COMPANION OR PET ANIMALS

Clinical and imaging features of suspected pituitary apoplexy in a domestic rat

Stephen James Everest,1,2 Tobias Schwarz,1, David Walker,1 Kevin Eatwell,1 Katia Marioni-Henry1

SUMMARY
A two-year-ten-month-old entire female fancy rat was evaluated for acute-onset neurological signs following a two-month history of lethargy and behavioural changes. Physical examination revealed generalised muscle atrophy. Neurological examination localised the lesion likely to the right thalamus based on suspected left unilateral hemineglect. The patient was euthanased over quality-of-life concerns, and postmortem MRI of the brain was performed, followed by postmortem examination. This showed a lesion in the region of the pituitary which was T1 hyperintense to the brain, T2 isointense to the white matter and hypointense on gradient echo sequences, suggesting subacute haemorrhage. The authors described the clinical presentation and imaging features (MRI) of suspected pituitary apoplexia secondary to a pituitary macroadenoma in an aged female rat. Of particular interest are the findings of unilateral hemineglect and blooming artefact on MRI gradient echo sequences that lead to suspicion of pituitary apoplexia confirmed on postmortem examination.

BACKGROUND
In this case report the authors described the clinical presentation and imaging features of suspected pituitary apoplexia secondary to a pituitary macroadenoma in an aged female rat.

Pituitary adenomas are a common, and sometimes incidental, postmortem finding in aged rats.1 It is reported that the incidence is twice as high in female entire rats compared with male entire rats (67.92 per cent and 35.42 per cent, respectively).2 The clinical presentation of pituitary adenomas in six rats has been described by Vannevel,1 and similar to the present case the most common clinical signs detected on physical examination were ataxia, head tilt and postural deficits.3 Interestingly, the present case also demonstrated unilateral hemineglect, a phenomenon in which a patient with brain damage (most commonly caused by cerebrovascular disease in people) ignores stimuli contralateral to the affected area of the brain.4 In rats, multimodal neglect has previously been induced via disconnection of the medial agranular cortex and the posterior parietal cortex. This suggests that hemispatial neglect may be associated with lesions affecting the pathways involving these regions; however, damage to the basal ganglia, the white matter of the internal capsule and the mesencephalic reticular formation has also been reported to produce neglect.5

A haemorrhagic appearance of pituitary tumours has previously been described in rats. An example of this was in a clinical trial carried out by Magnusson and others.6 The authors performed postmortem examinations on a total of 2609 rats (male and female). They noted pituitary neoplasms, which were dark red and haemorrhagic in appearance in 11 of the examined rats. The description of the neoplasms in these cases was similar to the appearance of the pituitary mass found during the postmortem examination in the present case.

Pituitary apoplexy is a term first used by Brougham and others in 1950.7 It describes a relatively rare, although potentially life-threatening, condition involving haemorrhage or infarction of the pituitary gland, often secondary to pituitary adenoma, the first case of which was described by Bailey.8 Pituitary apoplexy is a poorly understood condition, with very few studies investigating its incidence and clinical presentation in people. Zhu and others9 reported that there was sex predisposition, with 72.2 per cent of cases being male and 27.8 per cent female, which supported similar results in earlier studies.10,11 It is thought that poor cardiovascular function could play a role in the development of pituitary apoplexy in patients with pituitary adenoma, which could explain why there is a higher prevalence in males.9

CASE PRESENTATION
A two-year-ten-month-old female entire fancy rat (Rattus norvegicus domesticus) was evaluated due to a sudden onset of progressive neurological signs of six days’ duration. The owner noticed that the rat had developed a left head tilt and would intermittently stumble and fall into left lateral recumbency and struggle to right itself. History included two months of progressive lethargy, polyphagia, polydipsia, muscle atrophy and behavioural changes, in particular an increased tendency to bite when handled. The rat had also become progressively less mobile and less willing to climb the bars of its cage, remaining solely on the floor of the cage for approximately one month before presentation.

Medical history included a mammary mass, which had been removed approximately 1.5 years before this presentation. Following removal, there was no recurrence and there was no clinical suspicion that this was active at the time of, or related to, the presenting disease process.

On examination, poor body condition score and hair coat with abrasions on the dorsal aspect of the
feet and tail were noted. The patient’s mental status was dull and was poorly responsive to stimuli. In particular it was noted that the patient was less reactive to touch on the left side of its body and took more time to find food dropped on its left. On the contrary, it would attempt to bite when approached from the right and was able to prehend food dropped on this side without any difficulty. It resented any form of manipulation, and the owner reported the patient to be more aggressive than usual. A left head tilt of approximately 20°–30° and left-sided head turn were noted. On analysis of its gait, the patient appeared to intermittently stagger and fall towards the left side, consistent with left vestibular ataxia. The muscle mass and tone of the rat were generally poor. Postural reactions such as paw replacement and hopping were difficult to assess due to the temperament of the patient; however, visual placement and extensor postural thrust could be performed. Visual placement of the right forelimb appeared to be normal; however, it was inappropriately delayed in the left forelimb. Extensor postural thrust was reduced in both pelvic limbs. However, withdrawal reflexes were normal in all four limbs. Spinal palpation did not reveal any obvious abnormalities or areas of hyperaesthesia.

On cranial nerve examination, menace response (evaluating cranial nerves II and VII) was normal on the right but absent on the left eye. There was no facial asymmetry noted, suggesting that there was normal function of cranial nerve VII and that the menace deficit was most likely secondary to a lesion in the visual pathway. The pupillary light reflex (PLR) was difficult to assess due to the patient’s temperament, but pupil size appeared to be normal and symmetrical. Strabismus or pathological nystagmus was not observed. Cranial nerve V motor function appeared to be intact based on assessment of normal jaw tone; sensation was normal on the right side of the face but reduced on the left side. The patient did not appear to have difficulties with deglutition; therefore, it was suspected that functions of cranial nerves IX and X were not affected. The tongue appeared to be symmetrical with normal position and function.

Based on the neurological examination the lesion was localised to the forebrain, most likely the right thalamus or cerebral cortex based on a suspicion of left unilateral hemineglect. A multifocal lesion localisation affecting the cerebral cortex and brainstem was also considered possible. Based on the signalment and clinical history, the primary differential diagnosis was an intracranial neoplasia such as a pituitary macroadenoma, followed by an inflammatory/infectious or degenerative condition. Vascular aetiology was considered less likely due to the progressive nature of the clinical signs.

INVESTIGATIONS

After obtaining the owner’s consent, postmortem MRI of the patient’s skull was carried out using a 1.5T MRI system (Siemens Magnetom Avanto, Siemens, Erlangen, Germany) with a 15-channel transmit-receive knee coil. On transverse and sagittal T1, T2 and T2* weighted image sequences, a large, well-demarcated extra-axial mass lesion could be seen in the area of the sella turcica compressing the thalamus, cerebral hemispheres and cerebellum (figure 1A–D). The lesion was T1 hyperintense to the brain, and isointense if compared with the white matter or hypointense to the grey matter on T2 weighted images (figure 1A–C). In the gradient echo images, the mass was hypointense to the brain, with blooming artefact (figure 1D) due to paramagnetic effects of bleeding products (deoxyhaemoglobin and methaemoglobin). Blooming artefact occurs in the presence of paramagnetic substances and makes lesions appear larger than they truly are. In the T2 weighted sagittal MRI, hyperintensity of the spinal cord was also noted (figure 1A).

DIFFERENTIAL DIAGNOSIS

Based on the MRI findings a subacute haemorrhage of a pituitary macroadenoma or pituitary apoplexy was suspected.

OUTCOME AND FOLLOW-UP

Considering the suspicion of intracranial neoplasia and associated poor prognosis, the rat was euthanased on welfare grounds.

Postmortem examination

Grossly expanding the pituitary gland was an 8-mm diameter, soft, red globus mass. Histologically the tumour was characterised by an expansile mass, composed of sheets and islands of atypical polygonal cells, which was segmentally encapsulated by a thin, fibrous band of tissue, and which compressed a portion of pre-existing pituitary gland (presumed pars distalis). The cells also lined frequent vascular channels. The individual cells had variably distinct cell borders and a moderate amount of eosinophilic, granular to floccular cytoplasm. The nuclei were round and exhibited moderate anisocytosis and anisokaryosis; no mitotic figures were observed. Multifocally, there was extravasation of small to moderate numbers of erythrocytes (haemorrhage), and scattered at the periphery of the mass, and within the pre-existing pituitary gland, were moderate numbers of haemosiderophages. The final diagnosis was a pituitary adenoma with intraslesional haemorrhage. Histopathological examination of the cervical spinal cord.

Figure 1  MRI. (A) Sagittal T2 weighted MRI with a visible homogeneous lesion (indicated by arrow) at the level of the diencephalon and mesencephalon. Hyperintensity of the spinal cord was also noted. (B) Transverse T2 weighted MRI showing a white matter isointense and grey matter hypointense lesion (indicated by arrow) at the level of the diencephalon. (C) Transverse T1 weighted MRI showing a lesion (indicated by arrow) hyperintense to the brain at the level of the diencephalon. (D) T2 gradient echo MRI showing a hypointense lesion (indicated by arrow) with blooming artefact at the level of the diencephalon.

Veterinary Record Case Reports
revealed mild, multifocal Wallerian degeneration. There was also moderate, multifocal lymphoplasmacytic perivascular inflammation of the cervical spinal cord with a focal area of similar inflammation in the associated meninges; the aetiology was undetermined. These findings could be secondary to the pituitary adenoma; however, an immune-mediated or viral aetiology could not be ruled out. Mild, multifocal pineal gland mineralisation was also present, which was considered to be an age-related and incidental finding.

**DISCUSSION**

Pituitary apoplexy has previously been described in other veterinary species, with a report by Long and others describing the case of a seven-year-old female, neutered German short-haired pointer that presented for acute-onset collapse, peracute vomiting and generalised tonic-clonic seizures. Its owner had noted a four-week history of polyuria/polydipsia and urinary incontinence before the more severe, acute clinical signs. On clinical examination, profoundly obtunded mentation and hyperthermia were noted. Neurological examination revealed decreased direct and consensual PLRs, bilaterally absent menace response and positional nystagmus. Proprioceptive deficits in all four limbs with normal spinal reflexes were also noted. Based on this assessment the authors localised the lesion to the diencephalon. The patient was ultimately euthanased due to poor response to treatment. Subsequent postmortem examination revealed haemorrhage within, and surrounding, a pituitary adenoma. The authors noted that the presentation of this case, paired with the neoplastic and paraneoplastic changes to the pituitary, was very similar to cases of pituitary apoplexy in people.

A similar case was described in a seven-year-old male, neutered domestic shorthaired cat by Beltran and others. This patient presented with a five-month history of depression followed by acute-onset restlessness and blindness. Neurological examination revealed the patient to be obtunded and disorientated. On cranial nerve examination, the patient had bilaterally absent menace responses, and direct and consensual PLRs. The authors also noted bilaterally decreased physiological nystagmus. The cat’s postural reactions were decreased in all four limbs, with normal spinal reflexes. MRI revealed a large suprasellar lesion causing compression of the optic chiasm and thalamus. The mass was T1 hypointense and T2 isointense to the grey matter, with hyperintense foci within it. Gradient echo sequences performed revealed signal void in the caudal crescentic rim. The imaging and postmortem examination confirmed a diagnosis of pituitary adenoma with several focal areas of haemorrhage present within the tumour.

Both the cases reported by Long and others and Beltran and others share many similarities with the case discussed in this report. All cases describe acute-on-chronic neurological deficits, localising to the diencephalon. Pituitary adenoma with associated haemorrhage within the tumour was confirmed on postmortem in all three cases. Additionally, the imaging performed by Beltran and others reported similar findings to those described in the rat in this report. These findings suggest that cases of pituitary apoplexy may be expected to present with similar clinical signs and MRI findings in rats as in other domestic, mammalian species.

While pituitary adenoma is known to be relatively common in domestic rats, there are few reports of pituitary apoplexy-like disease in domestic rats. A case report by Mayer and others examining the extra-label use of cabergoline in a 24-month-old, entire albino pet rat, described MRI findings on T1 and T2 weighted MRI that could be compatible with the presence of haemosiderin from previous haemorrhage. However, the authors did not acquire a gradient echo sequence as part of their MRI study. T2* weighted gradient echo sequences are considered the most sensitive among the most commonly available sequences in veterinary medicine, and a study confirmed that the agreement between veterinary radiologists for detection of haemorrhages is poor when only routine T1 weighted, T2 weighted and fluid-attenuated inversion recovery (FLAIR) sequences are used. In the present case, the mass was T1 hyperintense if compared with grey or white matter of the brain, indicating the presence of either haemoglobin degradation products, or a lipid-containing or mineralised lesion, or a cystic lesion with high concentration of proteins (colloid cyst, craniopharyngioma), or a melanin-containing lesion (metastatic melanoma). However, the same lesion was also hypointense on the gradient echo sequence, which combined with the high signal on T1 weighted images was suggestive of a late subacute haemorrhage; this finding was confirmed on postmortem examination. The spinal cord hyperintensity noted on the T2 weighted sagittal image was suspected to be spinal cord oedema or syringomyelia secondary to foraminal crowding with compression of the fourth ventricle and obstruction of cerebrospinal fluid flow at the foramen magnum due to the substantial mass effect present in the rostral cranial fossa.

This case showed that gradient echo sequences are a sensitive modality for imaging intracranial haemorrhage in rats, and are a feasible option for diagnosing pituitary macroadenoma and apoplexy in rats with neurological signs suggestive of intracranial disease. A particularly interesting clinical sign noted in this case, given the lesion localisation, was hemispatial neglect, which led the authors to suspect a lesion affecting the thalamus.

**Learning points**

- Pituitary tumours are a relatively common, slowly progressive condition in domestic rats.
- Pituitary tumours may present with acute-onset neurological signs if associated with intracranial haemorrhage, as in pituitary apoplexy.
- This case highlights neurological examination findings in a rat with hemineglect secondary to a thalamic lesion.
- Gradient echo sequences acquired with a 1.5T MRI system may help in achieving an antemortem diagnosis of pituitary apoplexy in domestic rats.

**Contributors**  All authors made major contributions to the content and editing of the final report, and were all involved with the management of the case.

**Funding**  The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests**  None declared.

**Provenance and peer review**  Not commissioned; externally peer reviewed.

**Data availability statement**  All data relevant to the study are included in the article.

**ORCID iD**

Tobias Schwarz http://orcid.org/0000-0001-8412-573X

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