Pituitary-dependent hyperadrenocorticism in a cockatoo

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Case Description—A 13-year-old female intact Moluccan cockatoo (Cacatua moluccensis) was admitted because of coelomic distention, presumed to be secondary to an abdominal hernia. The patient also had a history of rapid weight gain and polyuria and polydipsia.

Clinical Findings—Ultrasoundography was used to confirm the existence of a pseudohernia that appeared to contain the small intestines, pancreas, and reproductive tract. Results of plasma biochemical analysis revealed hyperglycemia, hypophosphatemia, and high nonfasting bile acid concentrations and aspartate aminotransferase activity. A CBC revealed a relative heterophilia with a concomitant lymphopenia and mild monocytosis. Histologic evaluation of a liver biopsy specimen indicated chronic hepatic lipidosis. Despite a strong clinical suspicion of hyperadrenocorticism, ACTH stimulation test results were equivocal.

Treatment and Outcome—The pseudohernia was strengthened with a prolene mesh. Despite ongoing medical and surgical care, the patient developed complications associated with the herniorrhaphy and was euthanatized. The clinical suspicion of hyperadrenocorticism was confirmed on the basis of histologic evaluation of the pituitary gland by use of special stains.

Clinical Relevance—To our knowledge, pituitary-dependent hyperadrenocorticism has not been previously confirmed in Psittaciformes. The condition should be considered in birds with clinical signs consistent with those observed in mammals. For the cockatoo of this report, ACTH stimulation test results were equivocal and additional diagnostic tests should be developed for avian patients. (J Am Vet Med Assoc 2008;232:394–398)

A 13-year-old female Moluccan cockatoo (Cacatua moluccensis) was admitted to the Avian and Exotic animal service at the Cornell University Hospital for Animals for evaluation of a presumptive abdominal hernia. A hernia had been diagnosed by the referring veterinarian on the basis of physical examination and radiographic findings 10 days prior to admission. Historically, the owners reported sudden weight gain, dyspnea, polyuria, and polydipsia of approximately 2 months’ duration. Additionally, the bird had alopecia of the sternum and a sore on the keel of the sternum that were attributed to feather picking and self-mutilation, respectively. Dyspnea, polyuria, and polydipsia were temporally related to the abdominal distention, progressing conjointly in severity. At the time of hospital admission, the patient weighed 1,100 g (2.42 lb), which is an increase from the typical adult weight of the bird of approximately 750 g (1.65 lb). Severe coelomic distention was observed with the duodenum and pancreas visible through the ventral midline skin. The liver was palpably enlarged with mild sternal lift, increased caudal extension of the liver, and rounded hepatic borders. No abnormalities were detected upon auscultation of the heart, lungs, or air sacs.

Results of physical examination, evaluation of whole body radiographic views by the referring veterinarian, and diagnostic testing supported a diagnosis of abdomi-
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not be identified; however, generalized atrophy of the

abdominal musculature was observed. The duodenum,

pancreas, and ventriculus, as well as a large, mildly hy-

perechoic liver, were readily viewed within the coelom.

In addition, the ovary and oviduct were also identified
dorsal to these structures. These findings were corrobo-
rated by surgical exploration of the area that revealed a
diffusely thin, transparent abdominal musculature over-
lying the coelomic contents. Owing to the large size of
the liver, its rounded margins, and fatty appearance, as
well as the abnormal plasma aspartate aminotransferase
activity and bile acids concentration, a biopsy specimen
of the liver was obtained for histologic evaluation. De-
tailed exploration of the coelomic cavity during surgery
was limited by extensive coelomic fat accumulation.

Because of the diffuse and severe atrophy of the abdomi-
nal muscles, an 8 × 6-cm ovoid piece of prolene mesh4 was
used to replace the abdominal wall. The repair yielded
a reduction in the size of the abdominal distention by
approximately 15%. Anesthetic recovery was unevent-
ful. The patient was discharged from the hospital the
following day and was administered a 7-day course of
enroflaxacin (15 mg/kg [6.8 mg/lb], PO, q 24 h) and a
5-day course of meloxicam (0.3 mg/kg [0.14 mg/lb], PO,
q 24 h). A postoperative examination within 7 days was
recommended.

Histologic evaluation of the liver biopsy specimen
indicated severe, diffuse hepatic lipidosis with biliary
hyperplasia and extramedullary hematopoiesis. He-
patic portal areas and central veins were indistinct, and
multilocular areas of parenchymal collapse were identi-
fied within the examined sections, changes indicative
of chronic hepatic lipidosis.

The patient was reevaluated 17 and 24 days after
surgery. The bird was bright, alert, and responsive,
and by the second visit was approaching an ideal body
weight. The droppings continued to be voluminous;
however, the owners perceived that the frequency and
total volume had decreased slightly over time. On ini-
tial reexamination, evidence of delayed wound healing
of the skin was observed, particularly along the most
dependent two thirds of the incision.

During the first postoperative visit, CBC and plas-
ma biochemical analyses were repeated. The Hct had
decreased to 32%, and mild leukocytosis (11.8 × 103
WBCs/μL) was observed. When considering the WBC
differential, the proportion of heterophils was toward
the upper end of the reference range (72%), whereas
the proportion of lymphocytes was toward the lower
end (24%). Mild monocytesis (1.7%) was also present.
Plasma biochemical parameters were within reference
limits except for a mild to moderate hypouricemia (1.4
mg/dL; reference range, 3.5 to 10.5 mg/dL). By the sec-
ond visit, the cranial-most third of the skin incision had
healed; the caudal two thirds continued to be covered
by a dark-brown scab. However, owing to a lack of evi-
dence of disseminated systemic disease, odor, or dis-
charge, medical management consisting of enroflaxacin
(15 mg/kg, PO, q 24 h) and nonadherent dressings was
elected.

Review of clinical signs and history after the sec-
ond postoperative examination suggested that these
features were consistent with those seen in mammalian
hyperadrenocorticism.1 Thus, an ACTH stimulation
test was recommended to evaluate the hypothalamo-
pituitary-adrenal axis.

An ACTH stimulation test based on a previously
published protocol in Moluccan cockatoos2 was per-
formed 41 days after surgery. As per the published pro-
tocol, the patient received 0.15 mg (0.2 mg/kg [0.09
mg/lb]) of cosyntropin via IM injection into the pecto-
ral musculature. Baseline serum corticosterone concen-
tration was measured, as were concentrations at 1 and
3 hours after stimulation, with the aim of comparing
the degree of stimulation to that found in the work of
Walsh et al.2 The patient had a baseline serum corticos-
terone concentration of 13 ng/mL, with concentrations
of 87 and 92 ng/mL, at 1 and 3 hours after stimulation,
respectively. Given that the patient had a similar degree
of stimulation to that observed in the work of Walsh
et al,2 it was decided that the patient did not over stim-
ulate; thus, a diagnosis of hyperadrenocorticism was
not achieved via this test.

The patient continued to have delayed surgical
wound healing and was admitted twice over the next
2 weeks for management of the incisions. The prolene
mesh was found to be infected, and an abscess was re-
moved, but unfortunately, the patient's condition wors-
ened after the second surgery; the bird had 2 episodes
of cardiorespiratory arrest and was subsequently eu-
thanatized. Gross necropsy examination performed 24
hours after death revealed extensive fibrous adhesions
between the coelomic viscera and the prolene mesh as
well as multiple fibrous and fibrinous adhesions be-
tween caudally located coelomic viscera. Additionally,
fibrin was present in the cranial portion of the coelomic
cavity. In contrast to the normal anatomical situation in
birds in which the adrenal glands are flat and closely op-
oposed to the cranial poles of the kidneys, adrenal glands
in this bird were prominent, rounded, and bulged over
the ventral aspect of the renal surfaces.3 The adrenal
glands were roughly bilaterally symmetrical, measur-
ing 5 mm in diameter. The pituitary gland measured
3 mm in diameter, had caused mild compression of the
surrounding CNS structures, and was therefore consid-
ered enlarged. Thyroid glands were pale tan, smooth,
and bilaterally symmetrical and measured 2 mm in di-
ameter each. Because of the small size, symmetry, and
contour of the thyroid glands, they were judged to be
within reference limits. Representative sections of tis-
sues were fixed in neutral-buffered 10% formalin, pro-
cessed routinely, and stained with H&E for histologic
examination. Histologic sections from the CNS, includ-
ing the pituitary gland, measured 5 μm thick; all re-
main ing tissues were sectioned at 4-μm thickness. In
addition to routine staining, sections of the pituitary
gland were examined for ACTH immunoreactivity via
a streptavidin-biotin immunoperoxidase technique by
use of a rabbit anti-ACTH antibody4 and an automated
immunohistochemistry stainer in accordance with the
instructions of the manufacturer.5 An additional sec-
ton of pituitary gland was incubated with normal rab-
tbit IgG rather than rabbit anti-ACTH antibody to serve
as a negative control sample.

Histologically, diffuse bilateral hyperplasia of the
adrenal glands was found. Adrenal glands were com-
posed of approximately 85% inter-renal (cortical type) cells, recognized by abundant foamy eosinophilic cytoplasm. Fifteen percent of the adrenal gland was composed of chromaffin (medullary type) cells. The normal structure of the pituitary gland was replaced by a mass of largely agranular epithelial cells arranged in chords and acini supported by a fine fibrovascular stroma. Neoplastic cells had abundant pale, basophilic, foamy cytoplasm and round nuclei containing coarsely stippled chromatin. Moderate anisocytosis and anisokaryosis were observed. Rare, widely scattered cells contained small numbers of eosinophilic cytoplasmic granules. Scattered acini were filled by small amounts of homogeneous eosinophilic material. Small numbers of the neoplastic cells were immunoreactive for ACTH. Immunoactive cells were either solitary or present in small clusters.

These findings were consistent with a pituitary adenoma. Given the necropsy findings of a pituitary tumor with bilateral adrenal hyperplasia as well as the clinical signs at admission, a diagnosis of PDH was made.

Discussion

To our knowledge, a confirmed case of PDH has not been previously reported for birds. The patient in this report presented with several clinical signs and clinicopathologic features common to dogs with hyperadrenocorticism, such as polyuria and polydipsia, pendulous abdomen, abdominal muscle weakness, hepatomegaly, hepatic lipodisosis, increased intra-abdominal fat, weight gain, delayed wound healing, a relative heterophilia, lymphopenia, concurrent monocytosis, high liver enzyme activities, hyperglycemia, and hypophosphatemia. It was these clinical signs and clinicopathologic findings that directed us toward the consideration of hyperadrenocorticism as a potential diagnosis.

Despite a high index of clinical suspicion and an attempt to confirm the diagnosis with antemortem testing, a definitive diagnosis was not achieved in this bird until a necropsy examination had been performed. An ACTH stimulation test was performed on the basis of the published protocol of Walsh et al. The original study of 28 clinically normal adult Moluccan cockatoos revealed a mean basal serum corticosterone concentration among females of 18 ng/mL and a mean post-stimulation concentration of 110 ng/mL at 2.5 hours. Therefore, the typical degree of stimulation achieved was 6 times the baseline concentration. The patient in this report achieved a 7-fold increase in serum corticosterone concentrations in response to ACTH (13 ng/mL at baseline and 92 ng/mL at 3 hours after stimulation). Such a degree of stimulation was not considered appreciably greater than that reported by Walsh et al; thus, a diagnosis of hyperadrenocorticism was not obtained via this test.

Among dogs, ACTH stimulation tests have been reported to have a sensitivity of approximately 85% for the diagnosis of PDH; therefore, 15% of truly affected dogs are falsely declared negative for PDH by this test. The sensitivity of this test in birds is currently unknown, and despite a high degree of conservatism between the avian and mammalian endocrine system, it is unclear whether an exaggerated response should be expected. One possible explanation of the lack of aberrant ACTH stimulation could be that the bird had a cyclic form of hyperadrenocorticism (ie, Cushing’s disease). This condition occurs rarely in humans and is associated with intermittent secretion of ACTH hormone via functional pituitary adenomas. Clinical signs and clinicopathologic features may vary with this condition and wax and wane depending upon the degree of secretion of ACTH. Such a condition might explain the resolution in the biochemical parameters observed between the initial profile and that performed at the first recheck appointment of the patient in this report. As an alternative hypothesis, it is possible that ACTH responsiveness varies diurnally among cockatoos. Among rats, it has been shown that ACTH stimulation is greatest during the diurnal nadir of corticosterone concentrations. If such a phenomenon were to occur among cockatoos, then failing to perform an ACTH stimulation during the corticosterone nadir may lead to a spurious decrease in the degree of stimulation. Although this theory remains possible, it is somewhat less likely given previous work indicating that no evidence exists for diurnal responsiveness to ACTH stimulation in pigeons (Columbia livia domestica).

We considered the use of a dexamethasone suppression test to confirm the suspected diagnosis in vivo. However, although baseline data on the degree of suppression achieved by various doses of dexamethasone exist for pigeons, no published data exist for psittacines. We also considered advanced imaging modalities in the diagnostic process; however, the patient had developed complications associated with the herniorrhaphy prior to any such testing.

Necropsy findings of a pituitary adenoma along with bilateral adrenal gland hyperplasia are consistent with PDH. Additionally, the presence of ACTH immunoreactive cells within tumor indicates that the neoplasm may have been hormonally active. Despite certain structural and functional differences between birds and mammals, the avian hypothalamic-pituitary-adrenal axis shares many similarities with the mammalian axis. In their report on the microscopic and functional anatomy of the hypothalamic-pituitary-adrenal axis of the budgerigar (Melopsittacus undulatus), Kobayashi et al confirmed findings of earlier reports that the avian pituitary gland consists of an adenohypophysis and a neurohypophysis. However, unlike the situation in mammals, the adenohypophysis consists only of the pars distalis and the pars tuberalis; no functional pars intermedia exists. The pars distalis represents the largest portion of the adenohypophysis and is situated ventral to the neurohypophysis. The pars distalis consists of the cephalic lobe and the caudal lobe, which consist of 2 cytologically distinct cell types. The ACTH-secreting cells are located in the cephalic lobe and are under the positive influence of corticotrophin-releasing factor, produced by the hypothalamus. Corticotrophin-releasing factor is itself negatively regulated by corticosterone. The primary adrenal glucocorticoid of birds is cortisol. Although a number of birds with pituitary adenomas and adenocarcinomas have been reported in the literature, these reports lack the clinical, clinicopatho-
logic, and histopathologic features necessary for a definitive diagnosis of PDH.  

Previously reported putitary pathologic changes of birds include adenomas and adenocarcinomas with variable frequency, particularly in budgerigars.  

In 1999, Suchy et al reported on the occurrence of 6 putitary gland tumors among 286 necropsy examinations of birds obtained over a 10-year period in which the brain was examined histologically.  

Two of the lesions were classified as chromophobic putitary adenomas, 2 as chromophobic adenocarcinomas, and 2 as acidiophilic carcinomas. Although the 2 acidiophilic carcinomas had immunoreactivity to anti-growth hormone antibodies, no other putitary gland neoplasms were immunoreactive to anti-ACTH, anti-growth hormone, anti-melanocyte-stimulating hormone, or anti-prolactin antibodies. Thus, no immunohistochemical support of PDH was found among the members of that study population.  

Although clinical signs consistent with PDH, such as polyuria, polydipsia, hyperglycemia, and obesity, have been observed in a number of birds, the authors of these reports 13,16,18,19 were unable to determine the exact etiology of these clinical signs and thus could not confirm PDH. It has been suggested that the clinical signs observed among affected birds may be the result of growth hormone excess, decreased arginine vasotocin production, cerebral compression, or excess production of ACTH.  

The microanatomy of the avian adrenal gland is distinct from the mammalian adrenal gland. It is not divided into an outer cortex and an inner medulla; rather catecholamine-producing cells (chromaffin cells) and corticoid-producing cells (cortical [inter-renal] cells) are interspersed within the adrenal glands. Cortical cells are the major cell type and form cords that generate a subcapsular zone and an extensive inner zone within the gland.  

As reviewed by Lumeij, 22 various forms of primary putitary pathologic findings have been reported for a number of avian species. Reported putitary gland lesions include bilateral adenoma and cortical hyperplasia, unilateral adenoma, and unilateral adrenocortical carcinoma.  

However, in none of these affected birds was functional hyperadrenocorticism described clinically. To our knowledge, only 1 clinical report 23 of hyperadrenocorticism in a bird exists in the veterinary literature. This brief communication describes a scarlet macaw (Ara macao) found to have unilateral adrenal gland carcinoma on necropsy examination. The patient had clinical signs of emaciation, decreased appetite, and polyuria-polydipsia of a few weeks’ duration. The patient had high serum alkaline phosphatase activity and uric acid concentration, with a concurrent decrease in the PCV. An ACTH stimulation test was not performed in this bird. The patient’s basal serum corticosterone concentration was, however, measured and found to be 17.7 ng/mL, which was significantly greater than that measured in 5 clinically healthy conspecifics (mean, 5.1 ng/mL). Given the observed serum corticosterone concentration and histologic findings, the patient was considered to have hyperadrenocorticism secondary to a functional adrenal gland tumor.  

In conclusion, we contend that the patient of this report was affected with PDH on the basis of the observed clinical and clinicopathologic findings, in conjunction with the histologic findings. A small number of the neoplastic cells in the putitary gland were immunoreactive for ACTH. The presence of immunoreactivity in the atypical cell population, as well as the bilateral hyperplasia in the adrenal glands, suggests that the putitary gland tumor was endocrinologically active.  

Findings of a study 24 in domestic birds indicate that ACTH-secreting cells are normally present only in the cephalic lobe of the avian putitary gland. In the bird of this report, the neoplastic process had profoundly altered the anatomy of the gland such that anatomic origin of the tumor could not be determined. Detailed descriptions of the normal number and distribution of ACTH-secreting cells in putitary gland of cockatoos are lacking, and normal putitary glands from an age-matched bird were not available for comparison in this study. However, specific knowledge of the normal anatomy of the putitary gland for this species might be useful in interpreting the anatomic origin of neoplasms in the future. It is, however, recommended that the diagnosis of hyperadrenocorticism be considered among psittacines with clinical signs and laboratory findings analogous to those observed in dogs with hyperadrenocorticism. Given the inability of the ACTH stimulation test to obtain a definitive diagnosis in the bird of this report, it would seem prudent to perform advanced imaging techniques to quantify gross putitary gland lesions in suspect birds. It is also recommended that additional studies be performed to determine the viability of low-dose dexamethasone suppression testing in the diagnosis of this condition among psittacines.

References


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Effects of carprofen on the integrity and barrier function of canine colonic mucosa
Catherine A. Briere et al

**Objective**—To measure effects of carprofen on conductance and permeability to mannitol and histologic appearance in canine colonic mucosa.

**Sample Population**—Colonic mucosa from 13 mature mixed-breed dogs.

**Procedures**—Sections of mucosa from the transverse colon and proximal and distal portions of the descending colon were obtained immediately after dogs were euthanized. Sections were mounted in Ussing chambers. Carprofen (400 μg/mL) was added to the bathing solution for treated sections. Conductance was calculated at 15-minute intervals for 240 minutes. Flux of mannitol was calculated for three 1-hour periods. Histologic examination of sections was performed after experiments concluded. Conductance was graphed against time for each chamber, and area under each curve was calculated. Conductance X time, flux of mannitol, and frequency distribution of histologic findings were analyzed for an effect of region and carprofen.

**Results**—Carprofen significantly increased mean conductance X time, compared with values for control (untreated) sections for all regions of colon. Carprofen significantly increased mean flux of mannitol from period 1 to period 2 and from period 2 to period 3 for all regions of colon. Carprofen caused a significant proportion of sections to have severe sloughing of cells and erosions involving ≥ 10% of the epithelium, compared with control sections.

**Conclusions and Clinical Relevance**—Carprofen increased in vitro conductance and permeability to mannitol in canine colonic mucosa. Carprofen resulted in sloughing of cells and erosion of the colonic mucosa. These findings suggested that carprofen can compromise the integrity and barrier function of the colonic mucosa of dogs. (Am J Vet Res 2008;69:174–181)