Case Report

Asystole associated with cerebrospinal fluid collection in a 3-month-old foal under general anaesthesia

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Summary

A 3-month-old colt foal presented to the Philip Leverhulme Equine Hospital for investigation of progressive neurological signs. Diagnostic investigation included cerebrospinal fluid collection, which was performed under general anaesthesia. During this procedure, severe bradycardia which progressed to asystole occurred. Initial resuscitation was successful; however, the foal had clinical signs consistent with cerebral hypoxia post-resuscitation and was euthanased the following day due to deterioration of neurological function. Asystole was presumed due to a Cushing-type reflex as a result of changes in intracranial pressure during the sampling procedure.

Introduction

Collection of cerebrospinal fluid (CSF) is an invasive but routine procedure in veterinary medicine. Subarachnoid puncture in the horse can be performed in three locations: the atlanto-occipital (AO) space, between the first and second cervical vertebrae (C1-C2) and in the lumbo-sacral (LS) space (Aleman et al. 2007; Pease et al. 2012; Depecker et al. 2014). The procedure is generally considered safe, and although physiological reflexes to an alteration in intracranial pressure (ICP) can occur and have been documented in other species, these have never been described in a horse undergoing CSF collection. Both increases and decreases in ICP can have cardiovascular sequelae, which can range from mild to life-threatening. This is the first case report, to the authors’ knowledge, of severe cardiovascular consequences of CSF collection in a 3-month-old foal.

Case history

A 98 kg 3-month-old Thoroughbred colt foal was presented to the Philip Leverhulme Equine Hospital with a 3-week history of neck pain following microchip implantation, progressing to abnormal neurological signs, and was unresponsive to treatment with antimicrobials, as he had received 14 days of oral doxycycline which was then followed with erythromycin, rifampicin. The foal has also received corticosteroids (dexamethasone) and nonsteroidal anti-inflammatories (flunixin meglumine). Symptoms exhibited included behavioural changes, gait abnormalities, proprioceptive and sensory deficits of the hindlimbs and increasing periods of recumbency.

On initial examination, the foal was quiet and recumbent with multiple superficial skin abrasions. Heart rate was 116 beats/min, respiratory rate was 48 breaths/min and pyrexia was evident with a rectal temperature of 38.6°C. Assessment of cranial nerve function revealed a slow pupillary light response and an exaggerated menace response. No other cranial nerve abnormalities were noted. There was no response to assessing skin sensation over the coronary band of the hindlimbs, with reduced withdrawal reflex and deep pain responses, particularly in the left hindlimb. Forelimb reflexes and pain sensation were normal. Anal reflex was normal, although the perineal reflex was reduced and the tail tone was noted as minimal. The urinary bladder diameter was 10cm on transabdominal ultrasonographic examination. Peripheral blood analysis was performed (Table 1).

Diagnosis and investigation

A lesion within the L4-S3 spinal region was suspected based on clinical findings, although diffuse CNS pathology was also considered. General anaesthesia to permit spinal radiography and CSF collection was planned. Collection of CSF from the AO space was deemed most appropriate due to the possibility of diffuse CNS pathology being present and there was minimal concern regarding a traumatic aetiology or the colt having a raised intracranial pressure. Prior to anaesthesia, 20 mL/kg of Hartmann’s solution (Aquapharm 1111) was administered via an intravenous cannula placed in the right jugular vein. The foal was kept in left lateral recumbency. Diazepam (Diazepam injection5, 0.25 mg/kg bwt i.v.) and buprenorphine (Vetergesic3, 0.01 mg/kg bwt i.v.) were administered via an intravenous cannula placed in the right jugular vein. The foal was kept in left lateral recumbency. Diazepam (Diazepam injection5, 0.25 mg/kg bwt i.v.) and buprenorphine (Vetergesic3, 0.01 mg/kg bwt i.v.) were

Table 1: Significant blood results

| Parameter      | Result      | Normal range          |
|----------------|-------------|-----------------------|
| Total nucleated cell count | 25.27 × 10^3/L | 5.4–14.3 × 10^3/L |
| Lymphocytes  | 0.96 × 10^9/L [3.8%] | 1.5–7.7 × 10^9/L |
| Monocytes    | 1.14 × 10^9/L [4.5%] | 0.1–1.5 × 10^9/L |
| Neutrophils  | 23.16 × 10^9/L [91.7%] | 22.3–9.5 × 10^9/L |
| Hct          | 32.5% | 32–53% |
| Total protein| 79 g/L | 57–80 g/L |
| Albumin      | 27 g/L | 22–37 g/L |
| Globulin     | 52 g/L | 27–50 g/L |
| GGT          | 138 U/L | 5–24 g/L |
| Lactate      | 2.9 mmol/L | <2 mmol/L |
administered prior to induction of general anaesthesia with ketamine (Narketan®, 2.2 mg/kg bwt i.v.). Following orotracheal intubation with auffed 20 mm endotracheal tube, anaesthesia was maintained with sevoflurane (Sevoﬂo®) in 100% oxygen. Base apex ECG, pulse oximetry, capnography and respiratory gas composition (including volatile anaesthetic agent) and rectal temperature were monitored throughout the anaesthetic (Datex Ohmeda S/5®).

Cannulation of the right transverse facial and facial artery to permit invasive blood pressure monitoring was attempted, but was unsuccessful. Mechanical ventilation was initiated after 15 min of anaesthesia following arterial blood gas analysis (RapidPoint 500®) of a sample obtained by percutaneous puncture of the left median artery (see Table 2 for results). The anaesthetic was unremarkable with a heart rate between 40 and 72 beats/min, end tidal sevoflurane was maintained at 2–2.4% and end tidal carbon dioxide (ETCO₂) was 37–52 mmHg during spinal radiography.

Aseptic preparation for cisternal puncture was performed, and the head of the foal was flexed to a 90° angle with the neck. Initial needle placement, with a 20 gauge × 90 mm spinal needle, was nonproductive. On the placement of a second needle, grossly normal CSF was obtained by free flow (approximately 3 mL). Immediately following CSF collection, the heart rate dropped to 21 beats/min with unducted P waves alternating with normal complexes.

Treatment
Glycopyrrolate (Glycopyrronium Bromide®, 2 μg/kg bwt i.v.) was administered with no response, so atropine (Atropine Sulphate Injection®, 15 μg/kg bwt i.v.) was administered IV and heart rate increased to 30 beats/min, although alternating unducted P waves and ST segment depression was also evident (Fig 1). Atropine administration (15 μg/kg bwt i.v.) was repeated, shortly after which the foal went into 3rd degree AV block, initially with occasional ventricular escape complexes (14 per minute) then asystole followed. External cardiac compressions were initiated at 60 per minute and 10 μg/kg bwt adrenaline (Adrenaline Injection®) administered IV. Ventricular tachycardia (170 beats/min) developed 1 min later (Fig 2). Cardiac compressions were stopped, and the ventricular tachycardia resolved spontaneously into sinus tachycardia (153 beats/min). Heart rate continued to fall and when it reached 60 beats/min, a further 12 μg/kg atropine i.v. was administered. At this point, it was elected to recover the foal and sevoflurane was discontinued. The foal was extubated when signs of returning consciousness were noted. Arterial hypoxaemia was documented post-recovery (see Table 2) and supplemental oxygen therapy was initiated.

Outcome
Following recovery, the foal showed signs of forebrain disease, including seizures-like activity, which was suspected to be due to severe hypoxaemia during the period of asystole. Overnight the foal was kept sedated on a propofol infusion (PropoFlo Plus®, 6 mg/kg/hour i.v.). The diagnostic findings of an irregular radiolucency within the body of S1, consistent with infection or fracture, were discussed with the owner who elected to continue with treatment which also included carprofen (Rimadyl®, 0.7 mg/kg bwt i.v. s.i.d.) and sodium penicillin and gentamicin (Crystapen®, 10 mg/kg bwt i.v. q.i.d. and Genta-Equine®, 10 mg/kg bwt i.v. s.i.d.) Over the following 24 h, the calf developed complete paralysis of the hindlimbs, acute onset ascites and respiratory distress. The foal was humanely euthanased at this point.

Post-mortem findings
Severe suppurative osteomyelitis and lytic necrosis was identified within vertebra T1. This had resulted in fracture and collapse of the vertebral body with dorsal displacement of necrotic fragments, and purulent material into the spinal canal. There was also a focal area of osteonecrosis within the vertebral body of S1. Histopathological findings were consistent with the gross pathology. Additionally, in the spinal cord, diffuse grey and white matter malacia and neuronal death was evident at the T1 segment and mild multifocal perivascular inflammatory cuffs were observed within the grey matter at S1. No abnormalities of the cervical spinal cord or brainstem were noted. CSF analysis was unremarkable.

Severe acute uroperitoneum was present, due to rupture of the urinary bladder at the dorsocranial pole where marked thinning of the bladder wall surrounding the perforation was noted. There was minimal haemorrhage or oedema associated with the site of rupture suggesting this had occurred shortly before death. Potential causes include neurogenic bladder dysfunction, trauma secondary to CPCR or during seizures post-resuscitation. No microbiological culture was performed, due to the owner declining further post-mortem costs.

Discussion
CSF sampling has many potential complications, although they are rarely reported in veterinary species. Infection, spinal cord injury and venous puncture have all been described

| TABLE 2: Arterial blood gas analysis results |
|------------------------------------------|
| Intra-operative | Post-CPCR | 24 h following GA and CSF tap |
|-----------------|-----------|-------------------------------|
| pH              | 7.28      | 7.24                          | 7.24                          |
| PaCO₂ (mmHg)    | 49        | 44                            | 56                            |
| PaO₂ (mmHg)     | 521       | 46                            | 119                           |
| (mmol/L)        | 22.3      | 20.5                          | 23.2                          |
| B.E. (mmol/L)   | −3.4      | −5.0                          | −3.2                          |
| Lactate (mmol/L)| Not measured | Not measured            | 4.2                            |
| FiO₂            | 1         | 0.21                          | Supplemental O₂ administered   |
|                 |           |                               | but FiO₂ not measured          |

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Bradycardia can have physiological, pathological or pharmacological causes. Cardiovascular events during equine anaesthesia are a significant cause of mortality (Johnston et al. 2002; Bidwell et al. 2007). Vagal responses, which can cause profound bradycardia, are widely recognised in the human and veterinary fields, but this often resolves rapidly on cessation of the stimulus; whereas vasovagal reactions also lead to inappropriate vasodilatation and significant hypotension. As the foal was not responsive to anticholinergic drug administration but was adrenaline responsive, a primary vagally induced bradycardia is unlikely. There are many other causes of sinus bradycardia including hypoxaemia, hypothermia and electrolyte disturbances; none of which were present in the foal at the time of the event.

Inadvertent trauma to the brainstem or spinal cord due to the procedure is unlikely to have occurred as neither structure was reported damaged on post-mortem examination. Obstruction of the endotracheal tube can occur due to blockade or kinking, which is more likely with severe ventro-flexion of the neck as occurred during this procedure. Capnography however demonstrated no abnormalities when the rhythm disturbance occurred, ruling out occlusion of the airway or anaesthetic delivery equipment as a potential cause for bradycardia.

In the case described, the temporal association between bradycardia and CSF collection suggests this as the most likely cause. Intracranial pressure (ICP) is governed by many factors, and small changes in ICP can lead to devastating consequences. Cerebral blood flow and cerebral blood volume are critical influencers of ICP, and many mechanisms keep ICP tightly regulated (Tameem and Krovvidi 2013). Raised ICP is a common final pathway for various intracranial pathologies, including disturbances of CSF circulation, obstruction to major venous sinuses, diffuse brain oedema or swelling, brain masses and idiopathic causes can also occur (Dunn, 2002). ICP has been shown to be higher in anaesthetised horses in lateral recumbency compared to standing horses (Brosnan et al. 2002); therefore, a small but significant increase in ICP may occur when the horse is anaesthetised and placed in lateral recumbency. There was no clinical suspicion of a raised ICP in the foal, although clinical signs are often vague and are not documented in horses, so this cannot be ruled out as a possibility. Clinical signs of raised ICP in dogs include altered consciousness, absence of brainstem reflexes, abnormal posture and motor activity and the Cushing response (Platt et al. 2001) although these signs are not always present. In humans, raised ICP often initially presents as headache, papilloedema and vomiting (Dunn, 2002). Other factors which arose during the case could have led to an increase in ICP. Flexing of the head to 90°, to aid collection of CSF from the AO space (Johnson and Constantinescu 2000) may partly occlude the jugular veins, which can lead to a rise in ICP (Rangel-Castillo et al. 2008). Given the timings of the occurrence of the event and the anaesthetic protocol used, we believe it unlikely that the bradycardia was pharmacologically induced.

The Cushing response to raised ICP is a well-recognised sympatho-adrenal mechanism and is characterised by hypertension, bradycardia and respiratory irregularities or apnoea (Doba and Reis 1972; Fodstad et al. 2006). This response occurs due to brainstem pressure and ischaemia which drives sympathetic activity, often causing a terminal and irreversible event which is not as much a true reflex, but a “last attempt to protect the ischaemic brain” (Schmidt et al. 2018). It is possible that the cardiovascular signs seen in the foal could be due to a Cushing response, although logically as CSF was being collected, ICP would decrease. It is possible, however, that a reduction in pressure at the cisterna magna could generate a pressure gradient sufficient to lead to an increase in brainstem pressure. A 20-
gauge 90 mm spinal needle was used for CSF collection, the size regularly used for AO collection in adult horses (Depecker et al. 2014). There are documented flow rates through different needle types and gauges during CSF collection in humans (Carson and Serpell 1996), with 20–22 gauge being better tolerated than 16–19 gauge needles. Although CSF was collected slowly in the foal, the size and possible physiological differences are particularly relevant when considering ICP, and sample collection may lead to rapid development of a significant pressure gradient.

Intracranial hypotension is also a possibility to explain a Cushing-like response. The condition is described in humans (Wasnick et al. 1993; Jacka and Wood 1994; Shrikrishna et al. 2006; Moon et al. 2016) but not in the veterinary literature. The pathophysiology is unclear; however, cardiovascular disturbances have been shown to occur with application of negative pressure drainage systems, reduction of brain mass at the end of craniotomy, beta-blocker administration and dura mater stretching (Hernandez-Palazon et al. 1998). Intracranial hypotension may result in rostral movement of the brain or brainstem nuclei, which can lead to cardiovascular changes such as bradycardia and arterial hypotension (Alfery et al. 1980). Cardiac arrest associated with pneumocephalus has been reported in humans, caused by intrathecal injection of air during administration of spinal anaesthesia (Haj et al. 2020). However in the foal, free flow of CSF occurred following needle placement. Although entrainment of air into the subarachnoid space cannot be ruled out, we think it highly unlikely to have occurred or be the cause of the cardiac consequences.

CSF collection from the AO space was deemed more appropriate than collection from the LS space as a larger volume would likely be obtained (Schwarz and Piercy 2006), and it would allow ruling out of central disease. If the lesion was affecting the distal spinal cord, collection from the LS pace would have been more appropriate due to the caudal flow of CSF (Mayhew, 1975), although this could subsequently have been performed under standing sedation if no abnormalities had been found during the initial investigations.

Placement of a peripheral arterial cannula was unsuccessful, precluding invasive arterial blood pressure monitoring. Under these circumstances, a noninvasive technique, such as an oscillometric cuff, could have been used. There is adequate correlation between indirect measurement of mean arterial pressure (MAP) and direct measurement of MAP when the cuff is placed on the coccygeal artery of foals (Giguere et al. 2005). The usefulness of this under the circumstances of the event is debatable, due to the intermittent nature of the information gained as the incidence of rapid changes in blood pressure are often undetected unless continuous blood pressure measurement is performed (Siebig et al. 2009). The lack of invasive arterial blood pressure monitoring was frustrating, as real-time information regarding blood pressure would have been useful during decision-making and when reflecting on possible causes of the bradycardia and asystole.

Conclusion

To the authors’ knowledge, this is the first case report of life-threatening cardiovascular changes associated with CSF sampling in a horse. Anaesthetists should be aware of this as a potential complication of this procedure. The use of invasive arterial blood pressure monitoring should be considered in these cases, and caution applied regarding rate and volume of fluid collected in smaller patients.

Authors’ declaration of interest

There are no conflicts of interest declared.

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Authors

DB was the primary anaesthetist involved in the management of the case. AB and DB co-authored the manuscript.

Manufacturers’ addresses

1 Animalcare, York, UK.
2 Hameln, Gloucester, UK.
3 Ceva Animal Health, Buckinghamshire, UK.
4 Vetoquinol, Towcester, Northamptonshire, UK.
5 Zoetis, Parsippany, New Jersey, USA.
6 GE Healthcare, Chicago, Illinois, USA.
7 Siemens Healthcare, Erlangen, Germany.
8 Martindale, Elythpharm, Buckinghamshire, UK.
9 Hameln, Gloucester, UK.
10 Mercury Pharma International, London, UK.
11 Zoetis, Parsippany, New Jersey, USA.
12 Pfizer, New York, USA.
13 MSD Animal Health, Kenilworth, New Jersey, USA.
14 Dechra, Northwich, UK.

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