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## CONGENITAL PERIPHERAL VESTIBULAR SYNDROME IN A DOMESTIC FERRET (*MUSTELA PUTORIUS FURO*)

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### Abstract

A 3-month-old intact female ferret (*Mustela putorius furo*) was presented with a 2-month history of ataxia. On physical examination, the ferret had difficulty standing upright. During the neurologic examination, the patient had a left head tilt and positional strabismus, circled to the left, and was ataxic. Results of the complete blood count were consistent with a mild normocytic normochromic anemia. Initial treatment was supportive. Magnetic resonance imaging was performed and revealed an asymmetry of the inner ears. A brainstem auditory evoked response test was also performed. History, clinical signs, and diagnostic test results indicated that the ferret was suffering from congenital peripheral vestibular syndrome and left-sided deafness. Congenital disease should be considered in the differential diagnosis of young ferrets with peripheral vestibular syndrome. Supportive care and physiotherapy can improve balance and motor function, leading to an acceptable quality of life. Copyright 2014 Elsevier Inc. All rights reserved.

**Key words:** brainstem auditory evoked response; deafness; ferret; magnetic resonance imaging; vestibular ataxia; vestibular syndrome

**A** 3-month-old intact female ferret (*Mustela putorius furo*) was presented with a 2-month history of ataxia, circling, and left head tilt. The condition was obvious at 3 weeks of life, when the ferret's littermates started normal ambulation. The ferret was unable to maintain balance and often would fall on its left side. The ferret was not able to eat without help; therefore, it was fed a handmade chicken puree diet. The rest of the litter showed no clinical signs of illness.

On physical examination, the ferret presented with a poor hair coat, weighed 0.45 kg with a body condition score of 2/9, and showed difficulty in maintaining equilibrium. No other abnormalities were observed.

During the neurologic examination, the patient had a left head tilt, circled to the left, vestibular ataxia, and positional strabismus (Fig. 1). No deficits in proprioception were noted. Spinal reflexes were present and normal in all 4 limbs. Cranial nerves evaluation was normal, except for left vestibulocochlear nerve (cranial nerve VIII) deficits. Nevertheless, imbalance made further

neurologic evaluation difficult. Motor activity of the 4 limbs was apparently normal. No other abnormalities were noted during the neurologic examination.

The initial diagnostic workup included blood analysis. A complete blood count revealed a mild normocytic normochromic anemia. Serum chemistry results were within normal limits. At that time, a differential diagnosis was determined based on the peripheral location of the lesion (receptors in the membranous labyrinth and vestibulocochlear nerve), and included congenital defect, trauma, inflammatory/infectious disease,

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**FIGURE 1.** Peripheral vestibular syndrome in a ferret. Note the marked left head tilt.

toxicity, vascular defect, neoplasia, and idiopathic disease.

The ferret's owners declined further diagnostic tests during the initial visit owing to financial concerns. Supportive treatment was initiated. Nutrition was improved by switching to a complete nutritional hand-feeding product for carnivores (Carnivore Care; Oxbow Enterprises, Inc., Murdock, NE USA). Medical treatment included citicoline (10 mg/kg orally, every 12 hours, Somazina; Ferrer Internacional, Barcelona, Spain) for its neuroprotective and nootropic effects. Homeopathic antivertiginous plant-based medication (0.2 mL/ferret orally, every 12 hours, Vertigoheel gotas; Laboratorios Heel España, Madrid, Spain) and a vitamin and mineral supplement (Nutri-plus gel; Virbac Laboratories, Carros, France) were also added to the treatment. Physiotherapy exercises and swimming were also recommended to improve limb musculature.

The ferret was examined 3 weeks following the initial visit and appeared more alert, weighed 0.6 kg, and showed an improvement in body condition (score 3/9). Neurologic examination revealed a left head tilt, but circling was no longer present. No other abnormalities were noted.

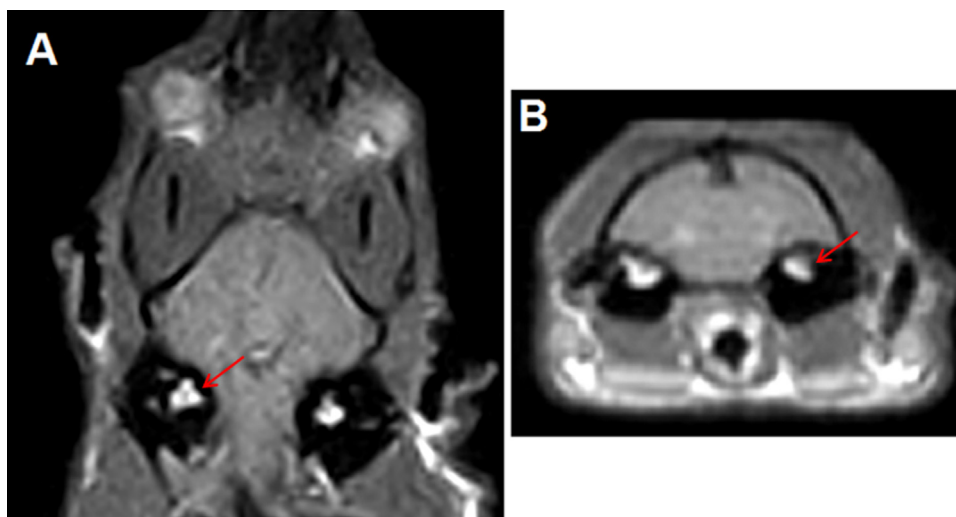
Diagnostic tests were once again recommended, and the owners consented to pursue magnetic resonance imaging (MRI). The ferret was premedicated with midazolam (0.5 mg/kg, intramuscular injection, Dormicum; Roche Farma, Madrid, Spain) and butorphanol (0.5 mg/kg, intramuscular injection, Torbugesic; Fort Dodge, IA USA). Anesthesia was induced and maintained with 0.5% to 1% isoflurane (Isoflo; Abbott Laboratories, North Chicago, IL USA) and 1-L flow of oxygen through a 2-mm (outer diameter) endotracheal tube. Crystalloid fluids (Lactated

Ringer's solution mixed with 5% glucose) were administered at the rate of 8 mL/kg/hour through a 24-g catheter located in the left cephalic vein. Capnography and pulse oximetry were used to monitor the patient during the procedure.

An MRI study of the cranium was performed on the ferret using a 0.2-T system (ESAOTE VetMR). It included sequences corresponding to sagittal, transverse, and dorsal T1-weighted (T1W); dorsal and transverse T2-weighted; transverse fluid attenuated inversion recovery; dorsal 3 dynamic contrast enhanced; and transverse and sagittal multiplanar reconstruction in 3 dynamic contrast enhanced. There were no signs of ischemic, demyelinating, or space-occupying lesions. Enlargement or asymmetry of ventricles was not observed. Bullae appeared air filled, and fluid or mass lesions were not observed within the tympanic bullae. The only abnormal MRI finding was a slight asymmetry in the morphology of inner ears (labyrinth and cochlea). This mild asymmetry was assessed cautiously, as it could have been related to patient positioning during the MRI procedure. T1W sequences after contrast-enhancement paramagnetic gadolinium-based medium (0.2 mL/kg, intravenously, Multihance; Laboratorio Farmacéutico Rovi, Madrid, Spain) did not reveal any enhancement (Fig. 2).

An otoscopic examination of both ears was performed under anesthesia using a portable otoscope. Physical abnormalities such as inflammation, stenosis, or masses were not observed in the external ear canals. Microscopic evaluation of samples from the ear canals was unremarkable. The ferret recovered uneventfully from anesthesia and was released from the hospital later that same day.

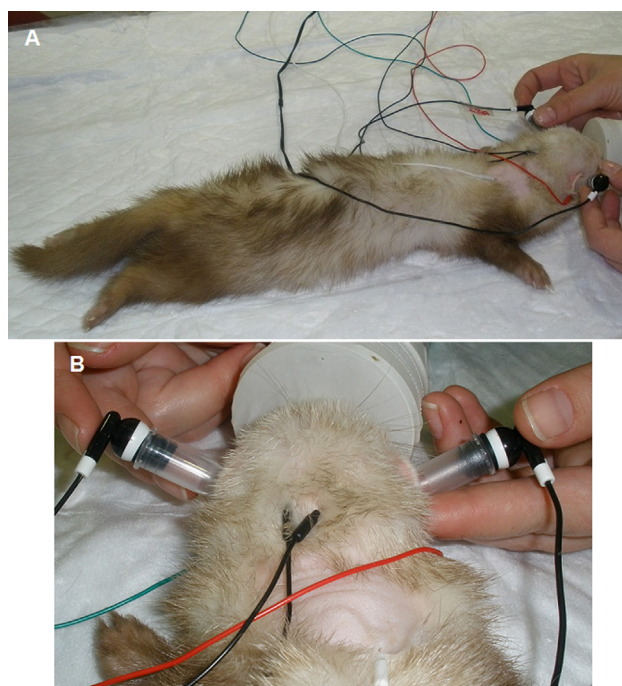
To evaluate the auditory system, a brainstem auditory evoked response (BAER) test was recommended. The BAER test was performed while the ferret was under general anesthesia. Again, the ferret was premedicated with midazolam (0.5 mg/kg, intramuscularly) and butorphanol (0.5 mg/kg, intramuscularly). Anesthesia was induced and maintained with 0.5% to 1% isoflurane via a facemask. The patient was then placed in ventral recumbency, and pulse oximetry was used to monitor oxygen saturation and heart rate. Subdermal electrodes were inserted using adapted needles. A recording electrode was applied to the vertex (dorsal aspect of the skull), reference electrodes in the base of the external ear canal, and a ground electrode in the nuchal crest. Electroacoustic transducers were inserted into



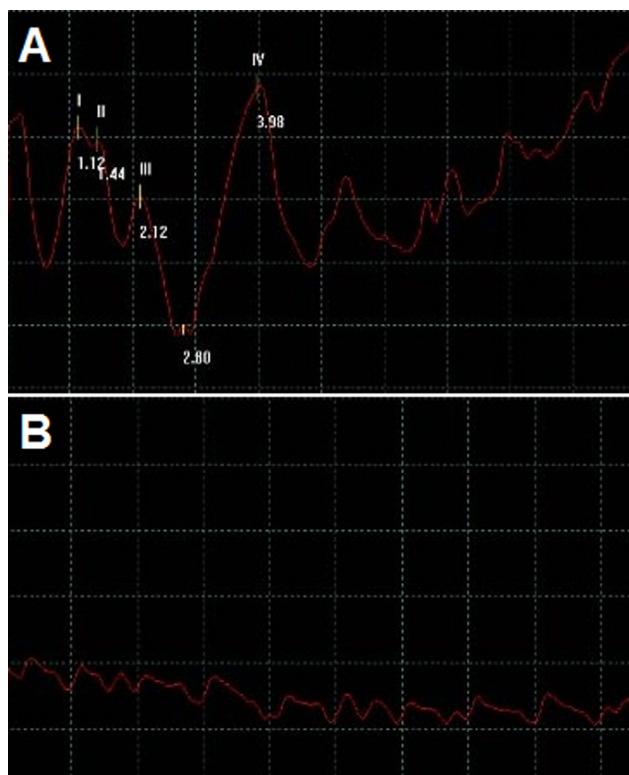
**FIGURE 2.** Magnetic resonance study images: (A) dorsal 3DCE sequence (TR = 34 ms, TE = 30 ms, slice thickness = 0.6 mm, FOV =  $14 \times 14 \times 4 \text{ cm}^3$ ) and (B) transverse MPR in 3DCE sequence (TR = 34 ms, TE = 30 ms, slice thickness = 0.8 mm, FOV = 15 cm). Note the asymmetry of the inner ears, with signal decrease of left inner ear (red arrows). 3DCE, 3 dynamic contrast enhanced; FOV, field of view; MPR, multiplanar reconstruction; TE, echo time; TR, repetition time.

the external auditory canals. Owing to small patient size, 2 Eppendorf tubes were adapted as earphones for the transducers, modified to fit securely over the ferret's external ears (Fig. 3). Alternating wave patterns were used for the test and had an increasing range of 50 to 90 dB normal hearing level. Click stimuli were employed, with a frequency range of 3 to 4 kHz

and 100- $\mu\text{s}$  length as well as a masking noise in the nonstimulated ear and 30 dB under the stimulated ear. An average of 1000 click stimuli were generated in each ear to get the tracing. Right ear BAER test recorded all the main waves (P1, P2, P3, P4, and P5), with P1 to P4 latencies of 1.12, 1.44, 2.12, and 3.98 ms. Right ear results were considered normal for a 3-month-old ferret,



**FIGURE 3.** Ferret positioned for a brainstem auditory evoked response test. Subdermal electrodes were placed using adapted needles (A). Electroacoustic transducers were placed into the external auditory canals, using two Eppendorf tubes adapted as earphones (B).



**FIGURE 4.** Brainstem auditory evoked response (BAER) test graphic results. The right ear BAER test (A) recorded all the main waves (I, II, III, IV, and V). The left ear BAER test (B) was not able to record any main wave.

as minor prolonged P1 and P4 latencies could be attributed to the use of adapted earphones. The left ear BAER test was unable to record any main wave (Fig. 4). These results were consistent with a sensorineural lesion causing left-sided deafness. The ferret recovered uneventfully from anesthesia, and it was released from the hospital later that same day.

The clinical signs and results of complementary tests were consistent with a diagnosis of peripheral vestibular syndrome, presumably of congenital origin considering the young age of the ferret and early onset of clinical signs, and the presence of left-sided deafness. Owing to the assumed congenital etiology of the lesion and mild improvement in clinical signs, no other diagnostic tests were indicated. Initial treatment and physiotherapy exercises were continued to improve muscle tone of the limbs. The ferret showed a slow progressive improvement of balance, and adapted by leaning on vertical surfaces to facilitate movement. Owing to difficulty of mastication, the ferret continued to be fed a liquid diet. Quality of life was judged adequate based on activity level, food and water consumption, and absence of pain or other

disease conditions. At last report, the ferret was alive with no increase of clinical disease signs 24 months after diagnosis.

## DISCUSSION

To the authors' knowledge, this is the first case report describing congenital peripheral vestibular syndrome in a ferret. In ferrets, several causes of vestibular diseases have been described, including toxins, infectious diseases (e.g., canine distemper virus, Aleutian disease, rabies, toxoplasmosis, and ferret systemic coronavirus), neoplasia (e.g., choroid plexus papilloma and granular cell tumor), trauma, and systemic disease (e.g., hypoglycemia).<sup>1-6</sup> Causes of vestibular disease in dogs and cats include neoplasia, trauma, toxin exposure, infectious disease, inflammatory disease, vascular disease, nutritional disorders, idiopathic disease, and congenital disorders.<sup>7-15</sup> For congenital causes, a hereditary origin is assumed as some breeds appear to be predisposed to vestibular disease. Nonetheless, pathogenesis of the disease is not well known. Onset of vestibular clinical signs in these animals can vary, ranging from birth to several weeks of age, with both unilateral or bilateral deafness being present.<sup>11,16</sup>

Vestibular disease can be classified as either peripheral or central, depending on the location of the lesion.<sup>7,8</sup> Lesions located in receptors of the membranous labyrinth and vestibulocochlear nerve deficits result in peripheral vestibular disease. Central vestibular disease results from lesions to the vestibular nuclei in the medulla or the vestibular projections to the cerebellum (cerebellar nuclei). Both peripheral and central vestibular disease can usually be distinguished by the presence of specific neurologic signs and diagnostic testing.<sup>7-9</sup> Common clinical disease signs of vestibular disease include ataxia, head tilt, nystagmus, and strabismus. Lesions affecting the central vestibular system typically produce clinical signs suggesting involvement of the medulla, including altered mentation, ipsilateral proprioceptive deficits, vertical nystagmus, and involvement of multiple cranial nerves. The anatomic diagnosis of peripheral vestibular disease is made in the absence of clinical disease signs associated with the medulla.<sup>10</sup>

Problems of balance resulting in incoordination are prominent in animals with both peripheral and central vestibular diseases.<sup>7-12</sup> Animals with both peripheral and central vestibular diseases often have decreased extensor muscle tone in the

forelimbs and rear limbs on the side of the lesion and increased extensor tone in the limbs on the contralateral side. These abnormalities result in a tendency for the animal to fall or roll toward the side of the lesion. However, animals with peripheral vestibular disease have no loss of general proprioception, which is assessed by performing postural reaction tests. Owing to impaired balance, postural reaction tests can be difficult to perform in affected animals. Ferrets with cochlear agenesis or hypoplasia show various degrees of imbalance associated with vestibular syndrome. In addition to this, these animals generally have poor muscle development, aggravating the inability to correctly stand.<sup>17</sup>

There is evidence that the development of the vestibular system is essential for correct neuromuscular development of the ferret during the initial neonatal period (first month of life).<sup>17,18</sup> Ferrets undergoing labyrinthectomies before complete development of mechanoreceptors showed delays in motor development and shorter and less contractile muscles.<sup>17</sup>

Antemortem diagnosis of congenital vestibular syndromes can be difficult. Compatible history and clinical disease signs are strongly suggestive. However, complementary tests are needed to rule out other common causes of vestibular ataxia, such as otitis media/interna.<sup>12</sup> MRI is the diagnostic imaging modality of choice for the central nervous system, as it allows the clinician to evaluate soft tissue, especially those surrounded by bone. Specific additional MRI sequences can be useful to detect hemorrhage (gradient echo sequences), ischemic disease (diffusion weighted imaging), peri-lesional edema and the presence of pure fluid (fluid attenuated inversion recovery sequences), and muscle, bone and nerve root abnormalities (short TI inversion recovery). Computed tomographic imaging provides excellent images of bony structures and is indicated where osseous changes are of greatest diagnostic importance. Computed tomography and MRI are complementary imaging studies of the middle ear, labyrinth, internal auditory canal, and their contents, but MRI is superior in imaging soft tissue components including intralabyrinthine fluid.<sup>19-23</sup> In this case, only one of the tests was available for economic reasons, and MRI was considered the imaging test of choice for better evaluation of the central nervous system and tympanic bullae.

Peripheral deafness is due to disorders of the peripheral auditory organ (middle/inner ear and cochlea). Peripheral deafness can be classified as sensorineural or conductive. Conductive deafness

results when sound is blocked from reaching the internal ear because of outer or middle ear pathologies. Sensorineural deafness occurs when there is damage to the hair cells or afferent neurons of the cochlea.<sup>16</sup> In dogs and cats, pigment-associated deafness is both the most common type of deafness and form of congenital deafness.<sup>16,24</sup> The white, deaf phenotype has been reported in multiple species, including the ferret, cat, dog, mouse, mink, horse, rat, Syrian hamster, alpaca, and human.<sup>16</sup> A hereditary basis is described, and the genes responsible for white or lightened pigmentation in skin and hair suppress melanocyte function. Suppression of melanocytes in the stria vascularis disrupts their regulation of the endolymph composition, and deafness ensues as a secondary effect.<sup>16,25</sup> Vestibular disease is not a finding in these animals. In ferrets, the pigment-associated hereditary defect has been described as Waardenburg syndrome.<sup>26</sup> Albino ferrets usually retain hearing for the very high frequencies, which may be of limited practical benefit. These animals demonstrate an abnormally small hearing mechanism in the middle and inner ear.<sup>27</sup>

Congenital peripheral vestibular syndrome accompanied by nonpigment-associated deafness has been documented in dogs.<sup>15</sup> These animals have cochlear and vestibular hair cell degeneration. Although the mechanisms for this type of deafness is not known in dogs, human and mouse models frequently show channelopathies (mutations in genes responsible for neuron membrane ion channels, especially potassium).<sup>28</sup> A similar condition unrelated to coat color was suspected in the ferret in this case report, owing to the presence of vestibular disease. Other nonhereditary congenital causes of both peripheral vestibular syndrome and deafness have been described, and these include perinatal anoxia, dystocia, and intrauterine ototoxin exposure.<sup>12,16</sup> Neither dystocia nor medical treatments administered during gestation were reported by the owners.

The BAER test is used for hearing assessment of people, dogs, and cats presenting for congenital deafness screening.<sup>29-31</sup> The BAER test allows for assessment of the cochlear division of vestibulocochlear nerve, the receptors, and various brainstem nuclei.<sup>32,33</sup> In puppies, BAER studies report both high sensitivity (100%) and specificity (78%) for diagnosing deafness.<sup>30</sup> In ferrets, BAER is a noninvasive test that can be performed in a similar way.<sup>34</sup> Sedation or anesthesia is recommended.

Ferrets have a relatively late onset of maturity of the auditory system, and adultlike BAER thresholds

are observed by postnatal day 40.<sup>32</sup> The normal BAER in adult ferret consists of four prominent positive peaks (P1 to P4) and a fifth peak of smaller amplitude and more variable latency. Published mean reference ranges for latencies in ferrets for P1 to P4 are 0.96, 1.83, 2.75 and 3.62 ms.<sup>34</sup> The absence of BAER waves in the left ear of this ferret indicated a sensorineural disease (deafness). The BAER test should be considered when a ferret presents with vestibular disease, and evaluation of inner ear function is required, or to confirm deafness.

Citicoline (cytidine diphosphate-choline) is a neurostimulant, which has neuroprotective and nootropic properties. Its mechanism of action is through biosynthesis promotion of neuronal membrane phospholipids and inhibiting apoptosis.<sup>35,36</sup> Recent studies suggest the neuroregenerative potential of citicoline.<sup>37-39</sup> The homeopathic antivertiginous plant-based medication Vertigoheel gotas contains the herbs *Conium maculatum*, *Ambra grisea*, *Petroleum rectificatum*, and *Anamirta cocculus*. Indications for the use of this compound in humans include nonspecific causes of vertigo and other related imbalance disorders, and related symptoms such as nausea.<sup>40,41</sup> Although the exact mechanism of action of Vertigoheel gotas is not fully understood, studies suggest that it activates the vestibular system in the brainstem area, which may facilitate more accurate communication between the peripheral vestibular system and the brain.<sup>42,43</sup>

Prognosis for congenital vestibular disease in mammals depends on location and the extension of the lesions.<sup>7-10</sup> Peripheral vestibular disease generally carries a better prognosis<sup>7</sup> when compared with central vestibular disease. In the authors' experience, ferrets suffering from congenital peripheral syndrome can progressively improve balance and thus, improve their ability to walk. Ferrets will likely benefit from supportive care and physiotherapy, including assisted exercise and swimming. The use of antivertiginous, neuroprotective, and nootropic drugs could help to improve balance and promote better quality of life in cases of peripheral vestibular diseases in ferrets.

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