Acute lead intoxication in a pregnant mare

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ABSTRACT

Lead (Pb) intoxication in horses is usually a chronic phenomenon with clinical signs associated with central nervous dysfunction. This report gives details of a case of acute Pb intoxication in a 9-year-old American Saddlebred mare with severe, progressive and ultimately fatal neurological deterioration. During the 4 days of hospitalisation, clinical signs progressed from intermittent headshaking and depression to severe, continuous, uncontrollable manic behaviour. At autopsy, three grey-coloured, hard metal particles were present in the gastrointestinal tract and subsequently found to contain 2614 ppm Pb. Lead concentrations in the brain, liver, stomach and kidney were 29, 4, 6 and 2 ppm wet weight, respectively.

Key words: cerebral dysfunction, equine, lead intoxication.

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INTRODUCTION

The toxic properties of lead (Pb) have been described since 300 BC. Historically, Pb has been one of the most common toxicants encountered in veterinary practice[4,5,9,18,20]. Cattle, horses, sheep, goats, household pets, waterfowl and raptors are some species that have been poisoned[12].

Lead intoxication (also known as plumbism) in horses is usually a chronic phenomenon with clinical signs associated with peripheral nerve dysfunction[5,8,12,13,20]. Clinical signs reported in horses may include: anorexia[5,6,9,15,20], weakness[5,15,20], ataxia[1,5], incoordination[6,7,9,15,20], depression[5,6,8,12,15,20], weight loss[1,5,6,8,9,12,15,20], hyperaesthesia[8], exercise intolerance[5,7], roaring or stridor[5,8,9,12,13,15], laryngeal and pharyngeal paresis[1,5,12,13,15,20], dysphagia[5,8,12,20], dysphonia[12,20], proprioceptive deficits[20], flaccidity of the rectal sphincter[5,6,20], paresis of the lower lip[5,6,20], facial paralysis[12,13], difficulty in prehension, mastication and deglutition[6,20], oesophageal paralysis[5], choke[6,7], tracheitis[9], secondary aspiration pneumonia[1,5,6,8,9,12,13,15,20], and intermittent fine muscle tremors[5,6,8,20]. Seizures may occur terminally[9,11,12,20]. Colic and diarrhoea present uncommonly[5,12,20] while foals may develop swollen, stiff joints[5,7,8]. Pulmonary oedema and haemorrhage have been observed sometimes in association with bilateral laryngeal paralysis[1,9]. Historically, central nervous system derangement with convulsions and excitation is not often seen in adult horses[5]. This report details a case of Pb intoxication with acute, severe, progressive cerebral dysfunction.

CASE HISTORY

A 9-year-old American Saddlebred mare that was 4 weeks in foal was presented for an examination of the upper respiratory tract to rule out obstruction as the cause of the respiratory embarrassment. This was preceded by depression, head-shaking and tongue-playing for 2 days which progressed to coughing with a mucopurulent nasal discharge and was treated with a trimethoprim-sulphadimethylpyrimidine (Amphoprim®, Virbac) (20 mg/kg, IV, q 12 h) and ketoprofen (Ketofen, Merial) (2.2 mg/kg, IV, q 24 h). *En route* to the Onderstepoort Veterinary Academic Hospital, the mare experienced a sudden episode of manic behaviour and had to be removed from the horse trailer.

Physical examination revealed normal cardiovascular and respiratory parameters, depression, absence of fever, bilaterally-delayed menace, pupillary-light reflexes and mild hyperaesthesia. There were multiple, superficial cuts and wounds on the face and limbs. Results of a complete blood count and serum biochemistry analysis showed a low-normal haematocrit (25 %; reference range 24–44 %), decreased total serum protein (65 g/ℓ; reference range 66–83 g/ℓ); leukopaenia (4.07 $\times 10^9$ cells/ℓ; reference range 6–12 $\times$ 10^9 cells/ℓ) due to neutropaenia (2.22 $\times$ 10^9cells/ℓ; reference range 3.54–7.32 $\times$ 10^9 cells/ℓ) and lymphopaenia (1.29 $\times 10^9$ cells/ℓ; reference range 1.8–3.6 $\times$ 10^9 cells/ℓ).

DIAGNOSIS AND OUTCOME

Following sedation with romifidine hydrochloride (Sedivet® Ingelheim Pharmaceuticals) (0.001 mg/kg, IV) for endoscopy, no abnormalities were seen following laryngoscopy and oesophagoscopy, while tracheoscopy revealed a moderate amount of mucopurulent fluid which consisted of activated macrophages and degenerate neutrophils. On evaluation of the abdomen, rectal examination was normal, while ultrasound showed progressive intestinal motility.

Within 2 hours of examination, the mare developed sudden neurological deterioration and demonstrated head-pressing, head-shaking, circling, loss of tongue tonus (Fig. 1) and coughed intermittently. The mare was placed in a dimly-lit, padded stall to prevent self-trauma and a clinical diagnosis of progressive cerebral disease due to a suspected viral encephalitis was made.

Following intravenous catheterisation (Milacath®, MILA International Inc., USA), the mare was treated with dexamethasone (Kortico Injectable, Bayer) (0.1 mg/kg, IV, q 6 h), flunixin meglumine (Cronyxin, Kyron Laboratories) (0.3 mg/kg, IV, q 6 h), mannitol 20 % (Mannitol 20 %, Intramed) (1g/kg, IV, q 24 h), furosemide (Salix®, Intervet SA) (0.5 mg/kg, IV, q 12 h), trimethoprim sulphadimethylpyrimidine (20 mg/kg, IV, q 12 h), thiamine (Vit B1, Kyron laboratories) (50 mg/kg, q 12 h), and dimethyl sulphoxide (DMSO 94 %, Kyron Laboratories) (2 mg/kg, IV, q 12 h) in 3 ℓ of balanced electrolyte solution (Sabax Plasma Vet, Adcock Ingram Critical Care). Cuts and abrasions due to the manic episode experienced in the horse trailer were cleaned and sutured.

Treatments were administered regularly during day 1 of hospitalisation. However, from day 2, therapy could only be admin-

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istered safely during periods when the mare was calm, as the mare's neurological status deteriorated such that manic episodes lasted longer, were more violent, and seemed to be exacerbated by handling. During hospitalisation, the mare intermittently showed three distinct behavioural patterns: depression, loss of tongue tonus, ptosis and ataxia (swaying from side to side); relatively alert mentation being able to prehend, masticate and swallow food and water; and violent mania (rearing up on hind limbs, running into walls and biting objects). Butorphanol tartrate (Torbugesic®, Fort Dodge Animal Health, USA) (0.06 mg/kg, I M and 0.01 mg/kg, IV) initially seemed to assist handling of the mare during manic episodes but failed to have an effect when neurological symptoms advanced.

Hepatocellular and hepatobillary enzymes (γ-glutamyl transferase and glutamate dehydrogenase), hepatic function tests (bile acids, conjugated and unconjugated bilirubin) as well as prothrombin time and partial thromboplastin time were within normal limits while hyperfibrinogenaemia (7 g/ℓ, reference range <4 g/ℓ) was identified. The leukogram had returned to normal 24 hours after admission. A standing, lumbosacral cerebrospinal fluid centesis was attempted, but was unsuccessful due to the mare's unpredictable behaviour.

Due to the uncontrollable manic episodes, the mare was humanely euthanased with sodium pentobarbitone (Euthapent, Kyron Laboratories) (100 mg/kg, IV) following chemical immobilisation using etorphine hydrochloride (M99® 9.8 mg/mℓ, Novartis SA) (0.01 mg/kg, IM) on day 4 of hospitalisation.

Since the behavioural abnormalities seen in this mare may have been caused by rabies virus, a full autopsy was undertaken only after an immunofluorescence test was performed on fresh brain and was found to be negative for rabies virus antigen. A toxicology screen for organophosphate, chlorinated hydrocarbon and carbamate pesticides on the stomach contents was negative. At autopsy, 3 grey, hard particles (diameter, 1–2 mm) were discovered, 2 in the stomach (Fig. 2) and 1 in the colon. These particles were subsequently found to contain 2614 ppm Pb by atomic absorption (AA) spectrophotometry (GBC 908 AA, Wilson Scientific Co., South Africa). Histopathology of the brain showed severe congestion, haemorrhage and oedema but no signs of leucoencephalomalacia. No intranuclear, acid-fast inclusion bodies could be found within the renal tubular epithelial cells[16]. Lead levels in the brain, liver, stomach and kidney were 29 ppm, 4 ppm, 6 ppm and
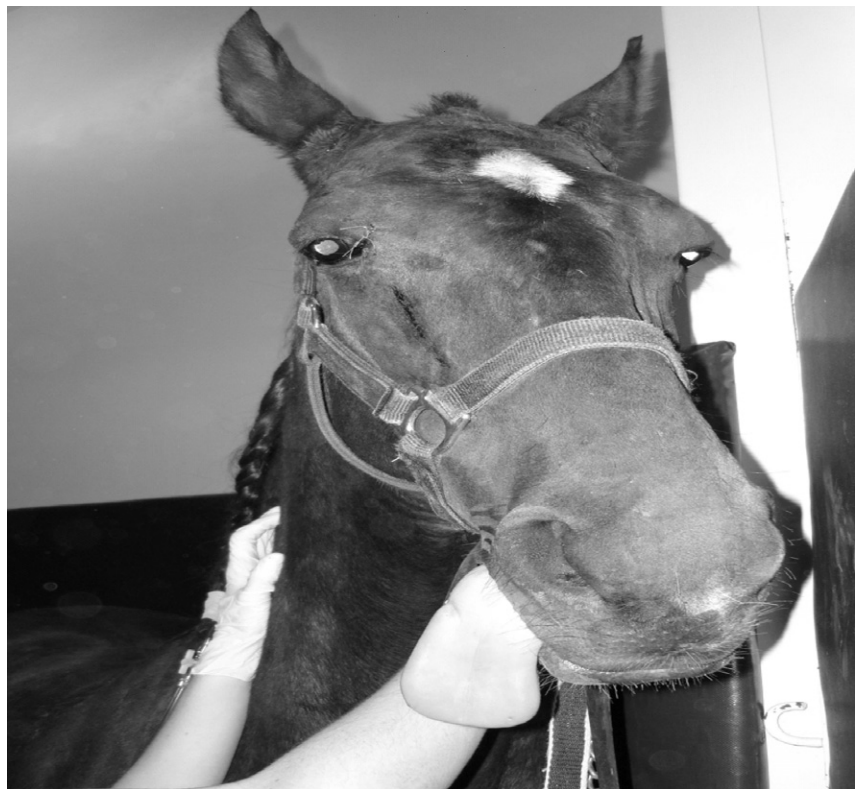

Fig. 1: **Acute lead intoxication in a pregnant mare: note the loss of tongue tonus and bilateral ptosis.**

2 ppm wet weight (wm), respectively, as determined by AA spectrophotometry (GBC 908 AA, Wilson Scientific, South Africa). Following an on-site inspection of the stud, haematology and whole blood lead determination on 8 randomly selected horses was normal. Analyses of multiple feed and water specimens for lead collected from the affected horse's stable and other sites, were within acceptable limits (<25 ppb Pb). It is suspected that the lead-containing pellets may have originated from extensive welding and soldering activities on the farm. Three months later, no additional horses have exhibited similar clinical signs.

DISCUSSION

Lead exposure usually occurs through the oral or respiratory route[15]. Animals have been poisoned by ingestion of lead-based paints[8,9,14,17,20], putty[9,14,20], greases[14,20], linoleum[9,14,17,20], leaded petrol[9,14,20], used motor oil[9,14,20], golf balls[9],

Fig. 2: **Acute lead intoxication in a pregnant mare: lead particles** (1–2 mm in diameter) **recovered from the stomach and colon.**

solder[14,20], lead shot[9,14], roofing materials[14,20], asphalt[14,18], industrial effluents[14,20], discarded motor vehicle batteries[8,14,20], lead arsenate pesticides[9], water from lead plumbing[14,20] and forage contamination near lead smelters[2,5,7,8,10,13,14,15,20]. In horses, Pb poisoning is most often associated with contamination of water and forage due to nearby mining and smelting operations[5,7]. Owing to the selective eating habits of horses, as well as their relative resistance to acute poisoning[9], horses are more likely to present with chronic lead intoxication[5].

There is some controversy in the literature regarding Pb toxicity in horses. Clinical signs of chronic Pb toxicity have been reported in horses ingesting as little as 1.7 mg Pb/kg/day[2]; however, horses that were fed 6.25 to 12.2 mg Pb/kg/day for 105 days failed to show any signs of Pb poisoning[9]. The latter study found that horses are less susceptible to chronic, low-level poisoning and do not respond to lead in a dose-response form, but according to individual susceptibility[9], which may explain the wide range reported for chronic Pb toxicity in horses (1–7 mg Pb/kg/day)[8,14,20]. In addition, many environmental dietary and physiological factors may affect toxicity, such as ingestion of additional Pb from soil during grazing[1,2,5], competitive inhibition of Pb absorption by diets high in calcium[3,5], age[14] and reproductive status[14]. Horses are relatively more resistant to acute intoxication, with an oral lethal dose of 500–750 g Pb[12,14].

In retrospect, the initial clinical signs reported in this case could be attributed to a peripheral neuropathy. In horses, a history of upper respiratory obstruction, ataxia, muscle fasciculation and loss of tongue tonus may be suggestive of Pb intoxication. In addition, Pb intoxication has been associated with mild haemolytic anaemia characterised by an inappropriately large bone marrow response in horses[11]. In this report, the haematocrit was low-normal at admission. However, this might have been incidental as the haematocrit increased to well within the reference range in subsequent laboratory tests and no metarubricytes or basophilic stippling was noticed. With chronic low-dose Pb exposure, absorbed lead is metabolised by the liver and excreted in bile, trapped in renal tubular epithelial cells and bound to the bone substance[14], thereby protecting the central nervous system. Lead damages the blood-brain barrier[14] resulting in cerebral oedema and haemorrhage, which is consistent with the postmortem findings of this case. Exposure to high concentrations of Pb results in overt CNS toxicity and colic[8].

There were no detectable signs of colic in this mare, but CNS derangements predominated (hyperaesthesia, head-pressing, circling to one side, manic behaviour, delayed and absent menace- and pupillary light reflexes). Based on the history, epidemiology, clinical signs and exceptionally high levels of lead contained by the particles in the gastrointestinal tract (2614 ppm Pb wm) and brain (29 ppm Pb wm)[19] this horse most likely suffered acute Pb intoxication.

In this report, the diagnosis of Pb intoxication was made following autopsy. In a horse that has been exposed to lead, clinical signs in conjunction with whole blood Pb concentrations greater than 0.35 ppm as well as 10 ppm Pb wm in liver and kidneys is considered diagnostic for Pb poisoning, although lower concentrations cannot definitively exclude Pb intoxication[5,8]. Measuring whole blood Pb concentration alone seems to be insensitive and non-specific for diagnosing acute and chronic Pb intoxication in horses[6,15], with a wide range of normal values being reported[13,21]. Tissue and blood Pb concentrations can eventually return to normal in more chronic cases due to slow bone sequestration[11]. In such cases, Pb exposure may be diagnosed by testing urine Pb concentration 6 to 12 hours after treatment with calcium disodium EDTA[8,11,12,15]. Increased erythrocyte aminolevulinic acid (ALA) and erythrocyte porphyrins as well as decreased activity of erythrocyte ALA dehydratase in blood may strengthen a diagnosis of Pb poisoning[11,20]. Although considered to be less diagnostic in cases of Pb exposure, urine may contain increased concentrations of coproporphyrins, uroporphyrins and ALA[5,11,20].

Treatment should include immediate identification and removal of the source of lead, and institution of chelation therapy with calcium disodium EDTA enabling rapid renal excretion[20]. Renal function tests and whole blood Pb concentration may help to identify whether therapy needs to be repeated[11,20]. British Antilewisite (BAL or dimercaprol) has been used in children and ruminants to decrease the risk of EDTA-induced exacerbation of Pb-induced encephalopathy[5,12] that may occur as a result of increased mobilisation of lead from bone and tissues, resulting in greater blood Pb concentrations and increased CNS toxicity[13]. D-penicillamine and thiamine is advocated in cases of Pb toxicosis in ruminants[5,12,14]. However, further studies are required to determine the efficacy of these drugs in horses. They may well have an application in horses, especially in acute Pb intoxication, since cattle most commonly show a similar CNS syndrome to that seen in acute equine Pb

intoxications such as the one described in this report[4,5,11]. Seizures may be controlled with barbiturates, and cerebral oedema may be treated with diuretics. Lucerne has a high calcium content[5,12] and may be beneficial as calcium supplementation may help to antagonise absorption of Pb within the gastrointestinal tract, because Pb and calcium share similar intestinal mucosal binding sites[3].

In animals with mild to moderate clinical signs, early diagnosis and appropriate therapy will yield a favourable prognosis if the source of Pb can be identified and removed. Animals with severe neurological derangements have a more guarded prognosis[12]. In South Africa, progressive cerebral disease in the adult horse may have various causes, including trauma, rabies, equine encephalosis, equine herpes virus-1, metabolic derangements (severe electrolyte disturbances or pyrrolizidine alkaloid-induced hepatic encephalopathy), leukoencephalomalacia, space-occupying lesions (abscess or tumour), bacterial meningitis, pesticides (organophosphates), poisons (strychnine or metaldehyde), and aberrant parasitic migration.

The authors conclude that Pb exposure in this mare overwhelmed the body's natural defence mechanism of local sequestration, causing severe damage to the blood–brain barrier, subsequently leading to progressive, fatal cerebral dysfunction.

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