

Effects of Aging on Vasopressin Production in a Kindred with Autosomal Dominant Neurohypophyseal Diabetes Insipidus Due to the $\Delta E47$ Neurophysin Mutation

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Postmortem examinations of the hypothalamus of patients with autosomal dominant neurohypophyseal diabetes insipidus (adNDI), which have been reported only on persons dying between the ages of 37–87 yr, reveal the presence of the arginine vasopressin (AVP)-producing parvocellular neurons but the absence of 95% of the expected AVP-producing magnocellular neurons. To determine whether the clinical course of adNDI is compatible with the hypothesis that the neuropathologic findings are attributable to a progressive loss of magnocellular neurons beginning in early life, we performed posterior pituitary magnetic resonance imaging and water deprivation tests, including plasma ACTH measurements, on 17 affected members of a kindred with the $\Delta E47$ neurophysin mutation whose ages ranged from 3 months to 54 yr. Nine adult nonaffected members (ages, 20–56 yr) underwent these tests as controls.

All six children undergoing magnetic resonance imaging demonstrated a posterior pituitary hyperintense signal

(PPHS). Eight of nine affected adults showed an absent or barely visible PPHS, whereas eight of nine age-matched nonaffected adults produced a normal size PPHS. During water deprivation tests, infants concentrated their urine normally, and a 3-month-old infant produced a high plasma AVP level of 15.7 pmol/liter. By school age, affected children were no longer able to concentrate their urine or prevent hypernatremia. Affected adults became dehydrated; their median plasma AVP level was less than 1.0 pmol/liter, but their median fasting plasma ACTH was 2-fold greater than the level of nonaffected adults (10.0 vs. 5.0 pmol/liter; $P = 0.008$).

These results suggest that adNDI is a progressive disease associated with chronic loss of the magnocellular neurons that supply AVP to the posterior pituitary but preservation of the parvocellular neurons that supply AVP and CRH to the median eminence and stimulate ACTH production during hypernatremia. (*J Clin Endocrinol Metab* 87: 870–876, 2002)

THE ARGININE VASOPRESSIN (AVP) gene, located on chromosome 20, encodes prepro-AVP (1–3). Prepro-AVP is translated in the hypothalamus on the ribosomes of the magnocellular and parvocellular neurons in the supraoptic nucleus (SON) and paraventricular nucleus (PVN). Prepro-AVP consists of its signal peptide, AVP, neurophysin II (NP), and copeptin domains. More than 30 mutations of the AVP gene leading to defects in the signal peptide, AVP and NP have been identified (4–27). All but one of the mutations are expressed clinically as autosomal dominant neurohypophyseal diabetes insipidus (adNDI) (25).

Postmortem neuropathologic examinations of patients with adNDI have been performed, including vasopressin immunohistochemical studies of the hypothalamus and pituitary gland (28–32). A marked reduction of AVP-containing magnocellular neurons was observed in the SON, an area normally occupied predominantly by these large neurosecretory cells. In the PVN, in which both AVP-containing magnocellular and parvocellular neurons are normally present, there was an even greater loss of the large neurons

but a relative preservation of the small neurosecretory cells. There was also a dramatic reduction of AVP in the posterior pituitary and in the neurosecretory axons projecting from the SON and PVN to the posterior pituitary (32).

We recently performed DNA sequence analysis of members of a large kindred in which postmortem examination of a middle-aged woman with adNDI in 1967 revealed the presence of less than 5% of the expected magnocellular neurosecretory cells in the SON and PVN (31). To determine whether the clinical laboratory and radiologic manifestation of adNDI over a wide age range are compatible with the hypothesis that the neuropathic findings are due to a progressive loss of magnocellular neurons beginning in early life, we performed posterior pituitary magnetic resonance imaging (MRI) and water deprivation tests including plasma ACTH measurements on affected and nonaffected members of the kindred, whose ages ranged from infancy to over 50 yr.

Subjects and Methods

Subjects

The neuropathologic findings and methods of study of the kindred member who died have been previously reported (31). The current studies were performed on 17 affected members (8 males and 9 females; mean age, 23 yr; range, 3 months to 54 yr) from four generations of an American kindred of English-Irish ancestry. Nine healthy nonaffected members (ages, 20–56 yr) of the kindred also participated in the project

Abbreviations: adNDI, Autosomal dominant neurohypophyseal diabetes insipidus; AVP, arginine vasopressin; MRI, magnetic resonance imaging or image; NP, neurophysin II; PPHS, posterior pituitary hyperintense signal; PVN, paraventricular nucleus; SON, supraoptic nucleus.

as adult controls. All studies performed were approved by the Children's Hospital and Regional Medical Center's Institutional Review Board. Water deprivation tests were performed during infancy; but, as required by the Institutional Review Board, MRI scans were not done during infancy because the procedure would have required sedation. The only controls for children were MRI brain scans selected from the Children's Hospital Radiology Department's files. The control brain scans had been performed on otherwise healthy, untreated children being evaluated for possible seizures. The children matched affected children in age and sex, and their scans, performed in the morning after an overnight fast, were reported as normal, including the presence of a posterior pituitary bright spot. Appropriate informed consents were obtained from adult subjects and from the parents of children participating in the study. The affected members or their parents completed a questionnaire form and were interviewed in person regarding the onset and clinical course of diabetes insipidus.

Nucleotide sequence analysis

Genomic DNA was extracted from whole blood using a DNA extraction kit (Puregene, Gentra Systems, Minneapolis, MN). As previously described (4), the AVP gene was amplified by PCR, and the PCR-amplified DNA was directly sequenced using a dRhodamine terminator cycle sequence kit and an ABI 377 automated DNA sequencer (PE Applied Biosystems, Foster City, CA).

Clinical procedures

Contiguous thin slice (3-mm thickness) T₁-weighted sagittal and coronal images of the posterior pituitary, with and without fat saturation, were performed during MRI scanning (33). The MRIs were interpreted and scored by an experienced neuroradiologist (E.W.) who was blinded as to whether the MRI was from a control or affected subject. Laboratory tests included blood electrolytes, creatinine, osmolality, AVP, oxytocin, ACTH, and cortisol measurements, and urinary specific gravity and osmolality determinations. Laboratory tests and MRI examination were performed only after each subject or parent of a minor subject stated that neither food nor drink had been ingested during the previous 12 h, and affected members did not take desmopressin acetate (DDAVP) on the night before the tests. The three subjects who admitted to breaking their fasts came back on another day for testing.

Nine affected adult members of the kindred and nine age-matched nonaffected members had MRI scans. Eight affected and eight nonaffected adults had blood and urinary measurements. Eight affected infants and children had blood and urinary determinations, including one child who was tested both during infancy and childhood. The six affected children, but not the two affected infants, had MRI scans.

Equipment and methods

Pituitary MRI was performed using the Magnetom Symphony scanner (Siemens Co., Munich, Germany) employing Numaris 3.5, Va 13c version software. AVP and oxytocin were extracted and measured by RIAs (34). Osmolality of both urine and blood was determined by freezing point measurements using the Advanced Microosmometer Model 3300 (Advanced Instruments, Inc., Norwood, MA). Fasting AM serum cortisol and plasma ACTH were measured by fluorometric and immunoradiometric assays, respectively (35, 36). Statistical significance determinations of comparisons of the median fasting ACTH and cortisol levels of affected and nonaffected adult members of the kindred were performed using the two-sample Wilcoxon rank-sum (Mann-Whitney U) test to obtain two-sided *P* values.

Results

Detection of mutation

Direct sequence analysis revealed a 3-bp deletion (AGG) of one of two consecutive AGG sequences (nucleotide position 1824–1829) in exon 2 of the AVP gene (Fig. 1). Sequence analysis of each allele after subcloning of PCR-amplified DNA confirmed the presence of this mutation in one allele (data not shown). This mutation, which has been previously

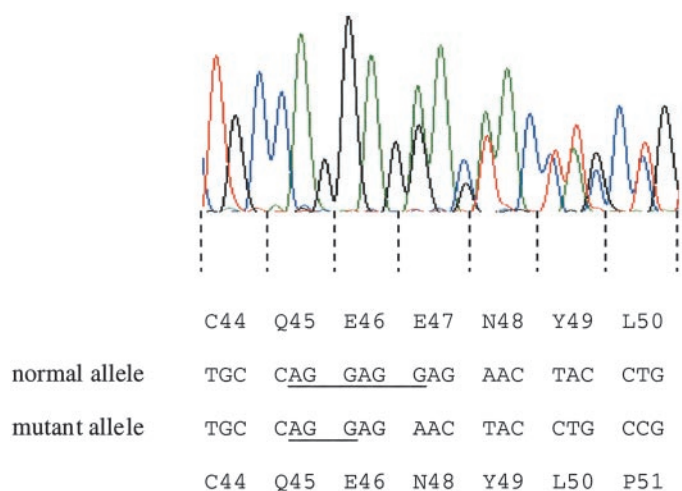


FIG. 1. Direct sequence analysis of the AVP gene. Color code for nucleotide elution curves: adenine, green; guanine, black; thymine, red; and cytosine, blue. PCR-amplified DNA was directly sequenced. Deletion of AGG out of two consecutive AGG sequences (nucleotide 1824–1829) in exon 2 of the AVP gene results in an elimination of glutamate at amino acid position 47 of the neurophysin moiety.

described, eliminates glutamate at amino acid position 47 of the neurophysin moiety (7). The pedigree in Fig. 2 represents all of the affected and nonaffected members of the Washington State arm of a large U.S. kindred of adNDI (31). All individuals positive for the mutation were symptomatic except for two infants (Fig. 2, IV-15 and V-4) who were less than 18 months old. All individuals negative for the mutation were over 3 yr of age and asymptomatic.

Clinical course

The parents noticed the onset of polyuria and polydipsia when their children were between 6 months and 3 yr of age. None of the children experienced an acute episode of dehydration or failure to thrive. Before the current study using genetic testing, the diagnosis of adNDI in this kindred was often delayed and was missed in two cases because the 8-h water deprivation tests, which had been performed during childhood, were interpreted as being equivocal or normal. All of the parents thought that the severity of polyuria and polydipsia increased during childhood, particularly during the first 10 yr of life. Affected mothers were able to breast-feed successfully. Plasma oxytocin determinations of fasting blood samples drawn from male subjects and from female subjects who at that time were not pregnant or lactating were in the normal range of 0.4–0.6 mU/liter in both affected and nonaffected members.

MRI findings

The PPHS of affected children was present, although smaller or slightly less intense than the PPHS of control children (Fig. 3 and Fig. 4, A and B). In young adults, the PPHS in five of six affected members was absent or barely visible in contrast to the normal size of the PPHS in nonaffected members (Fig. 3 and Fig. 5, A and B). By middle age, the bright spot was absent in three affected members, whereas it was absent in only one of three nonaffected mem-

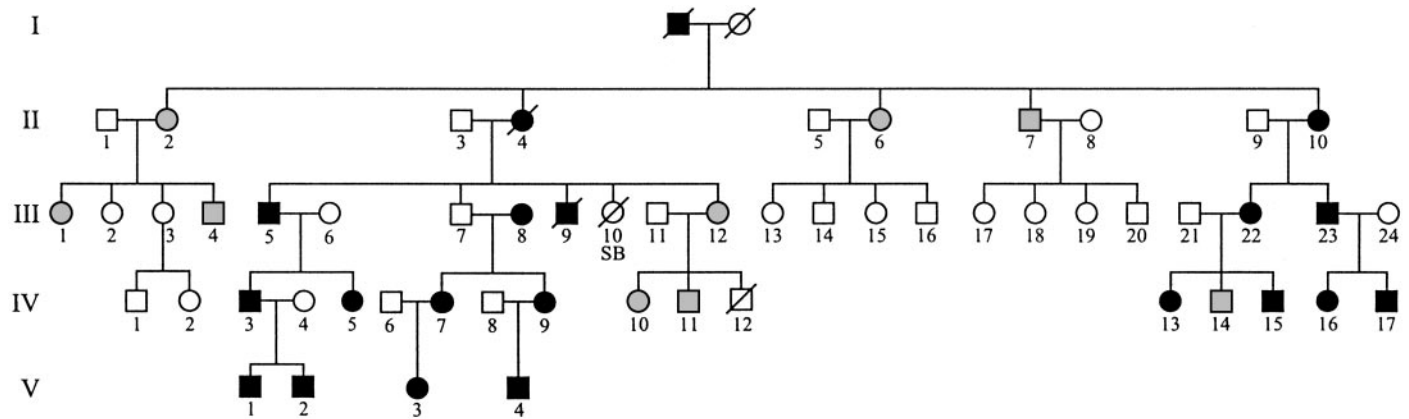


FIG. 2. *Blackened symbols* in pedigree indicate: 1) 3 deceased members who were clinically affected but not gene tested (I, II-4, and III-9); 2) 15 mutant gene-positive, clinically affected members; and 3) 2 mutant gene positive infants less than 18 months old (IV-15 and V-4) who were still asymptomatic. *Gray symbols* indicate clinically nonaffected members testing mutant gene-negative. *Open symbols* depict clinically nonaffected members not gene tested.

Posterior Pituitary hyperintense signal (PPHS): Affected members vs age matched controls

Groups	Prepubertal Children									Young Adults								Middle-age Adults									
Age in Years	1	2	3	4	5	6	7	8	9	20	22	24	26	28	30	32	34	36	40	42	44	46	48	50	52	54	56
PPHS Size & Intensity																											
4+				○	○	○		○	○						○	○	○	○									
3+				●	●	●																					
2+																											
1+																											
0																											

FIG. 3. The size and intensity of PPHS performed after 12 h of fasting were graded as follows: 0, no visible spot; 1+, barely visible spot; 2+, small but clearly visible spot; 3+, slightly smaller or less intense than normal; and 4+, normal size and intensity. *Closed circles* depict affected members of the kindred. *Open circles* indicate the following controls: for children, MRIs from age- and sex-matched unrelated children; and for adults, MRIs from age-matched nonaffected members of the kindred.

bers. The oldest nonaffected member being studied (age, 56 yr) failed to show a PPHS during two fasting MRIs even though he had a normal water deprivation test (Table 1). After drinking 240 ml of water at bedtime and several times daily for 5 d, including on the day of his third MRI, he produced a 3+ PPHS (normal size, but slightly less intense). In contrast, the oldest affected member (age, 54 yr) still failed to exhibit a PPHS on her second MRI after following the same regimen of increased fluid intake plus discontinuing DDAVP the night before the MRI and matching her fluid intake to her urinary output during the night.

Water deprivation tests

During infancy, urinary and plasma osmolality in affected individuals remained in the normal range of 200–1,192 and 275–295 mosmol/kg, respectively (Table 1). There was a progressive decline, particularly in the first decade of life, in the ability of affected individuals to withstand a 12-h fast, as illustrated by patient V-1. At 3 months of age, patient V-1 was not only able to concentrate his urine and prevent hyperosmolality, but he also increased plasma AVP to 15.7 pmol/liter (normal range, 1.0–12). By 7 yr of age, his serum sodium and plasma osmolality rose to 152 and 310, respectively, but plasma AVP rose only to 1.0 pmol/liter (Table 1).

Median plasma ACTH concentrations after 12 h of fasting

in affected and nonaffected members were 10.0 (range, 7.7–20.5) and 5.0 (range, 2.9–7.4) pmol/liter ($P = 0.008$). Median plasma cortisol levels in affected and nonaffected members were 572.5 (range, 515.9–670.4) and 355.9 (range, 182.0–573.8) nmol/liter ($P = 0.02$). The reference ranges for morning plasma ACTH and serum cortisol were 1.5–11.2 and 124.0–634.5 nmol/liter, respectively. In two affected adults tested in a nonfasting state and having normal serum sodium levels, morning plasma ACTH concentrations were 3.5 and 4.4 pmol/liter, and plasma cortisol levels were 253.3 and 275.9 nmol/liter.

Discussion

The origin of the PPHS has not been established, but the presence of some component of the AVP-NP-copeptin complex in the axons of the hypothalamohypophyseal tract is considered to be the most likely source (37–40). The PPHS has been demonstrated in 10 of 14 children in whom the diagnosis of adNDI has been established, including all six of the children in our series (Figs. 3 and 4A) (2, 41–43). In contrast, eight of nine affected adult members in our series, including a 31-yr-old woman who had never received anti-diuretic therapy, showed an absent or barely visible pituitary bright spot, whereas eight of nine nonaffected members produced a normal size PPHS (Figs. 3 and 5A). Of 29 previously

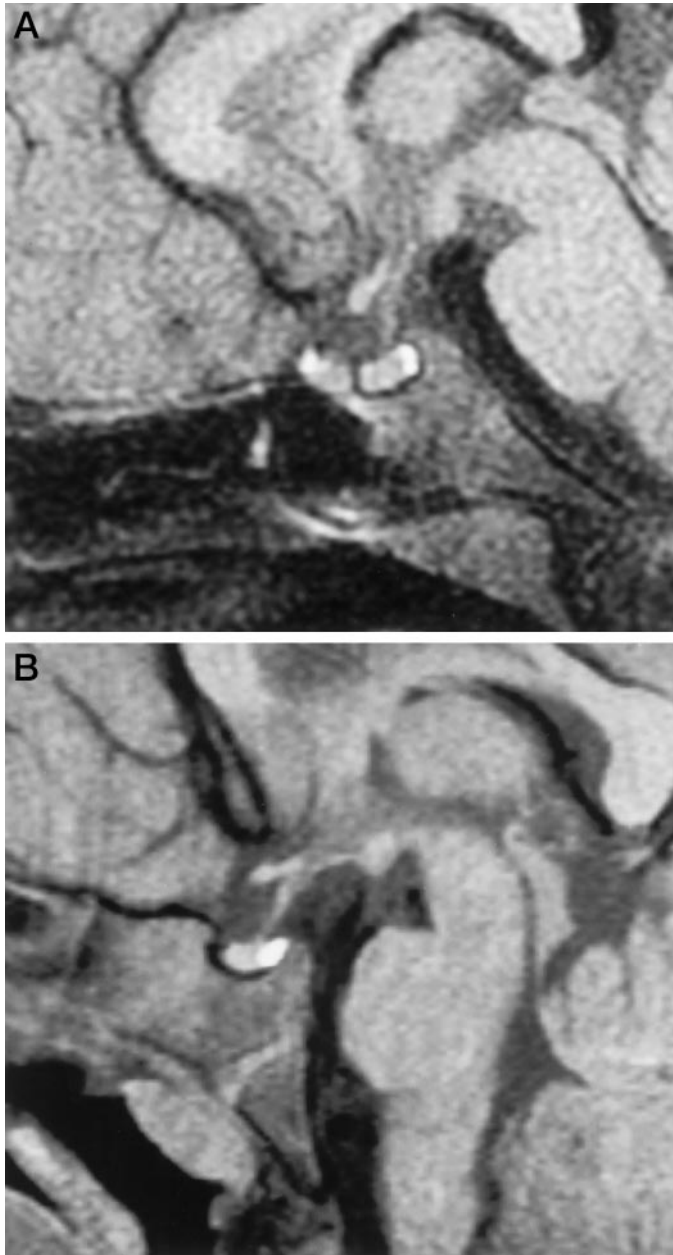


FIG. 4. Sagittal T₁-weighted images with fat saturation showing a 3+ PPHS in a 4-yr-old affected girl (A) and a 4+ PPHS in a control 4-yr-old girl (B).

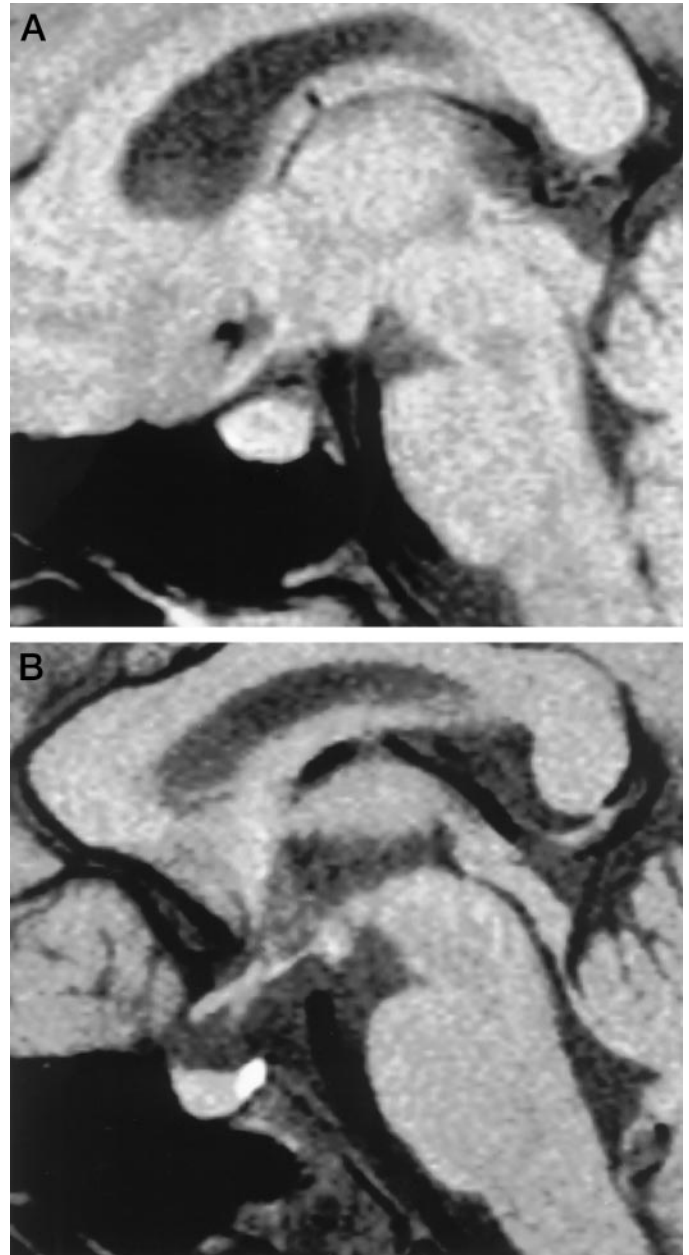


FIG. 5. Sagittal T₁-weighted images with fat saturation demonstrating absent PPHS in a 28-yr-old affected woman (A) and a normal PPHS in a 28-yr-old nonaffected woman (B).

reported adults with adNDI, only three exhibited a PPHS (2, 12, 18, 22, 41–44). When combined with our study, the results suggest that about 90% (37 of 41) of adults with adNDI may be expected to show only a barely visible or absent PPHS.

Disappearance of the PPHS alone cannot be used as evidence of loss of vasopressinergic cells. The PPHS is frequently absent in conditions of increased AVP secretion such as nephrogenic diabetes insipidus and renal failure treated with hemodialysis (37). Excessive release of AVP and secondary loss of PPHS may also occur with old age, apparently in response to diminished renal function and chronically raised plasma osmolality (45–47). The absence of the PPHS during two fasting MRIs in the oldest nonaffected member

(age, 56 yr) may have been due to aging because the PPHS was restored by 5 d of increased hydration, including on the day of the third MRI.

Measurement of plasma AVP as well as plasma and urinary osmolality in affected members after water deprivation provided confirmatory evidence that this form of adNDI is a progressive disease, especially during childhood. Infants were able to concentrate their urine and prevent plasma hyperosmolality. After infancy, affected children were no longer able to concentrate their urine; and by school age, they began developing hypernatremia and plasma hyperosmolality after fasting. The transition from infancy to school age is illustrated by the boy (Table 1, V-1) who, after exhibiting

TABLE 1. Laboratory tests after a 12-h fast in affected children and affected and nonaffected adults in the kindred

Pedigree no.	Age at time of tests	Urine		Blood		
		Specific gravity	mosmol/kg	Na ⁺ meq/liter	mosmol/kg	AVP pmol/liter ^b
Affected infants						
V-1 ^a	3 months	1.014	352	137	280	15.7
V-4	9 months	1.019	606	143	291	1.0
IV-15	14 months	1.012	503	144	292	2.0
Affected children						
V-2	3 yr	1.006	230	145	296	1.2
IV-16	4 yr	1.005	176	144	292	1.7
IV-13	4 yr	1.003	98	147	297	1.1
IV-17	5 yr	1.003	100	145	291	2.0
V-1 ^a	7 yr	1.007	256	152	310	1.0
V-3	9 yr	1.002	54	151	309	<1.0
Affected adults						
IV-5	26 yr	1.001	87	149	297	<1.0
IV-9	28 yr	1.001	48	150	300	<1.0
IV-3	29 yr	1.002	103	154	316	<1.0
IV-7	30 yr	1.001	60	151	308	1.0
III-22	31 yr	1.004	133	150	306	<1.0
III-23	32 yr	1.004	156	150	303	<1.0
III-8	45 yr	1.002	83	150	300	<1.0
II-10	54 yr	1.004	124	158	322	<1.0
Nonaffected adults						
IV-10	20 yr	1.025	828	139	284	3.0
IV-2	28 yr	1.025	926	140	280	5.3
III-16	29 yr	1.022	893	143	301	2.8
III-20	32 yr	1.024	965	143	294	8.0
III-19	33 yr	1.022	913	141	289	12.1
III-18	35 yr	1.023	849	141	289	3.9
III-4	48 yr	1.023	960	142	296	5.9
II-7	56 yr	1.024	965	143	297	5.4

^a Member V-1 of pedigree tested at 3 months and 7 years.

^b Normal range, 1–12 pg/ml.

a normal response to a water deprivation test including an elevated plasma AVP level at 3 months of age, showed the typical laboratory findings of diabetes insipidus at age 7 yr.

The number of neurons in the hypothalamus expressing AVP reaches the adult level as early as the second half of gestation (3). At birth, there still appears to be adequate remaining vasopressinergic cells in adNDI to maintain sufficient AVP production. The progressive decline between infancy and middle age of affected individuals to produce AVP and to withstand water deprivation suggests that the paucity of vasopressinergic neurons found at autopsy in later life stems from chronic loss (2, 13, 26). Consistent with the histologic changes of localized cellular destruction, postmortem examination of the brain of affected member II-4 in Fig. 3 in our series, as in other cases of adNDI, showed astrocytic proliferation restricted to the SON and PVN regions of the hypothalamus (28–32).

Previous studies suggest a potential cause for the loss of magnocellular neurons in this kindred of adNDI. DNA sequence analysis indicates that the gene mutation present in affected members produces an AVP precursor lacking GLU 47 in its NP moiety (7). GLU 47, as shown in the crystalline structure of bovine NP, is essential for this protein to form a salt bridge with AVP (48). Normal NP-AVP binding affinity is necessary for processing and trafficking the AVP precursors in neurons during axon transport from the SON and PVN to the posterior pituitary. Structural changes in NP have been associated with intracellular accumulation of mutant AVP precursors that have been postulated to be cytotoxic (2,

26, 49–53). In cell culture systems, structural changes in NP induced by the $\Delta E47$ mutation have been associated with retention of AVP precursors in the endoplasmic reticulum, altered processing, and decreased cell viability (50).

The reason that there is a selective loss in the hypothalamus of magnocellular neurons but preservation of parvocellular neurons is unclear because both produce AVP. On the basis of vasopressin immunohistochemical studies, Bergeron *et al.* (32) suggest that adNDI represents a selective degeneration of the magnocellular system that projects to the posterior pituitary with sparing of the parvocellular component projecting to the median eminence and central brain regions. Parvocellular neurons project to the median eminence and coexpress CRH and AVP (3, 54). During hypertonic saline infusion, and presumably during water deprivation tests that induce hypernatremia, parvocellular neurons augment the release of ACTH by secreting AVP and CRH into the pituitary portal capillaries (55–58). Consistent with preservation of this function of parvocellular neurons, the median fasting plasma ACTH level of the affected adults who developed hypernatremia in our study was 2-fold greater than that of nonaffected members of the kindred who did not develop hypernatremia.

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References

- Brownstein MJ, Russell JT, Gainer H 1980 Synthesis, transport and release of posterior pituitary hormones. *Science* 207:373–378
- Hansen LK, Rittig S, Robertson GL 1997 Genetic basis of familial neurohypophyseal diabetes insipidus. *Trends Endocrinol Metab* 8:363–372
- Swaab DF, Hofman MA, Lucassen PJ, Purba JS, Raadsheer FC, Van de Nes JA 1993 Functional neuroanatomy and neuropathology of the human hypothalamus. *Anat Embryol (Berl)* 187:317–330
- Ito M, Mori Y, Oiso Y, Saito H 1991 A single base substitution in the coding region for neurophysin II associated with familial central diabetes insipidus. *J Clin Invest* 87:725–728
- Bahnsen U, Oosting P, Swaab DF, Nahke P, Richter D, Schmale H 1992 A missense mutation in the vasopressin-neurophysin precursor gene cosegregates with human autosomal dominant neurohypophyseal diabetes insipidus. *EMBO J* 11:19–23
- Ito M, Oiso Y, Murase T, Kondo K, Saito H, Chinzei T, Racchi M, Lively MO 1993 Possible involvement of inefficient cleavage of preprovasopressin by signal peptidase as a cause for familial central diabetes insipidus. *J Clin Invest* 91:2565–2571
- Yuasa H, Ito M, Nagasaki H, Oiso Y, Miyamoto S, Sasaki N, Saito H 1993 Glu-47, which forms a salt bridge between neurophysin-II and arginine vasopressin, is deleted in patients with familial central diabetes insipidus. *J Clin Endocrinol Metab* 77:600–604
- McLeod JF, Kovacs L, Gaskill MB, Rittig S, Bradley GS, Robertson GL 1993 Familial neurohypophyseal diabetes insipidus associated with a signal peptide mutation. *J Clin Endocrinol Metab* 77:599A–599C
- Krishnamani MR, Phillips III JA, Copeland KC 1993 Detection of a novel arginine vasopressin defect by dideoxy fingerprinting. *J Clin Endocrinol Metab* 77:596–598
- Repaske DR, Browning JE 1994 A *de novo* mutation in the coding sequence for neurophysin-II (Pro24 224 Leu) is associated with onset and transmission of autosomal dominant neurohypophyseal diabetes insipidus. *J Clin Endocrinol Metab* 79:421–427
- Nagasaki H, Ito M, Yuasa H, Saito H, Fukase M, Hamada K, Ishikawa E, Katakami H, Oiso Y 1995 Two novel mutations in the coding region for neurophysin-II associated with familial central diabetes insipidus. *J Clin Endocrinol Metab* 80:1352–1356
- Rutishauser J, Boni-Schnetzler M, Boni J, Wichmann W, Huisman T, Vallotton MB, Froesch ER 1996 A novel point mutation in the translation initiation codon of the pre-pro-vasopressin-neurophysin II gene: cosegregation with morphological abnormalities and clinical symptoms in autosomal dominant neurohypophyseal diabetes insipidus. *J Clin Endocrinol Metab* 81:192–198
- Rittig S, Robertson GL, Siggaard C, Kovacs L, Gregersen N, Nyborg J, Pedersen EB 1996 Identification of 13 new mutations in the vasopressin-neurophysin II gene in 17 kindreds with familial autosomal dominant neurohypophyseal diabetes insipidus. *Am J Hum Genet* 58:107–117
- Repaske DR, Summar ML, Krishnamani MR, Gultekin EK, Arriaza MC, Roubicek ME, Blanco M, Isaac GB, Phillips 3rd JA 1996 Recurrent mutations in the vasopressin-neurophysin II gene cause autosomal dominant neurohypophyseal diabetes insipidus. *J Clin Endocrinol Metab* 81:2328–2334
- Ueta Y, Taniguchi S, Yoshida A, Murakami I, Mitani Y, Hisatome I, Manabe I, Sato R, Tsuboi M, Ohtahara A, Nanba E, Shigemasa C 1996 A new type of familial central diabetes insipidus caused by a single base substitution in the neurophysin II coding region of the vasopressin gene. *J Clin Endocrinol Metab* 81:1787–1790
- Rauch F, Lenzner C, Nurnberg P, Frommel C, Vetter U 1996 A novel mutation in the coding region for neurophysin-II is associated with autosomal dominant neurohypophyseal diabetes insipidus. *Clin Endocrinol (Oxf)* 44:45–51
- Repaske DR, Medlej R, Gultekin EK, Krishnamani MR, Halaby G, Findling JW, Phillips 3rd JA 1997 Heterogeneity in clinical manifestation of autosomal dominant neurohypophyseal diabetes insipidus caused by a mutation encoding Ala 224 Val in the signal peptide of the arginine vasopressin/neurophysin II/copeptin precursor. *J Clin Endocrinol Metab* 82:51–56
- Gagliardi PC, Bernasconi S, Repaske DR 1997 Autosomal dominant neurohypophyseal diabetes insipidus associated with a missense mutation encoding Gly 23 224 Val in neurophysin II. *J Clin Endocrinol Metab* 82:3643–3546
- Heppner C, Kotzka J, Bullmann C, Krone W, Muller-Wieland D 1998 Identification of mutations of the arginine vasopressin-neurophysin II gene in two kindreds with familial central diabetes insipidus. *J Clin Endocrinol Metab* 83:693–696
- Calvo B, Bilbao JR, Urrutia I, Eizaguirre J, Gaztambide S, Castano L 1998 Identification of a novel nonsense mutation and a missense substitution in the vasopressin-neurophysin II gene in two Spanish kindreds with familial neurohypophyseal diabetes insipidus. *J Clin Endocrinol Metab* 83:995–997
- Grant FD, Ahmadi A, Hosley CM, Majzoub JA 1998 Two novel mutations of the vasopressin gene associated with familial diabetes insipidus and identification of an asymptomatic carrier infant. *J Clin Endocrinol Metab* 83:3958–3964
- Kawakami A, Okamoto Y, Yamamoto T, Tatsumi Y, Miki T, Tanaka S, Fujii S 1998 Central diabetes insipidus associated with a missense mutation in the arginine vasopressin gene that replaces Ala at the carboxyterminus of the signal peptide with Thr. *Intern Med* 37:683–686
- Calvo B, Bilbao JR, Rodriguez A, Rodrigues-Arnan MD, Castano L 1999 Molecular analysis in familial neurohypophyseal diabetes insipidus: early diagnosis of an asymptomatic carrier. *J Clin Endocrinol Metab* 84:3351–3354
- Rutishauser J, Kopp P, Gaskill MB, Kotlar TJ, Robertson GL 1999 A novel mutation (R97C) in the neurophysin moiety of prepro-vasopressin-neurophysin II associated with autosomal-dominant neurohypophyseal diabetes insipidus. *Mol Genet Metab* 67:89–92
- Willcutts MD, Felner E, White PC 1999 Autosomal recessive familial neurohypophyseal diabetes insipidus with continued secretion of mutant weakly active vasopressin. *Hum Mol Genet* 8:1303–1307
- Siggaard C, Rittig S, Corydon TJ, Andreassen PH, Jensen TG, Andresen BS, Robertson GL, Gregersen N, Bolund L, Pedersen EB 1999 Clinical and molecular evidence of abnormal processing and trafficking of the vasopressin preprohormone in a large kindred with familial neurohypophyseal diabetes insipidus due to a signal peptide mutation. *J Clin Endocrinol Metab* 84:2933–2941
- Fugii H, Iida S, Moriwaki K 2000 Familial neurohypophyseal diabetes insipidus associated with a novel mutation in the vasopressin-neurophysin II gene. *Int J Mol Med* 5:229–234
- Forssman H 1945 On hereditary diabetes insipidus with special regard to a sex-linked form. *Acta Med Scand [Suppl]* 159:1–196
- Blotner H 1958 Primary or idiopathic diabetes insipidus: a systemic disease. *Metabolism* 7:191–200
- Braverman LE, Mancini JP, McGoldrick DM 1965 Hereditary idiopathic diabetes insipidus in a case report with autopsy findings. *Ann Intern Med* 63:503–508
- Green JR, Buchan GC, Alvord EC, Swanson AG 1967 Hereditary and idiopathic types of diabetes insipidus. *Brain* 90:707–714
- Bergeron C, Kovacs K, Ezrin C, Mizzen C 1991 Hereditary diabetes insipidus: an immunohistochemical study of the hypothalamus and pituitary gland. *Acta Neuropathol (Berl)* 81:345–348
- Mark L, Houghton V, Hendrix L 1991 High-intensity signals within the posterior pituitary fossa: a study with fat-suppression MR techniques. *AJNR* 12:529–532
- Robertson GL, Mahr EA, Athar S, Sinha T 1973 Development and clinical application of a new method for the radioimmunoassay of arginine vasopressin in human plasma. *J Clin Invest* 52:2340–2352
- Gotelli GR, Wall JH, Kabra PM, Marton LJ 1981 Fluorometric liquid-chromatographic determination of serum cortisol. *Clin Chem* 27:441–443
- Raff H, Findling TW 1989 A new immunoradiometric assay for corticotrophin evaluated in normal subjects and patients with Cushing syndrome. *Clin Chem* 35:596–600
- Sato N, Tanaka S, Tateno M, Ohya N, Takata K, Endo K 1995 Origin of posterior pituitary high intensity on T₁-weighted magnetic resonance imaging. *Invest Radiol* 30:567–571
- Kurokawa H, Fujisawa I, Nakano Y, Kimura H, Akagi K, Ikeda K, Uokawa K, Tanaka Y 1998 Posterior lobe of the pituitary gland: correlation between signal intensity on T₁-weighted MR images and vasopressin concentration. *Radiology* 207:79–83
- Fujisawa I, Asato R, Kawata M, Sano Y, Nakao K, Yamada T, Imura H, Naito Y, Hoshino K, Noma S, Nakano Y, Konishi J 1989 Hyperintense signal of the posterior pituitary on T₁ weighted MR images: an experimental study. *J Comput Assist Tomogr* 13:371–377
- Holder CA, Elster AD 1997 Magnetization transfer imaging of the pituitary: further insights into the nature of the posterior “bright spot.” *J Comput Assist Tomogr* 21:171–174
- Miyamoto S, Sasaki N, Tanabe Y 1991 Magnetic resonance imaging in familial central diabetes insipidus. *Neuroradiology* 33:272–273
- Maghnie M, Villa A, Arico M, Larizza D, Pezzotta S, Beluffi G, Genovese E, Severi F 1992 Correlation between magnetic resonance imaging of posterior pituitary and neurohypophyseal function in children with diabetes insipidus. *J Clin Endocrinol Metab* 74:795–800
- Maghnie M, Cosi G, Genovese E, Manca-Bitti ML, Cohen A, Zecca S, Tinelli C, Gallucci M, Bernasconi S, Boscherini B, Severi F, Arico M 2000 Central diabetes insipidus in children and young adults. *N Eng J Med* 343:998–1007
- Ozata N, Tayfun C, Kurtaran K, Yetkin I, Beyhan Z, Corakci A, Caglayan S, Alemdaroglu A, Gundogan MA 1997 Magnetic resonance imaging of posterior pituitary for evaluation of the neurohypophyseal function in idiopathic and autosomal dominant neurohypophyseal diabetes insipidus. *Eur Radiol* 7:1098–1102
- Brooks BS, El Gammal T, Allison JD, Hoffman WH 1989 Frequency and variation of the posterior pituitary bright signal on MR images. *AJNR* 10:943–948
- Goudsmit E, Neijmeijer-Leioux A, Swaab DF 1992 The human hypothalamo-neurohypophyseal system in relation to development, aging and Alzheimer's disease. *Prog Brain Res* 93:237–248
- Terano T, Seya A, Tamura Y, Yoshida S, Hirayama T 1996 Characterization

- of the pituitary gland in elderly subjects from magnetic resonance images: relationship to pituitary hormone secretion. *Clin Endocrinol (Oxf)* 45:273–279
48. **Chen L, Rose JP, Breslow E, Yang D, Chang WR, Furey Jr WF, Sax M, Wang BC** 1991 Crystal structure of a bovine neurophysin II dipeptide complex at 2.8 Å determined from the single-wavelength anomalous scattering signal of an incorporated iodine atom. *Proc Natl Acad Sci USA* 88:4240–4244
 49. **Olias G, Richter D, Schmale H** 1996 Heterologous expression of human vaso-pressin-neurophysin precursors in a pituitary cell line: defective transport of a mutant protein from patients with familial diabetes insipidus. *DNA Cell Biol* 15:929–935
 50. **Ito M, Jameson JL, Ito M** 1997 Molecular basis of autosomal dominant neurohypophyseal diabetes insipidus. Cellular toxicity caused by the accumulation of mutant vasopressin precursors within the endoplasmic reticulum. *J Clin Invest* 99:1897–1905
 51. **Ito M, Yu RN, Jameson JL, Ito M** 1999 Mutant vasopressin precursors that cause autosomal dominant neurohypophyseal diabetes insipidus retain dimerization and impair the secretion of wild-type proteins. *J Biol Chem* 274:9029–9037
 52. **Beuret N, Rutishauer J, Bider MD, Spiess M** 1999 Mechanism of endoplasmic reticulum retention of mutant vasopressin precursor caused by a signal peptide truncation associated with diabetes insipidus. *J Biol Chem* 274:18965–18972
 53. **Nijenhuis M, Zalm R, Burbach JP** 1999 Mutations in the vasopressin prohormone involved in diabetes insipidus impair endoplasmic reticulum export but not sorting. *J Biol Chem* 274:21200–21208
 54. **Dornhorst A, Carlson DE, Seif SM, Robinson AG, Zimmerman EA, Gann DS** 1981 Control of release of adrenocorticotropin and vasopressin by the supraoptic and paraventricular nuclei. *Endocrinology* 108:1420–1424
 55. **Milsom SR, Conaglen JV, Donald RA, Espiner EA, Nicholls MG, Livesey JH** 1985 Augmentation of the response to CRF in man: relative contribution of endogenous angiotensin and vasopressin. *Clin Endocrinol (Oxf)* 22:623–630
 56. **Rittmaster RS, Cutler Jr GB, Gold PW, Brandon DD, Tomai T, Loriaux DL, Chrousos GP** 1987 The relationship of saline-induced changes in vasopressin-releasing hormone-stimulated adrenocorticotropin and cortisol secretion in man. *J Clin Endocrinol Metab* 64:371–376
 57. **Irvine CHG, Alexander SL, Donald RA** 1989 Effect of an osmotic stimulus on the secretion of arginine vasopressin and adrenocorticotropin in the horse. *Endocrinology* 124:3102–3108
 58. **Antoni FA** 1993 Vasopressinergic control of pituitary adrenocorticotropin secretion comes of age. *Front Neuroendocrinol* 14:76–122