INVITED REVIEW ARTICLE

Nagoya J. Med. Sci. **78**. 349 ~ 357, 2016
doi:10.18999/nagjms.78.4.349

Central diabetes insipidus

Hiroshi Arima, Yoshinori Azuma, Yoshiaki Morishita and Daisuke Hagiwara

Department of Endocrinology and Diabetes, Nagoya University Graduate School of Medicine, Nagoya, Japan

ABSTRACT

Central diabetes insipidus (CDI), characterized by polyuria and polydipsia, is caused by deficiency of arginine vasopressin (AVP), an antidiuretic hormone which acts on V2 receptors in kidney to promote reabsorption of free water. CDI is classified into three subtypes; idiopathic, secondary and familial. A previous study suggests that infundibulo-neurohypophysitis might be an underlying cause of idiopathic CDI. Among secondary CDI, the tumors in the central nervous system such as craniopharyngioma and germ cell tumors are the most frequent causes. Familial CDI is inherited mostly in an autosomal dominant mode, and the number of causal mutations in the AVP gene locus reported so far exceeds 80. CDI is treated with desmopressin, an analogue of vasopressin, and the tablet is preferred to the nasal form because it is easier to administer. It is also shown that the oral disintegrating tablet formula increases QOL and decreases the incidence of hyponatremia in CDI patients. In some CDI patients, the osmoreceptors in the hypothalamus do not function and patients do not sense thirst. These adipsic CDI patients are treated with desmopressin and adjusting the amount of daily water intake based on body weight measurement; but controlling the water balance is extremely difficult, and morbidity and mortality are shown to be high in these patients.

Key Words: arginine vasopressin, polyuria, polydipsia, adipsia, desmopressin

INTRODUCTION

Arginine vasopressin (AVP) is an antidiuretic hormone which is synthesized in the magnocellular neurons of the supraoptic (SON) and paraventricular nuclei (PVN) in the hypothalamus. AVP is transported to the posterior pituitary through the axons, released into the systemic circulation, and plays a pivotal role in water balance by promoting reabsorption of free water through the V2 receptor in kidney. The release and synthesis of AVP are mainly regulated by plasma osmolality (or serum Na) in physiological conditions. The osmoregulation of the AVP neuron system is so precise that only 1–2% increases in serum Na levels significantly stimulate its release as well as the transcription of AVP gene in the SON and PVN.[1)] Serum Na levels are thus maintained around 140 mEq/L, the threshold level for AVP release.

The deficiency of AVP leads to hypotonic polyuria, a disorder called neurohypophysial or central diabetes insipidus (hereafter, we use CDI as the abbreviation). Water intake also increases in order to maintain water balance in patients with CDI, as long as their thirst sensation remains

Received: September 23, 2016; accepted: October 19, 2016

Corresponding author: Hiroshi Arima, MD, PhD

Department of Endocrinology and Diabetes, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho,Showa-ku, Nagoya 466-8550, Japan

Tel: +81-52-744-2142, Fax: +81-52-744-2212, E-mail: arima105@med.nagoya-u.ac.jp

intact.

In this review, the etiology, diagnosis, pathophysiology, treatment and prognosis of CDI are described.

ETIOLOGY

Most causes of CDI are acquired, and its prevalence of CDI is reportedly 1:25,000.[2] Table 1 indicates the etiology of 165 Japanese patients with CDI we reported previously.[3] The most frequent cause of CDI is the tumors in the central nervous system (CNS) including craniopharyngioma and germ cell tumors, which could damage the AVP neuron system. CDI is also caused by inflammatory diseases such as lymphocytic infundibulo-neurohypophysitis (LINH) and IgG4-related disease. CDI often manifests after pituitary surgery. In this case, polyuria appears in the first 2 days after surgery and sometimes resolves spontaneously, although it could persist permanently if AVP neurons are damaged substantially.[4] Idiopathic CDI, 13% of total CDI in Table 1, is diagnosed when the causes of CDI are unclear. It is of note that LINH has been sometimes regarded as idiopathic CDI in some studies. This is probably because LINH is reported to be a possible underlying cause of idiopathic CDI.[5] The rates of idiopathic CDI among total CDI thus vary among studies. Although rare, CDI also occurs genetically. This subclass of CDI is called familial neurohypophysial diabetes insipidus (FNDI), which is inherited mostly in an autosomal dominant mode.[6] More than 80 mutations that cause FNDI have been reported so far,[7-27] and they are mainly located in the coding region of neurophysin II, a carrier protein of AVP, in the gene locus (Table 2).

Table 1 Etiology of patients with CDI

Causes	No. of Patients (%)
idiopathic	22 (13)
germ cell tumor of CNS	38 (23)
craniopharyngioma	32 (19)
neurosurgery	21 (13)
inflammation	15 (9)
metastasis to pituitary	10 (6)
Rathoke's cleft cyst	6 (4)
empty sella syndrome	4 (2)
pituitary adenoma	4 (2)
cardiac arrest	4 (2)
malformation	2 (1)
other	7 (4)
total	165 (100)

CNS, central nervous system. "Inflammation" includes lymphocytic infundibulo-neurohypophysitis and IgG4 related diseases.

Table 2 Mutations causing FNDI

	Nucleotide Change	Exon	Amino Acid Change	Peptide	Japanese	Reference
1	c. -33_4del	1	p. M1_T4del *	SP1_4		7
2	c. -3A>C	1	p. M1_T4del *	SP1_4		8
3	c. 1A>G	1	p. M1_T4del *	SP1_4		9
4	c. 2delT	1	p. M1_T4del *	SP1_4		10
5	c. 3delG	1	p. M1_T4del *	SP1_4		9
6	c. 3G>A	1	p. M1_T4del *	SP1_4		9
7	c. 50C>T	1	p. S17F	SP17		9
8	c. 50C>A	1	p. S17Y	SP17		10
9	c. 52_54delTCC	1	p. S18del	SP18		11
10	c. 55G>A	1	p. A19T	SP19	✔	9
11	c. 56C>T	1	p. A19V	SP19	✔	9
12	c. 61T>C	1	p. Y21H	AVP2		9
13	c. 62A>C	1	p. Y21S	AVP2	✔	12
14	c. 64_66delTTC	1	p. F22del	AVP3		9
15	c. 77C>T †	1	p. P26L	AVP7		9
16	c. 123C>G	2	p. C41W	NP10		13
17	c. 127C>G	2	p. P43A	NP12		10
18	c. 132C>A	2	p. C44W	NP13		14
19	c. 133G>C	2	p. G45R	NP14		9
20	c. 133G>T	2	p. G45C	NP14		15
21	c. 143G>T	2	p. G48V	NP17		9
22	c. 151C>T	2	p. R51C	NP20		9
23	huge deletion (AVP-OT) † ‡	2_3	p. R51fs	NP20		16
24	c. 154T>C	2	p. C52R	NP21		9
25	c. 160G>C	2	p. G54R	NP23		9
26	c. 160G>A	2	p. G54R	NP23		9
27	c. 161G>T	2	p. G54V	NP23		9
28	c. 161G>A	2	p. G54E	NP23		17
29	c. 164C>T	2	p. P55L	NP24		9
30	c. 164C>A	2	p. P55H	NP24		18
31	c. 173G>T	2	p. C58F	NP27		9
32	c. 175T>C	2	p. C59R	NP28		9
33	c. 176G>A	2	p. C59Y	NP28		9
34	c. 177_179delCGC	2	p. C59delA60W	NP28_29		9
35	c. 188T>C	2	p. L63P	NP32		19
36	c. 193T>A	2	p. C65S	NP34		20
37	c. 194G>T	2	p. C65F	NP34		21

38	c. 200T>C	2	p. V67A	NP36		9
39	c. 207_209delGGC	2	p. T69delA70T	NP38_39		22
40	c. 230_232delAGG	2	p. E78del	NP47	✔	29
41	c. 232G>A	2	p. E78K	NP47	✔	9
42	c. 232_234delGAG	2	p. E78del	NP47		23
43	c. 233A>G	2	p. E78G	NP47		9
44	c. 242T>C	2	p. L81P	NP50		9
45	c. 251C>T	2	p. P84L	NP53		24
46	c. 260C>T	2	p. S87F	NP56		9
47	c. 260C>A	2	p. S87Y	NP56		21
48	c. 262G>A	2	p. G88S	NP57	✔	9
49	c. 262G>C	2	p. G88R	NP57		9
50	c. 262G>T	2	p. G88V	NP57		25
51	c. 274T>A	2	p. C92S	NP61		21
52	c. 275G>C	2	p. C92S	NP61		9
53	c. 275G>A	2	p. C92Y	NP61		9
54	c. 276C>A	2	p. C92X	NP61		9
55	c. 276C>G	2	p. C92W	NP61		13
56	c. 277G>T	2	p. G93W	NP62	✔	9
57	c. 286G>T	2	p. G96C	NP65		9
58	c. 287G>T	2	p. G96V	NP65	✔	9, 26
59	c. 287G>A	2	p. G96D	NP65		9
60	c. 289C>T	2	p. R97C	NP66		9
61	c. 290G>C	2	p. R97P	NP66		9
62	c. 292T>G	2	p. C98G	NP67		9
63	c. 292T>A	2	p. C98S	NP67		9
64	c. 293_294GC>CT	2	p. C98S	NP67		9
65	c. 294C>A	2	p. C98X	NP67	✔	9
66	c. 295G>C	2	p. A99P	NP68		9
67	c. 298G>C	2	p. A100P	NP69		18
68	c. 310T>G	2	p. C104G	NP73		9
69	c. 311G>T	2	p. C104F	NP73		9
70	c. 313T>C	2	p. C105R	NP74		9
71	c. 314G>A	2	p. C105Y	NP74	✔	9
72	c. 314G>C	2	p. C105S	NP74		14
73	c. 322G>T	2	p. ?/E108X §	NP77		27
74	c. 322+1delG	Intron 2	p. E108fs ‖	NP77		9
75	c. 329G>A	3	p. C110Y	NP79		10
76	c. 330C>A	3	p. C110X	NP79		9

77	c. 337G>T	3	p. E113X	NP82	9
78	c. 342_343CG>GT	3	p. E115X	NP84	9
79	c. 343G>T	3	p. E115X	NP84	9
80	c. 346T>G	3	p. C116G	NP85	9
81	c. 346T>C	3	p. C116R	NP85	9
82	c. 348C>G	3	p. C116W	NP85	9
83	c. 352G>T	3	p. E118X	NP87	9

*, Mutations affecting the initiator ATG are predicted to result in translation initiation at an alternative downstream ATG (codon 5), causing a deletion of the first 4 amino acid residues. †, Mutations associated with autosomal-recessive inheritance of FNDI. ‡, 10,396 base pair deletion involving the majority of the AVP gene as well as its regulatory sequences in the intergenic region between the AVP and the oxytocin gene. §, This mutation site is the final base of exon 2. If splicing of intron 2 is affected, the entire (in-frame) intron is inserted into the mRNA leading to an insertion of 58 amino acids into the AVP protein (p.?). If splicing is not affected, this mutation causes to change codon 108 to a premature termination codon (p. E108X). ‖, This mutation is predicted to cause retention of intron 2 during splicing. This will cause a frameshift from codon 108. ✔, Mutations reported in Japan.

DIAGNOSIS

CDI is characterized by hypotonic polyuria accompanied by polydipsia, as long as the thirst sensation is intact. Daily urine volumes exceed 3 liters in most cases. Daily water intake, which could be estimated by asking the subjects how many cups of water they take every day, is almost equal to daily urine volumes. If daily water intake seems to be less than 2 liters, the subjects are unlikely to have CDI. It is also important to ask the subjects how often they urinate and drink water at night, because only daytime polydipsia and polyuria suggest psychologic polydipsia rather than CDI. Information intake from the subjects is thus useful for the screening of CDI.

Final diagnosis of CDI is made by confirming that AVP release is hampered in response to increases in plasma osmolality or serum Na levels. For this reason, either injection of hypertonic saline or the water restriction test is performed. In the hypertonic saline examination, 5% NaCl at the rate of 0.05 ml/kg body weight (BW) /min is injected intravenously for 2 hours, and the serum Na and plasma AVP levels are measured before and every 30 minutes after starting the injection. The serum Na levels usually increase approximately by 10 mEq/L, and plasma AVP levels are increased in proportion to the increases in serum Na levels in normal subjects. In contrast, increases in AVP release are blunted or even abolished in patients with CDI (Figure 1). To perform this examination, it is essential to use a sensitive assay for plasma AVP.

In case no sensitive assays for plasma AVP are available, the water restriction test is performed. The subjects are deprived of water and food for about 6 hours or until their BW is decreased by 3%. In normal subjects, urine osmolality increases to levels more than 300 mOsm/kg. In contrast, urine osmolality remains to be below 300 mOsm/kg during the test in CDI patients. Injection of pitressin (vasopressin) at the end of the test could differentiate nephrogenic DI from CDI: urine osmolality increases in response to pitressin in patients with CDI but not in those with nephrogenic DI.

Pituitary MRI is also useful for the diagnosis of CDI. The high intensity in posterior pituitary in T1-weighted MRI images, which reportedly reflects the stock of pituitary AVP,[28] is observed in normal but not CDI subjects. However, as the AVP stock in the posterior pituitary could be

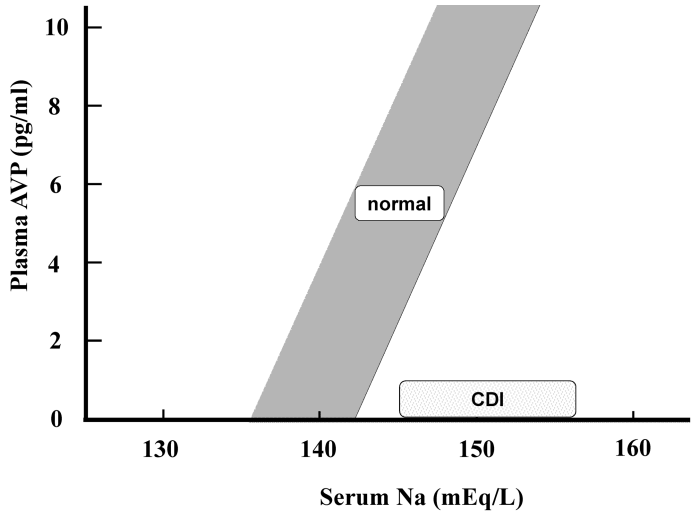

Fig. 1 Plasma AVP and serum Na levels in response to hypertonic saline injection. In normal subjects, plasma AVP levels increase in proportion to increases in serum Na levels. In CDI patients, the response of AVP is abolished. Note that serum Na levels are around 140 mEq/L in normal subjects but around 145 mEq/L in CDI patients before hypertonic saline injection.

decreased under chronically dehydrated conditions,[29] the lack of the high signal in T1-weighted pituitary MRI images is not specific to CDI. Pituitary MRI is also useful for the differential diagnosis of primary and secondary CDI. In case there is no abnormality except for the lack of the high signal in T1-weighted images, the subjects are diagnosed as idiopathic CDI. However, the follow-up of the imaging is necessary, particularly in children, since some abnormalities such as tumors in the CNS may appear later on.

PATHOPHYSIOLOGY

Due to the lack of AVP action on V2 receptors in kidney, patients with CDI show hypotonic polyuria and polydipsia. The amount of daily urine volume as well as water intake could exceed 10 liters when AVP release is almost completely abolished. In this situation, patients must urinate and drink water almost every 1–2 hours. Normal subjects feel thirsty when serum Na levels exceed 145 mEq/L, while the threshold of serum Na levels for AVP release is around 140 mEq/L. This would explain why serum Na levels are always kept around 140 mEq/L in normal subjects whereas they are around 145 mEq/L in CDI patients, in whom the action of AVP is lacking. Thus, CDI patients consume water until their thirst sensation ceases, but they will soon feel thirsty because serum Na levels exceed 145 mEq/L again due to the lack of AVP action. If the function of osmoreceptors in hypothalamus is also lost, the patients would not feel thirsty even if the serum Na levels exceed 145 mEq/L. In other words, they are adipsic and could show severe hypernatremia.

Patients with CDI sometimes have dysfunction of the anterior pituitary as well. If adrenal insufficiency exists, urine volumes could decrease in CDI patients. This is called “masked DI,” and substitution of adrenocortical hormones leads to increases in urine volume in patients with CDI accompanied by adrenal insufficiency. While several mechanisms have been suggested for

masked DI, one possibility is that AVP release, which is usually inhibited by adrenocortical hormones, is stimulated from the residual AVP neurons in CDI patients with adrenal insufficiency. However, it is still controversial whether or not glucocorticoid receptors are expressed in the AVP neurons.[30]

FNDI patients are born with normal water balance, but manifest progressive polyuria and polydipsia several months or years after birth.[31] The analyses of animal models for FNDI have demonstrated that accumulation of mutant AVP precursors in the endoplasmic reticulum (ER) causes ER stress and dysfunction of the neurons, which finally lead to loss of AVP neurons.[31-33] This is consistent with autopsy studies which showed that magnocellular neurons were lost in patients with FNDI.[34]

TREATMENT

Desmopressin, an analogue of AVP, is used for the treatment of CDI. The desmopressin formula is either intranasal liquid, intranasal spray, or tablets. In Japan, an oral disintegrating tablet (ODT)[35] was approved for the treatment of CDI in 2012, and the QOL of CDI patients has reportedly been improved by ODT.[36] Our study also showed that the incidence of hyponatremia in CDI patients treated with desmopressin is decreased after the switch from the nasal formula to ODT.[37] This is probably due to the fact that the absorption and efficacy of ODT are more stable than those of the nasal formula, making it easier to determine the required dose of desmopressin. Nevertheless, one should be aware that there is still a high incidence of hyponatremia in CDI patients treated with desmopressin,[37] and it is safe to start the treatment with a low dose of desmopressin.

The treatment of adipsic CDI patients is challenging. The recommended treatment is as below. The ideal BW for water balance should be determined based on the serum Na levels (BW is considered to be ideal when serum Na levels are within normal ranges), but this could vary over time and should be assessed periodically. The basal volume of water intake (for example, 1 liter/day) and the required dose of desmopressin (for example, 60 μg ODT desmopressin twice a day) to maintain the ideal BW should also be determined. However, one should recall that BW could substantially change from day to day in patients, and the scale of water intake must be set based on the BW changes. For example, if the BW is 58 kg in adipsic CDI patients whose ideal BW has been determined to be 60 kg, 2 kg water has been lost. In this situation, 2 liters of water should be consumed in addition to the basal volume (1 liter) of daily water intake; that would mean that patients must drink 3 liters of water on the day, but it could be difficult for adipsic patients to consume such a volume of water, given that they do not sense thirst.

PROGNOSIS

The prognosis of CDI due to tumors or inflammation depends on that of the primary diseases. On the other hand, the prognosis of idiopathic CDI patients is considered to be comparable to that of subjects without CDI, as long as the patients can drink water as necessary. However, the adipsic CDI patients are associated with significant morbidity,[38] and the incidence of serious infections requiring hospitalization and the risk of death have been shown to be higher in adipsic compared to non-adipsic CDI patients.[3]

CONCLUSION

The etiology has been clarified in most CDI patients. While most CDI patients are well treated with desmopressin, controlling water balance in adipsic CDI patients is still difficult.

CONFLICT OF INTEREST

H. Arima receives research funding from Kyowa Hakko Kirin Co., Ltd.

REFERENCES

1) Arima H, Kondo K, Kakiya S, Nagasaki H, Yokoi H, Yambe Y, *et al.* Rapid and sensitive vasopressin heteronuclear RNA responses to changes in plasma osmolality. *J Neuroendocrinol*, 1999; 11: 337–341.
2) Di Iorgi N, Napoli F, Allegri AE, Olivieri I, Bertelli E, Gallizia A, *et al.* Diabetes insipidus--diagnosis and management. *Horm Res Paediatr*, 2012; 77: 69–84.
3) Arima H, Wakabayashi T, Nagatani T, Fujii M, Hirakawa A, Murase T, *et al.* Adipsia increases risk of death in patients with central diabetes insipidus. *Endocr J*, 2014; 61: 143–149.
4) Hensen J, Henig A, Fahlbusch R, Meyer M, Boehnert M, Buchfelder M. Prevalence, predictors and patterns of postoperative polyuria and hyponatremia in the immediate course after transsphenoidal surgery for pituitary adenomas. *Clin Endocrinol (Oxf)*, 1999; 50: 431–439.
5) Imura H, Nakao K, Shimatsu A, Ogawa Y, Sando T, Fujisawa I, *et al.* Lymphocytic infundibuloneurohypophysitis as a cause of central diabetes insipidus. *N Engl J Med*, 1993; 329: 683–689.
6) Babey M, Kopp P, Robertson GL. Familial forms of diabetes insipidus: clinical and molecular characteristics. *Nat Rev Endocrinol*, 2011; 7: 701–714.
7) Lindenthal V, Mainberger A, Morris-Rosendahl DJ, Löning L, Mayer W, Müller HL. Dilatative uropathy as a manifestation of neurohypophyseal diabetes insipidus due to a novel mutation in the arginine vasopressin-neurophysin-II gene. *Klin Padiatr*, 2013; 225: 407–412.
8) Ilhan M, Tiryakioglu NO, Karaman O, Coskunpinar E, Yildiz RS, Turgut S, *et al.* A novel AVP gene mutation in a Turkish family with neurohypophyseal diabetes insipidus. *J Endocrinol Invest*, 2016; 39: 285–290.
9) Christensen JH, Rittig S. Familial neurohypophyseal diabetes insipidus--an update. *Semin Nephrol*, 2006; 26: 209–223.
10) Tian D, Cen J, Nie M, Gu F. Identification of five novel arginine vasopressin gene mutations in patients with familial neurohypophyseal diabetes insipidus. *Int J Mol Med*, 2016; 38: 1243–1249.
11) Perrotta S, Di Iorgi N, Ragione FD, Scianguetta S, Borriello A, Allegri AE, *et al.* Early-onset central diabetes insipidus is associated with de novo arginine vasopressin-neurophysin II or Wolfram syndrome 1 gene mutations. *Eur J Endocrinol*, 2015; 172: 461–472.
12) Kobayashi H, Fujisawa I, Ikeda K, Son C, Iwakura T, Yoshimoto A, *et al.* A novel heterozygous missense mutation in the vasopressin moiety is identified in a Japanese person with neurohypophyseal diabetes insipidus. *J Endocrinol Invest*, 2006; 29: 252–256.
13) Brachet C, Birk J, Christophe C, Tenoutasse S, Velkeniers B, Heinrichs C, *et al.* Growth retardation in untreated autosomal dominant familial neurohypophyseal diabetes insipidus caused by one recurring and two novel mutations in the vasopressin-neurophysin II gene. *Eur J Endocrinol*, 2011; 164: 179–187.
14) Chitturi S, Harris M, Thomsett MJ, Bowling F, McGown I, Cowley D, *et al.* Utility of AVP gene testing in familial neurohypophyseal diabetes insipidus. *Clin Endocrinol (Oxf)*, 2008; 69: 926–930.
15) Turkkahraman D, Saglar E, Karaduman T, Mergen H. AVP-NPII gene mutations and clinical characteristics of the patients with autosomal dominant familial central diabetes insipidus. *Pituitary*, 2015; 18: 898–904.
16) Christensen JH, Kvistgaard H, Knudsen J, Shaikh G, Tolmie J, Cooke S, *et al.* A novel deletion partly removing the AVP gene causes autosomal recessive inheritance of early-onset neurohypophyseal diabetes insipidus. *Clin Genet*, 2013; 83: 44–52.
17) Stephen MD, Fenwick RG, Brosnan PG. Polyuria and polydipsia in a young child: diagnostic considerations and identification of novel mutation causing familial neurohypophyseal diabetes insipidus. *Pituitary*, 2012; 15: S1–5.
18) Hrčková G, Jankó V, Kytnarová J, Čižmárová M, Tesařová M, Košťálová Ľ, *et al.* Two novel mutations

in seven Czech and Slovak kindreds with familial neurohypophyseal diabetes insipidus-benefit of genetic testing. *Eur J Pediatr*, 2016; 175: 1199–1207.
19) Birkegaard C, Christensen JH, Falorni A, Marzotti S, Minarelli V, Gregersen N, *et al.* A novel variation in the AVP gene resulting in familial neurohypophyseal diabetes insipidus in a large Italian kindred. *Pituitary*, 2013; 16: 152–157.
20) Luo Y, Wang B, Qiu Y, Zhang C, Jin C, Zhao Y, *et al.* Clinical and molecular analysis of a Chinese family with autosomal dominant neurohypophyseal diabetes insipidus associated with a novel missense mutation in the vasopressin-neurophysin II gene. *Endocrine*, 2012; 42: 208–213.
21) Paul DL. Novel human pathological mutations. *Hum Genet*, 2006; 118: 774–785.
22) Deniz F, Acar C, Saglar E, Erdem B, Karaduman T, Yonem A, *et al.* Identification of a novel deletion in AVP-NPII gene in a patient with central diabetes insipidus. *Ann Clin Lab Sci*, 2015; 45: 588–592.
23) Lee YW, Lee KW, Ryu JW, Mok JO, Ki CS, Park HK, *et al.* Mutation of Glu78 of the AVP-NPII gene impairs neurophysin as a carrier protein for arginine vasopressin in a family with neurohypophyseal diabetes insipidus. *Ann Clin Lab Sci*, 2008; 38: 12–14.
24) Jendle J, Christensen JH, Kvistgaard H, Gregersen N, Rittig S. Late-onset familial neurohypophyseal diabetes insipidus due to a novel mutation in the AVP gene. *Clin Endocrinol (Oxf)*, 2012; 77: 586–592.
25) Melo ME, Marui S, Brito VN, Mancini MC, Mendonca BB, Knoepfelmacher M. Autosomal dominant familial neurohypophyseal diabetes insipidus caused by a novel mutation in arginine-vasopressin gene in a Brazilian family. *Arq Bras Endocrinol Metabol*, 2008; 52: 1272–1276.
26) Kubota T, Yamamoto T, Ozono K, Shimotsuji T. Hyperintensity of posterior pituitary on MR T1WI in a boy with central diabetes insipidus caused by missense mutation of neurophysin II gene. *Endocr J*, 2001; 48: 459–463.
27) de Fost M, van Trotsenburg AS, van Santen HM, Endert E, van den Elzen C, Kamsteeg EJ, *et al.* Familial neurohypophyseal diabetes insipidus due to a novel mutation in the arginine vasopressin-neurophysin II gene. *Eur J Endocrinol*, 2011; 165: 161–165.
28) Kurokawa H, Fujisawa I, Nakao Y, Kimura H, Akagi K, Ikeda K, *et al.* Posterior lobe of the pituitary gland: correlation between signal intensity on T1-weighted MR images and vasopressin concentration. *Radiology*, 1998; 207: 79–83.
29) Arima H, Kondo K, Murase T, Yokoi H, Iwasaki Y, Saito H, *et al.* Regulation of vasopressin synthesis and release by area postrema in rats. *Endocrinology*, 1998; 139:1481–1486.
30) Berghorn KA, Knapp LT, Hoffman GE, Sherman TG. Induction of glucocorticoid receptor expression in hypothalamic magnocellular vasopressin neurons during chronic hypoosmolality. *Endocrinology*, 1995; 136: 804–807.
31) Arima H, Azuma Y, Morishita Y, Hayashi M, Hagiwara D. Formation of endoplasmic reticulum-associated compartment in vasopressin neurons: a mechanism by which endoplasmic reticulum stress is reduced. *Interdisciplinary Information Sciences*, 2015; 21: 173–180.
32) Hayashi M, Arima H, Ozaki N, Morishita Y, Hiroi M, Nagasaki H, *et al.* Progressive polyuria without vasopressin neuron loss in a mouse model for familial neurohypophysial diabetes insipidus. *Am J Physiol Regul Integr Comp Physiol*, 2009; 296: R1641–1649.
33) Hagiwara D, Arima H, Morishita Y, Wenjun L, Azuma Y, Ito Y, *et al.* Arginine vasopressin neuronal loss results from autophagy-associated cell death in a mouse model for familial neurohypophysial diabetes insipidus. *Cell Death Dis*, 2014; 5: e1148.
34) Green JR, Buchan GC, Alvord EC Jr, Swanson AG. Hereditary and idiopathic types of diabetes insipidus. *Brain*, 1967; 90: 707–714.
35) Arima H, Oiso Y, Juul KV, Nørgaard JP. Efficacy and safety of desmopressin orally disintegrating tablet in patients with central diabetes insipidus: results of a multicenter open-label dose-titration study. *Endocr J*, 2013; 60: 1085–1094.
36) Nozaki A, Ando T, Akazawa S, Satoh T, Sagara I, Horie I, *et al.* Quality of life in the patients with central diabetes insipidus assessed by Nagasaki Diabetes Insipidus Questionnaire. *Endocrine*, 2016; 51: 140–147.
37) Kataoka Y, Nishida S, Hirakawa A, Oiso Y, Arima H. Switch from intranasal to oral desmopressin decreased incidence of hyponatremia in patients with central diabetes insipidus. *Endocr J*, 2015; 62: 195–200.
38) Crowley RK, Sherlock M, Agha A, Smith D, Thompson CJ. Clinical insights into adipsic diabetes insipidus: a large case series. *Clin Endocrinol*, 2007; 66: 475–482.