**Unusual pathophysiological mechanisms of ptyalism in two horses**

Unusual causes of ptyalism

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**Summary**

This report outlines two cases of ptyalism that were not associated with oral conditions or primary dysphagia. The first, in a 9 year old thoroughbred gelding, was associated with left sided peripheral vestibular disease and bone modelling around the left tympanic bulla. The second, in a 7 year old Dutch warmblood mare, was associated with progressive bilateral laryngeal paralysis and a mediastinal T-cell lymphoma. In case 1, a neurological pathophysiology was proposed involving altered autonomic innervation of the salivary glands; whilst in case 2 the mechanism remains unclear but may have involved mechanical compression of the intra-thoracic oesophagus or stimulation of afferents within the vagus nerve. This case series highlights rare causes of ptyalism that have not been previously reported in the literature.

**Keywords**

Horse, Salivation, Mediastinal, Vestibular, Neurological

**Introduction**

The broadest definition of ptyalism is excessive salivation, which can be due to hypersalivation or as a consequence of difficulty in swallowing secretions. Elsewhere, the definition has been restricted to excessive secretion of saliva (Blood and Studdert, 1998) but here we use ptyalism to define increased salivation, recognised in the horse as overflow of saliva from the mouth.

Saliva production is mediated by autonomic innervation. Parasympathetic stimulation evokes the secretion of the majority of salivary fluid, including secretion of mucin from mucous glands; induces contraction of myoepithelial cells; and increases glandular blood flow as part of the salivary reflex (Proctor and Carpenter, 2006). Sympathetic stimulation acts to augment salivary production in salivary glands already under parasympathetic stimulation in a synergistic manner; increases exocytosis of proteins from salivary cells to alter the composition of saliva; induces contraction of myoepithelial cells; and can alter glandular blood flow but not as part of the salivary reflex (Proctor and Carpenter, 2006). There is no antagonism between the parasympathetic and sympathetic secretomotor nerve supply to salivary glands. Whilst the contribution of each system and the neuroactive substances involved varies depending on the species and salivary gland in question, nerve stimulation always acts to increase secretion (Emmelin, 1987).

Most commonly, ptyalism is associated with physical obstructions such as oral foreign body, oral neoplasia, oesophageal obstruction, and guttural pouch empyema, which lead to saliva overflow due to reduced swallowing ability (Hudson et al., 2006). Ptyalism should be differentiated from dysphagia due to deficits in somatic motor control of the pharynx and larynx, mediated via the glossopharyngeal nerve, vagus nerve or accessory nerve and originating in the nucleus ambiguous and nucleus solitarius in the caudal medulla oblongata (Mayhew, 2008). Neurological conditions including guttural pouch mycosis or lead poisoning, can affect these nerves and result in dysphagia, with clinical signs of quidding or nasal discharge of food (Dobesova *et al.*, 2012; Talcott, 2018).

Dysphagia has been defined as difficulty in swallowing (Blood and Studdert, 1998) although the literal translation is difficulty in eating and this definition is sometimes applied (Hudson et al., 2006).

**Case history**

*Case 1*

A 9 year old thoroughbred gelding developed sudden onset neurological signs following overnight pasture turnout, with evidence of trauma to his head (jaw) and pelvic limbs and serous discharge visible from the left external ear canal. Neurological examination shortly after the incident identified left-sided head tilt, ataxia and left-sided paresis, and ptyalism. Left-sided facial nerve involvement was suspected based on apparent drooping of the left ear. Dysphagia was not reported. Treatment with dexamethasone, doxycycline, penicillin, gentamicin and phenylbutazone was administered for two weeks before treatment was tapered to phenylbutazone only. Clinical signs improved over a seven week period until the gelding was considered safe to transport, when he was referred for further investigation.

*Case 2*

A 7 year old Dutch warmblood mare presented 8 days after the development of ptyalism, which began two days following a self-limiting episode of oesophageal obstruction. Endoscopy had identified right sided laryngeal hemiplegia. Haematology identified leucocytosis and neutrophilia. Persistent dysphagia was not reported. Treatment with dexamethasone, oxytetracycline and non-steroidal anti-inflammatory drugs was administered over the days preceding referral.

**Clinical findings**

*Case 1*

Clinical and neurological examination

The gelding was bright and alert with vital parameters within normal limits. Static neurological examination identified a moderate left-sided head tilt, exacerbated by changing light conditions, and ptyalism. Spontaneous or positional nystagmus was not observed and physiological nystagmus was normal. The owners reported the ptyalism to be variable since the initial onset of neurological signs and reported the saliva to be unusually non-viscous and apparently associated with increased arousal levels of the horse. The rest of the cranial nerve examination was normal, including facial nerve function. There was no evidence of dysphagia and tongue tone was normal. Dynamic neurological examination showed no gait deficits until entry into a darkened area, consistent with compensated vestibular ataxia.

Procedures

Endoscopy of the guttural pouches identified equivocal mild enlargement of the styloid process of the skull at the left temporo-hyoid articulation. There was no obvious change to the stylohyoid bone. Radiography of the skull was performed under standing sedation. On the dorso-ventral view, there was increased size and increased opacity of the left tympanic bulla, consistent with bone modelling (Figure 1).

*Case 2*

Clinical and neurological examination

The mare was quiet and responsive with reduced appetite. Clinical examination was unremarkable except for ptyalism. No specific cranial nerve deficits were detected and tongue tone was normal. Horner syndrome was not detected. Dynamic neurological examination revealed tremor and hyperflexion of the pelvic limbs when the mare was backed or the pelvic limbs lifted, consistent with ‘shivers’ syndrome; gait analysis was otherwise unremarkable. Oral examination was unremarkable. On observation of eating and drinking, there was no evidence of dysphagia. The mare was able to prehend and swallow food and was able to drink water but frequently coughed after drinking, suggestive of intra-tracheal irritation (aspiration) or extra-luminal tracheal compression.

Laboratory testing

Haematology was unremarkable on two occasions. Biochemistry identified bile acids to be at the upper end of the reference range (19.1µmol/l, reference 0-22µmol/l) and then later mildly increased (33.5µmol/l, reference 0-22µmol/l) and a moderate increase in total bilirubin (59µmol/l, reference 0-36µmol/l), although other liver enzymes and ammonia were within normal limits when measured on two separate occasions. Serum lead analysis was also within normal limits (<0.01µmol/l, reference 0-1.21µmol/l).

Procedures

Upper airway endoscopy on admission identified right sided laryngeal hemiplegia (grade IV/IV Havermeyer scale) with milder left arytenoid dysfunction (grade II/IV Havermeyer scale) at rest under light sedation. There was a bilateral poor response to the thoraco-laryngeal slap test. Guttural pouch endoscopy was unremarkable. Laryngeal ultrasonography identified moderate atrophy of the cricoarytenoideus lateralis (CAL) muscle on the left side and mild atrophy of the CAL muscle on the right side, consistent with chronic mild left laryngeal hemiplegia and recent onset severe right laryngeal hemiplegia. Upper airway endoscopy was repeated two days after admission and identified bilateral laryngeal paralysis with no movement of either arytenoid cartilage (grade IV/IV Havermeyer scale), including after stimulation of swallowing with a probe. Computed tomography of the head and upper neck was unremarkable.

Thoracic ultrasonography was performed three days after admission because the mare developed mild pyrexia. This identified focal pulmonary consolidation and mild focal pleural effusion (3cm depth in two intercostal spaces bilaterally). A mediastinal mass could not be identified. Differential diagnoses considered for the pleural effusion included bronchopneumonia progressing to pleuropneumonia, intra-thoracic neoplasia, and foreign body. Together with the pyrexia and pulmonary consolidation, mild pleuropneumonia secondary to aspiration was suspected, however pleural fluid aspiration for cytology was not performed to confirm this.

Liver biopsy was performed three days after admission, based on the presence of bilateral laryngeal paralysis and mild elevation in bile acids. There was insufficient sample for lead analysis but histopathology identified mild acute hepatocellular degeneration, characterised by diffuse mild swelling of hepatocytes with cytoplasmic clearing.

The mare developed a haemothorax following the liver biopsy procedure, confounding repeat assessment of the pleural effusion. Repeat thoracic ultrasonography five days after admission identified a moderate pleural effusion localised to the cranial lung (10cm depth in two intercostal spaces bilaterally).

**Diagnosis**

*Case 1*

Neuro-localisation

The left sided head tilt was most consistent with left sided peripheral vestibular disease. The parasympathetic innervation of the salivary glands is closely anatomically associated with the tympanic bulla. Parasympathetic innervation to the sublingual and mandibular salivary glands travels with the facial nerve and chorda tympani before synapsing in the mandibular ganglion, near the mandibular gland (Thomson and Hahn, 2012). Parasympathetic innervation to the parotid and zygomatic salivary glands travels with fibres of the glossopharyngeal nerve before synapsing in the otic ganglion, near the origin of the mandibular branch of the trigeminal nerve. Postsynaptic fibres then accompany fibres of the trigeminal nerve (Thomson and Hahn, 2012). The ptyalism could have resulted from excessive parasympathetic activation (perhaps due to focal inflammation). Alternatively, whilst experimental sympathectomy has been shown to increase cholinergically mediated protein secretion; experimental parasympathectomy in rats has been shown to increase sympathetically-mediated fluid secretion of saliva and so parasympathectomy could potentially explain the non-viscous salivation associated with stimulation of the horse (i.e. activation of the sympathetic system) (Carpenter *et al.*, 2005; Proctor *et al.*, 1990: in Proctor and Carpenter, 2007).

Differential diagnosis

Differential diagnoses considered included trauma and otitis media. The improvement prior to referral, as well as the initial history showing evidence of trauma, supported trauma as the most likely differential diagnosis.

*Case 2*

Neuro-localisation

The main neurological abnormalities were ptyalism and laryngeal paralysis. Ptyalism was more prominent than dysphagia. The absence of other cranial nerve deficits suggested adequate function of cranial nerves IX, X, and XI. ‘Shivers’ was also evident and considered an incidental finding. Shivers has been associated with neuroaxonal degeneration of the deep cerebellar nuclei (Valberg *et al.*, 2015).

Bilateral laryngeal paralysis was localised to lesions involving the recurrent laryngeal nerves that innervate the intrinsic muscles of the larynx. Motor axons originating in the nucleus ambiguous of the brain stem, exit with axons in the vagus and internal branch of the accessory nerve and run caudally in the vagosympathetic trunk; the recurrent laryngeal nerves separate in the cranial thorax: the right side courses around the right subclavian artery and the left side courses around the aortic arch before travelling cranially, each adjacent to the carotid arteries and trachea (Thomson and Hahn, 2012).

The sympathetic innervation to the head and neck originates in the lateral and intermediate horn of the thoracolumbar spinal cord before passing through the stellate ganglion, the ansa subclavia, the middle cervical ganglion and cranially in the vagosympathetic trunk to synapse in the cranial cervical ganglion (Thomson and Hahn, 2012). This is located deep to the medial compartment of the guttural pouch (Thomson and Hahn, 2012). Cervical dermatomes receive their sympathetic innervation via the paired vertebral nerves. However, in the absence of Horner syndrome or focal sweating of the head and neck, ptyalism due to sympathectomy of the salivary glands was unlikely. The parasympathetic innervation to the salivary glands has been described earlier and remains within the head.

Vagal afferent associated salivary gland stimulation has been reported in rats (Ueda *et al.*, 2016); given the historical episode of oesophageal obstruction, a lesion involving the paired vagus nerves with associated recurrent laryngeal motor axons remained a possibility. Alternatively, a partial functional obstruction of the oesophagus may have affected the ability to swallow excessive saliva produced, therefore resulting in drooling.

Differential diagnosis

Initial differential diagnoses considered for ptyalism were ‘slobbers’ caused by slaframine ingestion from *Rhizocturia leguminicola* (black fungus found on white or red clover) (Hagler and Behlow, 1981) and oral inflammation due to contact irritation. However, these were excluded because the mare’s clinical signs deteriorated despite a change in environment. Other physical causes of ptyalism such as oral foreign body were also excluded so, together with the progressive bilateral laryngeal paralysis, a neurological cause was suspected.

Reported causes of bilateral laryngeal neuropathy include hepatic encephalopathy, lead toxicity and organophosphate toxicity (Hughes *et al.*, 2009; Dollahite *et al.*, 1978; Duncan and Brook, 1985). There was no suggestion of polyneuritis equi or more generalised polyneuropathies. Normal serum liver enzyme activities and blood ammonia, and mild, non-specific histopathological hepatic abnormalities as well as normal mentation excluded hepatic encephalopathy. Analysis of liver tissue for lead is more sensitive than serum lead analysis (Dollahite *et al.*, 1978) therefore lead toxicity remained a differential. However the 1g of hepatic tissue required for the assay was not achieved despite obtaining multiple biopsy samples.

Space occupying or bilateral lesions of the ventral neck or cranial mediastinum could cause the laryngeal neuropathy. Ultrasonography of the cranial thorax through the triceps muscle did not identify a mediastinal mass, however thoracic radiography and ultrasonography via the thoracic inlet window were not performed. The progressive pleural effusion was supportive of a mediastinal mass and this remained a differential diagnosis.

**Treatment**

*Case 1*

In the absence of computed tomography of the skull or paediatric otoscope examination of the left ear to exclude otitis interna, a six week course of doxycycline was prescribed (10mg/kg BID PO) [Karidox1].

*Case 2*

Antimicrobial treatment with oxytetracycline (5mg/kg BID IV) [Engemycin2] and non-steroidal anti-inflammatory medication with phenylbutazone (2.2mg/kg BID IV) [Equipalazone3] were administered initially to treat suspected aspiration pneumonia.

Sodium calcium edetate (50mg/kg SID IV) was administered empirically from three days after admission as lead poisoning could not be ruled out.

Three days after presentation, the mare developed respiratory distress during placement of a nasogastric tube to provide enteral fluid therapy. It was necessary to induce general anaesthesia in order to place a tracheostomy tube. The mare recovered uneventfully from this procedure and the tracheostomy tube was maintained thereafter. Medications of penicillin (20mg/kg BID IM) [Depocillin4], gentamicin (6.6mg/kg SID IV) [Genta-Equine5], and flunixin (1.1mg/kg BID IV) [Meflosyl6] were administered to reduce exudation at the tracheostomy site and due to the suspected but unconfirmed presence of aspiration pneumonia.

**Outcome**

*Case 1*

Repeat examination of the gelding six months after onset of clinical signs identified persistence of the left sided head tilt, although the lesion was further compensated. Ptyalism was absent at rest but was stimulated by interaction with the gelding and in particular when the gelding was startled or excited by his environment.

*Case 2*

Five days after presentation, the mare continued to deteriorate. She showed more consistent inappetence, had lost weight and had developed a significant pleural effusion that required drainage. This, combined with the bilateral laryngeal paralysis and poor prognosis of the most likely differentials, prompted euthanasia on humane grounds.

**Post mortem findings**

*Case 2*

A partial post-mortem examination was performed. This identified a large, firm, slightly lobulated mass within the mediastinum and involving the heart base, compressing the adjacent structures of the trachea, cranial vena cava, and the aorta (Figure 2).

Histopathology identified a densely cellular and unencapsulated, infiltrative neoplasm with cells arranged in sheets within a fine, fibrous stroma. Neoplastic cells were round with distinct cell borders, scant cytoplasm and measuring approximately 10µm in diameter. Nuclei were central with coarsely stippled chromatin and inconspicuous nucleoli. Anisokaryosis and anisocytosis were mild and the mitotic rate was low (less than 1 per high power field). The neoplastic cells showed diffuse specific and membranous staining for CD3 antigen but were negative for CD79a antigen, yielding a diagnosis of a T-cell lymphoma.

**Discussion**

In case 1, the diagnosis of a traumatic lesion that caused the left peripheral vestibular disease secondary to a traumatic incident was relatively straightforward, and supported by the radiographic finding of bony modelling of the left tympanic bulla (Mayhew, 2008). On initial presentation, the drooling of saliva could have been incorrectly attributed to the injury to the jaw but once this resolved it was more clearly hypersalivation. Computed tomography might have been useful to reach a more specific diagnosis but was only available using standing sedation. This was not considered safe due to the gelding’s (non-pathological and long-standing) nervous and unpredictable temperament, therefore radiography was performed instead. Prescribing antimicrobials in the absence of a confirmed infectious cause is not good practice, but the risks of general anaesthesia or of withholding treatment to the individual patient were considered to outweigh the harm of possible unnecessary use of antimicrobials, in this case. Head MRI was not available (Dixon *et al.*, 2017). As stimulation of both autonomic systems acts to increase saliva secretion (Proctor and Carpenter, 2007), it is difficult to explain how dysfunction could cause ptyalism although a denervation hypersensitivity, for example enhancing the response to circulating catecholamines, is a possibility. The intermittent nature of the ptyalism, combined with the localised trauma-associated bone changes to the tympanic bulla, could support aberrant activation of the parasympathetic fibres in the vicinity supplying the salivary glands (Thomson and Hahn, 2012).

In case 2, a mediastinal lymphoma was ultimately identified at post mortem examination. It is possible that the neoplasm in case 2 could have been detected *ante mortem* utilising either ultrasonography of the heart base via the window of the thoracic inlet or cytology of the pleural effusion, however it would not have altered the eventual outcome of the case (De Clercq *et al.*, 2004; Garber *et al.*, 1994). The presence of asymmetrically progressive laryngeal paralysis and a mediastinal mass supports intra-thoracic compression of the recurrent laryngeal nerves or vagosympathetic trunks (or both) in case 2 (Thomson and Hahn, 2012). Mediastinal lymphoma has been reported to cause unilateral (left-sided) laryngeal paresis previously, but these cases were not associated with ptyalism (De Clercq *et al.*, 2004; Firth 1978).

The historical oesophageal obstruction and persistent ptyalism in case 2 might have been caused by a direct compression of the mass on the oesophagus or due to disruption of vagal motor axons that supply the oesophagus. Association of vagal afferents with salivation in rats (Ueda *et al.*, 2016) supports this neurological explanation for the ptyalism in this animal. Autonomic dysfunction due to mediastinal lesions has been reported previously. Compression of the vagus nerve has been associated with complete AV block in a horse with a mediastinal lymphoma (Sugiyama *et al.*, 2008). Malignant squamous cell thymoma was described in an 8 year old Quarter Horse cross Belgian mare with masses cranial to the heart and extending along the ventral neck from the intermandibular area to the thoracic inlet. Horner syndrome was reported to be present involving the left eye, which was attributed to disruption of sympathetic innervation (Whiteley *et al.*, 1986). Siegers *et al.* (2017) report a 15 year old Belgian Draught mare with multicentric B-cell rich T-cell lymphoma that had lesions involving the oesophagus and heart and presented with ptyalism. The lesions in this horse were widely disseminated and the authors attributed the ptyalism in this case to stomatitis, although it is possible that mechanisms similar to those postulated in Case 2 were in fact responsible.

In conclusion, although the majority of cases of ptyalism are secondary to a physical obstruction preventing saliva being swallowed; secondary to dysphagia; or due to equine dysautonomia, it is important to be aware of the neuroanatomy of the autonomic system controlling salivary gland activation and to be aware that extra-luminal compression of the intra-thoracic oesophagus by space occupying lesions in the mediastinum is possible.

**Manufacturer’s details:**

Karidox1 100mg/ml Oral solution, Nimrod Veterinary Products Ltd, Moreton-in-Marsh, Gloucestershire, UK: 01608 652593Engemycin2 200mg/ml Solution for injection, MSD Animal Health, Milton Keynes, Buckinghamshire, UK: 01908 685685
Equipalazone3 200mg/ml Solution for Injection, Dechra Veterinary Products, Shrewsbury, Shropshire, UK: 01939 211200Depocillin4 300mg/ml Suspension for Injection, MSD Animal Health, Milton Keynes, Buckinghamshire, UK: 01908 685685Genta-Equine5 100mg/ml Solution for Injection for Horses, Dechra Veterinary Products, Shrewsbury, Shropshire, UK: 01939 211200Meflosyl6 5% Solution for Injection, Zoetis, Leatherhead, Surrey, UK: 0845 300 8034

**Abbreviations:**

CAL: cricoarytenoideus lateralis muscle

**Declarations:**

Authorship: CMG managed case 1. CMG and RBO managed case 2. RJP consulted on both cases. GL performed post-mortem examination on case 2. RBO drafted the manuscript and RJP, GL and CMG revised it critically. All authors approved the final version of the manuscript.

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Ethical animal research: Informed client consent was obtained for use of clinical data for research purposes and for performing partial post-mortem examination on case 2. Institutional ethical approval RETH000689 was in place. In addition, both cases occurred prior to January 2017.

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**Figure legends**

*Figure 1: Radiographic dorsoventral image of the skull (caudal is to the top of the image and right is on the left of the image), demonstrating increased mineral opacity caudal and medial to the left petrous temporal bone (arrow), closely associated with the tympanic bulla.*

*Figure 2: Panel A - Part of the mass (arrowheads) in close association with the ascending aorta (\*). Panel B - Transverse section of the trachea at the level of the hilus, showing the lobulated mass on the ventral aspect of the trachea (arrowheads). Grid = 1 cm.*