[原著]Study on Twins with Hypertension and Cerebrovascular Disease in Japan

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Study on Twins with Hypertension and Cerebrovascular Disease in Japan

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Until the present, essential hypertension has presumed as a hereditary desease from the results of the study of families and twins (Weitz, 1923; Allan, 1933; Ayman, 1934; Hines, 1937; Platt, 1947, 1961; Miyao, Mimura, Terai, 1968). The comparison between monozygotic (MZ) twins and dizygotic (DZ) twins offers a convenient means for studying some problems of human heredity. Aa the results of previous genetic study of essential hypertension, it can be presumed that hypertension is transmitted by a mendelian dominant one-gene (Weitz,1923; Ayman, 1934; Miyao, 1953), therefore, this disease has been regarded as a clinical entity of qualitative character. But according to our recent genetic study and other investigators' results (Oshiro, 1964; Miyao, Mimura, Terai, 1968; Hamilton, Pickerling, Roberts, Sowrg, 1954), it has become apparent that blood pressure is a continuous character. If blood pressure, genetically, is a quantitative character, to classify blood pressure into hypertension, normotension and hypertension respectively at a certain level as a different qualitative character is questionable. But from the clinical points of view, hypertension will be diagnosed in the case of excessive blood pressure at a certain level, nevertheless blood pressure is a continuous character. One of the authors, Mimnra, reported the study of twins with hypertension, in 1973, on the basis of the mentioned opinion. In this paper, I'd like to state the average difference of blood pressure between MZ and DZ twins, the difference of blood pressure of MZ twins induced by the difference of environment, and the difference of concordance rate of hypertension between MZ and DZ twins, moreover, the difference of concordance rate of cerebrovascular disease between MZ and DZ twins.

Materials and methods

Eighty-nine pairs of MZ twins and 24 pairs of DZ twins were examined. In order to diagnose the zygosity in addition to anthropometrical measurement, we performed the following independent character test: blood typing (ABO, MN blood type and Rh factor), earwax, phenylthiocarbamide test and the mid-digital hair test. Moreover, finger printing and whether the twin parents were alike or not during childhood, were helpful factors in the diagnosis of the zygosity. Using the above mentioned method, the accuracy of diagnosis is 98.5%.

It is very difficult to evaluate whether or not the environment was the same. Therefore, the evaluation was determined by using the criteria as shown in Table 1. The evaluation was done by the mark of the eight items; education, composition of family, living in the same district or in a different district, assets and yearly income, plus the mutual opinion of the twins themselves as to whether or not they felt they had lived in the same environment. In the case where the average mark was less than 2, it was regarded as the same environment. And a different environment was decided when the average mark was two or more.

Table 1. Evaluation method of environmental factors

	Mark	1	2	3	4	5
1	Duration of living in the same house (year)	over 20	16~20	11~15	6~10	0~5
2	Occupation	same	almost same	different but substance of business is same	different	
3	Education	same	almost same	different		
4	Composition of family	same	almost same	different		
5	Living district	neighborhood	same town (city)	same prefecture	different prefecture	different country
6	Assets	same	almost same	different		
7	Yearly income (difference, million Yen)	0~0.5	0.51~1.00	1.01~1.50	1.51~2.00	2.01~
8	Mutual opinion of twins themselves	same	almost same	a little different	different	

Results and discussion

1. Mean intrapair difference of basal blood pressure between monozygotic twins and dizygotic twins.

The mean intrapair difference of basal blood pressure between MZ twins and DZ twins which were divided into three age groups is shown in Table 2. Significant differences were observed in only age groups of 20 to 49 years old, and total pairs between MZ and DZ twins, because the number of pairs of DZ twins was very few compared with that of MZ twins.

Table 2. Mean intrapair difference in basal systolic blood pressure and diastolic blood pressue in twins. pressure in twins.

Age Groups	Systolic Blood Pressure				Diastolic Blood Pressure			
	M Z		D Z		M Z		D Z	
	No. of Pairs	Difference in Blood Pressure mmHg, M ± SD	No. of Pairs	Difference in Blood Pressure mmHg, M ± SD	No. of Pairs	Difference in Blood Pressure mmMg, M ± SD	No. of Pairs	Difference in Blood Pressure mmHg, M ± SD
< 19	19	4.0± 4.62	3	8.7±13.32	19	6.6± 5.08	3	12.0± 6.00
20 – 49	45	6.6± 6.00**	16	17.1±23.07	45	5.7± 6.21*	16	11.0± 9.49
> 50	25	17.9±19.55	5	16.4±17.29	25	10.1± 9.32	5	11.6±10.33
Total	89	9.2±12.55*	24	15.9±21.01	89	7.1± 7.20*	24	11.3± 8.98

*……P < 0.01, **……P < 0.05

2. Mean intrapair difference of blood pressure after exercise test.

The mean intrapair difference of blood pressure, which was immediately measured after exercise between MZ and DZ twins, is shown in Table 3. Significant differences were also obtained in only age groups of 20 to 49 years old, and in total pairs between MZ and DZ twins.

Table 3. Mean an intrapair difference in systolic blood pressure and diastolic blood pressure Sfter exercise test in twins.

Age Groups	Systolic Blood Pressure				Diastolic Blood Pressure			
	M Z		D Z		M Z		D Z	
	No. of Pairs	Difference in Blood Pressure mmHg M ± SD	No. of Pairs	Difference in Blood Pressure mmHg M ± SD	No. of Pairs	Difference in Blood Pressure mmHg M ± SD	No. of Pairs	Difference in Blood Pressure mmHg M ± SD
< 19	19	7.4± 6.00	3	11.3±13.32	19	6.2± 5.69	3	9.3± 7.57
20 – 49	34	10.3± 8.77**	12	28.5±25.48	34	7.6± 5.82**	12	16.4±11.60
> 50	19	36.1±29.30	5	29.6±13.37	19	12.8±11.57	6	16.0± 4.69
Total	72	16.2±19.95**	20	26.2±21.76	72	8.6± 7.99**	20	15.3± 9.75

*……P < 0.01, **……P < 0.05

3. Mean intrapair difference of basel blood pressure and blood pressure after exercise test between monozygotic twins under the same environment and under a different environment.

The mean intrapair difference of basal blood pressure and blood pressure after exercise test between MZ twins, under the same environment and under a different environment, is shown in Fig. 1. As for the basal systolic blood pressure and the systolic blood pressure after exercise test, significant differences were observed between them, but significant differences were not found in the basal diastolic blood pressure and the diastolic blood pressure after exercise test between them.

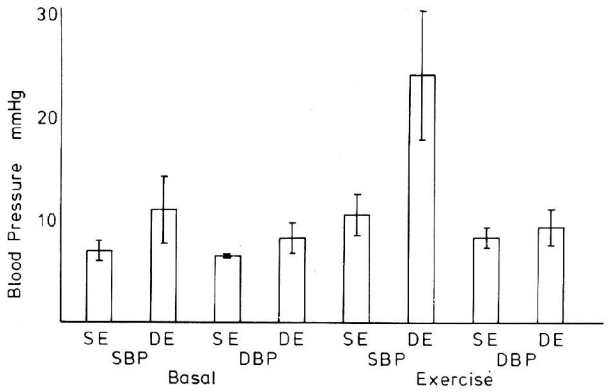

Fig.1 Mean intrapair difference of basal blood pressure and blood pressure after exercise in 60 pairs of monozygotic twins under the same environment and 53 pairs of monozygotic twins under a different environment.

4. Concordance rate of hypertension in Twins' essential hypertension.

Essential hypertension has been clinically diagnosed, in the case of excessive blood pressure at a certain level. Therefore, in the case of subjects over 40 years-old diagnosed as essential hypertension, if systolic blood pressure is over 150 mmHg and diastolic blood pressure is over 90 mmHg, then in the case of subjects under 40 years-old, diagnosis criteria of systolic blood pressure must be over 140 mmHg. In this study, we examined 113 pairs of twins. In these twins are found 13 pairs of MZ twins with hypertension. As shown in Table 4, out of 13 pairs of MZ twins concordance was found in 8 pairs (61.5%), while out of 5 pairs of same-sexed DZ twins, concordance was found in 1 pair (20%). From the results of our study, significant differences of concordance of hypertension was observed between MZ and DZ twins. Totalled other reports which were already published in Japan to our date, out of 47 pairs of MZ twins, concordance of hypertension was found in 31 pairs (66%), while out of 15 pairs of same-sexed DZ twins with hypertension was found only in 4 pairs (26.7%), and the significant difference between MZ and DZ twins was also observed.

Table 4. Concordance and discordance of hypertension in twins

Reporter	M Z			Same-sexed D Z			Opposite-sexed D Z		
	No. of pairs	Concordance	Discordance	No. of pairs	Concordance	Discordance	No. of pairs	Concordance	Discordance
Watanabe (1942)	1	1	0						
Oka (1952)	1	1	0				1	0	1
Misao & Yanase (1955)	1	1	0	1	0	1			
Awano & Takahashi (1966)	31	20	11	9	3	6	2	0	1
Mimura (1972)	(5)	(4)	(1)	(2)	(1)	(1)	(1)	(0)	(1)
Mimura et al (1978)	13	8	5	5	1	4	2	0	2
Total	47	31 (66%)	16	15	4 (26.7%)	11	5	0	5

Mimura's data, 1978, includes the data of Mimura 1972.

5. Environmental condition to development of hypertension in twins.

The difference between MZ twins and DZ twins is highly significant. The result suggests that the appearance or non-appearance of hypertension can be due mainly to genes of blood pressure, but there is no doubt that environmental factors will also affect its development. To solve the participation of environmental factors in the development of hypertension, it is necessary to compare the concordance ratio of hypertension in the same and different environments. Table 5 shows the environmental condition in development of hypertension which totalled above mentioned twin date of Japan, out of 24 pairs of MZ twins in the same environment concordance of hypertension was found in 15 pairs (62.5%), while out of 23 pairs of MZ twins in different environments, concordance of hypertension was found in 16 pairs (69.6%). Out of 8 pairs of DZ twins in the same environment, concordanc of hypertension was found in 3 pairs (37.5%) and out of 7 pairs of DZ twins in a different environment was found in 1 pair (14.3%). These results indicate that there is no significant difference of cnncordnace of hypertension in the MZ twins as regards environment. While in the DZ twins, in the same environment, the concordance of hypertension is found to be considerably larger than that of DZ twins in a different environment. These results suggest that there is a complicated relation between heredity and environment in the development of essential hypertension. In our twin study, out of 8 pairs of MZ twins witn the concordance of hypertension, only 2 pairs were under the same environment, three of four was the concordance of hypertension although under a different environment. On the contrary, in those DZ twins, the concordance of hypertension was observed in only under the same environment. From this result, we may be able to conclude that hereditary factors are superior to the environmental factors for the development of hypertension. Next, out of 5 pairs of MZ twins with discordance of hypertension which was diagnosed by basal blood pressure, 3 pairs were under a different environment. The rise of blood pressure by exercise was found in three persons of MZ twins with normal basal blood pressure as shown in Table 6. Therefore, it is fairly possIble that one of the twins having normal basal bloog pressure latently has the disposition of hypertension.

Table 5 Environmental condition to development of hypertension in twins.

Environment	M Z	D Z	
		Same-sexed	Opposite-sexed
Same environment	15／24 (62.5%)	3／8 (37.5%)	0／2 (0%)
Different environment	16／23 (69.6%)	1／7 (14.3%)	0／3 (0%)
Total	31／47 (66.6%)	4／15 (26.7%)	0／5 (0%)
		4／20 (20.0%)	

Table 6. Discordance of hypertension in monozgotic twins.

	Age	Sex	Height	Body Weight	Blood Pressure		Protein-uria	CTR	ECG	EG	50g GTT	TC	TG	Environ-ment
					Basal	Exercise								
E	49	F	150.7	54.0	128/70	164/84	(−)	49	IHD	I	B	152	163	D
Y			152.0	57.0	160/90	170/88	(−)	51	IHD	I	DM	144	130	
E	72	M	155.7	56.0	168/92	182/80	(−)	43	WNL	I	N	154	184	D
Y			162.5	65.0	120/68	140/76	(−)	59	WNL	I	N	163	204	
E	49	M	161.0	69.8	162/126	184/116	(−)	53.0	WNL	I	N	170	181	S
Y			162.2	56.1	148/80	174/94	(−)	42.8	WNL	I	N	174	106	
E	75	F	150.0	57.5	154/92		(−)	58.5	IHD	II	D	184	160	D
Y			149.6	54.5	140/80	174/94	(−)	56	WNL	II	B	242	154	
E	78	M	150.8	45.5	100/52	132/74	(−)	47.6	WNL	II	DM	225	96	S
Y			149.2	41.0	210/98		(−)	49.8	MI	II	DM	210	127	

CTR ····· Cardiothoracic Ratio. 50gGTT ····· 50gram Glucose Toleracnce Test.
ECG ····· Electrocardiogram. TC ····· Total Cholesterol.
EG ····· Eye-ground. TG ····· Triglyceride.
S ····· Same Environment. D ····· Different Environment.

6. What is the cause of discordance of hypertension in MZ twins ?

It is very difficult to clarify why there is the discordance of hypertension in MZ twins. Certainly, it may be said that the environmental difference may raise the blood pressure of one partner of MZ twins , or suppress the rise of blood pressure of other partner of MZ twins. Among the several environmental factors which raise the blood pressure, salt intake is regarded as most important factor from the experimental and epidemiological points of view. The mean intrapair difference of salt intake per day in the four age groups is shown in Table 7. The mean intrapair difference of salt intake per day in MZ twins in the under 19 year-old group is 1.52, in the 20-29 age group is 2.83, in the 30-49 age group is 3.50, over 50 age group is 3.79,g respectively. The mean intrapair difference of salt intake per day increases gradually in accordance with the duration of separation. Next, as for salt intake of the discordance of hypertension in 5 pairs of MZ twins, salt intake of four normotensive partners is lower than that of hypertensive partners. Therefore, it is presumed that the difference of salt intake will play an important role for the acceleration or the suppression of the rise of blood pressure. The mean intrapair and interpair difference of basal renin activity in MZ twins is shown in Table 8. If renin activity is the major factor for the raise of blood pressure, it must be the highest level of renin activity in MZ twins with discordance of hypertension, but unexpected results were obtained as shown in Table 8. The same result was obtained as for aldosteron level. From this result, it is difficult to draw a definite conclusion as for the participation of renin and aldosteron to the development of hypertension in MZ twins.

Table 7 Mean intrapair difference of salt intake per day in MZ twins.

Age	No. of Pairs	Difference in Salt Intake g. M±SD
< 19	13	1.52±2.09
20 − 29	11	2.83±2.66
30 − 49	15	3.50±3.05
50 >	11	3.79±2.87

Table 8 Mean intrapair and interpair difference of basal · renin activity in MZ twins.

	Concordance of Hypertension	Discordance of Hypertension	Both Twins with normal Blood Pressure
No. of Pairs	4	3	5
Intrapair Difference	0.46	0.66	0.90
Interpair Difference	0.80	0.78	1.13

7. Is hypertension main cause of cerebrovascular disease ?

Cerebrovascular disease---cerebral hemorrhage and thrombosis is the highest mortarity cause in Japan. It is not always clear is the risk factors for the stroke ;of apoplexy. But it has been generally accepted that hypertension is the main risk factor for the stroke.

If this is true, it must be high concordance of stroke in MZ twins with concordance of hypertension. As for this important problem, there is few reports in the world, because it is very difficult to find such twins and this study is necessary a long time follw-up examination. Sending a questionaire to the survivor of MZ twins or family of MZ twins where in the case of both twin-partners were dead, the cause of death of the twins and whether they had hypertension or not before their death will be clear. Whether the twin partners were alike or not during childhood, which was written in the questionaire, is the basis of diagnosis of zygosity. Out of 8 pairs of MZ twins, one pair was the discordance of renal failure; two pairs were the discordance of heart failure; four pairs were the discordance of stroke and in only one pair the concordance of stroke was observed. Other pareners without stroke are still alive and four partners out of five partners had hypertension. Table 9 shows the concordnace and discordance of cerebrovascular disease in twins which wese reported by Harvald and Hauge (1958), Miyao (1961), Awano (1976) and Mimura, et al. Out of 40 pairs of MZ twins, concordance of stroke was found in 14 pairs (35%), while out of 26 pairs of same-sexed DZ twins, concordance of stroke was found in 4 pairs (15%). The concordance in MZ twins was higher than that of DZ twins, but the concordance rate in MZ twins was lower contrary to our expectation. From this result, it is presumed that in the case where one partner with hypertension died due to cerebrovascular disease, the probability of death due to cerebrovascular disease in other partner with hypertension is not always high. Considering the cause of low concordance rate of stroke in MZ twins with hypertension, there are many factors including hypertension developing stroke but hypertension will be controlled by medication in many cases. Therefore, it is very difficult to draw a definite conclusion as for this important problem. It is necessary to carry out a long time follow-up study of twins with hypertension. Moreover, it is necessary to form an international cooperation system for study twin case in order to gather many pairs of twins with hypertension.

Table 9. Concordance and discordance of cerebrovasculer disease in twins.

Reporter	Year	M Z			D Z		
		No. of pairs	Concor-dance	Discor-dance	No. of pairs	Concor-dance	Discor-dance
Harvard & Hauge	1958	21	5	16	24	3	21
Miyao	1961	7	4	3	1	0	1
Awano	1976	7	4	3	1	1	0
Mimura et al	1978	5	1	4			
Total		40	14 (35%)	26	26	4 (15%)	22

Conclusion

Eghty-nine pairs of MZ twins and 24 pairs of DZ twins were examined and the following results were obtained.

1) Mean intrapair difference of basal blood pressur of the MZ twins was significantly smaller than that of the DZ twins.
2) Mean intrapair difference of blood pressure after exercise test of the MZ twins was also significantly smaller compared with the DZ twins.
3) Mean intrapair difference of basal blood pressure and the blood pressure after exercise test given the MZ twins under the same environment were significantly smaller than that of the MZ twins under a different environment.
4) Concordance rate of hypertension of the MZ twins was significantly higher than that of the DZ twins.
5) A significant difference was not observed in concordance rate of hypertension in MZ twins between same environment and different environment
6) Mean intrapair difference of salt intake in the MZ twins increases in accordance with the duration of separation.
7) In the present study, it is difficult to draw a definite conclusion as for the participation of renin and aldosteron to the development of hypertension.
8) The concordance rate of stroke of apoplexy in the MZ twins was higher that of the DZ twins, but it was lower than that of hypertension.

From our present study of twins, it is difficult to clarify by what mechanism does blood pressure rise and what is the environmental factors excluding salt intake which influences the level of blood pressure.

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