Original Article

Journal of Feline Medicine and Surgery
2021, Vol. 23(10) 883–891

DOI: 10.1177/1098612X20979706
journals.sagepub.com/home/jfm

This paper was handled and processed by the European Editorial Office (ISFM) for publication in *JFMS*

Retrospective evaluation of refeeding syndrome in cats: 11 cases (2013–2019)

Simon Cook[1], Emily Whitby[1], Neus Elias[2], Georgina Hall[1] and Daniel L Chan[1]

Abstract

Objectives The aim of this study was to describe the clinicopathological findings, management and outcome of cats with refeeding syndrome (RS) following prolonged starvation.

Methods Records from four referral hospitals were searched between May 2013 and November 2019 and retrospectively evaluated. Inclusion criteria were the presence of a risk factor for RS, such as severe weight loss or emaciation following a period of presumed starvation, hypophosphataemia or a delta phosphorous exceeding 30% reduction following refeeding, being treated on the basis of a clinical diagnosis of RS and one or more derangement of hypokalaemia, hypoglycaemia or hyperglycaemia.

Results Eleven cats were identified, which had been missing for a median of 6 weeks (range 3–104 weeks). Mean ± SD percentage weight loss was 46% ± 7% (n = 8). Eight of 11 cats developed hypophosphataemia with a mean delta phosphorous of –47% ± 9%. All cats were documented to be hypokalaemic. During hospitalisation, 10/11 cats developed hyperglycaemia and 7/11 cats developed hypoglycaemia. Cardiovascular, gastrointestinal and neurological signs were common. Eight of 11 cats displayed new or progressive neurological deficits after refeeding, including mentation changes and cerebellar dysfunction. All cats became anaemic and seven cats required a blood transfusion. Eight cats survived to discharge after a mean of 14 ± 4 days of hospitalisation. Six cats developed acute kidney injury (AKI; International Renal Interest Society stage 1). The presence of AKI ($P = 0.024$) was associated with non-survival and maximum bilirubin concentration was significantly higher in non-survivors ($P = 0.018$).

Conclusions and relevance Cats with RS in this cohort had been missing, presumed starved, for more than 3 weeks. In addition to hypophosphataemia and hypokalaemia, altered glucose homeostasis and organ damage involving the liver and kidneys were common. Cats with RS appear to have a good prognosis, but prolonged intensive care is required.

Keywords: Malnourishment; lipidosis; phosphorous; potassium; nutrition; starvation; emaciation

Accepted: 16 November 2020

Introduction

Refeeding syndrome (RS) is a complex condition that occurs following the reintroduction of nutrition after prolonged starvation or malnourishment.[1] It can occur in people and cats, regardless of whether feeding is enteral or parenteral,[2,3] and also appears to occur in ruminants and horses.[4,5] It is characterised by multiple metabolic derangements, most notably hypophosphataemia, hypokalaemia and hypomagnesaemia. Thiamine deficiency, altered glucose homeostasis and fluid shifts are also common.[1,6,7]

[1]Department of Clinical Science and Services, The Royal Veterinary College, London, UK
[2]Vets Now, Glasgow, UK

Corresponding author:
Simon Cook BSc, BVSc, MVetMed, DACVECC, DECVECC, FHEA, MRCVS, Queen Mother Hospital for Animals, Hawkshead Lane, Herts AL9 7TA, UK
Email: sdcook@rvc.ac.uk

The dyselectrolytaemias observed in RS are thought to develop as a consequence of the rapid shift between catabolic and anabolic metabolism that occurs in response to insulin release associated with refeeding. This increases intracellular demand for phosphorus, potassium and magnesium, causing a critical decline in their circulating concentrations. Cellular thiamine demand also increases in response to refeeding as it acts as a cofactor for enzymes such as pyruvate dehydrogenase and alpha ketoglutarate dehydrogenase.[8] Total body reserves of potassium, magnesium, phosphorous and thiamine are already depleted in states of chronic starvation so the sudden increase in demand creates a marked imbalance with clinically apparent deficiencies. Both impaired glucose tolerance and hypoglycaemia are described in people and in cats with RS.[3,6,9,10]

In people, this combination of abnormalities is often associated with neurological, cardiovascular, gastrointestinal and haematological abnormalities, including tremors, encephalopathy, arrhythmias, heart failure, anorexia, vomiting and haemolysis.[1,10,11] In the most severe cases, multi-organ failure and death can occur. RS typically develops 2–5 days after nutrition has been reinstated,[12] although signs can be observed within hours of refeeding or delayed for up to 10 days.[3,10]

RS has been infrequently reported in veterinary literature.[3,6] This study aimed to describe the characteristic clinicopathological findings associated with starvation associated RS in 11 cats, to better characterise disease presentation and outcome.

Materials and methods

Ethical approval was granted by the Social Science Research Ethical Review Board (reference number SR2019-0049). Electronic records from four referral populations (The Queen Mother Hospital for Animals [Royal Veterinary College], Vets Now [Glasgow], The Hospital for Small Animals [Royal (Dick) School of Veterinary Studies] and London Veterinary Specialists)[1] of client-owned cats were searched between May 2013 and November 2019 inclusive for the term 'refeeding' or stems 'malnourish-' or 'starv-' to identify retrospectively cats that were treated for RS. Cases were included if they satisfied all of the following criteria: (1) there was a risk factor for development of refeeding such as severe weight loss or emaciation following a period of presumed starvation; (2) they were documented as hypophosphataemic or had a delta phosphorous exceeding a 30% reduction during hospitalisation following refeeding; (3) they had one or more of the following abnormalities documented: hypokalaemia, hypoglycaemia or hyperglycaemia; and (4) they were treated on the basis of a clinical diagnosis of RS. Cases were excluded if their medical records were incomplete.

Data collected included signalment, body condition score (BCS), length of presumed starvation and percentage body weight loss (calculated using the last recorded weight in each cat's clinical history prior to starvation and their weight on admission). Date of refeeding was taken as the day of the first documented alimentation after starvation. Clinicopathological data not limited to phosphorus, potassium, sodium and glucose concentrations were collected, in addition to blood gases, packed cell volume (PCV) changes over time and blood component therapy administration. Delta phosphorous (ΔPhos) was defined as the maximum drop in phosphorus documented after refeeding. Delta sodium (ΔNa) was defined as the highest sodium minus the lowest sodium recorded. Where available, rates of nutrient supplementation and percentage of resting energy requirement (RER [defined as RER = 70 × (current body weight in kg)$^{0.75}$ kcal]) provided were recorded. The initial caloric target was defined as the first documented, intentional, proportion of RER delivered during hospitalisation. Case notes were explored for clinical evidence of cardiovascular, gastrointestinal and neurological dysfunction following refeeding, as well as haematological abnormalities and comorbidities. If neurological abnormalities were observed prior to refeeding, these were also recorded. Tachycardia was defined as a heart rate $\geqslant$240 beats per min (bpm), bradycardia was defined as $<$140 bpm, hypertension was defined as systolic blood pressure of $\geqslant$180 mmHg, hypotension was defined as a systolic blood pressure of $<$90 mmHg and hypovolaemia was documented when clinical examination and response to fluid resuscitation were consistent with this. Haematological analyses were assessed to identify the aetiology of any anaemia. Length of hospitalisation and outcomes were recorded. All data related to the entire treatment period after initial presentation, including prior to referral.

Statistical analysis

All continuous data were assessed for normality using a Shapiro–Wilk test and histogram inspection; descriptive data were calculated as appropriate using commercially available software (GraphPad Prism Version 8). Where a value was not available, the case was excluded from analysis for that particular variable. Continuous variables were compared using a student's *t*-test for parametric data and a Mann–Whitney U-test for non-parametric data. Fisher's exact test was used to compare categorical data.

Results

Eleven cases were identified, with a mean ± SD age of 83 ± 40 months. Table 1 details individual case signalment and BCS on presentation. All cats were reported to be in good health prior to going missing, with no clinically relevant underlying disease. Cats had been missing for a median of 6 weeks (range 3–104 weeks; n = 11) prior to presentation, with a mean percentage weight loss of 46% ± 7% (n = 8). All cats ate voluntarily within 2 days of being found.

Table 1 Clinicopathological findings, management and outcome

Cat	Age (months)	Sex (M/F)	Breed	Missing (weeks)	BCS (out of 9)	Weight loss (%)	Lowest phosphate (mmol/l) (RI)	ΔNa (mmol/l)	Highest ALT (U/l) (RI) and day post-refeeding	Highest total bilirubin (μmol/l) (RI)	AKI (Y/N)	Transfusion type	Nutrition route	Total length of hospitalisation (days)	Outcome
1	137	MN	DSH	6	1.5	48	0.72 (1.1–2.74)	20	439 (20–100) (5)	154 (2–10)	Y	pRBCs (feline)	Oral, syringe, PN	10	CPA
2	36	FN	DSH	4	1	NA	0.97 (1–2.42)	23	833 (12–130) (1)	148 (0–15)	N	pRBCs (feline)	Oral and NG	15	Discharge
3	84	MN	DSH	7	2.5	46	1.02 (1.1–2.74)	15	96 (12–130) (1)	8 (2–10)	N	NA	Oral, PN	19	Discharge
4	64	MN	DLH	3	2	46	0.75 (0.92–2.16)	7	218 (20–100) (9)	31 (2–10)	N	Whole blood (feline)	Oral, PN	18	Discharge
5	91	FN	BSH	6	3	NA	0.88 (1.1–2.74)	16	569 (12–130) (1)	39 (2–10)	Y	NA	Oral only	15	Discharge
6	100	FN	DLH	6	2	33	0.56 (1.1–2.74)	14	188.6 (5–60) (4)	7 (2–10)	N	NA	Oral only	14	Discharge
7	84	MN	DSH	104	1	NA	0.81 (1.1–2.74)	23	153.3 (5–60) (3)	283 (2–10)	Y	pRBCs (xeno) pRBCs (feline)	Oral and NG	22	Euthanasia
8	42	FN	DSH	7	NA	50	0.65 (1–2.42)	13	399 (20–100) (1)	7 (0–15)	N	NA	Oral only	8	Discharge
9	19	FN	DSH	3	1	55	1 (1–2.42)	10	130 (12–130) (3)	2 (0–15)	Y	Whole blood (feline)	Oral only	9	Discharge
10	138	FN	DSH	6	2	39	1.03 (1–2.42)	18	281 (12–130) (13)	55 (0–15)	N	Whole blood (feline)	Oral, syringe NG and O tube	18	Discharge
11	115	FN	Russian Blue	6	1	54	1.82 (1.1–2.74)	20	>1000 (12–130) (1)	60 (2–10)	Y	Feline pRBCs	Oral, O tube and PN	11	Euthanasia

M = male; F = female; BCS = body condition score; RI = reference interval; ΔNa = delta sodium; ALT = alanine transaminase; AKI = acute kidney injury; Y = yes; N = no; MN = male neutered; DSH = domestic shorthair; pRBCs = packed red blood cells; PN = parenteral nutrition; CPA = cardiopulmonary arrest; FN = female neutered; NA = not available; NG = nasogastric; DLH = domestic longhair; BSH = British Shorthair; xeno = xenotransfusion (dog to cat); O = oesophagostomy

Nutrients

No cats were hypophosphataemic on initial evaluation of electrolytes. Eight of 11 cats developed hypophosphataemia during hospitalisation, with the lowest phosphorous occurring a median of 5 days (range 1–13 days) after refeeding. The mean ΔPhos was –47% ± 9% occurring over a median of 1 day (range 0.5–7 days). Phosphorous was supplemented intravenously (IV) for a mean of 6 ± 3 days.

A mean lowest plasma potassium concentration of 2.6 ± 0.4 mmol/l occurred a mean of 7 ± 6 days after refeeding and cats were supplemented with potassium IV for a median of 7 days (4–19 days).

Ten of 11 cats were documented to be hyperglycaemic during hospitalisation, and 7/11 cats were documented to be hypoglycaemic. In those documented hypoglycaemic, all cats received dextrose supplementation for a mean of 3 ± 2 days. The highest level of IV glucose supplementation documented was 0.45 g/kg/h for several hours (10% dextrose at a rate of 4.5 ml/kg/h). Sepsis was considered to be a contributory cause of hypoglycaemia in one case (cat 1). There was no pattern in the development or progression of hypo- or hyperglycaemia, and no cats received insulin therapy.

Ten cats received IV magnesium supplementation for a mean of 6 ± 3 days. All cats received thiamine supplementation (injectable in 9/11 cases, oral in the other two). Thiamine supplementation ranged between 25 and 100 mg daily, with a mean length of supplementation of 7 ± 4 days. Calcium gluconate was supplemented as a continuous rate infusion for 3 and 9 days in cats 9 and 11, respectively.

Cardiovascular, gastrointestinal and neurological clinical signs

All cats showed clinical evidence of dysfunction of at least 2/3 evaluated organ systems (Table 2). Every cat developed cardiovascular abnormalities, the most frequent being hypotension (n = 6). Every cat developed gastrointestinal abnormalities, the most frequent being inappetence after initial appetence (n = 9). Six cats displayed neurological deficits prior to refeeding, most frequently vision loss (n = 4). Eight of 11 cats displayed new or progressive neurological deficits after refeeding, including mentation changes (n = 6) and cerebellar dysfunction (n = 4; Table 2). In surviving cats, all neurological clinical signs had resolved or were resolving at discharge.

Anaemia and haematological findings

No cats were anaemic on presentation, with a median PCV of 29% (range 26–44%). All cats became anaemic with the lowest PCV documented a mean of 8 ± 5 days after refeeding. Heinz bodies were detected in 5/9 cats for which an external haematology was available. Additional red blood cell abnormalities are described in Table 2. Seven cats required a blood transfusion a mean of 8 ± 6 days after refeeding. Four cats received a type-specific packed red blood cell (pRBC) transfusion, three cats received type-specific whole blood and one cat received a xenotransfusion in addition to a feline pRBC transfusion.

Comorbidities

Table 2 details the comorbidities identified. Skin wounds were present in 5/11 cats. Nine of 11 cats had biochemical (increased ALT activity) evidence of a hepatopathy documented. However, four of these were highest on presentation and five had increased since refeeding. One cat had hepatic lipidosis documented on fine-needle aspiration cytology. Six of 11 cats developed acute kidney injury (AKI; International Renal Interest Society stage 1)[13] in hospital.

Blood gas analyses were available for review in nine cases. When acidaemia or alkalaemia were documented, the most common abnormality was a metabolic alkalosis with alkalaemia in four cats, developing twice on day 2, once on day 3 and once on day 9 after refeeding. Additional blood gas abnormalities identified by the traditional Henderson–Hasselbach-based approach included respiratory acidosis with acidaemia in two cats, metabolic acidosis with acidaemia in two cats, a mixed-origin acidaemia in one cat and respiratory alkalosis with alkalaemia in one cat.

Nutrition

All cats ate voluntarily initially, with four cats eating entirely voluntarily throughout hospitalisation. Four cats received additional parenteral nutrition, and four cats were fed by nasogastric or oesophageal feeding tube (Table 1). The median initial caloric target in hospital was 10% (range 5–40%). Where delivery of 100% RER was achieved intentionally (n = 9), it occurred 13 ± 5 days after initial refeeding.

Outcome

Eight of 11 cats survived to discharge, one of which underwent CPA with successful return of spontaneous circulation. One cat died and two were euthanased (Table 1). Euthanasia was performed in both cases due to a protracted course of critical illness and financial considerations after 11 and 22 days in hospital. Surviving patients were hospitalised for a mean of 14 ± 4 days. The presence of AKI ($P = 0.024$) was associated with non-survival, and maximum bilirubin concentration was significantly higher in non-survivors ($P = 0.018$). ALT concentration (0.497), ΔPhos (0.678) and ΔNa ($P = 0.055$) had no association with outcome.

Table 2 Organ system abnormalities and comorbidities

Cat	Cardiovascular	Gastrointestinal	Neurological	RBC abnormalities	Comorbidities
1	Hypotension, hypertension, hypovolaemia, ventricular tachycardia, bradycardia, CPA	Inappetence after initial appetence, diarrhoea, vomiting	Before refeeding: vision loss, mydriasis After refeeding: seizure, obtundation, ataxia, cervical ventroflexion (K^+ 3.1 mmol/l)	Heinz bodies	AKI (IRIS grade 1)
2	Tachycardia, hypotension	Inappetence after initial appetence, diarrhoea, melaena	Before refeeding (owner reported): vision loss After refeeding: none	No specific abnormalities detected	None
3	Bradycardia	Inappetence after initial appetence, vomiting	Before refeeding: left head tilt After refeeding: intention tremor, hypermetria, wide-based stance, head pressing	Haemolysed serum, Heinz bodies, ghost cells, spherocytosis, ISAT positive, Coomb's negative	Skin wounds, immune mediated haemolytic anaemia (primary) developed in hospital
4	Hypotension, bradycardia, CPA	Vomiting	Before refeeding: obtundation, vision loss After refeeding: obtundation recurred, seizure (post-CPA)	Heinz bodies, echinocytosis, ghost cells, macrocytosis	Skin wounds
5	Hypertension	Inappetence after initial appetence, diarrhoea	Before refeeding: head tremors After refeeding: cervical ventroflexion (K^+ 3.7 mmol/l), obtundation, vestibular ataxia, nystagmus	No specific abnormalities detected	AKI (IRIS grade 1)
6	Bradycardia	Inappetence after initial appetence, diarrhoea	Before refeeding: loss of vision, mydriasis After refeeding: none	Haemolysed serum, macrocytosis, Heinz bodies	None
7	Intermittent ventricular premature complexes	Inappetence after initial appetence, vomiting	Before refeeding: cervical ventroflexion (K^+ 3.2 mmol/l) After refeeding: intention tremors, seizure, stupor	Macrocytosis, basophilic stippling, Heinz bodies, elliptocytosis	Skin wounds, AKI (IRIS grade 1)
8	Tachycardia	Inappetence after initial appetence	Before refeeding: none After refeeding: none	No external haematology performed	None
9	Bradycardia, hypotension, hypovolaemia	Melaena	Before refeeding: none After refeeding: hyperaesthesia, cerebellar ataxia	No external haematology performed	Skin wounds, AKI (IRIS grade 1)
10	Hypotension, tachycardia	Inappetence after initial appetence, diarrhoea, hypersalivation	Before refeeding: none After refeeding: intention tremors, ataxia (uncharacterised), cervical ventroflexion (K^+ 3 mmol/l)	No specific abnormalities detected	AKI (IRIS grade 1), O tube site infection, hepatic lipidosis on FNA
11	Hypotension, bradycardia, hypertension, systolic dysfunction, ventricular premature complexes, ST segment elevation on ECG	Melaena, inappetence after initial appetence, gastrointestinal stasis, regurgitation	Before refeeding: none After refeeding: obtundation progressing to coma, hypoventilation	Echinocytosis, elliptocytosis	Skin wounds, skull fractures, femoral and pelvic fractures, O tube site infection, AKI (IRIS grade 1)

RBC = red blood cell; CPA = cardiopulmonary arrest; AKI = acute kidney injury; IRIS = International Renal Interest Society; ISAT = in saline agglutination test; FNA = fine-needle aspiration; O = oesophagostomy; ECG = electrocardiogram

Discussion

This study documents the clinicopathological changes in chronically starved, missing cats that developed RS, and management of these cats in primary care and referral practice.

Starvation and weight loss

No case had any previous relevant medical history or underlying disease, being reported to be in good health prior to going missing and having been presumptively starved. However, with regard to cat 7, which had been missing for 2 years, a more complete investigation would have been necessary to completely exclude, for example, an underlying enteropathy as a contributor to chronic malnourishment.

Broadly, protein catabolism during starvation progresses through three phases: rapid initial depletion; a subsequent more gradual phase during which lean muscle mass is preserved in favour of fat mobilisation and ketone body production; and a final, preterminal rapid depletion of body protein. It is possible that protein catabolism in the cat persists at an accelerated rate vs other species,[14] although this is disputed.[15] Nonetheless, there appears to be a 'point of no return' after which a complete recovery is not possible, usually during or after the second wave of protein catabolism. Death is likely to occur when protein loss reaches 50% of normal.[16] Three of 11 cats in this study had lost >50% of their body weight, two of which survived to discharge; it appears that cats can survive after 50% weight loss.

Phosphorous

Degree of malnutrition has been correlated with severity of hypophosphataemia in people. In the same study, 81% of patients with anorexia nervosa (AN) monitored during refeeding developed their phosphorous nadir within the first week, but for some the nadir occurred as late as 14 or 20 days into hospitalisation.[17] A ΔPhos decrease of –30% or more in this current study was deemed significant based on previous use, and similar absolute or relative reductions utilised for diagnostic purposes.[18,19] The timescale to lowest phosphorous after refeeding was 5 days (range 1–13 days), suggesting that hypophosphataemia may develop acutely or later in hospitalisation, as is recognised in people. However, it is also possible that renal phosphate loss secondary to IV fluid therapy contributed to hypophosphataemia.[20,21]

Potassium

Hypokalaemia observed in RS is attributable to transcellular movement superimposed on chronically reduced intake.[22] Hypokalaemia may cause derangements in electrochemical membrane potentials, including delayed ventricular depolarisation, prolongation of action potentials and increased automaticity, potentiating the development and persistence of cardiac arrhythmias of both ventricular and supraventricular origin.[22] All three non-survivors had specific arrhythmias documented in this study, perhaps suggesting an association with illness severity, or that with continuous electrocardiogram monitoring of more stable patients, arrhythmias may appear more prevalent in cats with RS.

Cervical ventroflexion can be seen in hypokalaemic cats as a consequence of muscle weakness and the absence of a nuchal ligament. Forelimb hypermetria and a broad-based hindlimb stance are also possible.[22] Three cats in this study displayed cervical ventroflexion despite normal or only marginally low plasma potassium concentration at the time (Table 2). This was potentially attributable to thiamine deficiency.

Thiamine

Thiamine is a key coenzyme in the metabolism of carbohydrates and supply often becomes deficient after refeeding owing to increased cellular demand. The inhibition of carbohydrate metabolism in a thiamine-depleted state can cause energy deficits, neuronal dysfunction and necrosis affecting multiple sites, including the oculomotor, vestibular and lateral geniculate nuclei.[23] Reported clinical signs include vestibular ataxia, mentation changes, cervical ventroflexion and mydriasis with absent menace responses, with potential progression to coma and death.[24] This spectrum of neurological deficits was appreciated in the cats of this study (Table 2). One cat (cat 7) displayed cervical ventroflexion prior to refeeding, and four cats had apparent vision loss, supporting the notion that starvation without refeeding may result in clinical signs of thiamine deficiency.[23] However, signs are likely to worsen on refeeding without supplementation as suggested by the development of cervical ventroflexion, vestibular signs or both in six cats.

Absolute confirmation of thiamine deficiency is difficult, so a presumptive diagnosis is often made based on clinical signs and response to supplementation. In this study, all cats were supplemented with thiamine and this is also recommended in patients with AN being refed.[25]

Glucose

Hyperglycaemia is often referred to but rarely documented in people with RS.[9,12] Hypophosphataemia has been linked to impaired glucose homeostasis in both hyperglycaemic and normoglycaemic states, and this is thought to be a consequence of diminished tissue sensitivity to insulin.[26] Carbohydrate provision and critical illness may perhaps put cats at greater risk of hyperglycaemia,[27] but both hypoglycaemia and hypoglycaemia are reported,[3,6] and both abnormalities were demonstrated in this study. In people, hypoglycaemia has been reported upon refeeding in 36–44% of patients with AN, with 12% observed to have severe, protracted

hypoglycaemia lasting a median of 8 days.[9] Likely explanations for persistent hypoglycaemia include excessive insulin secretion, minimal capacity for glycogenolysis or sepsis. Considering the likely hyperinsulinaemia, dextrose restriction and avoidance of dextrose bolus therapy would seem prudent, but in the authors' experience this is difficult, and escalation very much appears to perpetuate hypoglycaemia.

Magnesium

Magnesium deficits are often a consequence of reduced dietary intake with concurrent excessive gastrointestinal or renal losses,[28] but they are common in RS owing to depleted reserves and a sudden increase in demand for magnesium.

In veterinary species, hypomagnesaemia can cause ventricular and supraventricular arrhythmias, seizures and hypertension.[29] In people, severe magnesium deficiency can result in cardiac arrhythmias, anorexia, tremors, seizures, weakness and ataxia.[30] All of these clinical signs have been observed in the cats in this study, although their aetiologies are likely multifactorial. Unfortunately, neither total nor ionised magnesium assays were commonly performed in the cats of this study, and interpretation is difficult due to a lack of reference intervals.

Organ dysfunction and comorbidities

In people, there is ongoing debate over whether hepatic injury in refed patients is due to autophagy during the starvation phase or lipidosis during refeeding. In these cats, a biochemical hepatopathy was appreciable both on presentation and on refeeding (Table 2), supporting both aetiologies. One cat (cat 10) had hepatic lipidosis confirmed and this may well have been an unappreciated comorbidity in other cases.

The documentation of AKI in six cases is novel and underlines the importance of extremely careful attention to fluid balance and dyselectrolytaemias. The mechanism is unclear but could involve oxidative damage, ischaemia–reperfusion injury, cellular hypoxia and iatrogenic damage via overzealous fluid therapy or positive fluid balance.

Broadly, the neurological deficits observed were likely attributable to a combination of metabolic aetiologies, including thiamine deficiency, hypophosphataemia-associated adenosine triphosphate (ATP) depletion, hypokalaemia and cellular hypoxia. Their resolving nature is also consistent with this, but vascular events cannot be completely excluded. Interestingly, four cats developed evidence of cerebellar dysfunction, including cerebellar ataxia and intention tremors, after refeeding. This does not appear to have been reported previously but may be consistent with Wernicke's encephalopathy in people with thiamine deficiency.[31]

The evidence of oxidative damage to RBCs, progressive hepatocellular injury and an association between hyperbilirubinaemia and a poor outcome warrant further mechanistic investigations but may support the use of antioxidant medications in such patients. It should also be noted that haemolysis of administered transfusions confounds the interpretation of hyperbilirubinaemia, particularly in cat 7, which received a xenotransfusion.[32]

Acid–base

This study also documented the presence of a presumptive refeeding alkalosis in four cats. Both metabolic alkaloses and acidoses, as well as respiratory alkaloses are described in people with RS,[1] but – to date – no veterinary evidence appears to exist.

Anaemia

Haemolytic anaemia is possible in RS as a consequence of decreased intra-erythrocytic ATP concentrations due to phosphorus depletion. Glycolysis is the only method of erythrocytic ATP generation, multiple steps of which are stimulated by phosphorus.[33] ATP depletion causes increased cellular fragility, shorter erythrocyte lifespan and subsequent haemolysis, although clinical evidence of this is uncommon.[34,35] A previous study of hypophosphataemic cats with associated haemolytic anaemia noted decreases in PCV within 24–48 h of hypophosphataemia first being documented.[36] Cats are thought to be particularly prone to severe hypophosphataemia-associated haemolysis, in conjunction with having haemoglobin that is particularly vulnerable to oxidation, denaturation and subsequent Heinz body formation.[37] Once formed, Heinz bodies may contribute to erythrocyte fragility and perpetuate haemolysis.

Development of anaemia in the cats of this study is likely multifactorial and not solely attributable to hypophosphataemic haemolytic crises. The timing of lowest phosphorous did not coincide with the lowest PCV documented. Two cats had haemolytic serum reported; one cat (cat 3) had developed immune-mediated haemolytic anaemia in hospital and the other (cat 6) had the lowest phosphorous of the study, recorded at 0.56 mmol/l at the time (Table 1). The immune-mediated haemolytic anaemia was considered primary, but a drug-induced secondary process could not be excluded. It is likely that oxidative damage evidenced by Heinz bodies in five cats is also a factor, while fluid resuscitation and hospital acquired anaemia are also possibilities.[38]

Alimentation-associated hypophosphataemia is reported in cats,[39] while refeeding-associated alkalosis and hypokalaemia are also anecdotally seen in patients that are refed after shorter periods of starvation, suggesting a spectrum of disease that is continuous with the cats

in this study, and which includes a mild disease phenotype without organ dysfunction.

Study limitations

This study is limited, in several ways, by its retrospective nature. The length of illness and reliance on thorough medical record-keeping in patients with varying illness severity reveals differences in levels of monitoring and documentation, with the potential for under-reporting. It is possible that more cats developed hepatic lipidosis than was recognised, and this would be a key area to explore in future studies. Although subjective, the availability of muscle condition scoring may have permitted stratification according to the degree of malnutrition and should be recorded for that purpose in populations such as this.

It was not possible to completely exclude an effect of comorbidities on clinical findings associated with RS in this study. For example, five cats had skin wounds as evidence of trauma, three of which developed an AKI. Nonetheless, the fact that missing, starved cats with RS often have concurrent evidence of trauma is an important finding that differentiates RS in cats from RS in people with AN.

It can be difficult to accurately characterise neurological clinical signs retrospectively, especially if complete, specialist neurological examinations had not been performed or repeated. It may have been possible to more precisely attribute clinical signs to deficiencies if these were consistently and sequentially performed, or may be possible in future analyses. This would be key to interrogating the starvation-associated and the refeeding-associated neurological signs.

Conclusions

RS is an uncommon condition necessitating prolonged intensive care, although cats appear to have a reasonable prognosis when aggressively managed. The observed clinical signs can provide an evidence base for diagnostic criteria in feline RS. As expected, cardiovascular, gastrointestinal and neurological clinical signs appear common in cats with RS, and a requirement for blood transfusion is common.

Despite the multifaceted, spectral nature of this disease, the defining clinicopathological changes in cats with RS appear to be hypokalaemia, hypophosphataemia and abnormal glucose homeostasis. Further work to stratify starved cats according to risk of RS is required, as well as efforts to predict the severity of the syndrome itself.

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

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

Ethical approval This work involved the use of non-experimental animals only (including owned or unowned animals and data from prospective or retrospective studies). Established internationally recognised high standards ('best practice') of individual veterinary clinical patient care were followed. Ethical approval from a committee was therefore not necessarily required.

Informed consent Informed consent (either verbal or written) was obtained from the owner or legal custodian of all animal(s) described in this work (either experimental or non-experimental animals) for the procedure(s) undertaken (either prospective or retrospective studies). No animals or humans are identifiable within this publication, and therefore additional informed consent for publication was not required.

ORCID iD Simon Cook https://orcid.org/0000-0003-4671-639X
Emily Whitby https://orcid.org/0000-0002-9808-7233
Georgina Hall https://orcid.org/0000-0001-6643-7262

References

1 Boateng AA, Sriram K, Meguid MM, et al. **Refeeding syndrome: treatment considerations based on collective analysis of literature case reports.** *Nutrition* 2010; 26: 156–167.
2 da Silva JSV, Seres DS, Sabino K, et al. **ASPEN consensus recommendations for refeeding syndrome.** *Nutr Clin Pract* 2020; 35: 178–195.
3 Armitage-Chan EA, O'Toole T and Chan DL. **Management of prolonged food deprivation, hypothermia and refeeding syndrome in a cat.** *J Vet Emerg Crit Care* 2006; 16: S34–S41.
4 Luethy D, Stefanovski D and Sweeney RW. **Refeeding syndrome in small ruminants receiving parenteral nutrition.** *J Vet Intern Med* 2020; 34: 1674–1679.
5 Witham CL and Stull CL. **Metabolic responses of chronically starved horses to refeeding with three isoenergetic diets.** *J Am Vet Med Assoc* 1998; 212: 691–696.
6 DeAvilla MD and Leech EB. **Hypoglycemia associated with refeeding syndrome in a cat.** *J Vet Emerg Crit Care (San Antonio)* 2016; 26: 798–803.
7 Chan DL. **Refeeding syndrome in small animals.** In: Chan DL (ed). Nutritional management of hospitalized small animals. Chichester: John Wiley & Sons, 2015, pp 159–164.
8 Abdou E and Hazell AS. **Thiamine deficiency: an update of pathophysiologic mechanisms and future therapeutic considerations.** *Neurochem Res* 2015; 40: 353–361.
9 Gaudiani JL, Sabel AL, Mascolo M, et al. **Severe anorexia nervosa: outcomes from a medical stabilization unit.** *Int J Eat Disord* 2012; 45: 85–92.
10 Hofer M, Pozzi A, Joray M, et al. **Safe refeeding management of anorexia nervosa inpatients: an evidence-based protocol.** *Nutrition* 2014; 30: 524–530.
11 Crook MA, Hally V and Panteli JV. **The importance of the refeeding syndrome.** *Nutrition* 2001; 17: 632–637.

12 Skipper A. **Refeeding syndrome or refeeding hypophosphatemia: a systematic review of cases.** *Nutr Clin Pract* 2012; 27: 34–40.
13 International Renal Interest Society (IRIS). **Grading of acute kidney injury.** http://www.iris-kidney.com/guidelines/grading.html (accessed July 21, 2020).
14 Rogers QR, Morris JG and Freedland RA. **Lack of hepatic enzymatic adaptation to low and high levels of dietary protein in the adult cat.** *Enzyme* 1977; 22: 348–356.
15 Russell K, Murgatroyd PR and Batt RM. **Net protein oxidation is adapted to dietary protein intake in domestic cats (*Felis silvestris catus*).** *J Nutr* 2002; 132: 456–460.
16 Guyton AC and Hall JE. Textbook of medical physiology. 12th ed. Philadelphia, PA: Elsevier Saunders, 2012.
17 Ornstein RM, Golden NH, Jacobson MS, et al. **Hypophosphatemia during nutritional rehabilitation in anorexia nervosa: implications for refeeding and monitoring.** *J Adolesc Health* 2003; 32: 83–88.
18 Friedli N, Stanga Z, Sobotka L, et al. **Revisiting the refeeding syndrome: results of a systematic review.** *Nutrition* 2017; 35: 151–160.
19 Goyale A, Ashley SL, Taylor DR, et al. **Predicting refeeding hypophosphataemia: insulin growth factor 1 (IGF-1) as a diagnostic biochemical marker for clinical practice.** *Ann Clin Biochem* 2015; 52: 82–87.
20 Knochel JP. **The pathophysiology and clinical characteristics of severe hypophosphatemia.** *Arch Intern Med* 1977; 137: 203–220.
21 Forrester SD and Moreland KJ. **Hypophosphatemia. Causes and clinical consequences.** *J Vet Intern Med* 1989; 3: 149–159.
22 Dibartola SP and De Morais HA. **Disorders of potassium: hypokalemia and hyperkalemia.** In: DiBartola SP (ed). Fluid, electrolyte, and acid-base disorders in small animal practice. 4th ed. St Louis, MO: Elsevier Saunders, 2012, pp 92–119.
23 de Lahunta A, Glass E and Kent M. Veterinary neuroanatomy and clinical neurology. 4th ed. St Louis, MO: Elsevier Saunders, 2015.
24 Dewey CW. **Encephalopathies: disorders of the brain.** In: Dewey CW and da Costa RC (eds). Practical guide to canine and feline neurology. 3rd ed. Chichester: Wiley Blackwell, 2016, pp 141–236.
25 Friedli N, Stanga Z, Culkin A, et al. **Management and prevention of refeeding syndrome in medical inpatients: an evidence-based and consensus-supported algorithm.** *Nutrition* 2018; 47: 13–20.
26 DeFronzo RA and Lang R. **Hypophosphatemia and glucose intolerance: evidence for tissue insensitivity to insulin.** *N Engl J Med* 1980; 303: 1259–1263.
27 Chan DL, Freeman LM, Rozanski EA, et al. **Alterations in carbohydrate metabolism in critically ill cats.** *J Vet Emerg Crit Care* 2006; 16: S7–S13.
28 Bateman S. **Disorders of magnesium: magnesium deficit and excess.** In: DiBartola SP (ed). Fluid, electrolyte, and acid-base disorders in small animal practice. 4th ed. St Louis, MO: Elsevier Saunders, 2012, pp 212–229.
29 Humphrey S, Kirby R and Rudloff E. **Magnesium physiology and clinical therapy in veterinary critical care.** *J Vet Emerg Crit Care (San Antonio)* 2015; 25: 210–225.
30 Ebel H and Gunther T. **Magnesium metabolism: a review.** *J Clin Chem Clin Biochem* 1980; 18: 257–270.
31 Sechi G and Serra A. **Wernicke's encephalopathy: new clinical settings and recent advances in diagnosis and management.** *Lancet Neurol* 2007; 6: 442–455.
32 Le Gal A, Thomas EK and Humm KR. **Xenotransfusion of canine blood to cats: a review of 49 cases and their outcome.** *J Small Anim Pract* 2020; 61: 156–162.
33 Rizzo SC and Eckel RE. **Control of glycolysis in human erythrocytes by inorganic phosphate and sulfate.** *Am J Physiol* 1966; 211: 429–436.
34 Amanzadeh J and Reilly RF, Jr. **Hypophosphatemia: an evidence-based approach to its clinical consequences and management.** *Nat Clin Pract Nephrol* 2006; 2: 136–148.
35 Dibartola SP and Willard MD. **Disorders of phosphorus: hypophosphatemia and hyperphosphatemia.** In: DiBartola SP (ed). Fluid, electrolyte, and acid-base disorders in small animal practice. 4th ed. St Louis, MO: Elsevier Saunders, 2012, pp 195–211.
36 Adams LG, Hardy RM, Weiss DJ, et al. **Hypophosphatemia and hemolytic anemia associated with diabetes mellitus and hepatic lipidosis in cats.** *J Vet Intern Med* 1993; 7: 266–271.
37 Christopher MM, White JG and Eaton JW. **Erythrocyte pathology and mechanisms of Heinz body-mediated hemolysis in cats.** *Vet Pathol* 1990; 27: 299–310.
38 Lynch AM, Respess M, Boll AE, et al. **Hospital-acquired anemia in critically ill dogs and cats: a multi-institutional study.** *J Vet Intern Med* 2016; 30: 141–146.
39 Justin RB and Hohenhaus AE. **Hypophosphatemia associated with enteral alimentation in cats.** *J Vet Intern Med* 1995; 9: 228–233.