvirus-1. J Am Vet Med Assoc. 2009;235:66–69.
19. de Matos R, Russell D, Van Alstine W, Miller A. Spontaneous fatal human herpesvirus 1 encephalitis in two domestic rabbits (*Oryctolagus cuniculus*). J Vet Diagn Invest. 2014;26:689–694.
20. Mäkitaipale J, Järvenpää E, Bruce A, Sankari S, Virtala AM, Näreaho A. Seroprevalence of *Encephalitozoon cuniculi* and *Toxoplasma gondii* antibodies and risk-factor assessment for *Encephalitozoon cuniculi* seroprevalence in Finnish pet rabbits (*Oryctolagus cuniculus*). Acta Vet Scand. 2022;64:2.
21. Furuoka H, Sato H, Kubo M, Owaki S, Kobayashi Y, Matsui T, et al. Neuropathological observation of rabbits (*Oryctolagus cuniculus*) affected with raccoon roundworm (*Baylisascaris procyonis*) larva migrans in Japan. J Vet Med Sci. 2003;65:695–99.
22. Hendrix CM, DiPinto LN, Cox NR, Sartin EA, Clemons Chevis CL. Aberrant intracranial myiasis caused by larval *Cuterebra* migration. Compend Contin Educ Pract Vet. 1989;11:550–59.
23. Walter KM, Bischoff K, de Matos R. Severe lead toxicosis in a lionhead rabbit. J Med Toxicol. 2017;13:91–94.
24. Shea A, Johnson P, Pivetta M, Beltran E. Congenital meningoencephalocoele in a rabbit. Vet Rec Case Rep. 2014;2:e000052.
25. García R, Añor S, de la Fuente C, Novellas R, Soler V, Martorell J. Paradoxical vestibular syndrome caused by a presumptive cerebellar infarction in a rabbit. Top Companion Anim Med. 2021;43:100509.
26. Solanes F, Bassan T, Cobos A, Frau M, Martorell J. Cerebral thromboembolism secondary to infective endocarditis in a pet rabbit (*Oryctolagus cuniculus*). J Exot Pet Med. 2022;40:41–44.
27. Richardson V. Torticollis (head tilt) in the rabbit. UK Vet. 2009;14:1–3.
28. Keeble E. Nervous system and musculoskeletal disorders. In: A Meredith, B Lord, editors. BSAVA manual of rabbit medicine. BSAVA; 2014. p. 214–31.
29. Meredith A, Richardson J. Neurological diseases of rabbits and rodents. J Exot Pet Med. 2015;24:21–33.
30. Oliveira CR, Ranallo FN, Pijanowski GJ, Mitchell MA, O'Brien MA, McMichael M, et al. The VetMousetrap a device for computed tomographic imaging of the thorax of awake cats. Vet Radiol Ultrasound. 2011;52:41–52.
31. Richardson J, Longo M, Liuti T, Eatwell K. Computed tomographic grading of middle ear disease in domestic rabbits (*Oryctolagus cuniculi*). Vet Rec. 2019;184:679.
32. Keeble E. Encephalitozoonosis in rabbits—what we do and don't know. In Pract. 2011;33:426–35.
33. Latney LTV, Bradley CW, Wyre NR. *Encephalitozoon cuniculi* in pet rabbits: diagnosis and optimal management. Vet Med. 2014;5:169–80.
34. Steinbach E, Gruninger G. Experimental production of cholesteatoma in rabbits by using non-irritants (skin tolerants). J Laryngol Otol. 1980;94:269–79.
35. Travetti O, Giudice C, Greci V, Lombardo R, Mortellaro CM, Di Giancamillo M. Computed tomography features of middle ear cholesteatoma in dogs. Vet Radiol Ultrasound. 2010;51:374–79.
36. Johnson JC, Burn CC. Lop-eared rabbits have more aural and dental problems than erect-eared rabbits: a rescue population study. Vet Rec. 2019;185:758–758.
37. Oglesbee BL, Lord B. Gastrointestinal diseases of rabbits. In: KE Quesenberry, CJ Orcutt, C Mans, JW Carpenter, editors. Ferrets rabbits and rodents: clinical medicine and surgery. 4th ed. Elsevier; 2020. p. 174–87.
38. Hartcourt-Brown FM, Holloway HKR. *Encephalitozoon cuniculi* in pet rabbits. Vet Rec. 2003;152:427–31.
39. Jass A, Matiasek K, Henke J, Küchenhoff H, Hartmann K, Fischer A. Analysis of cerebrospinal fluid in healthy rabbits and rabbits with clinically suspected encephalitozoonosis. Vet Rec. 2008;162:618–22.
40. Mygind SH. Head-nystagmus in human beings. J Laryngol Otol. 1921;36:72–78.
41. Collewijn H. Eye and head movements in freely moving rabbits. J Physiol. 1977;266:471–98.
42. Eatwell K, Mancinelli E, Hedley J, Keeble E, Kovalik M, Yool DA. Partial ear canal ablation and lateral bulla osteotomy in rabbits. J Small Anim Pract. 2013;54:325–30.
43. Wesche P. Clinical pathology. In: A Meredith, editor. BSAVA manual of rabbit medicine. BSAVA; 2014. p. 124–38.
44. Sieg J, Hein J, Jass A, Sauter-Louis C, Hartmann K, Fischer A. Clinical evaluation of therapeutic success in rabbits with suspected encephalitozoonosis. Vet Parasitol. 2012;187:328–32.
45. Suter C, Muller-Doblies UU, Hatt JM, Deplazes P. Prevention and treatment of *Encephalitozoon cuniculi* infection in rabbits with fenbendazole. Vet Rec. 2001;148:478–80.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Liatis T, Makri N, Czopowicz M, Richardson J, Nuttall T, Suñol A. Otitis media/interna and encephalitozoonosis are the most common causes of head tilt in pet rabbits in the UK: 73 cases (2009–2020). Vet Rec. 2024;e4267. https://doi.org/10.1002/vetr.4267