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CASE REPORT

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Long-term hormone replacement treatment in a horse with central diabetes insipidus

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Abstract

This case report describes the clinical presentation, and the diagnostic and therapeutic approaches of a 4-year-old gelding presented with severe polyuria and polydipsia. The horse was diagnosed with central diabetes insipidus. After diagnosis, different therapeutic regimens with intraocular desmopressin acetate (Minirin, Ferring GmbH, Kiel, Germany) (a synthetic arginine vasopressin analog) were tested, but without success. Only the subcutaneous injection of desmopressin acetate (Minirin, Ferring GmbH) led to an increase in urine specific gravity and a decrease in water intake and urine output. Daily subcutaneous treatment with desmopressin acetate (Minirin, Ferring GmbH) was initiated and maintained for at least 5 years. The horse did not develop adverse effects or re-occurrence of the initial complaints. This case report describes successful long-term treatment of central diabetes insipidus in a horse.

KEYWORDS

desmopressin acetate, equine endocrinology, hyposthenuria, PU/PD

1 | CASE

Diabetes insipidus (DI) is a medical condition characterized by production of hyposthenuric urine and profound polyuria/polydipsia (PU/PD). Although in central DI (CDI) the production or secretion of arginine vasopressin from the caudal pituitary gland fails, in nephrogenic DI the renal tubules fail to respond to arginine vasopressin.[1]

In horses, CDI has been described, but is considered a rare endocrine cause of PU/PD.[1] In the few cases described in literature, treatment has been conservative and directed at managing PU/PD by ensuring free access to water.[2] In humans and companion animals, CDI is treated with administration of desmopressin acetate, a synthetic arginine vasopressin analog.[3-5] There is 1 report describing the short-term use of desmopressin acetate eye drops in a foal, yet long-term treatment was not pursued.[6]

Abbreviations: BWT, body weight; CDI, central diabetes insipidus; DI, diabetes insipidus; PPID, pituitary pars intermedia dysfunction; PU/PD, polyuria/polydipsia; USG, urine specific gravity; WDT, water deprivation test.

2 | CASE HISTORY

A 4-year-old Warmblood gelding was presented to Strömsholm Equine Referral Hospital (Evidensia Specialisthästsjukhuset Strömsholm), for investigation of PU/PD. Eight months earlier, the horse had been imported from Latvia. Immediately on arrival, the owner noticed the horse showed excessive water consumption, consuming approximately between 240 and 320 mL/kg body weight (BWT) of water per day (150-200 L/day). The horse was stabled on straw, and the owner reported that the bedding was always excessively wet. There was no knowledge of disease before import. Diet consisted of a mixture of hay, haylage, and straw, and the horse had access to a salt block. One month before referral, a veterinarian examined the horse and did not find any abnormalities on physical examination. Hematology revealed no abnormalities: packed cell volume (PCV) 34% (30%-45%), leukocytes 11 $\times 10^3/\mu L$ (5.5-12.2 $\times 10^3/\mu L$) with normal distribution of neutrophils and lymphocytes. Biochemistry showed normal total protein (6.4 g/dL, 5.3-7.3 g/dL), albumin (3.2 g/dL, 2.9-4.1 g/dL), and fibrinogen

(160 mg/dL, 30-390 mg/dL) concentrations. Serum creatinine (1 mg/dL, 0.8-2.1 mg/dL) and blood urea nitrogen (12.8 mg/dL, 11-22 mg/dL) concentrations and gamma-glutamyl transpeptidase activity (11 IU/L, 0-47 IU/L) were within normal reference ranges. Serum aspartate aminotransferase (362 IU/L, 100-360 IU/L) and alkaline phosphatase (342 IU/L, 10-326 IU/L) activities were above reference ranges. A urine sample was collected after spontaneous voiding and revealed a urine specific gravity (USG) of 1.002 measured by refractometer. Dip stick analysis showed no signs of protein, blood, or glucose. Cytologic analysis of the urine showed no hematuria or pyuria, yet extracellular bacteria were seen. The horse was thereafter treated with oral trimethoprim-sulfadiazine (Hippotrim, Bayer Animal Health, Leverkusen, Germany; 30 mg/kg PO q12h for 10 days) but showed no clinical improvement.

3 | CLINICAL FINDINGS

On presentation at Strömsholm Equine Referral Hospital (Evidensia Specialisthästsjukhuset Strömsholm), the horse was bright, alert and responsive, and had a normal body condition score of 5/9 (BWT 625 kg) and normal haircoat. Abnormalities were not detected on physical examination. Blood analysis and urinalysis were partially repeated and showed normal serum creatinine concentration (0.9 mg/dL, 0.8-2.1 mg/dL), blood urea nitrogen (12.6 mg/dL, 11-22 mg/dL), and glucose (5.3 mmol/L, 4.2-7.5 mmol/L) concentrations. Serum electrolyte concentrations were sodium 134 mEq/L (124-142 mEq/L), potassium 3.2 mEq/L (3-5 mEq/L), and ionized calcium 6.5 mg/dL (5.8-6.8 mg/dL). Urine was collected after spontaneous voiding and USG measured by refractometer was 1.010. Urine dipstick analysis showed no traces of protein, blood, or glucose.

4 | DIAGNOSTIC WORKUP

Differential diagnosis for PU/PD and low USG in adult horses include pituitary *pars intermedia* dysfunction (PPID), diabetes mellitus, liver disease, acute or chronic renal failure, septicemia, endotoxemia, psychogenic salt consumption, iatrogenic (intravenous administration of fluids, administration of alfa2 adrenoreceptor agonists and others), DI, and primary/psychogenic polydipsia.[7]

Absence of signs of shock or endotoxemia, hirsutism and old age, previous or recent drug administration, hyperglycemia and glucosuria, increased liver enzymes, and azotemia ruled out shock or endotoxemia, PPID, iatrogenic causes, diabetes mellitus, liver disease, and renal failure. Although the horse had access to a salt block, based on the history there was no indication for excessive consumption of salt as the cause of the polydipsia. Moreover, serum electrolyte concentrations were normal, also making excessive salt consumption less likely. The horse had undergone recent management changes which made psychogenic polydipsia, related to stable confinement and boredom[7] a possible differential diagnosis. In addition, DI was considered.

After assessing the horse as normally hydrated and without azotemia, it was submitted to a water deprivation test (WDT). Every 6 hours a clinical examination was performed and BWT, blood urea nitrogen, serum creatinine concentration, and USG were measured (Table 1). After 18 hours, the BWT had dropped with 5.3% (Table 1) and the gelding exhibited signs of lethargy, tacky mucous membranes, and increased skin tent. The WDT was discontinued although it had failed to produce concentrated urine (Table 1). This outcome ruled out uncomplicated psychogenic polydipsia as the cause of PU/PD.[7] Water was thereafter gradually reintroduced. The horse then had free access to water and demonstrated excessive water consumption (Table 1) and urine output (overly wet bedding). Its vital signs and weight were normalized, whereas urine remained hyposthenuric (Table 1). To differentiate psychogenic polydipsia with medullary washout from DI, a modified WDT was performed.[7] This test consisted of restricted water access over a period of 24 hours, consisting of 7.8 L water every 6 hours (50 mL/kg BWT/d). Weight, hydration status, heart rate, blood urea nitrogen, serum creatinine concentration, and USG were assessed 12-hourly. After 24 hours and important weight loss (>5%), yet without increase in USG (Table 1), the test was discontinued. Blood samples were taken at the end of the WDT and submitted to a distant laboratory for measurement of plasma arginine vasopressin concentration, however, samples were unfortunately lost during shipping. Access to water was gradually increased again to 7.8 L at 3 hours interval (105 mL/kg BWT/d). In the afternoon of day 6, a desmopressin response test was performed[1,7] by administration of 0.05 μg/kg of desmopressin acetate (Minirin, Ferring GmbH, Kiel, Germany; 30 μg or 1.2 mL of the 25 μg/mL nasal spray solution) diluted in 10 mL of sterile saline IV. After desmopressin acetate (Minirin, Ferring GmbH) administration, there was an increase in USG (Table 1). The horse was also observed to urinate less frequently as the first urine sample was collected only 6 hours after the administration of desmopressin. This positive response supported the diagnosis of CDI. Further diagnostic procedures to investigate possible underlying causes of the CDI, like computed tomographic examination of the head and cerebrospinal fluid analysis, were declined by the owner.

5 | TREATMENT

Over the subsequent 2 days, the horse was gradually allowed ad libitum access to water. Different treatment options with desmopressin acetate (Minirin, Ferring GmbH), which could serve as long-term treatment options, were evaluated. The first therapeutic option consisted of the administration of 3 drops of desmopressin acetate (Minirin, Ferring GmbH) (equivalent 30 μg of the 100 μg/mL nasal drops solution) q24h in the conjunctival sac. Twelve hours after administration, USG continued to be low and water consumption was unchanged. The next day, the dose of intraocular desmopressin acetate (Minirin, Ferring GmbH) was doubled to 60 μg. In order to avoid overflow of the drug from the horse's eye, this dose was equally divided between both eyes: 3 drops (30 μg) in each eye. This treatment also did not have any effect. As a third option, the same dose of desmopressin acetate (Minirin, Ferring GmbH; 60 μg) was given q12h during the 2 subsequent days, meaning the horse received 3 drops (30 μg) in the left and right eye in the

TABLE 1 Variables measured during diagnostic workup and treatment

Day	Time (hours)	BWT (kg)	Water consumption (mL/kg/bwt/24 hours)	USG	Serum creatinine concentration (μmol/L)	BUN (mmol/L)
1: Afternoon: WDT	0	625	0	1.010	71	4.5
	+6	612		1.005	77	4.8
	+12	599		1.008	80	4.8
2: Reintroduction water	+18	592	200	1.007	83	4.6
3: Free access to water	-		230			
4: Free access to water	-		266			
5: Modified WDT	0	629	50	1.002	106	2.4
	+12	608		1.004		
6: Reintroduction water	+24	595	105	1.005	120	3
6: Afternoon: desmopressin response test	0	595		1.005	132	3.4
	+6	584		1.018		
7: Reintroduction water	+18	600	180	1.029	126	4.1
	+39	613		1.003		
8: Free access to water	-	618	233	1.005		
9: Desmopressin 30 μg q24h IO	0	612	180	1.003		
	+12			1.005		
10: Desmopressin 60 μg q24h IO	0	610	213	1.003		
	+12			1.009		
11: Desmopressin 60 μg q12h IO	0	612	157	1.002		
	+12			1.005		
12: Desmopressin 60 μg q12h IO	0	614	130	1.005		
	+12			1.010		
13: Desmopressin 30 μg q24h SC	0	612	104	1.005		
	+13			1.032		
	+24			1.031		
14: Desmopressin 25 μg q24h SC	0	612	92	1.031		
15: Discharge	+18			1.030		
	+22			1.028		

Abbreviations: BUN, blood urea nitrogen; BWT, body weight; IO, intraocular; USG, urine specific gravity; WDT, water deprivation test.

morning and again 3 drops (30 μg) in the left and right eye in the evening. After 2 days of treatment, USG and water consumption had declined, showing a partial response to this therapeutic regimen (Table 1). As it was impossible to increase the dose even more because of overflow of fluid from the eye and the lack of commercial solutions with higher concentration, a trial with subcutaneous administration of desmopressin acetate (Minirin, Ferring GmbH) was started. On day 13, the horse received 0.3 mL of desmopressin acetate (Minirin, Ferring GmbH) (equivalent 30 μg of the 100 μg/mL nasal drops solution) q24h SC. Water intake and USG responded favorably (Table 1). As the horse had shown dramatic increase in USG, the risk of overdosing and fluid retention was considered, and therefore the dose was slightly decreased from 30 to 25 μg q24h on day 14. Urine specific gravity and water intake remained stable (Table 1). The horse was discharged on day 15 with the instruction to treat the horse with 0.25 mL of desmopressin acetate (Minirin, Ferring GmbH; equivalent 25 μg of the 100 μg/mL nasal drops solution) q24h SC bilaterally in the neck and shoulder area, and to follow up the horse's water intake and urine output.

6 | OUTCOME

One week after discharge, the owner was contacted by telephone. The owner reported that the horse tolerated the treatment well. The horse drank 50-60 L water/d (81-98 mL/kg BWT per day). During the subsequent months and years, the owner was regularly contacted, and she continued to report resolution of PU/PD, good health, and no issues with treatment. The horse was used for recreative jumping and dressage.

After 34 months of treatment, the owner reported that she noted more frequent urination for a couple of days. She was advised to switch

to another injection site and to increase the dose of desmopressin acetate (Minirin, Ferring GmbH) to 30 μg q24g SC because of growth and weight gain of the horse. These measures resolved the more frequent urination.

After 5 years of treatment, a control blood and urine analyses were performed. Serum creatinine (114 μmol/L, 71-187 μmol/L), blood urea nitrogen (5.1 mmol/L, 4-8 mmol/L), and serum electrolyte concentrations (sodium 137 mmol/L (124-142 mmol/L), potassium 4.7 mmol/L (3-5 mmol/L), and total calcium 3.1 mmol/L (2.5-3.4 mmol/L)) were all within normal reference ranges. When measured 12 and 24 hours after administration of desmopressin acetate,[7] USG was respectively 1.030 and 1.005. Average water intake was 45 L/d (approximately 70 mL/kg BWT/d).

7 | DISCUSSION

The diagnosis of DI in this horse was supported by exclusion of other differentials for PU/PD, the finding of ongoing hyposthenuria and weight loss after a standard and a modified WDTs.[1] A low level of plasma arginine vasopressin concentration after WDT would further have supported CDI,[1] but unfortunately samples were lost during shipping. However, a positive response to administration of exogenous arginine vasopressin or desmopressin as a diagnostic tool has been proposed as a good diagnostic alternative.[1,4]

In humans, both hereditary and acquired forms of CDI have been described.[1,5] Although in small animals, CDI is often acquired and idiopathic, it is also associated with trauma, pituitary neoplasia, PPID, and encephalitis.[3,4,8] In horses, CDI has been described as an idiopathic syndrome,[6,9] in association with encephalitis[10] or PPID.[11] The cause of CDI in the horse in the current case report was not further investigated, but because of the young age and lack of other clinical signs or laboratory abnormalities, the PPID, pituitary neoplasia, and encephalitis were considered unlikely. Also, the fact that the horse remained neurologically normal over a period of 5 years makes neoplasia very unlikely. Advanced medical imaging of the brain in combination with cerebrospinal fluid analysis could have been useful to further exclude pituitary neoplasia but were declined by the owner. In human infants affected by the hereditary form of CDI, progressive loss of magnocellular neurons in the hypothalamus and consequently arginine vasopressin production leads to clinical signs of PU/PD usually developing after the first few years of life. Considering that the horse showed clinical signs at a young age and since arrival, with lacking information from before importation, a hereditary form of CDI is an important differential diagnosis, beside idiopathic CDI.

In humans and companion animals with CDI, hormone replacement with desmopressin acetate is the treatment of choice.[1,3-5] Desmopressin, a synthetic analog to arginine vasopressin, has increased antidiuretic activity, prolonged duration of action, and fewer adverse effects than the natural hormone (which is no longer commercially available).[8,12] Desmopressin acetate is available as an injectable solution, an intranasal spray/drops solution, or as tablets.[13] The desmopressin tablet formulation, commonly used in humans,[5] is expensive and was financially not feasible for the long-term treatment in this horse. The intranasal route, commonly used in human infants,[5] is for practical reasons not recommended in dogs and cats[3,4] and was not evaluated in this horse. Dogs and cats are commonly treated with desmopressin acetate nasal spray/drops solution applied to the conjunctival sac[8,13] and 1 report describes the same approach used in the short-term treatment of a 10-day-old Friesian filly with congenital CDI.[6] In the horse in the current case report, several dosing regimens of this ocular approach were attempted, yet the horse failed to respond satisfactorily. In companion animals, the subcutaneous route of administration has been reported as the most effective and the one with the longest duration of action.[13] An injectable solution of desmopressin acetate for parenteral use is commercially available but is expensive.[13] The nasal spray/drops solution formulation administered SC is a less expensive alternative and has been used in small animals with excellent results.[4,13] As the nasal spray/drops solution formulation is not sterile, it is recommended to use bacteriostatic syringe filters for administration.[13] In this horse, the nasal solution formulation was the only financially feasible option. Subcutaneous administration resulted in a dramatic reduction in water intake. Bacteriostatic syringe filters were not used for financial reasons, but no adverse reactions were observed. The horse has tolerated the daily injection well over a period of several years. Even in small animals, it is often noted that the parenteral injection is tolerated better compared to eye drops or oral medication.[13]

In dogs and cats, dosage and regimes are based on individual response.[8] The duration of action varies from 8 to 24 hours,[13] explaining why in some companion animals twice-daily administration is required. During initial treatment of this horse, USG continued to be increased 24 hours after administration, as was also described in another horse with PPID and CDI.[11] However, urine samples taken after 5 years of treatment showed that USG was satisfactory (1.030) 12 hours after desmopressin administration, but low (1.005) 24 hours after injection. Twice-daily administration could therefore be considered. Nevertheless, this was not pursued for economical and practical reasons and because the horse continued to show normal water intake and urinary output.

Desmopressin is considered safe for long-term treatment.[13] Adverse reactions are rare. Overdose could potentially lead to fluid retention and dilutional hyponatremia.[13] No adverse reactions or clinical signs indicating overdose were reported during the 5-year treatment period of this horse. Serum sodium concentrations have remained normal, thus confirming absence of dilutional hyponatremia as a complication of overdosage. Like dogs and cats with idiopathic CDI that are often managed successfully for several years,[8] the horse in the case report has been well for several years.

A limitation of this case report is the lack of diagnostic tests to further investigate the underlying cause of the CDI.

This is a report of long-term hormone replacement treatment of a horse with CDI. No adverse reactions were seen, and the horse's PU/PD was successfully controlled over several years. The only disadvantages of the treatment were the cost (yearly cost of approximately 1000 USD) and the horse not being able to attend competitions because of antidoping regulations. Desmopressin acetate should therefore be considered a valuable option for the long-term treatment of horses with CDI.

CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Authors declare no IACUC or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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