Emergency Management Of

Metabolic Encephalopathies

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Metabolic encephalopathy is a clinical syndrome resulting from disorders of metabolism. Metabolic encephalopathies typically cause diffuse, symmetrical forebrain signs. Typical characteristics of metabolic encephalopathy include:

- Altered mental state
    - Seizures
    - Coma, stupor
    - Behaviour change
        - Anxiety
        - Aggression
        - Dementia
        - Mania
- Blindness with normal PLR
- Symmetrical neurological deficits

Other symptoms that may co-exist with encephalopathy include

- Vomiting
- Diarrhoea
- Alterations in appetite
- Pica
- Dermatological signs
- Tremor

Clinical signs may become apparent acutely, may be chronic, or may appear to wax and wane, with varying severity.

Metabolic encephalopathy is a syndrome that has many possible causes. The most common causes are listed as follows:

Causes of Metabolic Encephalopathy in the Dog and Cat

Electrolyte Disorders	Hypernatraemia Hyponatraemia Hypocalcaemia
Endocrine disorders	Hypothyroid myxoedema coma Thyrotoxicosis (Thyroid storm) Hyperparathyroidism
Liver disease	Porto-systemic shunt Acute liver necrosis
Glucose Disorders	Hypoglycaemia
Kidney failure	Chronic kidney failure
Systemic Disease	Sepsis Heat stroke
Nutritional disease	Thiamine deficiency
Congenital disorders	Organic acidopathies e.g. L-2 hydroxyglutaric aciduria

When approaching these patients, the goals of patient management are to

1. Identify and treat the underlying cause
2. Manage the encephalopathy
3. Monitor and manage life-threatening disorders

Electrolyte Disorders

Hyponatraemia

When a patient is being evaluated for hyponatremia, the following steps should be followed to establish the cause, and then effect treatment.

Step 1: Obtain Osmolality Data

1. Determine the calculated plasma osmolality

   Calculated Plasma Osmolality = 2Na + BUN (mmol/L) + Glucose (mmol/L)

2. Determine the effective plasma osmolality – this measurement removes urea from the osmolality equation – given urea readily crosses the cell membrane, and therefore does not exert an osmotic shift between intracellular and extracellular environments. The term "effective plasma osmolality" is therefore a more clinically relevant measurement than measured osmolality in determining the effect of an abnormal osmolality on the extracellular and intracellular environments.

   Effective Plasma Osmolality = Calculated Plasma Osmolality – BUN (mmol/L)

3. Determine the osmolal gap - Once the calculated osmolality has been obtained, this should be compared to the measured or actual osmolality, determined by freezing point depression, determined by your pathology laboratory. This is an important step in guiding treatment, because although hyponatremia implies hypo-osmolality, actual measured osmolality may be low, normal, or even high in patients with hyponatremia.

   Osmolal gap = measured osmolality – calculated osmolality

Step 2: Determine the Aetiology

Once both calculated and measured serum osmolality has been determined, a rational approach to determining the cause of hyponatraemia can be made.

Measured osmolality should not exceed the calculated osmolality by more than 10 mOsm/L. If it does, an abnormal **osmolal gap** is present. This occurs when solutes not present in the osmolality equation are present in a large quantity in the plasma. Examples of these unmeasured solutes include mannitol, alcohol, and metabolites of ethylene glycol. An abnormal osmolal gap may also be present in patients with hyperlipidemia or Hyperproteinemia (pseudo-hyponatremia)

A list of causes of hyponatraemia, based on measured serum osmolality follows.

Aetiology of Hyponatraemia in the Dog and Cat

Normal Plasma Osmolality	High Plasma Osmolality	Low Plasma Osmolality
Hyperlipidemia – will decrease measured sodium in non-ion-selective electrode measurements **Hyperproteinemia** - will decrease measured sodium in non-ion-selective electrode measurements	**Hyperglycemia** **Mannitol infusion** **Glycerol** **Ethylene Glycol metabolites** **Ethanol**	**Hypovolaemia** Gastrointestinal loss ▪ Vomiting ▪ Diarrhea Third space loss ▪ Pancreatitis ▪ Peritonitis ▪ Uroabdomen ▪ Pleural or abdominal effusion Cutaneous Losses – burns Renal losses ▪ Hypoadrenocorticism ▪ Diuretic administration ▪ Nephropathy **Hypervolaemia** Congestive heart failure Severe liver disease Nephrotic syndrome Acute Renal failure Chronic Renal failure Severe hypo-proteinemia secondary to nutritional or gastrointestinal disease **Normo-volaemia** Psychogenic polydipsia Administration of hypotonic fluids Myxedema coma of hypothyroidism Stress, adrenal insufficiency Syndrome of inappropriate ADH secretion (SIADH) ADH potentiation ▪ Nitrous Oxide ▪ Barbiturates ▪ Narcotic analgesia ▪ NSAID's ▪ Vincristine, cyclophosphamide

Step 3: Consider Pathophysiology of Low Plasma Osmolality based on Volume Status

- **Low Plasma Osmolality with Hypovolemia – total body loss of sodium exceeds that of water**
    - Volume depletion resulting from gastrointestinal fluid loss or third-space loss results in decreasing renal blood flow, and glomerular filtration rate. This stimulates secretion of Renin, and activation of the renin-angiotensin-aldosterone system, which increases renal sodium and water resorption, and impaired excretion of water. Volume depletion also leads to vasopressin release, which results in resorption of water, and stimulation of thirst. The net result is water resorption in greater proportion than sodium, diluting body fluids, and leading to hyponatremia.

    - Hypoadrenocorticism leads to loss of both sodium and water. Release of aldosterone cannot occur, and renal sodium and water loss continues as a result. This causes blood volume contraction, and a non-osmotic stimulus for vasopressin release. Vasopressin release results in water retention, and dilution of remaining body fluids.

- **Low Plasma Osmolality with Hypervolemia – decrease in effective circulating blood volume**
    - The body perceives a decreased **effective circulating blood volume**, despite the presence of an increase in total body sodium and water (due to ascites, or edema), which causes the following
        - Decreased renal perfusion activates the RAAS, leading to increased sodium and water resorption
        - Decreased circulating blood volume also stimulates vasopressin release, via non-osmotic stimulation) leading to water retention/impairment of water excretion
    - Liver cirrhosis leads to arteriovenous shunting of blood, portal hypertension, and hypoalbuminemia, leading to the development of ascites, and a reduction in effective circulating blood volume
    - Hypoproteinemia results in decreased colloid oncotic pressure due to hypoalbuminemia
    - Congestive heart failure and falling cardiac output stimulate baroreceptors in the carotid and aortic sinuses, and results in non-osmotic release of vasopressin

- **Low Plasma Osmolality and Normal Blood Volume – inappropriate retention or intake of hypotonic fluid**
    - Inappropriate retention or intake of hypotonic fluid results in blood volume expansion, increasing glomerular filtration rate, and decreased proximal tubular reabsorption of sodium and water. Ongoing inappropriate hypotonic fluid intake or excessive secretion of vasopressin (as in SIADH or Hypothyroidism) leads to chronic hypo-osmolality and a new steady state.

Clinical Signs of Hyponatremia

Clinical signs of hyponatremia relate to the rapidity of onset of hyponatremia. Decreasing serum osmolality results in an influx of water into cells, resulting in cell swelling and death. When serum osmolality falls rapidly – at a rate of greater than 0.5 mEq/L - water influx into cells exceeds the rate at which cells can reduce production of osmotically active particles (most commonly amino acids) to compensate. When this occurs, cell swelling, and cell death occurs.

- Clinical signs relate to intracellular swelling within the central nervous system (CNS), because the brain is contained within the confined of an inelastic bony skull. Cell swelling within the cranial vault results in central nervous system dysfunction.
- Clinical signs include the following
    - Depression
    - Mild lethargy, weakness, incoordination
    - Nausea
    - Slight increases in bodyweight
    - Seizures
    - Coma
    - Death
- If hyponatremia develops slowly, the CNS either inactivates or loses osmotically active particles to compensate for decreasing serum osmolality. Clinical signs may or may not be present in these patients, depending on the underlying cause. It is important not to raise sodium concentrations too quickly in patients in which hyponatremia is suspected to have developed slowly, as this can result in intracellular dehydration, and cell death – see "Treatment of Hyponatremia" below

Treatment of Hyponatremia

- Isotonic hyponatremia
    - dependent on the underlying etiology
- Hypertonic hyponatremia - Diabetic ketoacidosis/non ketotic hyperosmolar diabetes mellitus
    - Correct hypovolemia
    - Slow reduction in glucose with insulin constant rate infusion
    - Hypotonic saline to correct free water deficits over 4-12 hours
    - Correct underlying disorder related to mannitol or glycerol use
- Hypotonic hyponatremia
    - Hypovolemia - use 0.9% NaCl
    - Hypervolemia/isovolemia - restrict free water access to less than urine output

Step 1: Treat Hypovolemic Shock

1. place a peripheral intravenous catheter and begin infusion of an isotonic crystalloid solution with a sodium concentration similar to that of the patient (< 10 mEq/L difference) using a small volume resuscitation protocol, until symptoms of hypovolemia have resolved
    - Dogs – 10 ml/kg of fluid is administered intravenously over 10 minutes. The patient is evaluated for symptoms of shock (heart rate, pulse quality, mucous membrane characteristics, mentation etc.). The boluses of fluid are repeated until the patient no longer displays symptoms of hypovolemia
    - Cats – 5-7 ml/kg of fluid is administered in the same manner as for dogs

To make a fluid solution of similar sodium concentration to the patient, for acute resuscitation, we will need to dilute an isotonic solution such as lactated Ringer's solution, with a hypotonic fluid such as 5% glucose. To illustrate this, we will use a desired sodium concentration of 105 mEq/L

a. Desired sodium concentration of fluid = 105 mEq/L
b. Concentration of sodium in lactated Ringer's solution = 130 mEq/L. We need to remove 25 mEq sodium from the bag of lactated Ringer's solution. 25/1000 = 0.192 L = 192 ml
    i. Remove 192 ml fluid from a 1 L bag of lactated Ringer's solution
    ii. Add 192 ml 5% glucose to dilute the remaining sodium to a concentration of 105 mEq/L.

2. following correction of hypovolemia, place the patient on 0.9% NaCl at 2-3.5 ml/kg/hr. (unless cardiac failure is present) until fluid calculations can be made (see below)

Step 2: Determine the Sodium Required to Normalize Levels

1. Re-measure the sodium concentration - Following correction of hypovolemia, the sodium concentration should be re-measured.
2. Determine the sodium deficit so that accurate calculations on fluid replacement may be made using the following formula. In most patients, the desired sodium concentration will be 130 mEq/L.

[Na] deficit (mEq) = 0.6 x BWt (kg) x (normal (desired) serum [Na] - patient serum [Na])

3. Determine the rate of sodium correction – sodium should not be corrected at a rate faster than 0.5 mEq/hr in dogs and cats, to prevent CNS cellular dehydration and myelinolysis within the brain (particularly in the pons). A sodium deficit of 30 mEq/L therefore may take 60 hours (2.5 days) to correct to the normal/desired sodium concentration (130 mEq/L)

Step 3: Determine the Volume of Fluid Required to Normalize Sodium Levels

1. Determine the volume of sodium chloride required to normalize (to 130 mEq/L) sodium concentrations using the following formula

$$\text{Required volume (L)} = 0.6 \times \text{BWt (kg)} \times \frac{[\text{Na}]_{\text{desired}} - [\text{Na}]_{\text{current}}}{[\text{Na}]_{\text{in fluid}} - [\text{Na}]_{\text{current}}}$$

This is the volume of sodium chloride that would be required to normalize the sodium concentration. Typically, we use a sodium concentration of 130 mEq/L as the desired or "normal" level

2. **For dehydrated patients -** Alternatively a more practical approach can be used in patients that are dehydrated, by calculating the effect a given volume of a particular fluid type will have on blood sodium concentrations, using the following formula

$$\text{Change in Serum [Na]} = \frac{\text{infused fluid [Na]} - \text{current [Na]}}{[\text{BWt (kg)} \times 0.6] + 1}$$

This estimates the effect of one litre (1L) of infused fluid on serum sodium concentration.

Step 4: Calculate the Total Patient Fluid Requirement

1. The total patient fluid requirement involves correction of hydration deficits, maintenance of normal fluid intake, and replacing ongoing losses from the patient as they arise, according to the following formula

Fluid requirement (L) = maintenance (60 ml/kg/24hrs) + % dehydration + ongoing losses

2. Hydration deficits are best corrected over 8-24 hours, depending on how quickly dehydration has occurred – with faster rates of rehydration indicated for patients that have become dehydrated rapidly (between 1-12 hrs.), and slower rates for patients in which dehydration has occurred over more than 24 hrs.
3. Once the total fluid requirement is determined, and an assessment of the effect of infusion of different fluid types will have on the rate of change in sodium concentration, we can now determine the best fluid to use to both correct hydration deficits over the desired time, and correct the sodium concentration at a rate of no greater than 0.25 mEq/hr (chronic hyponatraemia) or 0.5 mEq/hr (acute hyponatraemia)

What If the Sodium Rises Too Fast?

Rapid increase in sodium usually occurs in patients in which the rate of sodium correction is faster than 0.25-0.5 mEq/hr. In cases of acute hyponatremia, developing over less than 12 hrs., the rate of correction may initially be allowed to occur at up to 0.5 mEq/hr. However, if hyponatremia develops over longer than 12 hrs., the cells in the CNS (glial cells, Schwann cells etc.) excrete amino acids and other solutes to decrease the osmolality within the intracellular environment, as an adaptation to a hypotonic extracellular environment. Rapid correction of extracellular sodium concentrations therefore in these patients can result in an increase in osmolality of the extracellular environment relative to the intracellular environment. This results in an osmotic fluid shift from the ICF to the ECF, causing cellular dehydration and osmotic damage and lysis.
Symptoms include depressed mentation, small to pinpoint pupils, poor PLR and seizure activity. If these symptoms are noted to develop, or worsen during correction of hyponatremia, conduct the following

1. obtain a sodium concentration and determine an hourly rate of increase greater than 0.25-0.5 mEq/hr
2. administer short-acting anti-epileptic medication as a bolus – e.g. diazepam 0.25 mg/kg IV to control seizure activity
3. Administer 0.25 ml/kg 50% glucose (diluted to a 10% solution) as a bolus over 5-10 minutes, followed by a CRI of 5% glucose (to provide free water) @ 1-3 ml/kg/hr.
4. Re-check sodium concentration 60 minutes following glucose administration to determine a drop in sodium concentration to a level that determines an overall increase in sodium concentration over the previous 12 hrs. of less than 0.25 mEq/hr (chronic hyponatraemia) or 0.5 mEq/hr (acute hyponatraemia).

Note that for patients with severe clinical signs (both acute and chronic hyponatraemia patients), 3% NaCl may be administered in small boluses of 1-2 ml/kg; repeated up to 3 times to increase the serum sodium concentration by 4-6 mEq/L. It is important to note that sodium concentration increases should be limited to a maximum of 10 mEq/L for the first 24 hours and 18 mEq/L above baseline sodium for the first 48 hours of treatment (including the hypertonic saline bolus) to avoid osmotic demyelination risk in the brain.

Hypernatremia

Hypernatremia is defined as plasma or serum sodium concentration above the standard reference range. As is the case with hyponatremia, patients with hypernatremia most commonly present with either no specific signs,

or displaying signs of central nervous system dysfunction, because of cellular dehydration of neuronal cells, as water moves out of the intracellular space, and into the extracellular space along an osmotic gradient caused by excessive extracellular sodium.
When considering the causes of hypernatremia, loss of water from the body is a far more common cause of hypernatremia than gain of, or excessive retention of sodium

Aetiology

Gain of sodium

- Salt poisoning
- Hypertonic fluid administration
- Hyperadrenocorticism
- Hyper-aldosteronism

Loss of hypotonic fluid

- Post-obstructive diuresis
- Diabetes mellitus
- Mannitol
- Chronic renal failure
- Non-oliguric acute intrinsic renal failure
- Vomiting/diarrhea
- Small intestinal obstruction
- Peritonitis, pancreatitis
- Burns

True water deficit

- Decreased/inadequate access to water
- Hyperthermia
- Diabetes insipidus, fever

Pathophysiology

Pure water loss - results in increasing osmolality of ECF relative to Intracellular fluid, resulting in fluid shift from the Intracellular space to the Extracellular space. This causes the following

- Intracellular dehydration
- Slight/mild decreases in ECF osmolality
- Vasopressin release, thirst stimulation occurs to restore normal osmolality

Hypotonic fluid loss - increases the osmolality of ECF (but not as much as with pure water loss) resulting in some movement of fluid from ICF to the ECF (once again, not as much as with pure water loss) Because less fluid moves from the ICF to the ECF, these patients are much more likely to manifest signs of ECF and blood volume depletion. As the tonicity of the fluid loss increases (towards being isotonic), patients rapidly show signs of volume depletion from the ECF, due to the decreased stimulus for an osmotic shift of fluid from the ICF to the ECF

Gain of an impermeant solute - e.g. mannitol or glucose. An impermeant solute in large quantities displaces sodium in the renal tubules, and may potentially cause hypernatremia. Initially, glucose or mannitol will cause an increase in the osmolality of the extracellular fluid, leading to a shift of fluid from the ICF to the ECF, causing an increase in the ECF and intravascular volume, which will act as a trigger for natriuresis. However, if the solute displaces sodium in the tubules, hypernatremia may result.

Clinical Signs of Hypernatremia

- Clinical signs relate to the movement of water out of cells, resulting in a decrease in cerebral volume. If this occurs rapidly, cerebral dehydration, rupture of cerebral vessels, and focal hemorrhage may occur
- Clinical signs are generally seen when Na > 170 mEq/l
- Clinical signs include
    - CNS depression
    - Lethargy
    - Vomiting
    - Muscle weakness
    - Altered behavior and mentation
    - Ataxia
    - Seizures, coma
    - Death
    - With associated fluid loss, dehydration, tachycardia, weak pulses may be present

NOTE: if hypernatremia develops slowly (over 2-4 days), neurons retain intracellular osmotically active solutes called "idiogenic osmoles" (amino acids etc.) that reduce the extent of neuronal cellular hydration. These idiogenic osmoles accumulate gradually over 2-3 days, and are not thought to present in acute (<24hr) hypernatraemic patients

Diagnosis

The history and physical examination can provide important information in diagnosing the cause of the hypernatremia. Urine osmolality and urine electrolytes should be obtained, along with serum biochemistry and electrolytes.

Treatment

General Recommendations

- Most patients with hypernatremia have water loss. Gradual correction of this deficit with fluid therapy requires calculation of the water deficit, and replacement of this deficit with free water in intravenous fluids, or, in some cases, oral intake.
- Correct to a sodium concentration of 150 mEq/L
- Mild hypernatremia (Na < 160 mEq/l) - if patient is capable of drinking, give free access to water

Step 1: Correct Hypovolemia

If hypovolaemia is present, it is safest to use a crystalloid solution with a sodium concentration that is similar to the patient (within 10 mEq/L). This may necessitate making a specific fluid by adding hypertonic saline to a commercially available crystalloid such as 0.9% NaCl.

The following is an example of how to make a fluid with a sodium concentration of 170 mEq/L:

1. 0.9% NaCl has a sodium concentration of 150 mEq/L – meaning we need to add 20 mEq of sodium to achieve a sodium concentration of 170 mEq/L
2. 7% NaCl has a sodium concentration of 1166 mEq/L.17 ml of this solution will contain 20 mEq sodium… therefore we need to do the following

a. Remove 17 ml 0.9% NaCl from the normal saline bag we will be administering to the patient
b. Add 17 ml 7% NaCl to the 0.9% NaCl fluid bag

Note, that if hypernatraemia has a documented onset of within the previous 48 hours, rapid correction of hypernatraemia is indicated using a 5% dextrose solution at a rate of 3-6 ml/kg/hr to achieve a correction rate of 1-2 mEq/L/hr; with complete correction of hypernatraemia within 24 hrs.

Step 2: Calculate the Free Water Deficit

The free water deficit may be calculated using the following formula, and determines the amount of sodium-free water that is required to correct the sodium concentration. In most cases, desired sodium is 160 mEq/L.

$$\text{Water deficit} = 0.6 \times \text{BWt} \times \frac{([\text{Na}]\ \text{actual} - [\text{Na}]\ \text{desired})}{[\text{Na}]\ \text{actual}}$$

Step 3: Determine the volume of fluid required to replace the free water deficit

$$\textbf{Required volume (L)} = 0.6 \times \text{BWt (kg)} \times \frac{([\text{Na}]\ \text{desired} - [\text{Na}]\ \text{current})}{([\text{Na}]\ \text{in fluid} - [\text{Na}]\ \text{current})}$$

In addition, determine the expected change in sodium concentration if 1 litre of a fluid (for example 5% dextrose, 0.45% NaCl+ 2.5% glucose, LRS or 0.9% NaCl) was administered.

$$\textbf{Change in Serum [Na]} = \frac{\text{infused fluid [Na]} - \text{current [Na]}}{[\text{BWt (kg)} \times 0.6] + 1}$$

Step 4: Calculate the Total Patient Fluid Requirement

The total patient fluid requirement involves correction of hydration deficits, maintenance of normal fluid intake, and replacing ongoing losses from the patient as they arise, according to the following formula

Fluid requirement (L) = maintenance (60 ml/kg/24hrs) + % dehydration + ongoing losses

Hydration deficits are best corrected over 8-24 hours, depending on how quickly dehydration has occurred – with faster rates of rehydration indicated for patients that have become dehydrated rapidly (between 1-12 hrs.), and slower rates for patients in which dehydration has occurred over more than 24 hrs.
Once the total fluid requirement is determined, and an assessment of the effect of infusion of different fluid types will have on the rate of change in sodium concentration, we can now determine the best fluid to use to both correct hydration deficits over the desired time, and correct the sodium concentration at a rate of no greater than 0.5 mEq/hr

What If the Sodium Falls Too Fast?

Rapid decline of sodium usually occurs in patients in which the rate of sodium correction is faster than 0.5 mEq/hr. In cases of acute hypernatremia, developing over less than 12 hrs., the rate of correction may initially be allowed

to occur at up to 1 mEq/hr. However, if hypernatremia develops over longer than 12 hrs., the cells in the CNS (glial cells, Schwann cells etc.) retain amino acids and other solutes to increase the osmolality within the intracellular environment, as an adaptation to a hypertonic extracellular environment. Rapid correction of extracellular sodium concentrations therefore in these patients can result in a decrease in osmolality of the extracellular environment relative to the intracellular environment. This results in an osmotic fluid shift from the ECF to the ICF, causing cells swelling and cerebral edema.

Symptoms include depressed mentation, small to pinpoint pupils, poor PLR and seizure activity. If these symptoms are noted to develop, or worsen during correction of hypernatremia, conduct the following

1. obtain a sodium concentration and determine an hourly rate of decrease greater than 0.5 mEq/hr
2. administer short-acting anti-epileptic medication as a bolus – e.g. diazepam 0.25 mg/kg IV to control seizure activity
3. Administer mannitol @ 0.25-0.5 g/kg slow IV over 10-20 minutes to increase ECF osmolality. Place on a CRI of 2 g/kg/day if required

- The rate of sodium correction should roughly parallel the rate at which the hypernatremia developed. For example, Hypernatremia that has developed rapidly (<24hrs) - correct sodium concentrations at a rate not exceeding 1 mEq/l/hr; Chronic hypernatremia (developing over > 24 hrs.) must be corrected at a rate not exceeding 0.5 mEq/l/hr to avoid neurological osmotic disequilibria
- Control seizures with diazepam/phenobarbital
- Hypernatremia caused by excessive salt intoxication is treated with intravenous fluid therapy and furosemide
- Dogs with primary adypsia require their daily water requirements to be added to their food

Hypocalcaemia

Hypocalcaemia is defined as an abnormal reduction in the concentration of calcium in the extracellular fluid. Plasma calcium is present in 3 major forms: ionised calcium (55% of total calcium); non-ionised (Chelated) (10%

of total calcium) and protein-bound (35% of total calcium). Ionised calcium is the physiologically active form of calcium, and therefore is the most useful when determining whether calcium is the cause of clinical signs observed.

Aetiology:

The causes of hypocalcaemia are outlined below:

Common causes of Hypocalcaemia	Occasional causes of Hypocalcaemia	Uncommon Causes of Hypocalcaemia
Hypoalbuminaemia Chronic kidney disease Eclampsia Acute kidney injury Acute pancreatitis	Soft tissue trauma/rhabdomyolysis Hypoparathyroidism Ethylene glycol toxicity Phosphate enema Bicarbonate administration	Laboratory error Dilution Intestinal malabsorption Hypovitaminosis D Large volume blood transfusion Hypomagnesemia Intralipid infusion

Eclampsia is the most common cause of hypocalcaemia observed in clinical practice, and is a syndrome of low blood calcium in what is called the "peri-parturient period" – that is, the period around parturition. Most commonly, Eclampsia develops in the weeks after parturition, although it may develop prior to parturition as well.

In order to understand a little more about what is happening in hypocalcaemia, we need to know a bit about how blood calcium concentrations are regulated.

> **Calcium concentrations** in blood are tightly regulated. This is because too much calcium in circulation will lead to calcium deposits being formed within the blood vessels and tissues, causing kidney failure, abnormal heart rhythms, and other tissue damage. Insufficient circulating calcium will result in muscle tremors and abnormal neurological function, among other symptoms.
>
> **Parathyroid hormone** is produced in the parathyroid gland. Parathyroid hormone increases calcium absorption in the intestine, promotes calcium retention by the kidney, and also increases release of calcium from bone in order to increase serum calcium levels.
>
> **Calcitonin** is another hormone, made in the thyroid gland, which counteracts the actions of parathyroid hormone, to lower serum calcium levels
>
> Normally these two hormones – parathyroid hormone and calcitonin act in balance to regulate – on a minute-to-minute basis – the amount of calcium in the blood.

Eclampsia - also called "milk fever" or "puerperal tetany" may result from a number of factors, which eventually lead to low blood calcium concentrations. Causes of eclampsia are listed below –

- Increased calcium loss or utilization by the dam
    - Calcium is excreted and "lost" from the body in milk during lactation

    - Calcium is used to mineralize the skeletons of foetuses during pregnancy
- Decreased calcium uptake
    - Reduced appetite in late pregnancy may reduce calcium intake by the dam
    - Reduced appetite in early lactation or due to stress may reduce calcium intake by the dam
- Inadequate parathyroid hormone secretion
    - Excessive calcium supplementation in late pregnancy and during lactation reduces the stimulus for parathyroid hormone secretion, which can lead to parathyroid gland atrophy
- Increased calcium binding to albumin
    - Hyperventilation during dystocia or as a result of stress will increase binding of calcium to albumin.

Clinical Signs

The clinical signs of hypocalcaemia, a seen in eclampsia, for example, can be quite varied – but they usually involve nervous tissue and muscle tissue – because calcium is involved in the normal activity of the nervous system and muscle contractions. The most common clinical signs include the following…

- Neurological symptoms
    - Poor maternal behaviour
    - Restlessness, nervousness, pacing
    - Disorientation
    - Paraesthesia (especially facial pruritis)
    - Panting
    - Hyperthermia
    - Vocalisation
    - Ataxia
    - Convulsions
    - Pupillary dilatation; slow PLR
- Musculoskeletal signs
    - Muscle tremors
    - Muscle fasciculation
    - Twitching
    - Tetany/sustained muscle contraction
- Cardiovascular signs
    - Hypertension
    - Arrhythmias
- Other signs
    - Vomiting
    - Diarrhoea
    - Pyrexia
    - Tachypnoea

Diagnosis

The diagnosis is usually based on typical presenting signs, ionised calcium blood tests, serum biochemistry and, in the case of eclampsia, a history of a recent litter or pregnancy. Standard blood tests (if desired) may include a

chemical blood profile, complete blood count and an electrolyte panel. As soon as the electrolyte panel is ready, the total serum calcium will be verified by a blood test. Low blood glucose and low blood magnesium levels may also be present. These can also be supplemented in the patient during treatment if required.

Treatment

Treatment is based on management of the underlying cause, and administering parenteral calcium gluconate to control or manage overt clinical signs. 10% calcium gluconate may be administered at a dose of 0.5-1.5 ml/kg slow IV over 1-5 minutes. For persistent hypocalcaemia, a continuous infusion of 0.25-1 ml/kg/hr 10% calcium gluconate can be administered.

Hypoglycaemia

Hypoglycaemia is not a specific diagnosis, but a manifestation of various systemic abnormalities that may involve

- Intestinal absorption of nutrients
- Hepatic production of glucose

- Normal function of liver enzymes, including gluconeogenesis and glycogenolysis enzymes
- Adequate peripheral utilization of glucose

In the normal fasting dog, the primary source of energy is ketones derived from fatty acids, and glucose synthesized from pyruvate and alanine. Low levels of pyruvate and alanine can lead to the inability of the liver to synthesize adequate levels of glucose.

The origin of the clinical signs of hypoglycaemia centre around the dependency of the brain on glucose oxidation for energy, its inability to store quantities of glucose, and the increased secretion of catecholamines in hypoglycaemic patients. This combination leads to clinical signs of depression, weakness, tremors, nervousness, polyphagia, tachycardia, ataxia, in coordination and seizures.

Whipples Triad - is used in the definition of hypoglycaemia, and consists of

- Clinical signs of hypoglycemia
- Low glucose levels
- Response of clinical signs to glucose administration

Aetiology

Accelerated glucose removal	Failure of glucose secretion

• Excess secretion of insulin or insulin-like factors
  ○ Insulinoma
  ○ Islet cell hyperplasia
  ○ Paraneoplastic syndromes
  ▪ Hepatocellular carcinoma
  ▪ Hepatoma
  ▪ Leiomyosarcoma
  ▪ Oral melanoma
  ▪ Haemangiosarcoma
  ▪ Lymphoma
  ▪ Pulmonary, mammary, salivary carcinoma
• Drug-associated causes
  ○ Ethanol poisoning
  ○ Salicylate poisoning
  ○ Propranolol
  ○ Oral hypoglycemia agents
  ○ Xylitol
• Renal glycosuria
• Endotoxaemia, septic shock
• Babesia
• Pregnancy; eclampsia, lactation
	• Functional hypoglycemia (including toy breed, neonatal, hunting dog, starvation)
	• Hepatic disease
	  ○ Enzyme deficiencies
	  ○ Acute liver failure
	  ○ Porto-systemic shunt
	  ○ Chronic fibrosis
	  ○ Cirrhosis
	  ○ Glycogen storage disease
	  ○ Liver abscess
	• Adrenal insufficiency
	• Malabsorption and starvation
	• Sepsis
	• Renal failure

Clinical signs

Clinical signs of hypoglycaemia are usually referable to the neurological system, and include the following:

- Symptoms of depression/dullness
- Lethargy
- Ataxia, incoordination

- Seizures
- Stupor and coma.

Diagnosis

STAT database collection including PCV/TP and glucose assessment should be performed on admission in any patient showing these clinical signs. A low blood glucose test is diagnostic for hypoglycaemia.
The documentation of hypoglycaemia, the presence of supportive clinical signs, and a visible response to therapy form the basis of Whipples Triad, and can be used in conjunction with the aforementioned diagnostics to confirm hypoglycaemia as a cause for observed clinical signs

Treatment

- Begin infusion of 0.45% NaCl/2.5% glucose
- 1-4 ml/kg of 50% glucose is administered slow IV over 10-15 minutes; dilute to 10% solution prior to administration
- Measure potassium - supplement as required to aid in glucose movement into cells following initial stabilization.
- Begin frequent administration of food
- Adjunctive therapy
    - Glucocorticoid administration - stimulates gluconeogenesis; antagonizes insulin release
    - Glucagon – 50 ng/kg IV followed by continuous infusion @ 5-40 ng/kg/min IV to effect
- Determine aetiology

Hypothyroid Myxoedema Coma

Definition

Hypothyroid myxoedema coma is a rare condition, characterized by acute decreases in thyroid hormone, and the development of severe clinical signs. The clinical signs observed are an extension of the characteristic symptoms

of hypothyroidism, and are precipitated by prolonged, untreated hypothyroidism, and may be triggered by development of concurrent disease

Clinical synopsis

Patients with hypothyroid myxoedema coma have the following characteristics…

- decreased exercise tolerance
- mental apathy
- lethargy
- constipation
- obesity
- dermatological signs
    - Alopecia (hair loss)
    - chronic skin changes – hyper-pigmented, thickened skin
    - yeast skin infection
- patients usually present in acute decompensation in association with myxoedema
- profound mental depression
- hypothermia
- hypo-reflexia
- hypoventilation
- bradycardia

Blood tests usually indicate the following…

- normocytic, normochromic anemia, hypercholesterolemia

Blood gas and cardiovascular assessment reveals the following

- hypoventilation produces hypercapnoea
- depressed cardiac output, low blood pressure
- azotaemia

Treatment

Treatment is urgent, and involves aggressive

- IV fluid therapy - isotonic fluids to treat hypovolaemia, improve blood pressure, improve renal blood flow and urine output etc., followed by rehydration fluid therapy
- oxygen therapy and assisted ventilation (some patients may require mechanical ventilation support)
- thyroxine supplementation
- dexamethasone indicated due to endogenous corticosteroid deficiency that may be induced following commencement of thyroxine supplementation
- diagnose and manage any co-morbidities

Thiamine Deficiency (Wernicke's Encephalopathy)

Thiamine (vitamin B_1) is an essential dietary component in small animals. It is a coenzyme for pyruvate dehydrogenase, alpha-ketoglutarate dehydrogenase, and transketolase – all enzymes involved in carbohydrate metabolism. Thiamine deficiency impairs oxidation of keto-acids, resulting in the following:

- impaired cerebral utilisation of ketone for energy production

- NMDA receptor-mediated neuronal excitation
- Increased blood brain barrier permeability

Thiamine deficiency causes polioencephalomalacia, resulting in bilaterally symmetrical spongiosis, necrosis, and brainstem nuclei haemorrhage.
The causes of thiamine deficiency are listed below:

- Feeding of sulphur-dioxide preserved meat
- Feeding of fresh fish diets containing thiaminase
- Decreased food intake/anorexia
- Impaired thiamine absorption – diarrhoea, intestinal malabsorption etc.
- Hepatic dysfunction
- Increased urinary loss (chronic kidney failure, diuresis etc.)
- Increased utilisation (fever, infection etc.)

Clinical Synopsis

Clinical signs typical of thiamine deficiency include:

- Dogs
  - Dilated, poorly responsive pupils
  - Ataxia (mild)
  - Altered mentation
  - Hyperesthesia
  - Tetraparesis
  - Seizures
  - Opisthotonus
- Cats
  - Central vestibular symptoms
  - Head tremors
  - Mydriasis
  - Cervical ventroflexion

Diagnosis

The diagnosis of thiamine deficiency is usually made on the basis of history and clinical symptom evaluation. Other tests that may be used include measurement of thiamine metabolites in the blood or my measurement of erythrocyte transketolase activity.
Response to therapy has also been used as a diagnostic tool. MRI and post-mortem evaluation have also been utilised.

Treatment

Treatment involves supplementation with thiamine hydrochloride, at a dose of 5-50 mg/dog IV/IM/PO q 24 hr (dogs); 1-20 mg/cat slow IM or IM (cat).
Management of the underlying disorder is of paramount importance in preventing recurrence.

Hepatic Encephalopathy

Definition

Hepatic encephalopathy is a clinical syndrome characterized by abnormal mental status, altered state of consciousness, and impaired neurological function in a patient with advanced liver disease of any cause, or most frequently, porto-systemic vascular shunts.

Aetiology

The underlying diseases responsive for hepatic dysfunction, and the subsequent development of hepatic encephalopathy include…

- Inherited congenital abnormalities of portal vascular system (most common)
- Acute fulminant hepatic failure (acute hepatic necrosis)
- Chronic progressive liver disease leading to end-stage liver failure (cirrhosis)
- Hepatic toxins
- Viral infections e.g. feline enteric coronavirus (FIP); canine adenovirus Type I (Infectious canine hepatitis)

Clinical signs

Clinical signs of hepatic encephalopathy are frequently superimposed on those of the underlying liver disease. The severity of clinical signs seen appears dependent on the rapidity with which the liver disease developed, the extent of functional liver capacity, and the degree of porto-systemic shunting present. Symptoms include…

- Hepatic failure signs
  - Anorexia, depression, weight loss, lethargy, PUPD, nausea, hyper-salivation, vomiting, diarrhoea
- Neurological signs
  - Bizarre behavior/dementia, including pacing, aggressiveness
  - Ataxia
  - Compulsive pacing
  - Circling
  - Cortical blindness
  - Intermittent deafness
  - Tremors
  - Seizures
  - Coma (end stage)

Predisposing factors include

- Protein overload and gastrointestinal hemorrhage provide substrates for bacterial production of ammonia.
- Constipation can increase retention and absorption of ammonia and other encephalopathic substances.
- Anaesthesia or sedative drug administration: patients who develop hepatic encephalopathy have increased brain sensitivity to sedative, analgesic, and anesthetic agents. Administration of many of these drugs may induce coma in animals with PSS, even when normal dosages of the drugs are used.
- Development of azotemia, electrolyte disorders (including hypokalemia, hyponatremia), hypoglycaemia, and disorders of acid-base status – particularly alkalosis.
- Hypoxia, sepsis
- Viral infections affecting the liver
- Hepatic toxins

- Transfusion of stored red blood cells: Blood which has been stored for 24 hours contains up to 170 ug of ammonia/dL, and ammonia concentrations will continue to increase with prolonged storage.

The Pathophysiology of Hepatic Encephalopathy

The pathophysiology of hepatic is incompletely understood, but is thought to result from a combination of multiple factors that produce disordered central nervous system function. Broadly, the pathogenesis of hepatic encephalopathy falls into two categories.

1. The diseased liver fails to remove toxic products of gut metabolism and body metabolism from the portal blood, leading to elevated concentrations of potential neuro-toxins in systemic circulation.
2. The diseased liver fails to synthesis factors (including glucose) that are essential for normal brain function

There are a number of neuro-toxins that accumulate in the circulation of patients with porto-systemic shunts and liver disease that can affect the function of the central nervous system. Of these, ammonia is the most studied, and it is known that ammonia can disrupt cell metabolism energy production and cellular processes. Among other compounds that are implicated in the pathogenesis of hepatic encephalopathy are methionine-derived compounds called mercaptans, aromatic amino acids, short chain fatty acids and GABA-ergic compounds

Ammonia

Blood ammonia arises primarily from the colon where intraluminal urea and glutamine is converted to ammonia by urease-producing bacteria. Additionally, ammonia is formed from renal tubular synthesis from glutamine (acid base buffer).

In the intestine, ammonia diffuses readily out of the colon into the portal vein, and is delivered to the liver as ammonium (NH_4^+). The normal liver extracts 85% of ammonia from the bloodstream, converting it to urea via the Krebs-Henseleit cycle, with the resultant production of glutamine.

Ammonia levels rise when there are insufficient hepatocytes to convert normal daily ammonia load to urea, or when portal shunts direct colonic derived ammonia into the systemic circulation. Ammonia readily crosses the blood brain barrier, where is known to cause toxicity. Ammonia reacts in the brain with glutamate to form glutamine, a reaction requiring ATP. This may lead to decreased availability of ATP for the production and maintenance of membrane potentials, cellular metabolism; and may increase Gamma-amino-butyric acid (GABA) and aspartate synthesis (inhibitory neurotransmitters), and reduce activity of the TCA cycle, and ATP production within brain cells.

Methionine/Mercaptans

Mercaptans are bi-products of methionine degradation by intestinal bacterial flora. The products are specifically methanethiol, ethanethiol, and dimethyl sulfide. In experimental studies, then these compounds, are administered intravenously, they can cause nervous system depression and coma. Oral treatment of patients with antibiotics suppresses gut flora and reduces mercaptan production

Short Chain Fatty Acids

The short-chain fatty acids butyric acid, octanoic acid, and valeric acid, arise from dietary medium chain triglycerides. They appear to act synergistically with ammonia and mercaptans to augment nervous system depression. Effects are augmented in the presence of aromatic amino acids in blood.

Branched Chain vs. Aromatic Amino Acid Imbalance

The normal ratio of branched chain amino acids (leucine, isoleucine, and valine) to aromatic amino acids (phenylalanine, tyrosine, and tryptophan) is approximately 3:1. In hepatic failure, this ratio is often 1.5:1. This results because, in liver failure, there is increased uptake of BCAA by muscle tissue, and also decreased removal

of AAA by liver. Both branched chain amino acids, and aromatic amino acids compete with the same membrane pump for entry into the brain. BCAA are used for synthesis of normal excitatory neurotransmitters norepinephrine and dopamine. With reduced BCAA in circulation, more AAA enter brain, where they are utilized in synthesis of weak neurotransmitters, and inhibitory neurotransmitters which may contribute to central nervous system depression. Clinical studies involving supplementation of BCAA to hepatic encephalopathy patients do not appear effective, however.

Gamma Amino Butyric Acid (GABA) Agonists

Disruption in the fine balance between inhibitory and excitatory neurotransmitters in the brain may have an important role in hepatic encephalopathy. The principal inhibitory mediators in the brain are GABA and glycine. The brain is the principle site of GABA production. In the brain, GABA receptors are complexed with barbiturate and benzodiazepine receptor sites. In hepatic failure and PSS, the following occur

- There is an increased density of GABA receptor sites present in brain tissue
- Products with GABA-like activity are produced by gastrointestinal bacteria such as E coli and Bacteroides species and are present in portal circulation, and under normal circumstances, are removed from portal circulation by the liver. In liver failure and porto-systemic shunts, these compounds are present in higher quantities in systemic circulation where they can act as false neuro-transmitters at GABA receptor sites. Additionally, gastrointestinal hemorrhage also results in increased GABA-like product absorption.

The GABA-ergic theory is supported t some extent by the improvement in clinical signs in patients given the benzodiazepine receptor antagonist, flumazenil – although improvement in clinical signs of encephalopathy may occur in less than half of hepatic encephalopathy patients receiving the drug.

Manganese

Manganese is a trace element that is a constituent of many anti-oxidant metalloenzymes including superoxide dismutase. Manganese is excreted by the hepatobiliary system – and its serum concentration increases in liver disease. Patients with chronic liver disease and hepatic encephalopathy are known to have increased brain manganese concentrations. Increased manganese concentrations potentiate production of TNF-alpha (see below). Manganese-induced neurotoxicity causes astrocyte dysfunction, gliosis and neuron loss.

TNF-alpha

Tumour necrosis factor-alpha concentrations are known to be elevated in many patients with hepatic encephalopathy – particularly those with acute liver necrosis/acute liver failure. TNF-alpha is thought to have the following role in the pathophysiology of hepatic encephalopathy:

- Elevated TNF-alpha concentrations increase ENS endothelial ammonia diffusion rate
- Elevated TNF-alpha concentrations increase/augment glutamate-receptor-mediated neuro-toxicity
- Elevated TNF-alpha concentrations are associated with increased levels of GABA, and also increases peripheral benzodiazepine receptor activation

Summary of the Pathophysiology of Hepatic Encephalopathy.

Much of the evidence for these proposed mechanisms of central nervous system dysfunction in hepatic encephalopathy is derived from experimental studies. In reality, it is considered most likely that there is an additive or synergistic relationship between ammonia, short chain fatty acids, and mercaptans, and possibly

aromatic amino acids, and manganese that leads to central nervous system dysfunction. In inflammatory liver disease, the role of inflammatory cytokines, vasoactive mediators and vascular permeability and cerebral perfusion likely play a role in neurological dysfunction also.
Importantly, from a therapeutic standpoint, patients with hepatic encephalopathy have increased sensitivity to benzodiazepines, and barbiturates owing to increased numbers of GABA receptor sites, and increased circulating GABA-ergic substances, making dose adjustments important to factor, particularly when benzodiazepines are administered to control seizures.

The Diagnosis of Hepatic Encephalopathy

The diagnosis of hepatic encephalopathy is based on recognition of a clinical syndrome of bizarre neurological behaviour in a patient with no previous history of disease, and the presence of laboratory data suggesting hepatic dysfunction or failure. Serum bile acids and ammonia tolerance test are used to assist in confirming laboratory suspicion of inadequate hepatic detoxification. Radiography, CT/MRI imaging and ultrasonography may further assist in characterizing the type of liver disease present e.g. porto-systemic shunt, cirrhosis etc.

Therapy for Hepatic Encephalopathy

The therapy for hepatic encephalopathy involves the same principles as have been described for the pre-surgical management of the patient with porto-systemic shunt, namely to recognise the underlying disease, reduce production and absorption of gastrointestinal factors known to augment hepatic encephalopathy, and to provide supportive care, in the form of intravenous fluid support, maintenance of normal electrolyte and acid-base status and control excessive central nervous system excitation with judicious use of anti-epileptic mediations and anaesthetic agents.

Administration of the following can greatly assist in improving neurological function

- Control seizures
    - Diazepam: despite the GABA-ergic theory, diazepam remains one of the most effective therapies for the front-line management of seizures in patients with hepatic encephalopathy. Diazepam is metabolised in the liver, so it is reasonable to expect a longer half-life than normal. Additionally, GABA-ergic neurotoxicity may result in benzodiazepines having a profound effect following administration. For these reasons, it is wise to consider starting with low-range therapeutic doses when managing acute seizures, and titrating upwards to effect.
    - Potassium bromide – may be used as a maintenance therapy, as it does not require hepatic metabolism and appears well tolerated. A loading dose of 600 mg/kg may be delivered per rectum over 6 divided doses in the first 24 hours of therapy, followed by maintenance therapy.
    - Status epilepticus may be managed with an intravenous infusion of propofol (1-4 mg/kg IV for induction, then 6-10 mg/kg/hr continuous infusion
- Reduce absorption or production of neuro-toxic metabolites:
    - Fasting for 12-24 hrs.; then re-introduction of feeding, using a low protein diet to reduce dietary sources of ammonia, toxic amines and aromatic amino acids, as well as short chain fatty acids
    - Catharsis of the colon – reduces numbers of colonic bacteria and removes the potentially toxic bi-products of intestinal bacterial metabolism. Water enemas, 10% iodine enemas, or lactulose enemas have been used. Lactulose is hydrolysed by enteric bacteria to lactic, acetic, and formic acids, which lower colonic pH, ionize ammonia to ammonium, and also lead to creation of unabsorbed solutes, which cause an osmotic diarrhoea. Additionally, lactulose provides a carbohydrate source for bacteria, which reduces the percentage of protein used for bacterial metabolism, reducing ammonia production. Up to 90% of humans show improvement with lactulose enemas (20 ml/kg; retain for 30 minutes, and then release and flush) when compared to 20% improvement with warm water enema alone.

  - Antibiotics such as neomycin, metronidazole or amoxycillin have been used to reduce the population of urease-producing bacterial in the intestinal lumen
  - Oral lactulose at a dose of 2-3 ml/kg PO q 8 hrs. to produce mild catharsis is recommended for patients tolerating oral medication, following enema administration.
  - Omeprazole 1 mg/kg q 24 hrs. may be used to reduce gastric haemorrhage
- Glucose infusion reduces peripheral metabolism of proteins to maintain normoglycaemia.

Following diagnosis of hepatic encephalopathy (based on clinical signs, liver disease etc.) every attempt should be made to adequately manage the underlying disorder. This includes constriction of porto-systemic shunts, supportive care and hepatic anti-oxidant therapy for acute hepatopathies; liver biopsy for chronic hepatopathies to diagnose and manage diseases such as copper toxicosis, antibiotic therapy for infectious causes etc.

Other Metabolic Disorders Causing Hepatic Encephalopathy

Urea cycle enzyme deficiencies

- A rare condition resulting in hyperammonemia and clinical signs of hepatic encephalopathy. BUN is often normal due to increased activity of other enzymes in the cycle, other liver enzymes are usually normal.