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Descriptive Clinical Reports

Diagnosis and treatment of confirmed and suspected primary hyperparathyroidism in equids: 17 cases (1999–2016)

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Summary

Background: Primary hyperparathyroidism is uncommon in equids.
Objectives: To describe the diagnostic findings and efficacy of treatment in equids with primary hyperparathyroidism.
Study design: Retrospective case series describing 16 horses and one mule.
Methods: Cases were identified by retrospective review of records at Cornell University and via an ACVIM listserv query. Inclusion criteria were an equid with hypercalcemia, normal renal function and high parathyroid hormone (PTH) or histopathological diagnosis of a parathyroid adenoma. Equids with normal PTH and PTH-related protein (PTHrP) in the face of hypercalcemia were included as suspect cases.
Results: The most common presenting complaints were weight loss (12/17) and hypercalcemia (10/17). PTH was above reference range in 12/17 cases. Suspected parathyroid tumours were localised in 12/14 equids imaged using ultrasonography alone (2/3), technetium 99m Tc sestamibi scintigraphy alone (1/1) or both modalities (9/10). Three horses did not have imaging performed. Surgical exploration successfully excised tumours in six of 10 cases. Five were located at the thoracic inlet, and surgery resulted in complete cure. One tumour was excised from the thyroid lobe, and the horse remained hypercalcemic. Four other cases explored surgically, four treated medically and three that were not treated also remained hypercalcemic.
Main limitations: The small study size prohibited statistical analysis.
Conclusions: Parathyroid adenomas in equids can be successfully localised with ultrasonography and scintigraphy. Surgical excision appears more likely to be successful for single gland disease at the thoracic inlet.

Keywords: horse; parathyroid adenoma; parathyroidectomy; parathyroid imaging; technetium Tc 99m sestamibi scan; equine endocrinology

Abbreviations

IQR	Interquartile range
PHPT	Primary hyperparathyroidism
PTH	Parathyroid hormone
PTHrP	Parathyroid hormone-related protein
USD	United States Dollars

Introduction

Primary hyperparathyroidism (PHPT) is an uncommon endocrinopathy in horses that historically has been difficult to treat; however, a recent case study has elucidated potential novel diagnostic methods and surgical treatment success [1]. This retrospective study was undertaken to evaluate the outcome of these methods in a larger cohort.

Hyperparathyroidism is characterised by inappropriately high production of parathyroid hormone (PTH) by the chief cells of the parathyroid gland and subsequent derangements in calcium and phosphorous homoeostasis [2]. Clinical signs include anorexia, weight loss, osteodystrophia fibrosa of the facial bones, osteopenia and lameness [1,3–7]. Both primary [1,3–7] and secondary [8,9] hyperparathyroidism have been reported in equids. Two reports of secondary hyperparathyroidism, both in ponies, were suspected to be nutritional in origin and no definitive reports of renal secondary hyperparathyroidism in equids exist in the literature. In contrast to other domestic species, equids with chronic renal failure commonly develop hypercalcemia [10] and there is evidence that in the horse this disease process induces a hypoparathyroid state [11].

Primary hyperparathyroidism results from hyperplasia or neoplasia of the parathyroid gland itself and can involve single or multiple glands, leading to excessive production of PTH that is unresponsive to physiologic negative feedback mechanisms. PTH acts to increase osteoclast activity via an indirect process resulting in bone resorption and calcium release, as well as to promote renal calcium reabsorption and phosphorous wasting [2]. In most species PTH also increases circulating calcitriol, though the relationship between vitamin D metabolites and calcium homoeostasis appears to differ in horses and is not fully understood [12].

Hyperparathyroidism in horses must be differentiated from other causes of hypercalcemia, such as chronic renal disease, hypervitaminosis D and hypercalcemia of malignancy, in which paraneoplastic production of parathyroid hormone-related protein (PTHrP) results in an increase in blood calcium concentration due to its ability to bind to the PTH receptor and mirror many of the actions of PTH [2].

Treatment of single-gland PHPT in people is often straightforward with surgical success rates ranging from 92 to 99% [13]; however, treatment has been limited in horses due to the difficulties in identifying the abnormal gland. Recently, both ultrasonography and technetium Tc 99m sestamibi scintigraphy have aided in localisation and removal of parathyroid

adenoma resulting in a clinical cure in a pony [1]; however, surgical failures have also been documented [3,6,7]. In the equine literature, documented medical therapy has been limited to short-term diuresis with intravenous and oral fluid therapy as well as furosemide in an effort to lower plasma calcium concentrations [1,6,7]. Our objectives were to 1) characterise the clinical and laboratory findings in equids with PHPT, 2) evaluate the utility of ultrasonography and scintigraphy as diagnostic modalities, 3) document potential intra- and post-operative complications and 4) document the efficacy of surgical and medical treatments.

Materials and methods

Cases were identified via retrospective review of records at one institution and an ACVIM listserv query, including medical records from 1999 to 2016. Inclusion criteria were an equid with persistent hypercalcemia, presumptive normal renal function as assessed by serum creatinine concentration, and high serum PTH concentration or histopathologic identification of parathyroid adenoma. Equids with normal serum PTH and PTHrP concentrations in the face of hypercalcemia likely reflect abnormally high PTH secretion and were included as suspect cases [2]. PTHrP was not required in cases with high serum PTH, as serum PTH is expected to be low in cases of hypercalcemia of malignancy [1], though it is possible for a functional parathyroid adenoma and PTHrP-secreting neoplasia to be present in the same animal. Information was recorded for signalment, presenting complaint, physical examination findings, clinicopathologic data, pertinent diagnostics including ultrasonography, radiography, scintigraphy and histopathology, surgical and medical treatment, case complications, outcome, case follow-up and total hospital bill.

Descriptive statistics were used to report findings. Numerical values are reported as medians and ranges, unless otherwise indicated.

Results

Seventeen equids that fulfilled the inclusion criteria were submitted for inclusion in this study, including two previously documented cases (Case 1 and 6) [1,6], with 12/17 having an increased PTH concentration and 6/17 having histopathological confirmation of parathyroid adenoma. Five had a normal PTH and PTHrP, only one of which had definitive diagnosis by histopathology. Signalment of all cases are summarised in Supplementary Item 1.

Clinical findings

Presenting complaints and physical examination findings are shown in Supplementary Item 1. The most common presenting complaints were weight loss (12/17) and hypercalcemia (10/17; the remaining seven cases did not have serum chemistry performed before presentation). Clinicopathologic findings are summarised in Table 1. Consistent with the inclusion criteria, cases were presented with high ionised and total calcium concentrations. Serum phosphorus concentration was decreased in 12/17 cases.

The PTH concentration was increased in 12/17 cases (Table 1). Five cases (Cases 5, 11, 13, 15, 16) had a serum PTH concentration within reference range and were considered suspect for PHPT, though Case 5 was later confirmed with histopathology. Plasma PTHrP concentrations were available for 12/17 cases and were low when reported. The two cases with a measurable PTHrP concentration had low values in conjunction with increased PTH concentrations, thus hypercalcemia of malignancy was considered unlikely. Serum 25-hydroxyvitamin D concentrations were available for 7/17 cases and were abnormal in 3/7.

Diagnostic imaging

Suspected abnormal parathyroid tissue was noted in 7/13 horses examined by ultrasonography. Increased radiopharmaceutical uptake consistent with abnormal parathyroid tissue was observed in 10/11 cases examined by technetium Tc 99m sestamibi scintigraphy [1,3,7]. Representative scintigraphy and ultrasonography from two confirmed cases are shown in Figure 1. Case attributes and location of abnormal tissue are shown in Table 2.

In the 10 cases that were examined by both ultrasonography and scintigraphy, findings agreed in 6/10 cases and differed in 4/10 cases. In all five cases with positive findings on both ultrasonography and scintigraphy, locations of suspected abnormal parathyroid glands agreed. All four cases with discrepant results had a negative ultrasonography but positive scintigraphy. Fine needle aspiration was performed in Case 2 at the thoracic inlet, which yielded a diagnosis of endocrine/neuroendocrine tumour. Biopsy was performed in Case 11 which was inconclusive.

Radiographs of the skull, limbs or both were obtained to screen for bony changes in 8/17 animals, with abnormalities seen in 7/8 animals including osteopenia of the limbs or skull (5), dystrophic mineralisation (2), laminitic changes of unknown cause (1) and focal loss of the lamina dura of the first molars (1). Pleural changes were observed on ultrasonography of Case 2. Thoracic radiographs revealed focal lung masses. Paraneoplastic hypercalcemia of malignancy considered unlikely in this case due to normal PTHrP concentration and histopathological confirmation of parathyroid adenoma following surgical excision. Thoracic radiographs performed on a second animal were normal (Case 6).

Treatment and complications

Surgical excision was attempted in 10/17 cases, 6/10 of which were histopathologically confirmed as cases of PHPT. Histopathologic diagnoses are described in Table 2. Five of six horses with a diagnosis of parathyroid adenoma had tumours localised to the thoracic inlet on ultrasonography (5/5), scintigraphy (4/4) or both (4/4) preoperatively. The sixth adenoma was removed via hemithyroidectomy in Case 6 and had been identified by ultrasonography. Though the 4/10 animals receiving unsuccessful surgeries all had unequivocally increased PTH concentrations, histopathological confirmation of PHPT was not obtained.

One surgery was performed under standing sedation to remove a tumour embedded in the thyroid lobe (Case 6). Median anaesthetic time for the remaining nine cases was 90 min, with a range of 60–143 min (IQR 85–105). In six of 10 cases anaesthetic complications were reported, which are detailed in Table 2 and included hypotension (5), hypoxaemia (2), hypercapnia (2) and transient arrhythmia consisting of ventricular premature contractions (1). Intraoperative hypocalcemia was not noted in any case. All horses undergoing surgical excision with general anaesthesia had a normal recovery. Median ionised calcium at the time of surgery was 2.5 mmol/L, ranging from 2.04 to 3.87 mmol/L (IQR 2.33–2.60, reference range 1.44–1.74). Though diuresis with balanced isotonic fluids was utilised preoperatively in seven of 10 horses undergoing surgical excision in an attempt to reduce anaesthetic complications, ionised calcium remained equal or above 2.04 mmol/L in these animals.

Hypocalcemia was noted in 2/6 cases after removal of parathyroid adenomas. Post-operative hypocalcemia was first documented at 42 and 52 h following surgery (Cases 1 and 4). Muscle tremors, stiffness and cardiac arrhythmias were seen in both cases, with Case 4 additionally showing a grimacing facial expression and synchronous diaphragmatic flutter, and Case 1 showing laryngeal spasm and hyperresponsiveness. In Case 1, clinical signs of tetany preceded documented hypocalcemia by 18 h despite frequent monitoring of serum ionised calcium concentration. Both horses were treated with oral and intravenous calcium supplementation, with calcium values normalising in 2.25 (Case 1) and 15 days (Case 4) post-operatively and clinical signs of tetany resolving in 22 (Case 1) and 12 days (Case 4). Three additional cases undergoing surgical excision received prophylactic calcium supplementation with oral (2) or intravenous (1) calcium, with no documented hypocalcemia or signs of tetany. Sources of oral calcium varied and included calcium oxide, calcium propionate, calcium carbonate and/or alfalfa hay.

Post-operative hypophosphatemia occurred in five out of six cases with parathyroid adenoma removal. Clinically, hypophosphatemia can cause muscle fasciculations and weakness, neuromuscular irritability, intestinal ileus, cardiac arrhythmias, rhabdomyolysis and haemolysis [14]. Two hypophosphatemic cases developed signs of muscle dysfunction (cases 1 and 4), though they also had concurrent hypocalcemia. Case 1 also developed concurrent mild anaemia, though definitive evidence of haemolysis was not noted. Cases were treated with oral and intravenous

TABLE 1: Clinicopathologic data of horses diagnosed with PHPT

Case	Ionised calcium (mmol/L)	Total calcium (mmol/L)	Phosphorus (mmol/L)	PTH[a] (pmol/L)	PTHrP (pmol/L)	Vitamin D (nmol/L)	PHPT diagnosis[b]
Median	2.66	4.35	0.45	N/A	0	15.0	
Range	2.14–4.95	3.65–6.65	0.29–0.99	N/A	0–0.40	0–19.0	
IQR	2.5–2.8	4.2–5.2	0.32–0.84	N/A	0–0	11.4–17.2	
Reference[c]	1.44–1.74	2.70–3.22	0.68–1.52	0.60–11.0	<1.0[d]	13.0–40.0	
1	**2.52**	**5.37**	0.99	**129**	N/A	N/A	Confirmed
2	**3.0**	**5.35**	**0.29**	**30.8**	0	N/A	Confirmed
3	**2.48**	**4.2**	0.90	**119**	0	19.0	Confirmed
4	**2.82**	**4.57**	**0.43**	**73.6**	0	N/A	Confirmed
5	**2.24**	**4.35**	0.87	3.90	N/A	N/A	Confirmed
6	**2.62**	**4.60**	**0.32**	**14.1**	N/A	17.0	Confirmed
7	**2.46**	**3.87**	0.70	**23.7**	0	N/A	Consistent
8	**2.77**	**4.22**	**0.45**	**62.8**	0	N/A	Consistent
9	N/A	**5.30**	**0.48**	**41.1**	N/A	N/A	Consistent
10	**4.95**	**6.65**	**0.32**	**44.2**	0.40	**9.50**	Consistent
11	**2.62**	**4.27**	**0.32**	6.70	0	**12.0**	Suspect
12	**3.10**	**5.20**	**0.39**	**39.3**	0	N/A	Consistent
13	**2.14**	**3.70**	0.77	6.20	0	**0**	Suspect
14	N/A	**5.20**	**0.51**	**20.5**	0.10	N/A	Consistent
15	**2.66**	**3.65**	**0.42**	4.60	0	13.0	Suspect
16	**2.77**	**4.05**	**0.61**	3.90	N/A	N/A	Suspect
17	**2.77**	**4.27**	**0.32**	**11.7**	0	17.0	Consistent

Values that were outside the laboratory-specific reference range are indicated in bold font. IQR, interquartile range; PHPT, primary hyperparathyroidism; PTH, parathyroid hormone; PTHrP, parathyroid hormone related protein.

[a]PTH testing methods varied over the study years and values are not directly comparable.

[b]Cases were classified as 'Confirmed' if histopathologic confirmation was achieved, 'Consistent' if PTH was above reference range and 'Suspect' if PTH and PTHrP were both normal in the face of hypercalcemia.

[c]Individual laboratory-specific reference ranges varied and general reference ranges are supplied from the New York State Animal Health Diagnostic Center for ionised calcium, total calcium and phosphorus concentrations, and from the Michigan State University Veterinary Diagnostic Laboratory for PTH, PTHrP and Vitamin D concentrations.

[d]Reference range is for canines and felines, as no range exists in equids.

therapy (3/5), intravenous therapy alone (1/5) or oral therapy alone (1/5). Post-operative complications were seen in 7/10 surgical cases, as shown in Table 2.

Seven cases received medical therapy either as sole treatment (Cases 11–14) or as an adjunct to surgical treatment (Case 6, 9 and 10). Three cases were not treated and were returned to prior management. Out of the four equids receiving only medical therapy and the three not treated, 4/7 were suspect cases. Reasons for not pursuing surgical treatment were reported in six cases and included lack of localisation of lesion (3/6), age of patient (2/6) and financial concerns (1/6). Medical treatments and complications are detailed in Table 2.

Outcome

Surgical success was defined as cases in which a parathyroid tumour was removed resulting in resolution of the patient's hypercalcemia. The calcium concentration normalised in 5/10 cases that underwent surgical treatment (Cases 1–5), improved but did not normalise in 1/10 (Case 9), improved initially but relapsed over time in 2/10 (Cases 8 and 10) and did not improve in 2/10 (Cases 6 and 7). All five horses whose calcium normalised post-operatively had a single parathyroid adenoma removed from the thoracic inlet. Case 6 had a parathyroid adenoma removed via hemithyroidectomy, but remained hypercalcemic following surgical excision. Multiple tumours were suspected, as the PTH concentration also remained increased after surgery.

PTH concentrations of nine cases with increased PTH were re-measured after surgical treatment. Four of nine cases showed normal PTH concentrations following treatment (Cases 1–4), all of which had a parathyroid adenoma removed from the thoracic inlet. As stated, the PTH concentration remained increased in Case 6 after excision of parathyroid adenoma. Two out of nine cases showed reduction but not normalisation of the PTH concentration, the first after removal of normal parathyroid and branchial cyst with medical therapy and diet change (Case 9), and the second after removal of lymphoid tissue and medical therapy with intravenous fluids, diuretics and tiludronate disodium (Case 10), though the cause of this reduction is unknown.

In addition to resolution of their hypercalcemia, all cases of successful surgical treatment demonstrated improvement in clinical abnormalities if they were evaluated post-operatively, except for Case 3 who showed persistent lameness. However, this abnormality was not definitively attributable to the patient's PHPT and may have been multifactorial given the patient's age and concurrent poor foot conformation. Case 1 was also lame pre-operatively and showed improvement after treatment. Radiographs were repeated in Case 1 3 months after discharge, which showed improvement in bone density. Three cases showed improvement in body condition following successful surgery (Cases 2, 3 and 4); post-operative body condition was not noted for Case 1 and was not abnormal prior to surgery in Case 5. Of the three cases showing anorexia prior to treatment that were successfully treated, all improved (Cases 2, 3 and 4) with one case showing complete resolution of marked preoperative anorexia just 24 h after successful surgery (Case 3). Case 5 was subclinical at presentation.

Seven cases received medical treatment, in four cases as sole therapy. Success was gauged by improvement in clinicopathologic values and clinical signs. Medical therapy was reported as unsuccessful in five out of seven cases (Cases 6, 9, 10, 11 and 12) and to have improved the clinical status in two out of seven cases (Cases 13 and 14). Cases 13 and 14 were treated with diet change to reduce calcium intake and showed reported improvement but not normalisation of blood calcium concentrations (Case 13) and body condition (Cases 13 and 14). Administration of tiludronate sodium in Case 10 resulted in a mild reduction in blood calcium concentration. All animals treated medically remained hypercalcemic (median, 2.63 mmol/L; range, 2.07–3.11; reference range, 2.70–3.22 mmol/L).

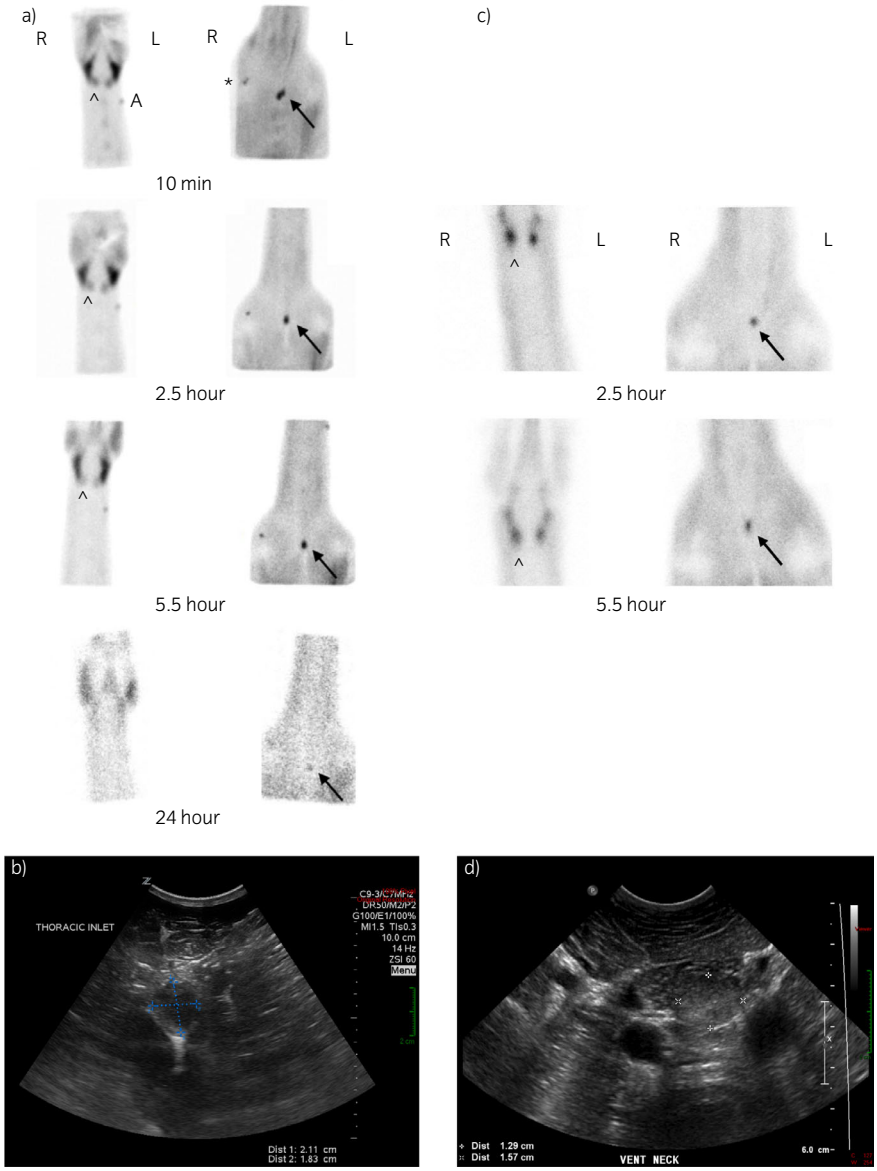

Fig 1: a) Sequential technetium Tc 99m sestamibi scintigraphy images of the thoracic inlet and neck of a 22-year-old Morgan mare with a parathyroid adenoma at the thoracic inlet (Case 3). Adenoma was confirmed by surgical excision and histopathology. Ventrodorsal views from the ramus of the mandible to the thoracic inlet are shown. The ovoid area of uptake at the thoracic inlet (arrows) represents the parathyroid adenoma and persists through the 24-h image. Uptake is seen in the thyroid glands (carets) through the 5.5-h image. A marker is utilised at the point of the shoulder (asterisk), and a small area of pharmaceutical uptake is noted at the level of the catheter hub (A). b) Ultrasonographic study from the same case, showing a 2.11 × 1.83 cm hypoechoic nodule at the level of the thoracic inlet consistent with a parathyroid adenoma. c) Sequential technetium Tc 99m sestamibi scintigraphy images of the thoracic inlet and neck of a 30-year-old Quarter Horse gelding (Case 2) with a parathyroid adenoma at the thoracic inlet. Adenoma was confirmed by surgical excision and histopathology. Ventrodorsal views from the ramus of the mandible to the thoracic inlet are shown. The ovoid area of uptake at the thoracic inlet (arrows) represents the parathyroid adenoma. Uptake is seen in the thyroid glands (carets) through the 5.5-h image. d) Ultrasonographic study of the same case, showing a 1.29 × 1.57 cm echoic nodule at the level of the thoracic inlet consistent with a parathyroid adenoma.

Median duration of hospitalisation was 9 days, ranging from 0 (outpatient) to 60 days (IQR, 3–14). The total bill was available for 15 cases, with a median of 6000 US dollars (USD) (range, 540–11,057 USD; IQR, 3108–7959).

Sixteen horses survived to discharge, with one horse euthanised after two unsuccessful surgeries to remove suspected abnormal parathyroid tissue (Case 9). Follow-up was available for nine horses. Median duration of follow-up was 11 months (range, 1–25 months). Seven of nine were still alive (Cases 2, 3, 10, 12, 13, 14 and 16), two of which had successful surgical removal of parathyroid adenoma. Two horses (Cases 8 and 15) were euthanised for colic 3 days and approximately 1 month after discharge; one horse was surgically treated unsuccessfully (Case 8), and one was not treated (Case 15).

Discussion

This is the first comprehensive case series describing diagnosis and treatment of PHPT in equids. We find an overall 50% PHPT cure rate after attempted surgical excision of parathyroid adenoma and a 100% cure rate

TABLE 2: Diagnostic and histopathologic findings, treatment, subsequent calcium status and complications in equids diagnosed with primary hyperparathyroidism

Case	PHPT diagnosis[a]	Sonographic localisation	Scintigraphic localisation	Number of glands affected	Treatment	Histological diagnosis	Calcium after treatment	Complications	Clinical outcome
1	Confirmed	Thoracic inlet	Thoracic inlet	Single	Surgical excision	Parathyroid adenoma	Normal	Intra-op: hypotension Post-op: hypocalcemia, tetany, hypophosphatemia, anaemia, renal injury, hypertriglyceridemia, sinus tachycardia	Cure
2	Confirmed	Thoracic inlet	Thoracic inlet	Single	Surgical excision	Parathyroid adenoma	Normal	Intra-op: hypotension, hypercapnia Post-op: hypophosphatemia	Cure
3	Confirmed	Thoracic inlet	Thoracic inlet	Single	Surgical excision	Parathyroid adenoma	Normal	Intra-op: hypotension, ventricular premature contractions Post-op: diarrhoea, colic, hypophosphatemia, hypertriglyceridemia, renal injury	Cure
4	Confirmed	Thoracic inlet	N/A	Single	Surgical excision	Parathyroid adenoma	Normal	Intra-op: hypotension Post-op: hypocalcemia, tetany, hypophosphatemia, cardiac arrhythmia, colic, oral ulcerations from calcium gel, renal injury	Cure
5	Confirmed	Thoracic inlet	Thoracic inlet	Single	Surgical excision	Parathyroid adenoma	Normal	Intra-op: hypoxemia Post-op: hypophosphatemia, renal injury	Cure
6	Confirmed	Intra-thyroid	N/A	Single	Surgical excision, diuretics	Parathyroid adenoma	Increased	Post-op: hypothyroidism	Not Improved
7	Consistent	Nondiagnostic	Peri-thyroid	Single	Surgical excision	Thyroid, fibroadipose tissue, lymph node	Increased	None	Not improved
8	Consistent	Mid-neck	Mid-neck	Single	Surgical excision	Thyroid adenoma	Increased	Intra-op: hypotension, hypercapnia Post-op: colic, diarrhoea	Not improved
9	Consistent	N/A	Peri-thyroid	Multiple	Surgical excision, diet change, fluid therapy	Branchial cyst, normal parathyroid	Increased	None	Not improved, euthanised
10	Consistent	Nondiagnostic	Thoracic inlet	Multiple	Surgical excision, bisphosphonate, i.v. fluids, diuretics	Lymph tissue	Increased	None	Not improved
11	Suspect	Nondiagnostic	Peri-thyroid	Single	Diet change, i.v. fluids	N/A	Increased	None	Not improved
12	Consistent	N/A	N/A	Unknown	Diet change	N/A	Increased	Colic	Not improved
13	Suspect	Nondiagnostic	Peri-thyroid	Single	Diet change	N/A	Increased	Reduced exercise tolerance	Improved
14	Consistent	Nondiagnostic	N/A	Unknown	Diet change	N/A	Increased	None	Improved
15	Suspect	N/A	N/A	Unknown	Not treated	N/A	N/A	N/A	Not improved
16	Suspect	Nondiagnostic	Nondiagnostic	Unknown	Not treated	N/A	N/A	N/A	Not improved
17	Consistent	N/A	N/A	Unknown	Not treated	N/A	N/A	N/A	Not improved

PHPT, primary hyperparathyroidism; Intra-op, during surgery; Post-op, after surgery.
[a]Cases were classified as 'Confirmed' if histopathologic confirmation was achieved, 'Consistent' if PTH was above reference range and 'Suspect' if PTH and PTHrP were both normal in the face of hypercalcemia.

for surgical excision of single gland adenomas at the thoracic inlet. All cases treated surgically either had high PTH concentration or definitive histopathologic diagnosis, suggesting surgical failure was more likely due to inadequate identification of abnormal tissue than to misdiagnosis. There were no equids in this series that showed complete resolution of signs following medical therapy.

Diagnosis

Older patients appear overrepresented in our case population, with a median age of 21 years. Additionally, nearly twice as many mares were present as geldings. Women and older patients of both sexes have a higher risk of developing PHPT in humans [15]. In dogs, the disease is also more common in older animals [16]. It is difficult to know if the presenting complaints seen in this study resulted entirely from PHPT as opposed to other co-morbidities, as it is possible for the disease to be silent in other species [17].

Ultrasonography and technetium Tc 99m scintigraphy are both valuable imaging modalities for the diagnosis of PHPT in equids, though multi-gland disease might hinder successful diagnosis. Formal sensitivity and specificity of each test could not be calculated due to the lack of a gold standard diagnosis and low case numbers. Overall sensitivity of ultrasonography to identify suspected abnormal parathyroid tissue among the included cases was low (54%). Risks of solely using ultrasonography are that abnormal glands could be missed and that other structures such as lymph or thyroid tissue could be misidentified as abnormal parathyroid glands. Both ultrasonography and scintigraphy are used in human patients for PHPT diagnosis, with one prospective study showing a combined sensitivity of 97.4% for patients with a single adenoma [18]. False-negative ultrasonographic and scintigraphic examinations have been reported in human patients with small or ectopic parathyroid glands, multi-gland disease, conditions causing delayed washout from the thyroid such as goitre and nonadenomatous morphologic changes to the parathyroid [13]. Ultrasonography is utilised in dogs to localise parathyroid tumours, with a study showing a nodule found in 96% of cases [16]. The apparently higher sensitivity of sonography in canine and human patients is likely due to the more restricted anatomical location of the caudal parathyroid glands in those species compared to equids, where the glands can be located as far caudally as the thymus [3].

Overall sensitivity of scintigraphy was higher than ultrasonography at 90%. However, scintigraphic identification of abnormal tissue did not guarantee successful surgical identification or excision of tumours, especially when the uptake was not in a single location at the thoracic inlet. This indicates that scintigraphy may lack sensitivity for multigland disease or specificity for parathyroid adenoma. Optimally, the standard of care in human patients suggests that ultrasonography and scintigraphy should be used in concert for diagnostic accuracy in equid patients with PHPT.

Prognosis

In this study, identification of a single abnormal gland at the thoracic inlet appears to be associated with surgical success, with five out of five patients with single gland disease at the thoracic inlet having confirmed excision of parathyroid adenoma and clinical cure. In contrast, the single case with suspected multiple gland disease at the thoracic inlet had an unsuccessful surgery with only lymphoid tissue excised (Case 10). This case illustrates the difficulty of differentiating lymphoid and parathyroid tissue during surgery. A significant challenge to successful diagnosis and surgical excision of abnormal parathyroid tissue in humans is the presence of multi-gland disease. The sensitivity of sestamibi scans is lower in human patients with multi-gland disease [18–21], and intra-operative PTH measurement can be used in these cases to judge surgical success. Additionally, complete bilateral neck exploration often must be performed to locate all abnormal tissue [18,19]. Neither intraoperative PTH testing nor complete neck exploration are feasible in equid patients, likely reducing the prognosis for surgical success in cases with multi-gland disease. However, a recent study found that concordant ultrasonographic and sestamibi results showing one enlarged gland indicated a high likelihood of single-gland disease in people [22]. Our data agree, suggesting that concordant ultrasonographic and sestamibi results showing single gland disease and thoracic inlet location could be useful criteria to assess surgical prognosis.

No cases in which abnormal tissue was located in the mid-neck or intra-thyroid areas resulted in successful resolution of laboratory values or all clinical signs, despite excision of a parathyroid adenoma embedded in the thyroid in Case 6. An additional case report of PHPT exists in which the horse showed increased radiopharmaceutical uptake at both the thyroid and the thoracic inlet, and surgical exploration of the thyroid region was unrewarding. Post-mortem examination later revealed a parathyroid adenoma at the thoracic inlet [7]. The reasons for the surgical failures in this study could include the presence of multi-gland disease, misidentification of abnormal tissue on ultrasonography or scintigraphy and misidentification of adenomatous tissue at surgery. Differentiating between normal and abnormal radiopharmaceutical uptake in the cranial parathyroid and thyroid glands, as well as between thyroid, lymphoid and adipose tissue ultrasonographically in the cranial neck of the horse can be difficult, especially given the prevalence of thyroid adenomas in aged equids. Intraoperative impression smears and cytology of excised tissue might be useful in assessing surgical success, and could dictate the need for further exploration if neuroendocrine tissue is not removed in the first attempt.

This study illustrates that surgical cure can be achieved in cases of PHPT with normal PTH concentrations (Case 5). In human patients, lower PTH concentrations are correlated with lower tumour weights, higher incidence of multi-gland disease and a higher risk of surgical failure when excision is attempted [13]. However, in canine patients, up to 73% of animals with confirmed PHPT have a PTH value within the normal reference range compared with 7.4% in human patients [17,23,24]. While more work is needed to evaluate whether PTH concentration is a predictor for surgical success in horses, at this time all horses with suspected PHPT warrant further diagnostic investigation and surgical intervention, as this could be curative.

Medical therapy was noted to have partially improved the clinical status in only two out of seven animals in which it was attempted. Surgical therapy is the preferred therapy in dogs, with medical therapies such as fluid diuresis, bisphosphonates and glucocorticoids utilised only as short-term treatment of deleterious hypercalcemia, such as in animals with concurrent azotemia or a calcium-phosphorous product >70 [25]. Though dietary restriction of calcium was utilised in 5/7 cases, it should be noted that this therapy is not recommended in humans due to the possibility of triggering additional PTH release and subsequent increases in bone resorption [26].

Complications

Surgical excision resulted in treatable intraoperative complications. Diuresis did not reduce calcium concentrations below 2.04 mmol/L in any case, but no significant arrhythmias were noted under anaesthesia aside from single rare ventricular premature contractions in one horse. Though some tumours were located adjacent to critical vasculature, no significant intraoperative haemorrhage was noted. Additionally, there were no complications in anaesthetic recovery, even despite documented osteopenia.

Post-operative complications were difficult to predict. The varying derangement in calcium homoeostasis following excision in these patients was likely due to the degree of suppression of the remaining parathyroid glands, as the patient with prolonged hypocalcemia had an undetectable PTH concentration following excision. A recent study of dogs with PHPT undergoing either percutaneous ethanol ablation or parathyroidectomy showed a moderate correlation between the magnitude of hypercalcemia pretreatment and the development of postoperative hypocalcemia [27]. In equids the response to excision is difficult to predict at this time; thus, owners should be warned of the possibility of this complication following surgery. Though this study did not investigate the chronicity of the patients' hypercalcemia prior to surgical excision, this parameter warrants further study.

Acute renal injury, defined by an increase in serum creatinine of >25% over baseline, was noted in four out of six cases following surgical excision of a parathyroid adenoma, the reason for which is also unknown and in all cases resolved with short-term enteral and/or intravenous fluid therapy. Clinicians must be aware of the risk of postoperative acute renal injury in these patients and should monitor renal function accordingly.

A surprising finding in this study was the prevalence of hypophosphatemia in patients undergoing successful surgical excision. Increased PTH concentrations should promote increased phosphaturia; thus, removal of a hyperfunctional gland and reduced PTH would be expected to result in normal or even increased phosphorus concentrations [2]. The reason for postoperative hypophosphatemia in these cases is

unclear and could be multifactorial. Five out of six cases with successful parathyroid adenoma excision received preoperative diuretics, which promote hyperphosphaturia, in an attempt to lower blood calcium concentrations. Although acute renal tubular damage can lead to hypophosphatemia, it is more common with chronic renal disease in horses [10,28]. Two of these cases developed transient post-operative hypertriglyceridemia that was treated with intravenous glucose supplementation. Hyperglycaemia and subsequent insulin release drives phosphorus into cells, leading to hypophosphatemia. Additionally, accelerated uptake of phosphorus into muscle and bone occurs in human patients post-surgically [2]. This study suggests that blood phosphorus concentrations should be closely monitored in the post-operative period and clinicians should be prepared to initiate treatment if necessary.

Limitations

Limitations of this study included the lack of gold standard diagnosis for all cases, variability in testing methods, small study size and subsequent lack of substantial statistical analysis. It is possible that the cases with normal PTH concentrations did not have PHPT, as no gold standard test (such as post-mortem examination) was applied. Prospective study with post-mortem examination to assess sensitivity and specificity of PTH concentration and the imaging modalities would be beneficial. Over the study period there were multiple improvements in PTH testing methods, making it difficult to compare values between cases or associate PTH concentration with outcome in the current data set. The potential association between PTH concentration at diagnosis, single-gland disease and surgical success are areas for continued investigation. Additionally, minimally invasive treatment modalities such as percutaneous ultrasound-guided heat or chemical ablation have been described in dogs [29,30] and warrant further attention. Finally, though this study did not investigate the presence of concurrent endocrine diseases, further elucidation of associations of PHPT in horses with pituitary pars intermedia dysfunction, pheochromocytoma and neoplasia of the thyroid is warranted, given that PHPT is a component of multi-endocrine neoplasia in humans [2].

Conclusions

In summary, PHPT in horses can be diagnosed with a combination of laboratory findings, ultrasonography and scintigraphy. The disease can be successfully treated with surgical excision of hyperfunctional parathyroid tissue, leading to normalisation of blood calcium and PTH concentrations and improvement in clinical signs. Surgical treatment appears to be most successful when a single tumour is identified at the thoracic inlet.

Authors' declaration of interests

The authors have declared no competing interests.

Ethical animal research

Research ethics committee oversight not required by this journal: retrospective analysis of clinical data.

Owner informed consent

Explicit owner informed consent for inclusion of animals in this study was not stated.

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Authorship

E. Gorenberg and J. Tomlinson contributed to study design, study execution, data analysis and interpretation, preparation of the manuscript and final approval of the manuscript. A. Johnson, G. Magdesian, F.-R. Bertin, L. Costa, M. Theelen, S. Durward-Akhurst, C. Cruz Villagran, H. Carslake and N. Frank contributed to study execution, data acquisition, preparation, and final approval of the manuscript.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Supplementary Item 1. Signalments, body condition scores and presenting complaints of equids diagnosed with primary hyperparathyroidism.