

Pituitary pars intermedia dysfunction (equine Cushing's disease) in a Thoroughbred stallion: a single report

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Equine pituitary pars intermedia dysfunction (PPID) generally occurs in older horses showing hirsutism, delayed molting, weight loss, polydipsia, polyuria, laminitis, and reproductive disorders (in broodmares), but there have been no reports on stallions. This report presents a case of a 21-year-old Thoroughbred stallion that developed hirsutism and experienced delayed molting. There were no abnormal findings for semen quality or the stallion's sexual desire. The horse was diagnosed with PPID based on dexamethasone suppression test and plasma levels of adrenocorticotrophic hormone. It was then medicated with pergolide mesylate. Since the horse died due to humerus fracture, an autopsy was conducted, and pituitary adenoma was confirmed. No pathological findings were defined in the testicles; therefore, reproductive activity might not have been impaired.

Key words: hirsutism, pituitary pars intermedia dysfunction, stallion, Thoroughbred

J. Equine Sci.
Vol. 26, No. 4
pp. 125–128, 2015

Twenty-year-old stallions are not uncommon in the recent Leading Sires list in Japan. Although there is an increase in the occurrence of geriatric disorders at more advanced ages, pituitary pars intermedia dysfunction (PPID), also known as equine Cushing's disease (ECD), is a common endocrine diseases of horses. The incidence of PPID is 15–30% in aged horses and shows no difference between sexes [8]. The pathogenesis of PPID is poorly understood, but the available evidence supports a loss of dopaminergic inhibition of the melanotroph of the pars intermedia [7]. PPID is a clinical syndrome of aged horses associated with hirsutism, delayed molting, poor hair coat, laminitis, polyuria and polydipsia, and so on [8]. PPID in female Thoroughbreds can become a serious economic problem, since broodmares with PPID are reported to become subfertile [5, 6]. On the other hand, male reproductive dysfunction induced by PPID has never been reported.

A male Thoroughbred stallion that had been at stud since 9 years of age was initially examined by the author for persistent hirsutism and delayed molting in May (spring) 2014 at the age of 21 years (Fig. 1a and 1b). No abnor-

malities were detected in previous routine hematology tests including CBC, PCV, and hemogram and blood biochemistry including AST, ALT, GGT, LD, CK, T-Bil, D-Bil, BUN, CRE, and blood glucose, which were conducted every 1–2 months. Furthermore, no abnormalities were found in routine semen examinations (semen volume, 110 ml; sperm count, 1.05×10^8 /ml; pH 7.4; and active motility of sperms). The author suspected this to be a case of equine PPID and performed a dexamethasone suppression test (DST) in June 2014. Before the dexamethasone injection (40 μ g/kg, i.m.) and 15 hr and 19 hr after the injection, blood samples were collected, and plasma cortisol levels were measured. The cortisol levels were 22.1, 21.4, and 24.3 ng/ml, respectively. The cortisol levels at 15 hr and 19 hr were higher than the reference values (less than 10 ng/ml), and there were few changes in comparison with the cortisol level from before the dexamethasone injection; therefore, we determined that the DST was positive because there was no negative feedback. To support the DST result, the stallion's plasma adrenocorticotrophic hormone (ACTH) level was measured at rest in July 2014. The ACTH level was 259 pg/ml and was higher than that in three other horses (controls) living with the patient, (i.e., 12.8, 18.0, and 20.0 pg/ml at the ages of 14, 18 and 24 years, respectively). Based on these laboratory data and clinical signs, administration of pergolide mesylate (1 mg/head per day per os) was started in August 2014.

Since the stallion died following anastasia because of a fractured humerus in September 2014, we had the oppor-

Received: July 14, 2015

Accepted: September 4, 2015

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Fig. 1. Appearance of the stallion before (a) and after (b) the onset of pituitary pars intermedia dysfunction (PPID). The stallion had already molted by May 31, 2013, at the age of 20 years (a), but it had not molted by May 31, 2014, at the age of 21 years (b).

tunity to perform an autopsy as well as autopsy imaging. Following computed tomography imaging of the head, the pituitary gland was observed to be enlarged (Fig. 2). The crucial macroscopic findings were swelling of the pituitary gland ($3.8 \times 3.0 \times 2.2$ cm), which protruded from the pituitary fossa (Fig. 3), and atrophy of the anterior lobe (adenohypophysis) and the posterior lobe (neurohypophysis; Fig. 4). The intermediate lobe was hyperplastic in the vertical section (Fig. 4). Histopathological analysis demonstrated a proliferation of tumor cells that were derived from the intermediate pituitary and excluded the anterior and posterior lobes. The tumor cells had an oval nuclei and a highly spindle-shaped cytoplasm that was amphophilic and/or eosinophilic, and the alignments of cells were radial at the center of small vessels with a palisade or acinar alignment (Fig. 5). No enlargement of the adrenal gland or macroscopic abnormality of the testicles was observed, and no histopathological abnormalities were seen in the testicles.

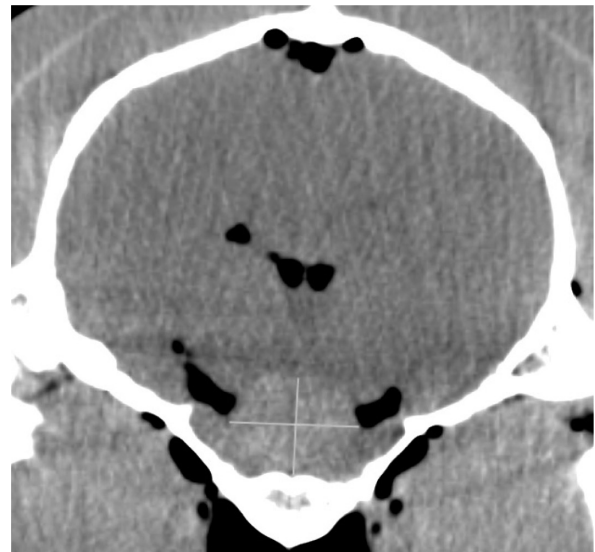


Fig. 2. CT scan cross-sectional findings of the enlarged pituitary gland of the stallion. The lengths in the vertical and horizontal directions were 2.05, and 2.72 cm, respectively.

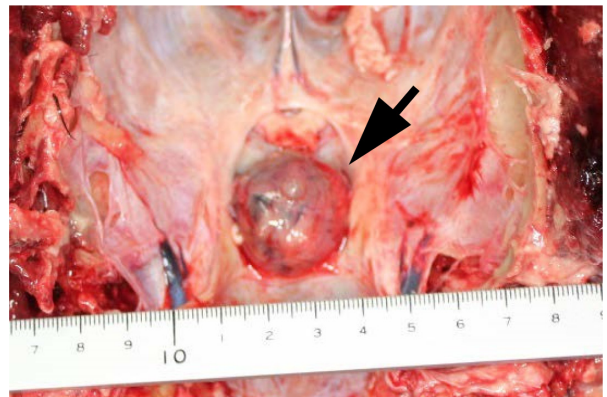


Fig. 3. Macroscopic findings of the stallion's enlarged pituitary gland, which protruded from the pituitary fossa.

In Japan, cases of PPID in Thoroughbred stallions are rare because the number of male horses kept for breeding is very low (2.64%, 266 male horses/10,060 breeding horses, according to Japan Association for International Racing and Stud Book, 2014). Equine PPID is a general endocrine disease that has been diagnosed in 7- to 40-year-old horses, and no sex-related differences have been reported [8]. The previously reported clinical symptoms of PPID include hirsutism, delayed molting, poor hair coat, laminitis, polyuria, polydipsia, weight loss, docility, lethargy, hyperhidrosis, narcolepsy, blindness, lower response to a painful stimulation, increased appetite, recurrent infection, and reproductive dysfunction (in broodmares) [8]. In this

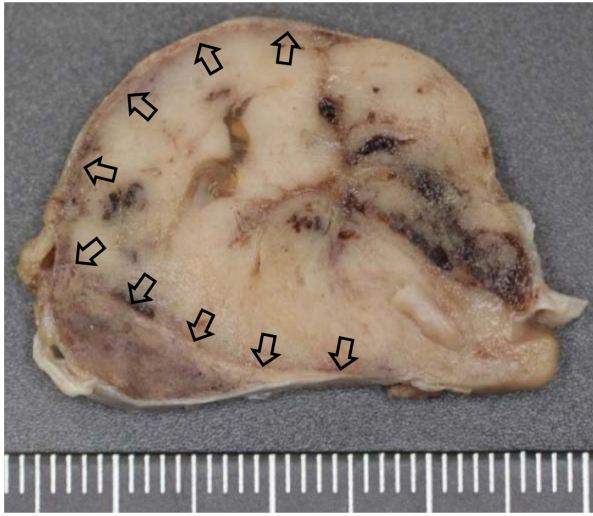


Fig. 4. Vertical section of the stallion's pituitary gland. Pituitary adenoma was noted in the intermediate lobe and the excluded anterior and posterior lobes. The open arrows indicate the boundary of the anterior lobe and intermediate lobe.

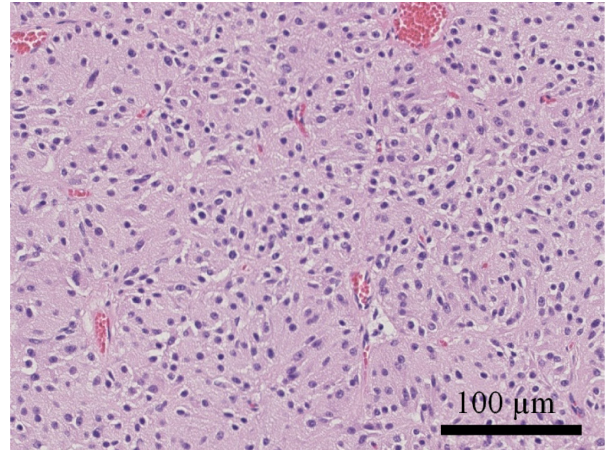


Fig. 5. Histopathological image of the tumor cells that were derived from the intermediate lobe in the pituitary. The tumor cells had an oval nuclei and a highly spindle-shaped cytoplasm that was amphophilic and/or eosinophilic, and the alignments of cells were radial at the center of small vessels with a palisade or acinar alignment.

case, the stallion was presented with hirsutism and delayed molting. A DST and assay of plasma ACTH levels have been generally accepted as the standard diagnosis for equine PPID because of their high reliability, convenience, and low costs [2, 8]. However, as pseudo-positive reactions can be increased in autumn, the timing of the implementation of tests should be carefully considered [3]. In this case, the DST and the plasma ACTH assay were performed in June and July 2014, respectively, and therefore, the results of both have high reliability. Oral administration of pergolide mesylate, a dopamine receptor agonist, has been recommended for treating equine PPID over a horse's lifetime [9, 10]. We could not evaluate the effect of the medication after DST and ACTH measurements, however, as the horse died after 21 days of administration.

The pathology of equine PPID has been previously reported to include macroscopic enlargement of the pituitary gland accompanied by hypertrophy, hyperplasia, and adenoma [1, 4, 11]. The histopathology of equine pituitary adenoma was reported as columnar or spindle-shaped tumor cells originating in the intermediate lobe and showing palisaded and/or acinar alignment along with their infiltration into the anterior or posterior lobes [1, 4, 11]. These findings could be consistent with this case. Therefore, we pathologically diagnosed equine PPID.

Broodmares with PPID present abnormal estrous cycles, heat restraint, and low fertility. These symptoms could be induced by the unusual release of sex hormones in association with the decreased secretion of dopamine and a hypothalamo-pituitary system affected by an enlarged

intermediate lobe [6, 8]. Although reports on PPID of stallions is lacking, gonadotropic hormone released from the anterior lobe may affect the male genital system and reproductive behavior as well as the testicles. As described above, in July 2014, this stallion showed no abnormalities in a routine semen examination or in sexuality. As there were no abnormal pathological findings in the testicles, we assumed that the stallion had normal fertility. The clinical symptoms, laboratory data, and pathology as presented here were consistent with previous reports on horses except for sex (male). More cases need to be studied to constructively discuss the fertility of stallions with PPID.

References

1. Boujon, C.E., Bestetti, G.E., Meier, H.P., Straub, R., Junker, U., and Rossi, G.L. 1993. Equine pituitary adenoma: a functional and morphological study. *J. Comp. Pathol.* **109**: 163–178. [Medline] [CrossRef]
2. Couëtil, L., Paradis, M.R., and Knoll, J. 1996. Plasma adrenocorticotropin concentration in healthy horses and in horses with clinical signs of hyperadrenocorticism. *J. Vet. Intern. Med.* **10**: 1–6. [Medline] [CrossRef]
3. Donaldson, M.T., McDonnell, S.M., Schanbacher, B.J., Lamb, S.V., McFarlane, D., and Beech, J. 2005. Variation in plasma adrenocorticotrophic hormone concentration and dexamethasone suppression test results with season, age, and sex in healthy ponies and horses. *J. Vet. Intern. Med.* **19**: 217–222. [Medline] [CrossRef]
4. Heinrichs, M., Baumgärtner, W., and Capen, C.C. 1990. Immunocytochemical demonstration of proopiomelano-

- cortin-derived peptides in pituitary adenomas of the pars intermedia in horses. *Vet. Pathol.* **27**: 419–425. [[Medline](#)] [[CrossRef](#)]
5. Love, S. 1993. Equine Cushing's disease. *Br. Vet. J.* **149**: 139–153. [[Medline](#)] [[CrossRef](#)]
 6. McCue, P.M. 2007. Ovarian abnormalities. pp. 87–92. *In*: Current Therapy in Equine Reproduction. (Samper, J.C., Pycock, J.F., and McKinnon, A.O. eds.), W. B. Saunders, Philadelphia.
 7. McFarlane, D., Dybdal, N., Donaldson, M.T., Miller, L., and Cribb, A.E. 2005. Nitration and increased alpha-synuclein expression associated with dopaminergic neurodegeneration in equine pituitary pars intermedia dysfunction. *J. Neuroendocrinol.* **17**: 73–80. [[Medline](#)] [[CrossRef](#)]
 8. McFarlane, D., and Toribio, R.E. 2010. Pituitary pars intermedia dysfunction. pp. 1262–1270. *In*: Equine Internal Medicine, 3rd ed. (Reed, S.M., Bayly, W.M., and Sellon, D.C. eds.), W. B. Saunders, Philadelphia.
 9. Perkins, G.A., Lamb, S., Erb, H.N., Schanbacher, B., Nydam, D.V., and Divers, T.J. 2002. Plasma adrenocorticotropin (ACTH) concentrations and clinical response in horses treated for equine Cushing's disease with cyproheptadine or pergolide. *Equine Vet. J.* **34**: 679–685. [[Medline](#)] [[CrossRef](#)]
 10. Schott, H.C., Graves, E.A., and Refsal, K.R. 2005. Diagnosis and treatment of pituitary pars intermedia dysfunction (classical Cushing's disease) and metabolic syndrome (peripheral Cushing's syndrome) in horses. *Adv. Derm.* **5**: 159–169.
 11. van der Kolk, J.H., Heinrichs, M., van Amerongen, J.D., Stooker, R.C., in de Wal, L.J., and van den Ingh, T.S. 2004. Evaluation of pituitary gland anatomy and histopathologic findings in clinically normal horses and horses and ponies with pituitary pars intermedia adenoma. *Am. J. Vet. Res.* **65**: 1701–1707. [[Medline](#)] [[CrossRef](#)]