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Factors Associated with Blood Pressure in Females with Heavy Exposure to Cadmium

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Animal experiments have implicated cadmium(Cd) as a possible factor in hypertension (Schroeder et al 1966; Perry and Erlanger 1974). Autopsy studies in the United States and in other countries have ascertained that most human subjects dying from hypertensive complications show increased concentrations of Cd in their kidneys, compared with subjects dying from a variety of other major diseases (Schroeder 1965). However, in addition to the data supporting this effect of Cd on blood pressure, contradictory reports have appeared (Holden 1969; Hammer et al 1972). Recently differences in susceptibility among animal strains and in the intake of other metals have been implicated as important factors in the development of hypertension (Friberg et al 1974; Perry et al 1980). In Japan, a cross-sectional study on females with clinical symptoms of Itai-Itai disease from chronic Cd poisoning (Friberg et al 1974) demonstrated that they had lower blood pressure than the reference group (Nogawa and Kawano 1969; Shinoda and Yuri 1981). In the present study, longitudinal observations of blood pressure and certain contributory factors associated with it were measured in females with heavy exposure to Cd in order to obtain further information on the relationship between Cd and blood pressure in human beings.

MATERIALS AND METHODS

The study group consisted of 61 female Itai-Itai disease observation patients aged 60 years or more with kidney symptoms but no bone symptoms due to Cd, as defined by Shiroishi et al (1977). They have been registered as people deeply suspected of having Itai-Itai disease following diagnostic standard for the disease (Friberg et al 1974). In the endemic districts located along the Jintsu River, they are supposed to experience heavy Cd exposure through rice, vegetables and drinking water polluted by Cd from Kamioka mine around the Ist and IInd world war (Kawano et al 1981; Watanabe et al 1981). The patients were examined at least once in November from 1980 to 1982. The health examination consisted of blood pressure measurement, 24-hour specimen urine analysis ; protein (biuret method), glucose (glucose-oxidase method), beta 2 microglobulin (single radical immuno-diffusion

method), lysozyme (lysophate method), Cd(atomic absorption method with dithizone-chloroform extraction), amino acid (2,4,6-trinitron benzene sulfonic acid) and inorganic phosphorus (Fiske-Subba Row method), and blood chemistry; hemoglobin (Cyanmethemoglobin method), hematocrit(microtube method), alkaline phosphatase(modified Bessey-Lowry method), inorganic phosphorus (Fiske-Subba Row method), calcium (atomic absorption method), glucose (glucose-oxidase method), urea nitrogen (diacetyl-monoxine method), uric acid (Folin method) and creatinine (Folin Wu method). For these 61 subjects, blood pressure measurement data obtained 10 years previously in November 1971 to 1973 were added in order to assess the changes in the interim period. The distribution and mean of the blood pressure readings were compared with data from the national survey on circulatory system diseases (the national survey) in Japan carried out in October, 1971 and in November, 1980 respectively (Ministry of Health and Welfare 1971; 1983). In comparing the blood pressure of these subjects with that of the national survey, the mean of the Hokuriku-Tokai area which includies the districts where the subjects live, was used as the reference.

For the analytical study on the contributory factors relating to blood pressure in these subjects, the standard partial regression coefficient and the multiple correlation coefficient were obtained with multivariate regression analysis of data from 1980 to 1982.

RESULTS AND DISCUSSION

The distribution and mean of blood pressure readings with age (mean age 75 years ; range 60-86 years) are shown in Table 1 for all patients, except one receiving hypotensive drugs, with the addition of the mean blood pressure data from the national survey. The mode of the systolic blood pressure values for patients between 60-69 years old, examined from 1980 to 1982, was located between 110 and 119 mmHg and the mean was 122 mmHg (SD=23). The latter value corresponded to the mean for females aged 30 years in the national survey 1980. Furthermore, the mode for patients more than 70 years old located between 120 and 129 mmHg, and the mean was 127 mmHg (SD=20) which corresponded to that for females aged about 40 years in the national survey. The mode of diastolic blood pressure values for patients aged 60-69 years old was located between 60 and 69 mmHg, and the mean was 72 mmHg (SD=14). The latter reading was almost identical to the mean for females aged 30 years in the 1980 national survey.
For subjects aged 70 years or more, the mode was located between 70 and 79 mmHg, and the mean diastolic blood pressure value was 71 mmHg (SD=13). These results therefore confirm that the systolic and diastolic blood pressure of patients was significantly lower than that of the national survey. In order to know whether the lower blood pressure was sustained or not, readings from the same patients examined 10 years previously were

Table 1. The distribution and mean of blood pressure values in Itai-Itai disease observation patients (1980-1982) and the mean in the 1980 national survey.

Female Itai-Itai disease observation patients

Systolic blood pressure (mmHg)

Age(year)	n	mean (SD)	-99	100-109	110-119	120-129	130-139	140-149	150-159	160-169	170-179	180-
60-69	13	122 (23)	1	3	5	-	1	1	1	-	-	1
70-	47	127 (20)	1	2	4	15	10	9	4	1	1	-

Diastolic blood pressure (mmHg)

Age(year)	n	mean (SD)	-59	60-69	70-79	80-89	90-99	100+
60-69	13	72 (14)	1	5	3	3	1	-
70-	47	71 (13)	3	8	19	14	2	1

Female subjects in the national survey

Systolic blood pressure (mmHg)				Diastolic blood pressure (mmHg)			
Age(year)	n	mean	SD	Age(year)	n	mean	SD
30-39	353	120	14	30-39	353	74	11
40-49	292	129	18	40-49	292	79	11
50-59	293	139	23	50-59	293	82	12
60-69	196	141	20	60-69	196	81	11
70-	122	146	24	70-	122	79	11

analyzed retrospectively from records. As shown in Table 2, the mode of systolic blood pressure values was located between 120-129 mmHg for patients aged 50-59 years, between 130-139 mmHg for the 60-69 years age group and between 130-149 mmHg for 70 years or more. Their mean values were 129 mmHg (SD=17) for patients aged 50-59 years, 134 mmHg (SD=23) for 60-69 years and 131 mmHg (SD=23) for patients more than 70 years old. With regard to diastolic blood pressure, the mode was located between 80-89 mmHg for every age group, and their mean values were 83 mmHg (SD=11) for patients aged 50-59 years, 80 mmHg (SD=12) for these aged 60-69 years and 81 mmHg (SD=8) for patients more than 70 years. Both systolic and diastolic blood pressure values for patients almost correspond to reference values for females aged 40 years in the 1971 national survey (Table 2), which suggests that their

Table 2. The distribution and mean of blood pressure values in Itai-Itai disease observation patients (1971-1973) and the mean in the national survey.

Female Itai-Itai disease observation patients

Systolic blood pressure (mmHg)

Age(year)	n	mean (SD)	-99	100-109	110-119	120-129	130-139	140-149	150-159	160-169	170-179	180-
50-59	13	129 (17)	-	1	2	4	3	2	-	1	-	-
60-69	31	134 (23)	1	3	3	4	9	4	3	2	1	1
70-	16	131 (23)	1	-	1	3	4	4	1	2	-	-

Diastolic blood pressure (mmHg)

Age(year)	n	mean (SD)	-59	60-69	70-79	80-89	90-99	100-
50-59	13	83 (11)	-	1	3	5	3	1
60-69	31	80 (12)	1	7	8	9	4	2
70-	16	81 (8)	-	1	5	8	2	-

Female subjects in the national survey

Systolic blood pressure (mmHg)				Diastolic blood pressure (mmHg)			
Age(year)	n	mean	SD	Age(year)	n	mean	SD
30-39	298	125	15	30-39	298	76	12
40-49	204	133	20	40-49	204	81	13
50-59	215	146	29	50-59	215	86	15
60-69	144	154	26	60-69	144	86	14
70-	60	161	27	70-	60	85	14

lower blood pressure values have been sustained in the recent decade.

Because Cd increases sodium retension (Foulke et al 1974, Perry and Erlanger 1982), it was assumed that hypertension might develop among subjects with chronic Cd poisoning in the Japanese rural district where excess sodium intake is also common. The Cd polluted district in the present study belongs to the Hokuriku area where mean sodium intake is 242 mEq (14.2g of salt) per adult person per day accordings to the national nutrition survey (Ministry of Health and Welfare 1982). In contradiction to this, lower blood pressure was found in patients when compared with a

reference population of females with identical age. It was also observed that the pressor effect of Cd could be prevented by several metals, most notably selenium (Perry et al 1980). However, the present authors have found a lower blood concentration of selenium in female Itai-Itai disease observation patients (0.116 ± 0.022 μg/g, n=37) compared with that of a reference population (0.149 ± 0.030 μg/g, n=28). This will be published elsewhere. Akabori et al (1984) reported that a higher intake of Cd resulted in a tendency for lower blood pressure in Rhesus monkeys fed with food including 3, 10, 30 and 100 μg Cd chloride per gram over 5 years. Blood pressure may therefore also be reduced in human beings suffering from heavy exposure to Cd. As mentioned already, it is assumed that the patients studied experienced heavy Cd exposure around the Ist and IInd world war (Kawano et al 1981; Watanabe et al 1981).

Cd was first suggested as a possible cause of human hypertension after animal experiments (Schroeder et al 1955) and the necessity for life-long low-dose Cd feeding was emphasized in order to produce a significant increase in blood pressure (Schroeder et al 1962). However, because the subjects in the present study have probably had a different type of exposure from the animals used in Schroeder's experiment mentioned above, this might explain why hypertension has not developed among them. In addition to this, differences in the mechanisms of the development of hypertension among various races should be taken into consideration in future research.

The multivariate regression analysis between blood pressure and laboratory data associated with Itai-Itai disease (Friberg et al 1974) is shown in Table 3. The combination of age, urinary lysozyme, urinary Cd, hemoglobin, serum calcium, blood glucose, serum uric acid and serum creatinine showed the best multiple correlation coefficient with both systolic and diastolic blood pressure (0.51 for systolic blood pressure, 0.53 for diastolic blood pressure; $p < 0.05$).

In adding any of the other laboratory data mentioned above, the correlation coefficient was not much improved. Among these contributory factors associated with blood pressure, urinary Cd, hemoglobin, serum calcium and serum creatinine did not show an identical relationship with systolic and diastolic blood pressure. This might be due to different mechanisms between systolic and diastolic blood pressure regulation. Urinary lysozyme and blood glucose showed significant standard partial regression coefficients with both systolic and diastolic blood pressure. The negative standard partial regression coefficient for urinary lysozyme which is increased in Itai-Itai patients (Nogawa et al 1979a) indicates that a higher concentration of urinary lysozyme is related to lower systolic and diastolic blood pressure. Furthermore, the positive standard partial regression coefficient for blood glucose which is decreased in Itai-Itai patients (Nogawa et al 1979b) indicates that the lower

concentration of blood glucose is related to lower systolic and diastolic blood pressure. These results from the multiple regression analysis support the theory that lower blood pressure among subjects in the present study is significantly associated with the pathogenesis of Itai-Itai disease.

Table 3. Standard partial regression coefficients and multiple correlation coefficients of multivariate regression analysis between blood pressure and its associated factors in Itai-Itai disease observation patients.

	Age (year)	Urinary lysozyme (mg/dl)	Urinary Cd (ug/l)	Hemoglobin (g/dl)	Serum calcium (mg/dl)
Mean ± SD	75±7	2.48±1.9	9.5±5.1	11.2±2.4	9.5±0.6
Systolic	-0.005	-0.301	-0.096	-0.06	+0.148
Dyastolic	-0.048	-0.177	-0.195	+0.392	+0.030

Blood Sugar (mg/dl)	Serum uric acid (mg/dl)	Serum creatinine (mg/dl)	Multiple correlation coefficient
99 ± 40	3.0 ± 0.8	2.2 ± 1.2	
+0.275	+0.146	-0.081	0.51 ($p < 0.05$)
+0.211	-0.111	+0.201	0.53 ($p < 0.05$)

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