Water Intake and 24-hour Blood Pressure Monitoring in a Patient with Nephrogenic Diabetes Insipidus Caused by a Novel Mutation of the Vasopressin V2R Gene


Abstract

A 47-year-old man presented with polydipsia, which had had since childhood, and recent onset of hypertension. Genetic analysis proved that he had nephrogenic diabetes insipidus caused by a novel mutation (deletion of 6 amino acids between G107 and C112) in the vasopressin V2 receptor gene. Results of 24-hour blood pressure monitoring disclosed a greater dipping pattern and greater blood pressure variability during waking hours than in male patients with only essential hypertension. This characteristic blood pressure profile may result from daily occurrence of free water depletion, as further observation indicated that water deprivation was associated with a reduction in blood pressure.

(Measurement and Calculations)

To evaluate the patient’s blood pressure profile, ambulatory blood pressure monitoring (ABPM) was performed for 24 hours at intervals of 30 minutes (TM-2421, A&D, Tokyo) (2). The dipping ratio (2) and blood pressure variation (3) were estimated from the ABPM data. The dipping ratio was calculated by dividing the mean sleeping blood pressure (22:00-05:30) by the mean awake blood pressure (06:00-21:30). The variation of blood pressure during waking hours or sleep was defined as the standard deviation of blood pressure measurements during the respective periods.

Orthostatic blood pressure measurements were taken to assess autonomic function (4). After 5 minutes in a supine position, the patient remained upright for 5 minutes. Blood pressure was recorded while supine and while standing at intervals of 1 minute using a semiautomated device (BP-80, Ninon Korin, Tokyo). The values are indicated as the mean±SD.

Informed consent for DNA analysis was obtained from the patient and his parents. Genomic DNA was prepared from peripheral leukocytes by standard methods. DNA sequencing was performed as previously described (5). Genomic DNA was subjected to nested PCR to obtain the final 2 kb PCR product which covered the exons, introns, about 140 bp of the 5'-translated region, and about 220 bp 3'-untranslated region of the AVPR2 gene. A total of 12 different primers (sense and antisense) were used for direct sequence of the PCR product. The sequence was performed by an automated DNA sequencer model 373S (Applied Biosystems Japan, Chiba) using the PRISM dye termination kit (Applied Biosystems Japan) ac-
A 47-year-old man was referred to our hospital in September 1998 for evaluation of hypertension diagnosed at a routine annual health examination. He complained of polydipsia since childhood. He has a high school education and works as a head chef. His body weight had increased by 5 kg over the last 3 years. He was admitted to our hospital for evaluations of hypertension and polydipsia.

**Family history**

His pedigree is depicted in Fig. 1. Although his mother had no polydipsia, his elder brother apparently did but died of an unknown febrile illness at 6 months of age. A cousin also has polydipsia.

**Physical examination**

His height and body mass index (BMI) were 158 cm and 26.0 kg/m², respectively. His blood pressure was 178/100 mmHg. No other abnormalities were noted on physical examinations.

**Laboratory investigation**

Table 1 shows laboratory data obtained on admission. The daily urine volume was abnormally high, and hypernatremia and hyperosmolarity were observed. The calcium (albumin corrected) concentration was normal (8.2 mg/dl). An endocrine work-up revealed elevated plasma renin activity and serum concentration of AVP. Restriction of free water intake according to the method of Dashe et al (6) caused only negligible changes in urinary osmolality from 69 mOsm/l to 67 mOsm/l and urinary volume from 460 ml/h to 440 ml/h. Nasal inhalation of 1-deamino-8-arginine vasopressin was associated with minimal increases in urinary osmolality (70 mOsm/l) and urinary volume (430 ml/h). Although renovascular hypertension was suspected because of the elevated high renin activity, no abnormalities were found by the captopril-loaded renogram using 99mTc-diethylene triamine pentaacetic acid, or by magnetic resonance angiography. Other secondary causes of hypertension were ruled out by biochemical and endocrine testing. He had no abnormal findings on chest radiograph or electrocardiogram, computed tomograph of the brain, no proteinuria on urinary analysis and normal chemistries on creatinine clearance (106 ml/min), total cholesterol (206 mg/dl) and fasting plasma glucose concentration (98 mg/dl).

**DNA analyses**

Direct DNA sequencing of the patient showed the presence of 18 bp deletion in the exon 2 (680–697; the numbers refer to the nucleotides in the genomic sequence in GenBank accession no. L22206; the initial base of the initial codon is denoted as nucleotide 1) resulting in deletion of 6 amino acids between G107 and C112 (Fig. 2). The sequence of the father was normal (Fig. 2) and the mother was heterozygous for the mutation (data not shown).

**Table 1. Laboratory Data on Admission**

<table>
<thead>
<tr>
<th>Peripheral blood count</th>
<th>Endocrines</th>
<th>(Normal range)</th>
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</thead>
<tbody>
<tr>
<td>White blood cells</td>
<td>Plasma</td>
<td>5.1 ng/ml/h (0.2–2.7)</td>
</tr>
<tr>
<td>Red blood cells</td>
<td>Serum</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>Aldosterone</td>
<td>75 pg/ml (30–159)</td>
</tr>
<tr>
<td>Serum chemistry</td>
<td>Cortisol</td>
<td>19 μg/ml (2–25)</td>
</tr>
<tr>
<td>Total protein</td>
<td>Arginine vasopressin</td>
<td>25 pg/ml (0.3–3.5)</td>
</tr>
<tr>
<td>Creatinine</td>
<td>Thyroid stimulating hormone</td>
<td>3.36 μU/ml (0.41–4.13)</td>
</tr>
<tr>
<td>Sodium</td>
<td>Free triiodothyronine</td>
<td>3.16 mg/ml (2.27–3.90)</td>
</tr>
<tr>
<td>Potassium</td>
<td>Free thyroxine</td>
<td>1.08 mg/dl (0.95–1.74)</td>
</tr>
<tr>
<td>Chloride</td>
<td>Urine</td>
<td></td>
</tr>
<tr>
<td>Osmolality</td>
<td>17-hydroxycorticosteroid</td>
<td>7.7 mg/day (3.1–8.7)</td>
</tr>
<tr>
<td>Urine</td>
<td>17-ketosteroid</td>
<td>5.2 mg/day (4.2–12.4)</td>
</tr>
<tr>
<td>Output</td>
<td>Metanephrine</td>
<td>0.20 mg/day (0.05–0.23)</td>
</tr>
<tr>
<td>Osmolality</td>
<td>Normetanephrine</td>
<td>0.24 mg/day (0.07–0.26)</td>
</tr>
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</table>
Blood Pressure Profile in Nephrogenic DI

Findings by ABPM

Based on all the findings, the patient was diagnosed with nephrogenic diabetes insipidus and essential hypertension. During the hospitalization he maintained normal sodium intake (120 mEq per day) under a regular schedule determined as was previously reported (2). ABPM was measured at the 3rd-week. The patient recorded the timing and amount of water intake during ABPM. The mean blood pressure measured over the 24-hour period was 128/83 mmHg. The blood pressure profile indicated blood pressure lability and a tendency toward an elevation in blood pressure after food and water intake (Fig. 3). The dipping ratio was 0.84, and the variation in blood pressure during awake and asleep was 10.7 and 9.3, respectively.

To examine the effect of volume depletion on blood pressure, we performed a water deprivation test. On a day in the 4th week, the patient was maintained in a recumbent position from 8:00 to 8:30 AM (Phase I) following breakfast. He then collected urine and refrained from drinking water until 11:30 AM. He was again kept in a recumbent position from 11:30 AM to 12:00 PM (Phase II). In these two phases, the blood pressure was measured at intervals of 2.5 minutes by a device used for autonomic function testing, with cardiac output and heart rate continuously measured by impedance cardiography (NCCOM3-R7, Bomed, Los Angeles, CA, USA) by the methods of Kubicek et al (7). At the end of each phase, blood was drawn and the body weight measured. On a day during the fifth week, a similar evaluation was performed under conditions of water supplementation. The patient consumed enough water to supplement the amount of water lost by urinary excretion during the interphase. Water deprivation was associated with a reduction in blood pressure, body weight, and cardiac output, while the serum AVP concentration increased during this time (Table 2). With water supplementation, these parameters were similar between Phases I and II (Table 2). On an-

Figure 2. Direct sequencing data of the patient and the father. Deletion of 18 bp underlined in the father’s sequence was observed in the patient, which causes a deletion of 6 amino acids between G107 and C112.

Figure 3. Twenty-four hour blood pressure profile, and the time and amount of water intake. Blood pressure was measured by ambulatory blood pressure monitoring under a regular schedule and a constant sodium intake at the 3rd week of admission.
other day during the 5th week of testing, orthostatic response in blood pressure was performed. A maximal change in reduction of systolic blood pressure of 4 mmHg was observed after 1 min standing up.

Before we examined the relation between water intake and blood pressure in the patient, he was provided with detailed information about the protocol and gave informed consent before participating. Our investigation was approved by the ethics committee of Iwate Medical University.

Discussion

Genetic analysis indicates that the patient has NDI with a mutation in the vasopressin V2 receptor gene, which matches his family history. Since the molecular identification of the human V2 receptor gene responsible for congenital NDI by Rosenthal et al in 1992 (8), more than 100 different types of mutations, insertions, or deletions in the gene has been reported (9). This mutation has not been reported yet, thus, the mutation is novel for NDI. Although we have not examined the function of this mutation, we speculate that the deletion of cysteine 112 disrupts the correct binding between the second and third extracellular domains, which are required for structural or functional integrity of the receptor (10).

Hypertension is not generally observed in NDI. Although the patient’s hypertension is classified as essential, the recent increase in body weight may have contributed to the onset of disease. His BMI qualifies as overweight (11), and the association of overweight with hypertension is well documented (12). It is unlikely that the high serum concentration of AVP induced hypertension in this patient for two reasons. First, even high concentrations (120 pg/ml) of serum AVP do not cause an elevation in blood pressure if baroreflex regulation is intact (13, 14); the autonomic function in this patient was found to be normal by orthostatic blood pressure measurements. Second, the duration of known hypertension was less than 1 year, while AVP concentrations likely were present since childhood.

To compare the dipping ratio and variation in blood pressure obtained from ABPM with those from patients with essential hypertension, ABPM was performed on 21 age- and BMI-matched males among the admitted patients with hypertension (WHO classification of stage I or II) admitted to hospital between 1998 to 2000. We performed ABPM under the same conditions as for the patient presented in order to eliminate the effect of lifestyle differences which are known to affect the blood pressure pattern (15). The mean age was 44±5 years, BMI was 26.1±0.5 kg/m², and 24-hour mean blood pressure was 107±10 mmHg. The mean dipping ratio was 0.92±0.05, and the mean variation in blood pressure was 8.0±2.0 mmHg while awake and 8.4±2.2 mmHg while asleep. The dipping ratio (0.84) of the patient was greater than 1 SD below the mean control value, and the variability of awake blood pressure was greater than 1 SD of the mean control value. Thus, the patient has a greater dipping pattern and a greater variability in comparison with controls with essential hypertension. These findings may predispose him to cardiovascular disease since larger variability and excessive reductions in blood pressure while asleep have been shown to be associated with cardiovascular events (16, 17).

The findings of a greater dipping pattern and a greater blood pressure variability appear to result from recurrent water deprivation, which was associated with a reduction in blood pressure (Table 2). Data from the water deprivation test suggest that a reduction in blood pressure was caused by a decrease in cardiac output resulting from a lower heart rate and likely from a decreased peripheral venous return. The decreased heart rate may be caused by the increased concentration of AVP, because an increase in the serum concentration of AVP is reported to augment feedback to baroreflex receptors, leading to a decrease in the heart rate (18). On the other hand, the total vascular index did not change during water deprivation, while an increase in the serum concentration of AVP from 7.5 pg/ml to 20.0 pg/ml was observed. These data also support the idea that a high serum AVP concentration is not responsible for vasoconstriction in this patient.

The mean blood pressure (128/83 mmHg) measured over the 24-hour period was quite lower than casual blood pressure (178/100 mmHg) at admission. This may result not only from

Table 2. Results of the Water Deprivation Test

<table>
<thead>
<tr>
<th>Variables</th>
<th>Water deprivation</th>
<th>Water supplementation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Phase I</td>
<td>Phase II</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>64.8</td>
<td>63.3</td>
</tr>
<tr>
<td>Serum arginine vasopressin (pg/ml)</td>
<td>7.5</td>
<td>20.0</td>
</tr>
<tr>
<td>Heart rate (/min)</td>
<td>62</td>
<td>55</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>108</td>
<td>101</td>
</tr>
<tr>
<td>Cardiac output (/min)</td>
<td>4.4</td>
<td>4.0</td>
</tr>
<tr>
<td>Total vascular resistance index</td>
<td>26.6</td>
<td>27.3</td>
</tr>
</tbody>
</table>

Heart rate, cardiac output, and mean arterial pressure from the two phases represent mean values. Total vascular resistance index was calculated from the mean arterial pressure (mmHg) divided by cardiac output (/min). See Case Report's Section for details.
white coat effect (19) but also from spontaneous hypotensive effect by admission (20). Because it has been proposed that the upper limit of normal ABPM was 125/80 mmHg (21), the present value still belongs to the category of hypertension.

As thiazide diuretics are the most useful in reducing urine volume (22) in patients with NDI, this treatment may ameliorate a greater dipping pattern and greater blood pressure variability of 24-hour blood pressure monitoring through a lesser change of body water balance.

In conclusion, we presented a patient with NDI having a novel mutation and essential hypertension, whose ABPM profile showed a greater dipping pattern, as well as a greater blood pressure variability while awake. This characteristic blood pressure profile may result from repeated volume depletion, as water deprivation was associated with a reduction in blood pressure.

References