Topical Review

Pituitary Deficiencies

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A B S T R A C T

Diabetes insipidus, arising from damage to or congenital abnormalities of the neurohypophysis, is the most common pituitary deficiency in animals. Hypopituitarism and isolated growth hormone or thyrotropin deficiency may result in growth abnormalities in puppies and kittens. In addition, treatment of associated hormone deficiencies, such as hypothyroidism and hypoadrenocorticism, in patients with panhypopituitarism is vital to restore adequate growth in dwarfed animals. Secondary hypoadrenocorticism is an uncommon clinical entity; however differentiation of primary versus secondary adrenal insufficiency is of utmost importance in determining optimal therapy. This article will focus on the pathogenesis, diagnosis and treatment of hormone deficiencies of the pituitary gland and neurohypophysis.

The pituitary gland is composed of the adenohypophysis (pars distalis, or anterior lobe), the neurohypophysis (pars nervosa, or posterior lobe), the pars intermedia (intermediate lobe), and the pars tuberalis. The adenohypophysis is formed from an area of the roof of the embryonic oral ectoderm called *Rathke's pouch*, which extends upward to meet the neurohypophysis, which extends downward as an outpouching of neural ectoderm from the floor of the third ventricle. Hypopituitarism can arise from the adenohypophysis (dwarfism, secondary hypothyroidism, secondary hypoadrenocorticism) or from the neurohypophysis (central diabetes insipidus) as a result of neoplastic, congenital, traumatic, vascular, infectious or inflammatory conditions in the brain and surrounding structures.

Neurohypophyseal Dysfunction

The neurohypophysis is composed of axons that originate within the supraoptic and paraventricular nuclei of the hypothalamus. The main activity of vasopressin which is produced by the neurohypophysis is the enhancement of water retention by the kidney. As a consequence, the hormone is often called antidiuretic hormone (ADH). Vasopressin is the most important hormone for the control of water balance. The control of vasopressin secretion is a result of changes in plasma osmolality. An increase in osmolality activates cells in the hypothalamus that synthesize vasopressin.

ADH, an octapeptide synthesized in the hypothalamus, is packaged into membrane-limited granules with a corresponding binding protein and transported to the pars nervosa, where it is released into the circulation. ADH binds to specific receptors in the distal part of the nephron and collecting duct of the kidney; it increases the renal tubular reabsorption of water from the glomerular filtrate. Overhydration of the body inhibits release of ADH, while dehydration favors release of ADH, which in turn causes increased water resorption from the glomerular filtrate, resulting in dilution and decreased osmolarity of body fluids.

Central Diabetes Insipidus

Diabetes insipidus (DI) is a disorder of water metabolism characterized by polyuria, urine of low specific gravity or osmolality, and polydipsia. It is caused by defective secretion of antidiuretic hormone (central DI) or by the inability of the renal tubule to respond to antidiuretic hormone (nephrogenic DI). Deficiency of antidiuretic hormone (ADH or vasopressin) can be partial or complete and has been reported in both dogs and cats.

Central DI is characterized by an absolute or relative lack of circulating ADH and is classified as primary (idiopathic and congenital) or secondary.[1] Secondary central DI usually results from head trauma, after transphenoidal hypophysectomy or neoplasia.[2-7] The lesions responsible for the disruption of ADH synthesis or secretion in central diabetes insipidus include large pituitary neoplasms, a dorsally expanding cyst or inflammatory granuloma, and traumatic injury to the skull with hemorrhage.

Central DI may appear at any age, in any breed, and in either gender of dogs or cats[8]; however, young adults (6 months of age) are most commonly affected.[9,10] The major clinical signs of DI are profound polyuria and polydipsia (more than 100 ml/kg/day; normal, 40 to 70 ml/kg/day), nocturia, and incontinence usually of several months duration. The severity of the clinical signs varies since DI may result from a partial or complete defect in ADH secretion or action. Other less consistent signs include weight loss because these animals are constantly seeking water and dehydration. Urine osmolality is decreased below normal plasma osmolality (>300 mOsm/kg) in both the central and nephrogenic forms, even if the animal is deprived of water.

Routine CBC, serum biochemical and electrolyte profiles are usually normal; however, plasma osmolality will often be high (>310 mOsm/l) in central DI as a result of *dehydration*.[11] Animals with primary polydipsia will exhibit low plasma osmolality (<290 mOsm/l) as a result of *overhydration*. When abnormalities, such as slightly increased hematocrit or hypernatremia, are present on initial evaluation they are usually secondary to dehydration from water restriction by the pet owner. In animals with central DI, the urinalysis is unremarkable except for the finding of a persistently dilute urine (urine specific gravity 1.001-1.008).

Diagnostic tests to confirm and differentiate central DI and psychogenic polydipsia include the modified water deprivation test or response to ADH supplementation (Table 1). The modified water de-

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Table 1
Procedures for the modified water deprivation test and the ADH supplementation test

Modified Water Deprivation Test
1. The animal is confined to a cage with no food or water and is weighed at 1- to 2-hour intervals after emptying the urinary bladder and obtaining an initial body weight.
2. When greater than 5% of body weight has been lost, the urinary bladder should be completely emptied and the urine checked for specific gravity or osmolality.
3. A urine-specific gravity greater than 1.025 or urine osmolality greater than 900 mOsm/L is generally considered an adequate response to water deprivation.
4. Failure to concentrate urine to this degree in the absence of renal disease indicates either central or nephrogenic DI, and/or medullary washout.
5. Immediately after water deprivation, if the animal fails to concentrate urine adequately after losing 5% or more of its body weight, an ADH response test is performed.
6. A synthetic form of ADH (desmopressin acetate [DDAVP]) may be administered subcutaneously or intravenously, or 20 μg of DDAVP (approximately 4 drops of the 100 μg/mL intranasal preparation) can be administered as intranasal or conjunctival drops.
7. Urine concentrating ability is then monitored every 2 h for 6-10 h.
8. Increases in urine-specific gravity greater than 1.025 or urine osmolality greater than 900 mOsm/L after administration of aqueous vasopressin or DDAVP is suggestive of central DI.
9. An inability to concentrate urine after ADH administration indicates nephrogenic DI or severe medullary washout.

Frequent patient monitoring is essential because severe dehydration, possible neurologic complications, and even death could ensue.

DDAVP Therapeutic Trial
1. The owner should measure the animal's 24-h water intake 2 to 3 d before the therapeutic trial with DDAVP is initiated, allowing free-choice water intake.
2. The intranasal preparation of DDAVP is administered in the conjunctival sac (1-4 drops every 12 h) for 3 to 5 d.
3. A dramatic reduction in water intake (greater than 50%) during the first few treatment days would strongly suggest an ADH deficiency.
4. When the polyuria is due to other causes, the decrease is seldom more than 30%.

privation test is designed to determine whether endogenous ADH is released in response to dehydration and whether the kidneys can respond to ADH. To evaluate the ability to concentrate urine, a water deprivation test should be done if the animal is not dehydrated and does not have renal disease. The bladder is emptied, and water and food are withheld (usually 3-8 hr) to provide a maximum stimulus for ADH secretion. The animal should be monitored carefully to prevent a loss of >5% body wt and severe dehydration. Either urine and plasma osmolality or urine specific gravity may be used to monitor the response to water restriction. At the end of the test, urine specific gravity is >1.025 in normal animals or those animals with only a partial ADH deficiency. There is little or no change in specific gravity in those animals with a complete lack of ADH activity.[11] The plasma vasopressin response to hypertonicity is a more recent provocative test to measure the pituitary response to increased sodium concentration in the blood in dogs with unexplained polydipsia and polyuria.[12]

As an alternative to the water deprivation test, or in cases in which this test fails to establish a definitive diagnosis, a closely monitored therapeutic trial with desmopressin can be performed (Table 2). Again, all other causes of polyuria and polydipsia should initially be ruled out, limiting the differential diagnosis to central diabetes insipidus, nephrogenic diabetes insipidus, and psychogenic polydipsia. For this test, the owner should measure the animal's 24-hr water intake 2-3 days before the therapeutic trial with desmopressin, allowing free-choice water intake. The intranasal preparation of desmopressin is administered in the conjunctival sac (1-4 drops, BID) for 3-5 days. A dramatic reduction in water intake (>50%) during the first treatment day would strongly suggest an ADH deficiency and a diagnosis of central diabetes insipidus.[11] If the test is being run in the veterinary hospital, urine specific gravity is determined at the start of the test; desmopressin acetate is administered (2-4 drops in the conjunctival sac); the bladder is emptied at 2 hr; and urine specific gravity is measured 4, 8, 12, 18, and 24 hr after ADH administration. Specific gravity peaks at >1.026 in animals with a primary ADH deficiency, is significantly increased above the level induced with water deprivation in those with a partial deficiency in ADH activity, and shows little change in those with nephrogenic diabetes insipidus.

Polyuria may be controlled using desmopressin acetate, a synthetic analog of ADH. The initial dose is 2 drops applied to the nasal mucosae or conjunctivae; this is gradually increased until the minimal effective dose is determined.[11] Maximal effect usually occurs in 2-6 hr and lasts for 10-12 hr. Water should not be restricted. Treatment should be continued once or twice daily for the life of the animal.

Abnormalities of Growth

Many pediatric endocrine disorders are manifested as abnormalities of statural growth. Causes of inadequate growth can be divided into two broad catagories. Intrinsic defects of growing tissues (skeletal dysplasias, chromosomal abnormalities, dysmorphic dwarfism) and abnormalities in the environment of growing tissues (nutritional, metabolic, environmental and endocrine). Intrinsic defects of growing tissues include most of the genetic and chromosomal abnormalities that result in growth failure. Genetic disorders may be suspected on the basis of clustering of disease in certain breeds and or lines of dogs and cats (i.e. chondrodystrophy of Alaskan malamutes). Diagnosis may require pursuing pedigree analysis, genetic testing or both.

Abnormalities of the environment of growing tissues are the most common and easily identified disorders. A thorough dietary history will reveal inadequate quantity and/or quality of feeding. Metabolic disorders such as portosystemic shunting, pancreatic insufficiency, congenital heart disease, and chronic renal failure, may be identified by characteristic clinical signs and laboratory data. Endocrine causes of growth retardation include juvenile hypothyroidism, hyperadrenocorticism and hypopituitarism.

Table 2
Comparison of the clinical features of typical and atypical hypoadrenocorticism

Typical Hypoadrenocorticism	Atypical Hypoadrenocorticism
Pathogenesis	
Primary adrenal insufficiency—late	Primary adrenal insufficiency—early
Primary adrenal—high ACTH	Secondary—ACTH insufficiency
Signalment	
Young (< 5 y)	Young (< 5 y)
Dogs: female, cats either sex	Dogs: female
Standard poodles, Leonbergers	Any breed
Clinical signs	
Weakness	Anorexia
Lethargy	Lethargy
Depression	Vomiting
Vomiting	Depression
Diarrhea	Chronic diarrhea
Anorexia	Waxing and waning course
Previous response to therapy	Previous response to therapy
Collapse	Hair loss
Shock	
Hypothermia	
Shaking	
Polydipsia/polyuria	
Painful abdomen	
Melena	
Hair loss	
Laboratory findings	
Lack of stress leukogram	Lack of stress leukogram
Eosinophilia	Eosinophilia
Hyponatremia	Lymphocytosis
Hyperkalemia	Hypoglycemia
Hypochloremia	
Na/K ratio < 27	
Azotemia	
Hypercalcemia	
Metabolic acidosis	
Hypoglycemia	
Endocrine testing	
Undetectable cortisol after ACTH	Decreased cortisol after ACTH
High endogenous ACTH	Secondary: low endogenous ACTH