



SPONTANEOUSLY ARISING DISEASE

Age-related Qualitative Histological and Quantitative Stereological Changes in the Equine Pituitary

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Summary

The aim of this study was to characterize the age-related morphological changes in the equine pituitary and to identify features that allow distinction between pituitary pars intermedia dysfunction (PPID)-associated and non-functional/age-associated pars intermedia (PI) adenoma. Pituitary glands of all horses submitted for necropsy examination at the Institute of Veterinary Pathology, Ludwig Maximilians University Munich, between 2008 and 2012 were examined. The pituitary glands of 124 horses were weighed, cut into ~2 mm slices and examined histologically. A slightly modified grading scheme (grades 1–5) was applied to evaluate histological alterations of the PI semiquantitatively. The volume fractions and total volumes of the three pituitary lobes, PI, pars distalis (PD) and pars nervosa (PN), as well as the total number and mean size of PI cells (PICs), were determined using state-of-the-art quantitative stereological methods.

There were significant associations between histological grade, the appearance of PI adenomas, follicles and cysts in the PI, lipofuscin in the PN ($P < 0.001$) and focal hyperplasia of chromophobes in the PD and age. In contrast, the appearance of follicles and cysts in the PD, invasion of basophil cells into the PN, haemorrhage and necrosis were not age dependent. PI adenomas were observed in 18% (22/124) of the animals, but only four horses were evidently suffering from PPID, therefore clinically overt/PPID-associated PI adenomas were found in 3% (4/124) of all horses. Most PI adenomas were incidental and considered non-functional. Pituitary weight, PI volume, total number and mean volume of PICs increased with age in all horses. The total PI volume and the number of PICs of horses exhibiting PPID-associated PI adenomas were significantly higher, while the mean size of PICs was smaller compared with that of horses showing non-PPID-associated adenoma, which suggests that different growth processes are responsible for adenoma formation. The present study demonstrated various age-associated lesions of the PD and PN and revealed a high frequency of incidental, non-PPID-associated PI adenomas in aged horses. Therefore, post-mortem diagnosis of PPID in horses is possible, by determination of pituitary weight and by demonstration of PIC hyperplasia, using quantitative stereological methods.

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Introduction

Equine Cushing's syndrome (ECS) is considered to be a neurodegenerative disorder of the hypothalamus, resulting in the loss of dopaminergic inhibition of

the pituitary pars intermedia (PI) and is therefore referred to as pituitary pars intermedia dysfunction (PPID) (Dybdal *et al.*, 1994; Schott, 2002). Adenoma formation in the PI is thought to cause the clinical syndrome of PPID in horses, by changing the hormone profile (Orth *et al.*, 1982; Wilson *et al.*, 1982; Boujon *et al.*, 1993). In other

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species (e.g. man and dog), Cushing's disease is accompanied by hypercortisolism and is often due to excessive secretion of adrenocorticotropic hormone (ACTH) by a functional pituitary tumour (Bertagna *et al.*, 2009; Melián *et al.*, 2010). Horses suffering from PPID have increased levels of ACTH in addition to elevations in α -melanocyte stimulating hormone (MSH), corticotropin-like intermediate peptide (CLIP) and β -endorphin; all of which influence the development of clinical signs (Orth *et al.*, 1982; Wilson *et al.*, 1982; Millington *et al.*, 1988; Heinrichs *et al.*, 1990). Degeneration of dopaminergic neurons innervating the PI is thought to lead to tumourigenesis, as dopamine concentration is decreased in adenomatous PI tissue of horses with PPID (Millington *et al.*, 1988). Furthermore, administration of dopamine agonists restores the PPID-induced hormone imbalance to normal and is therefore currently the treatment of choice for horses with PPID (Orth *et al.*, 1982; Schott *et al.*, 2001; Donaldson *et al.*, 2002). Enlargement of the PI and adenoma formation remain the most reliable indicators for post-mortem confirmation of the clinical diagnosis of PPID (Schott, 2002; McFarlane, 2011). However, morphological changes in the PI are found in aged horses without clinical signs of the disease (van der Kolk *et al.*, 2004; McFarlane *et al.*, 2005; Miller *et al.*, 2008), so the histological diagnosis of PPID remains challenging and depends on the ability to discriminate between PPID- and age-associated alterations in the PI (van der Kolk *et al.*, 2004; McFarlane *et al.*, 2005).

The aim of the present study was to characterize age-related and PPID-associated changes in the equine pituitary using qualitative histological and quantitative stereological analyses.

Materials and Methods

Horses

Pituitary glands from 124 horses (58 geldings, 48 mares and 18 stallions) submitted for necropsy examination to the Institute of Veterinary Pathology, Ludwig Maximilians University Munich, between 2008 and 2012 were collected for the study. The age of the animals ranged from 1 day to 36 years (median 14 years; mean 13.5 ± 7.6 years). As PPID defines a clinical syndrome, the diagnosis was based on detailed preliminary reports and clinical findings of specialists in equine internal medicine as well as post-mortem findings of specialists in veterinary pathology. The clinical diagnosis was established by observation of hirsutism/hypertrichosis together with at least one other classical sign (i.e. hyperhidrosis, weight loss, lethargy,

loss of muscle mass, deposition of fat along the crest of the neck, supraorbital fat deposition, laminitis, polydipsia/polyuria and delayed wound healing). According to these criteria, four of the 124 horses in this study had PPID. Adenomas in the PI were classified as PPID-associated adenomas (clinically overt cases) and non-PPID-associated adenomas (non-functional, age-associated), depending on the evidence of clinical signs of PPID in the respective horses.

Some of the horses with pituitary enlargement and tumour formation without clinically overt PPID may have had subclinical/early stages of PPID.

Twenty-one glands were collected in the autumn (September–November), 39 in the winter (December–February), 36 in the spring (March–May) and 28 in the summer (June–August). Pituitary glands from all four horses with clinically overt PPID were collected in months other than during autumn.

Pituitary Gland Processing

The pituitary glands were fixed in 4% neutral buffered formalin for 24 h and weighed to the nearest 0.01 g. The pituitaries were cut into sagittal slices of ~ 2 mm thickness and evaluated for gross alterations. The slices were scanned on a plastic transparency with the right cut surface facing downwards, using a HP Scanjet 7400c (HP Deutschland GmbH, Böblingen, Germany). The middle slice, with fractions of all three pituitary lobes, was embedded in plastic containing glycol methacrylate and methyl methacrylate, as described previously (Hermanns *et al.*, 1981). All other slices were embedded in paraffin wax.

Histological Examination

A slightly modified semiquantitative grading scheme was applied to evaluation of histological sections stained by haematoxylin and eosin (HE) of all 124 pituitaries (Miller *et al.*, 2008): grade 1 (within normal limits), grade 2 (focal or multifocal enlargement of the PI), grade 3 (diffuse enlargement of the PI), grade 4 (diffuse enlargement of the PI with microadenomas, diameter ≤ 5 mm) or grade 5 (diffuse enlargement of the PI with macroadenomas, diameter > 5 mm). PI adenomas were classified as non-functional/age-associated or PPID-associated adenomas, depending on the evidence of clinical signs of PPID (see above). Pituitary glands were additionally evaluated for histological features that were not part of the grading scheme, such as colloid-filled follicles (diameter ≤ 1 mm) or cysts (diameter > 1 mm) in the PI and pars distalis (PD), focal hyperplasia of chromophobes in the PD, infiltration of basophil cells into the pars

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