Central diabetes insipidus unveiled by glucocorticoid therapy in a patient with an empty sella

A case report and literature review

Lei-Yi Yang, MM, Sang Lin, MM, Qi-Bing Xie, MD, Geng Yin, MD*

Abstract

Rationale: Some diseases contribute to hypopituitarism without clinical manifestations and the glucocorticoid therapy may unveil central diabetes insipidus. The condition is rare and usually causes problems for clinical physicians.

Patient concerns: A 59-year-old woman presented to our hospital due to facial numbness and persistent eyelid heaviness.

Diagnosis: Physical examination and cerebrospinal fluid examination supported a diagnosis of Guillain–Barré syndrome. Magnetic resonance imaging showed an empty sella. Hormone test indicated hypopituitarism.

Interventions: The patient received intravenous immunoglobulin and glucocorticoid. Central diabetes insipidus appeared after 20 days. Subsequently, the patient was prescribed 1-desamino-8-D-arginine vasopressin and prednisone.

Outcomes: During 6 months' follow-up, the patient's urine output was gradually reduced to normal level.

Lessons: This case indicated that hypopituitarism may be caused by an empty sella and be masked by adrenal insufficiency. Central diabetes insipidus may present after glucocorticoid therapy.

Abbreviations: ACTH = adrenocorticotropic hormone, AVP = arginine vasopressin, CDI = central diabetes insipidus, CRH = corticotropin releasing hormone, CSF = cerebrospinal fluid, DDAVP = 1-desamino-8-D-arginine vasopressin, GBS = Guillain–Barré syndrome, GC = glucocorticoid, GFR = glomerular filtration rate, SG = specific gravity.

Keywords: central diabetes insipidus, glucocorticoid, empty sella, Guillain–Barré syndrome

1. Introduction

Empty sella is one of the causes of hypopituitarism, and refers to an intrasellar herniation of the subarachnoid space through a congenital defect in the diaphragm sellae or pituitary involution.[1] Central diabetes insipidus may be masked by adrenal insufficiency and uncovered by subsequent steroid therapy, due

to involvement of arginine vasopressin (AVP)-dependent and AVP-independent mechanisms.[2] Here, we report a rare case of a patient with empty sella who developed central diabetes insipidus following glucocorticoid (GC) administration.

2. Case report

A 59-year-old woman presented to the Neurology Department in July 2019 with a history of numbness of the face and persistent eyelid heaviness for 10 days. Physical examination revealed an attenuated tendon reflex, negative pyramidal sign, and progressively worsening symmetrical weakness of the extremities. Her family and past histories were unremarkable. Magnetic resonance imaging of the brain showed an empty sella (Fig. 1) and electrophysiologic evidence of neurogenic injury in the extremities was also discovered. Hormone tests demonstrated decreased levels of adrenocorticotropic hormone (ACTH), serum free triiodothyronine, and free thyroxine, thus indicating hypopituitarism. Cerebrospinal fluid (CSF) examination revealed no abnormal findings. According to the diagnostic criteria for Guillain-Barré syndrome (GBS) proposed by the National Institute of Neurological Disorders and Stroke in 1978,[3,4] the symptoms of progressively worsening symmetrical weakness of the extremities along with a reduced tendon reflex in this patient were consistent with a diagnosis of GBS. According to a study by Asbury et al,[3] unremarkable CSF findings were not an exclusion criteria, since CSF examination in some patients did not reveal typical albuminocytologic dissociation within 1 to 10 weeks from
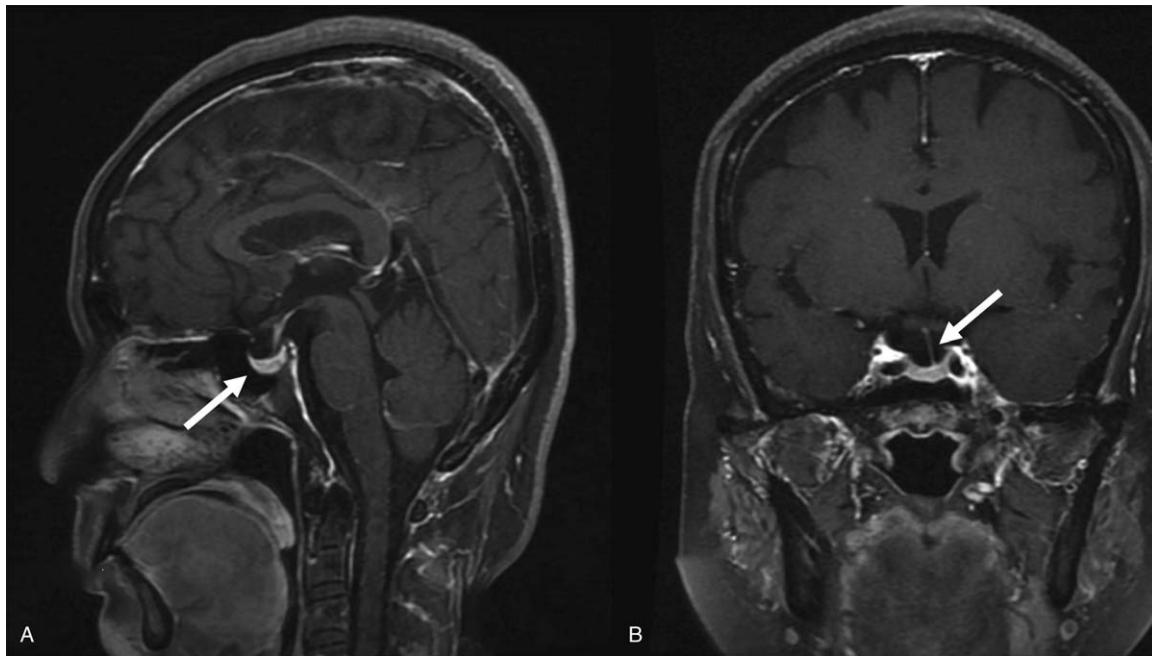
Figure 1. Magnetic resonance images. (A) T1-weighted image in sagittal section view shows that the pituitary gland is pressed downwards, and the thickness is about 0.4 cm (white arrow). (B) T1-weighted image in coronal section view shows that the pituitary stalk is shifted to the left (white arrow).

the onset of the symptoms. Once the diagnosis was confirmed, the patient received intravenous immunoglobulin (20g × 5 days), methylprednisolone (1000mg × 5 days and then 500mg × 5 days), and dosage-tapered oral prednisone. Her 24-hour urine output increased (4000–10000ml/day) after 20 days, and urinalysis showed low specific gravity (SG) of the urine (1.005) along with normal renal function. Subsequently, a high dosage of 1-desamino-8-D-arginine vasopressin (DDAVP) was administered which decreased the 24-hour urine output. In order to identify the etiology, she underwent an 8-hour fluid deprivation-vasopressin test (Table 1). During the test, symptoms of hypovolemia were observed; however, there was little increase in the urinary osmotic pressure and the urine SG remained below 1.010, suggesting a deficiency of AVP. On administration of 5 U of exogenous AVP, the urinary SG increased rapidly with doubling of the urine osmolality, and the ratio of urinary osmotic pressure to plasma osmotic pressure was more than 1.0, indicating that the patient responded appropriately to AVP. Thus, these findings supported a diagnosis of central diabetes insipidus (CDI). Although an increase in the serum sodium is a feature of CDI, it may be normal at the time of clinical diagnosis.[5] Consequently, the patient was prescribed daily DDAVP and prednisone. After six months, her urine output reduced to normal and the weakness of the extremities disappeared.

3. Discussion

CDI is characterized by a failure to maximally concentrate the urine along with a deficiency of AVP.[6] Occasionally, it may be masked by adrenal insufficiency caused by hypopituitarism and uncovered by corticosteroid therapy. The phenomenon of polyuria due to CDI masked by a GC deficiency has been described in other case reports.[2,7–22] The reported patients had hypopituitarism attributable to different diseases and did not manifest polyuria in the early stage; however, the typical manifestations of CDI appeared after the administration of GCs (Table 2).

The mechanisms of CDI and hypopituitarism are interconnected. It is difficult to identify CDI before starting GC therapy in patients with hypopituitarism because they do not manifest the characteristic symptoms of CDI. In the present case, hypopituitarism was caused by an empty sella. Empty sella compresses the pituitary and causes pituitary hormone deficiency in 8% to 60% of the patients,[23] particularly leading to a defective anterior pituitary function.[24] There are also a few case reports of posterior empty sella in children presenting with CDI, and in these cases the symptoms may be seen in the early years. Nevertheless, the pathogenic mechanisms remain unclear.[25]

AVP, also known as antidiuretic hormone, is synthesized by both the supraoptic and paraventricular nuclei in the hypothalamus. AVP is transported within secretory granules through the

Table 1

Results of an 8-hour fluid deprivation-vasopressin test.

	Urine Output	Urine Osmotic Pressure	Plasma Osmotic Pressure	Urine Specific Gravity
Fluid deprivation test	about 250ml/h	239 mOsm/kgH$_2$O	301 mOsm/kgH$_2$O	1.007
Vasopressin test	–	486 mOsm/kgH$_2$O	292 mOsm/kgH$_2$O	1.014

Table 2

A summary of previously published studies of CDI followed by GC therapy in patients with hypopituitarism.

References	Sex/Age, yr	Causes of Hypopituitarism	Reasons for Administrating GC	Dosage of GC	Duration of GC therapy before CDI
Tamasawa et al[5]	M/34	Acromegaly (a functioning pituitary tumor)	Secondary adrenocortical failure	GC 1200 mg/day, followed by a gradually decreased dosage	5 days
Ohta et al[6]	M/37	Malignant lymphoma	Hypopituitarism	Dexamethasone 0.5 mg/day	Immediately
Endo et al[7]	M/68	Acute myeloid leukaemia with trilineage myelodysplasia	Neoplastic fever	Methylprednisolone 40mg/day	3 days
Toftegaard and Knudsen[8]	F/15	Primitive neuroectodermal tumor	After induction of anaesthesia	Dexamethasone 4 mg	Immediately
Tien et al[9]	M/18	Intracranial germinoma	Adrenal crisis	Hydrocortisone and then cortisone acetate subsequently (dosage NA)	NA
Chin et al[10]	F/71	Lung carcinoma with cerebral metastases	Bronchospasm and perilesional edemas surrounding the cerebral metastases	Hydrocortisone 100 mg /8h and then dexamethasone subsequently	NA
Fujiwara et al[11]	M/38	Idiopathic giant cell granulomatous hypophysitis	Hypothalamic hypocortisolism	Dexamethasone 0.5mg/day	Immediately
Iida et al[12]	M/52	Lymphocytic hypophysitis	Hypopituitarism	Hydrocortisone 15 mg/day	5 days
Ogawa et al[13]	M/81	Lymphocytic hypophysitis	Erythroderma	Prednisolone 20mg/day	NA
Huang et al[14]	M/72	Lymphocytic hypophysitis	Adrenal insufficiency	NA	4 days
Arai et al[15]	F/37	Lymphocytic panhypophysitis	Hypopituitarism	Hydrocortisone 10 mg/day	5 days
Sasaki et al[16]	M/56	IgG4-related infundibulohypophysitis	Lowered the serum IgG4 level	Prednisolone 40 mg/day	14 days
Yoshioka et al[17]	M/28	Sarcoidosis	Hypopituitarism	Hydrocortisone 20 mg/day	NA
Non et al[18]	F/45	Neurosarcoidosis	Secondary adrenal insufficiency	Hydrocortisone 100 mg /8h	3 days
Yoshioka et al[19]	M/50	Rathke's cleft cyst	Correcting hyponatremia	Hydrocortisone from 5 mg to 20 mg over 4 days	10 days
Asakawa et al[20]	F/73	Rathke's cleft cyst	Adrenal insufficiency	Hydrocortisone 10 mg/day	NA
Asano et al[21]	F/73	Rathke's cleft cyst	Anterior pituitary hormones insufficiency	Hydrocortisone 15 mg/day	4 days
Present case	F/59	Empty sella	Guillain–Barré syndrome	Methylprednisolone 1000 mg/day × 5 days, 500 mg/day × 5 days and dosage-tapered oral prednisone subsequently	20 days

F = female, GC = glucocorticoid, M = male, NA = not available.

supraoptic-hypophyseal tract to the posterior pituitary gland, where the granules are stored and secreted on osmotic stimulation.[26] The mechanisms of GC deficiency that impair renal water excretion are both AVP-dependent and AVP-independent. First, cortisol induces relative resistance of the V2 receptor to AVP, which decreases the translocation of type 2 aquaporins for water reabsorption. Thus, in case of GC deficiency, the effects of AVP are amplified.[27] Second, corticotrophin-releasing hormone (CRH) neurons in the para-ventricular nucleus stimulate the release of ACTH and AVP. Additionally, CRH is upregulated in states of GC deficiency and, thus, causes release of AVP.[2] Third, hypocortisolism results in renal sodium loss and volume depletion, which are potent stimulators for appropriately increasing the release of AVP. Lastly, GC deficiency also leads to a decrease in the stroke volume and cardiac output, resulting in non-osmotic stimulation of AVP secretion.[28] Green et al found that adrenalectomised rats with hereditary diabetes insipidus showed decreased free water excretion, which was later rectified with GC replacement.[29] This indicates mechanisms that are independent of AVP. GC dilates both afferent and efferent resistances resulting in an increase in the glomerular filtration rate (GFR); consequently, the rate of water flow into the nephron increases.[30] Furthermore, an increase in the water permeability of the distal tubules was found

in adrenalectomized Brattleboro rats, suggesting a direct action of GC on renal tubules.[31] Hayamizu et al reported that GC can stimulate atrial natriuretic peptide secretion to enhance the diuretic effects.[32] As such, ameliorating GC deficiency can lead to a reversal of these compensatory mechanisms, and diabetes insipidus ensues (summarized in Fig. 2). Moreover, the timing of GC deficiency may play a role in the mechanisms of CDI. Linas et al studied the role of AVP in defective water excretion in rats with diabetes insipidus and demonstrated that an AVP-dependent impairment in water excretion after 24 hours of GC deficiency played a role. Additionally, an AVP-independent factor was observed after 2 weeks of GC deficiency.[33]

We further hypothesized that the dosage and duration of GC administration played a role in the development of CDI. Unfortunately, since the data concerning dosage and duration of GC in some previous studies were not available (summarized in Table 2), the statistical results may be biased. We can conclude that either the maintenance dosage or stress dosage of GC can unmask CDI. However, no cases have been reported in which CDI was induced only when greater than the maintenance dosage of GCs was given.

In conclusion, empty sella is one of the causes of hypopituitarism, and GC replacement in patients with hypopituitarism can unveil CDI. Our report is the first to describe the two mechanisms
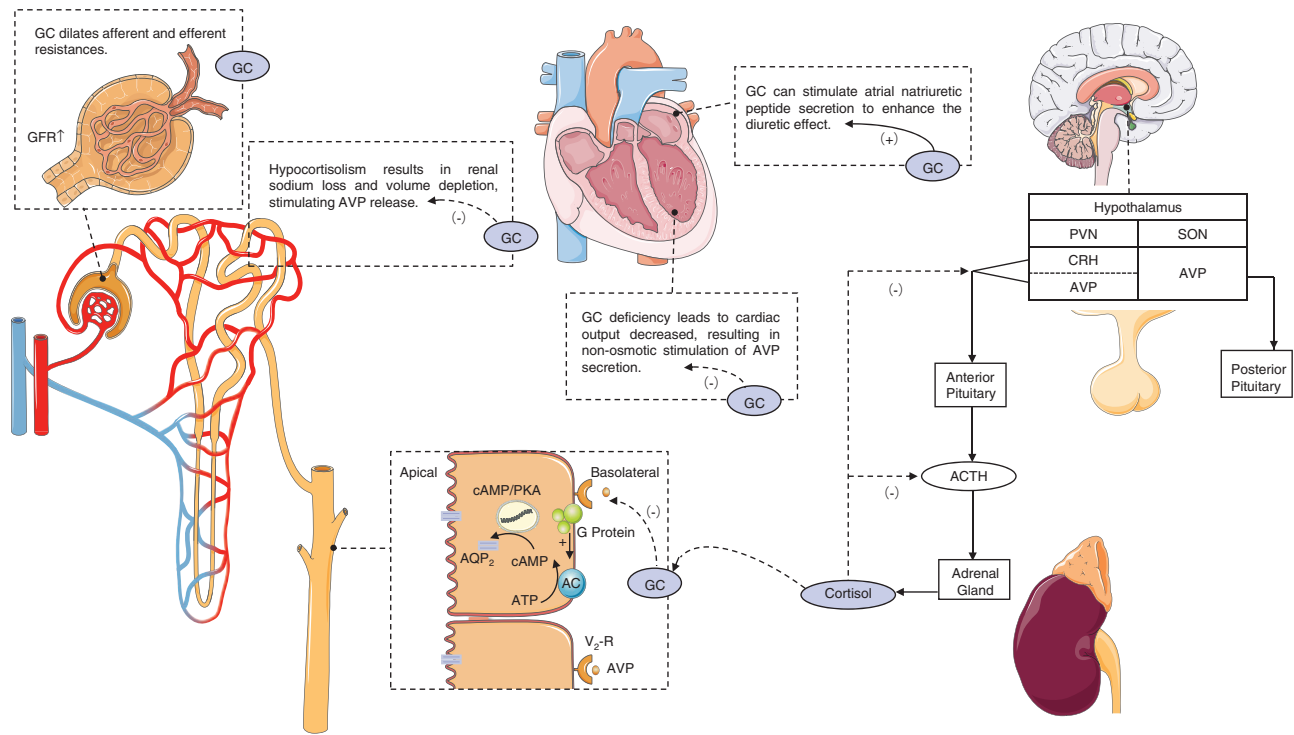
Figure 2. Schematic figure demonstrating the reasons for central diabetes insipidus after glucocorticoid administration.

mentioned above seen together in a patient with an empty sella. GC deficiency may lead to impaired water excretion, which is mediated by AVP-dependent and AVP-independent mechanisms. Therefore, attention should be paid when hypopituitarism is encountered in the clinic as CDI may present on administration of GC.

Author contributions

Conceptualization: Lei-Yi Yang
Data curation: Sang Lin
Methodology: Geng Yin
Supervision: Qi-Bing Xie
Writing – original draft: Lei-Yi Yang
Writing – review & editing: Geng Yin

References

[1] Chiloiro S, Giampietro A, Bianchi A, et al. Diagnosis of endocrine disease: Primary empty sella: a comprehensive review. Eur J Endocrinol 2017;177:R275–85.

[2] Chin HX, Quek TP, Leow MK. Central diabetes insipidus unmasked by corticosteroid therapy for cerebral metastases: beware the case with pituitary involvement and hypopituitarism. J R Coll Physicians Edinb 2017;47:247–9.

[3] Asbury AK, Cornblath DR. Assessment of current diagnostic criteria for Guillain-Barré syndrome. Ann Neurol 1990;27Suppl:S21–4.

[4] Leonhard SE, Mandarakas MR, Gondim FAA, et al. Diagnosis and management of Guillain-Barré syndrome in ten steps. Nat Rev Neurol 2019;15:671–83.

[5] Garrahy A, Moran C, Thompson CJ. Diagnosis and management of central diabetes insipidus in adults. Clin Endocrinol (Oxf) 2019;90:23–30.

[6] Babey M, Kopp P, Robertson GL. Familial forms of diabetes insipidus: clinical and molecular characteristics. Nat Rev Endocrinol 2011;7:701–14.

[7] Tamasawa N, Kurahashi K, Baba T, et al. Spontaneous remission of acromegaly after pituitary apoplexy following head trauma. J Endocrinol Invest 1988;11:429–32.

[8] Ohta M, Kimura T, Ota K, et al. Glucocorticoid-induced central diabetes insipidus in a case of malignant lymphoma. Tohoku J Exp Med 1991;163:245–54.

[9] Endo T, Tamai Y, Takami H, et al. Acute myeloid leukaemia with trilineage myelodysplasia complicated by masked diabetes insipidus. Clin Lab Haematol 2000;22:233–5.

[10] Toftegaard M, Knudsen F. Massive vasopressin-resistant polyuria induced by dexamethasone. Intensive Care Med 1995;21:238–40.

[11] Tien KJ, Wang SY, Yang CY, et al. Hypernatremia-associated coma caused by glucocorticoid replacement for adrenal crisis in an unrecognized central diabetes insipidus patient. Kaohsiung J Med Sci 2013;29:519–20.

[12] Fujiwara T, Ota K, Kakudo N, et al. Idiopathic giant cell granulomatous hypophysitis with hypopituitarism, right abducens nerve paresis and masked diabetes insipidus. Intern Med (Tokyo, Japan) 2001;40:915–9.

[13] Iida M, Takamoto S, Masuo M, et al. Transient lymphocytic panhypophysitis associated with SIADH leading to diabetes insipidus after glucocorticoid replacement. Intern Med 2003;42:991–5.

[14] Ogawa N, Takamatsu T, Miyake T, et al. Masked diabetes insipidus manifested by administration of adrenocortical steroid hormone for erythroderma. J Jap Soc Intern Med 2004;93:2639–42.

[15] Huang C-H, Chou K-J, Lee P-T, et al. A case of lymphocytic hypophysitis with masked diabetes insipidus unveiled by glucocorticoid replacement. Am J Kidney Dis 2005;45:197–200.

[16] Arai Y, Nabe K, Ikeda H, et al. A case of lymphocytic panhypophysitis (LPH) during pregnancy. Endocrine 2007;32:117–21.

[17] Sasaki Yatabe M, Watanabe K, Hayashi Y, et al. Overlap of post-obstructive diuresis and unmasked diabetes insipidus in a case of IgG4-related retroperitoneal fibrosis and tuberoinfundibular hypophysitis: a case report and review of the literature. Intern Med (Tokyo, Japan) 2017;56:47–53.

[18] Yoshioka K, Tanaka N, Yamagami K, et al. Arginine vasopressin-independent mechanism of impaired water excretion in a patient with

sarcoidosis complicated by central diabetes insipidus and glucocorticoid deficiency. Case Rep Med 2011;2011:145856.

[19] Non L, Brito D, Anastasopoulou C. Neurosarcoidosis-associated central diabetes insipidus masked by adrenal insufficiency. BMJ Case Rep 2015;2015.

[20] Yoshioka K, Minami M, Fujimoto S, et al. Incremental increases in glucocorticoid doses may reduce the risk of osmotic demyelination syndrome in a patient with hyponatremia due to central adrenal insufficiency. Intern Med 2012;51:1069–72.

[21] Asakawa M, Chin R, Niitsu Y, et al. A case of Rathke's cleft cyst associated with transient central adrenal insufficiency and masked diabetes insipidus. Case Rep Endocrinol 2014;2014:1–6.

[22] Asano T, Yamada H, Yoshida M, et al. Hypothalamic type of hypopituitarism and central diabetes insipidus probably linked to Rathke's cleft cyst. Int Med (Tokyo, Japan) 2015;54:935–40.

[23] Zuhur SS, Kuzu I, Ozturk FY, et al. Anterior pituitary hormone deficiency in subjects with total and partial primary empty sella: do all cases need endocrinological evaluation? Turk Neurosurg 2014;24:374–9.

[24] Ascoli P, Cavagnini F. Hypopituitarism. Pituitary 2006;9:335–42.

[25] Lambert M, Gaillard RC, Vallotton MB, et al. Empty sella syndrome associated with diabetes insipidus: case report and review of the literature. J Endocrinol Invest 1989;12:433–7.

[26] Huang CH, Chou KJ, Lee PT, et al. A case of lymphocytic hypophysitis with masked diabetes insipidus unveiled by glucocorticoid replacement. Am J Kidney Dis 2005;45:197–200.

[27] Ishikawa S, Saito T, Fukagawa A, et al. Close association of urinary excretion of aquaporin-2 with appropriate and inappropriate arginine vasopressin-dependent antidiuresis in hyponatremia in elderly subjects. J Clin Endocrinol Metab 2001;86:1665–71.

[28] Schrier RW, Berl T, Anderson RJ. Osmotic and nonosmotic control of vasopressin release. Am J Physiol 1979;236:F321–32.

[29] Green HH, Harrington AR, Valtin H. On the role of antidiuretic hormone in the inhibition of acute water diuresis in adrenal insufficiency and the effects of gluco- and mineralocorticoids in reversing the inhibition. J Clin Invest 1970;49:1724–36.

[30] Baylis C, Handa RK, Sorkin M. Glucocorticoids and control of glomerular filtration rate. Semin Nephrol 1990;10:320–9.

[31] Hirsch DJ, Hirtle RW. Effect of adrenalectomy on distal tubule water permeability of the Brattleboro rat. Can J Physiol Pharmacol 1986;64:1170–6.

[32] Hayamizu S, Kanda K, Ohmori S, et al. Glucocorticoids potentiate the action of atrial natriuretic polypeptide in adrenalectomized rats. Endocrinology 1994;135:2459–64.

[33] Linas SL, Berl T, Robertson GL, et al. Role of vasopressin in the impaired water excretion of glucocorticoid deficiency. Kidney Int 1980;18:58–67.