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Follow-up Study on Chemical Childhood Diabetes

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From the results of our diabetes detection survey, in 1962 in the general population, of 847 children over 6 years old, there was no overt diabetes, except for one case of chemical diabetes without glycosuria. But since then, clinically speaking, it would appear that the incidence of childhood diabetes has gradually increased. Therefore, the Ministry of Education has taken note of this important trend and has legislated the system of urinary test for all pupils. In Kumamoto Prefecture, urinary test, as for albuminuria and glycosuria, was carried out since 1973. The incidence rate of childhood diabetes in Kumamoto Prefecture was reported by Mimura in 1975. Namely, the incidence of diabetes in children under 6 and up to 15 years old found 18 cases of overt diabetes and 10 cases of chemical diabetes. The ratio of overt diabetes to chemical diabetes in children under 6 and up to 15 years old was 64.3 versus 35.7 per cent. In 1972, Rose-nbloom, et al reported that 10.6 per cent of the chemical childhood diabetics who were followed, progressed to the overt diabetes. Therefore, it is very interesting to note how many per cent of our chemical childhood diabetics do progress to the overt diabetics. From this follow-up study, it will be expected that the mode of development of diabetes will be clarified, and whether there is a different character between juvenile-onset diabetes (JOD) and maturity-onset diabetes in the young people (MODY) or not.

Experimental materials and methods

As shown in Table 1, the number of chemical childhood diabetics is 14 cases in Kumamoto Prefecture, in addition to one case in Okinawa. The total number amounts to 15 cases. In the

urinary examination of diabetes in school, positive glycosuria was found in 12 cases, and by the family examination of diabetes, positive glycosuria was found in 3 cases. Chemical diabetes was diagnosed by a 50g oral glucose tolerance test. Chemical childhood diabetes was determined, both in the case where the peak level or the blood sugar value one hour after glucose loading was over 200mg/100ml, and in the case where the blood sugar value two hours after glucose administration was over 140mg/100ml. Normal glucose tolerance was decided both in the case where the peak level or the blood sugar value one hour after glucose loading was below 180mg/100ml, and where the blood sugar value two hours after glucose administration was less than 120mg/100ml. The cases which did not meet the above mentioned criteria, were diagnosed as border-line. Even if the fasting blood sugar is over the normal range, in the case of asymptomatic state, the child was diagnosed as having chemical diabetes. Determination of blood sugar was made on capillary whole blood by the autoanalyzer. Determination of serum immunoreactive insulin (IRI) was made by the one antibody method. The follow-up study has been carried out once a month on Sunday. All chemical diabetics and their parents received the instruction of diet therapy periodically by the dieticians.

Table 1. Follow-up cases of chemical childhood diabetes

No.	Name	Sex	Present Age	Date of Detection	Duration of Follow-up (month)	Initial Fasting Blood Sugar	Family History	Motive of Finding of Glycosuria
1	H.T.	f	17	5/73	52 (27)	132	(+)	Urinary examination in school
2	T.M.	f	17	6/74	39 (21)	108	(+)	same
3	K.M.	m	17	5/72	64	134	(+)	same
4	K.U.	f	17	8/73	49	162	(-)	same
5	M.T.	f	16	12/71	69 (40)	98	(+)	same
6	K.I.	f	16	11/74	34	140	(+)	same
7	A.N.	f	16	8/75	41	138	(+)	same
8	K.T.	f	16	6/75	39	122	(+)	same
9	N.S.	f	15	10/71	77	152	(-)	same
10	Y.S.	m	15	5/76	14	88	(-)	same
11	A.I.	f	10	6/76	15	88	(+)	same
12	N.N.	f	14	6/77	3	100	(-)	same
13	K.N.	f	18	11/74	34	142	(+)	Family examination
14	A.T.	f	13	9/74	37	96	(+)	same
15	N.N.	f	13	9/74	36	112	(+)	same

No. 1, 2 and 5 progressed to overt diabetes, the number in the parenthesis is the duration of chemical diabetes.

Experimental results

Among 15 children, 13 cases are female and 2 cases are male. As for sex difference, the incidence of female was much higher than that of male. The average age of diagnosis of diabetes was 11 years old. The duration of follow-up ranged from 3 months to 77 months, the average follow-up month was 35 months. In the fasting blood sugar from 88mg/100ml to 162mg/100ml, the average fasting blood sugar was 120mg/100ml. Among 15 children, 3 female children showed slightly over weight but by the diet therapy the body weight reduced to the normal range in the course of follow-up study. Out of 15 children, 3 children, No. 1, 2 and 5 progressed from chemical

diabetes, (Maturity-onset type of diabetes in the young people, MODY) to overt diabetes, (Juvenile-onset diabetes, JOD). Figure 1 shows the initial and the follow-up glucose tolerance test of an 11 year old girl. Her glycosuria was found by the urinary examination in school. In December, 1971, her glucose tolerance showed chemical diabetes. In 1972, her glucose tolerance took a turn for the worse a little. In 1973, she did not receive the examination. From the beginning of 1974, she complained of typical diabetic symptoms. But she did not agree with insulin therapy. In summer camp, 1974, the fasting blood sugar remarkably raised at 416mg/100ml and urinary keton body was positive. Therefore, she initially received an insulin injection.

Fig. 2 shows the initial and the follow-up glucose tolerance test of a 14 year old girl. Her glycosuria was also found in the urinary examination in the school, in June, 1974. Her fasting blood sugar and the blood sugar 60, 90, and 120 minutes after glucose loading, were found to be 107, 197, 206 and 156mg/100ml, respectively, as shown in this figure. The response of Immuno-reactive insulin (IRI) showed delayed type and low response. Insulinogenic index was found to be 0.17. In 1975, she did not have the examination, because she did not have any complaint. But in the following year, she gradually complained of thirst, polydipsia, polyuria and the weight-loss. The fasting blood sugar raised to 246mg/100ml, and the insulin secretion showed very low response compared with that of 1974. From this time, she received insulin injection.

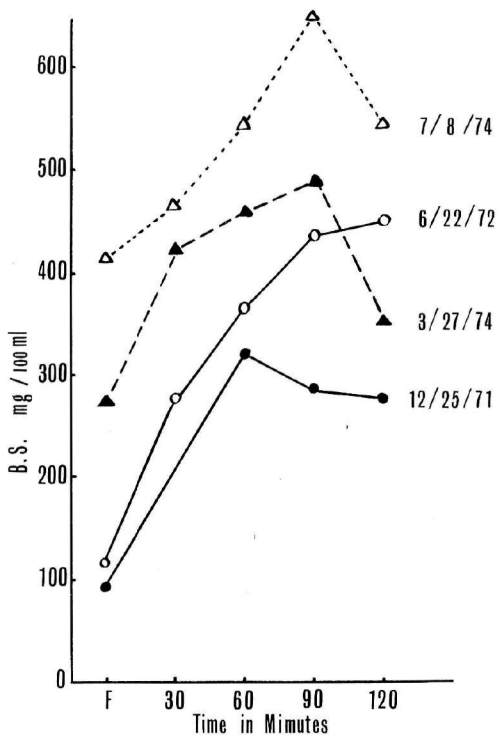


Fig. 1. Initial and follow-up glucose tolerance test of 11 years old girl

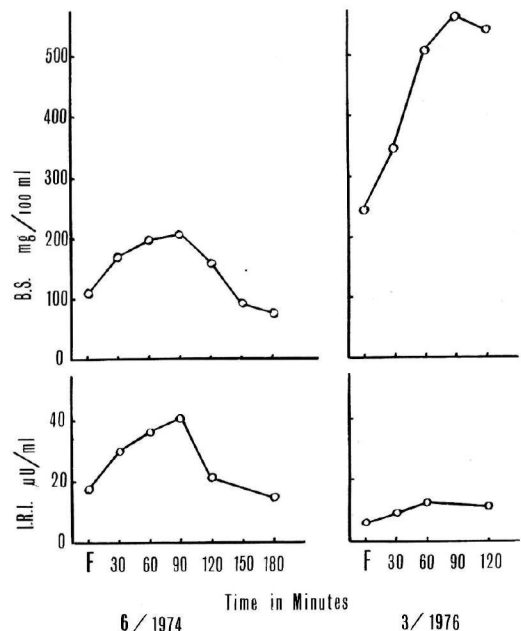


Fig. 2 Initial and follow-up glucose tolerance test of 14 years old girl

Figure 3 shows the initial and the follow-up glucose tolerance test of a 13 year old girl. Her glycosuria was found in the urinary examination in the school, in 1973, The fasting blood sugar and the blood sugar 1 hour and 2 hours after glucose administration were found to be 131, 250 and 160mg/100ml, respectively. Next year, her glucose tolerance was improved by the administration of tolbutamide. IRI response showed the delayed type, but insulin secretion was not so impaired, insulinogenic index was 1.42. In 1975, she did not complain of any diabetic symptoms and the fasting blood sugar was less than 140mg/100ml. But in 1976, the fasting blood sugar raised over 200mg/100ml and the insulin secretion showed remarkably low response compared with that of 1974. As shown in this figure, from 1976, the fasting blood sugar raised over 200 mg/100ml, and she complained of diabetic symptoms. Therefore, she received insulin injections since the end of 1976. Three girls did not suffer from viral infections prior to progression to overt diabetes. Figure 4 shows the initial and the follow-up fasting blood sugar and the blood sugar 2 hours after breakfast of a 12 year old boy. In 1972, glycosuria was found in the urinary examination in the school. The fasting blood sugar gradually raised since 1975, but at the present time the fasting blood sugar remained under 160mg/100ml. Figure 5 shows the initial and the follow-up glucose tolerance test of this boy. His glucose tolerance was chemical diabetes, in 1972 and 1973. In 1974, his glucose tolerance became normal, but IRI response showed the delayed type. But in 1975, his glucose tolerance showed chemical diabetes, and IRI secretion became low response, insulinogenic index was 0.16. In the following year, his glucose tolerance was almost the same as compared with last year. But the insulinogenic index decreased to 0.08. But his glucose tolerance in 1978, remained chemical diabetes.

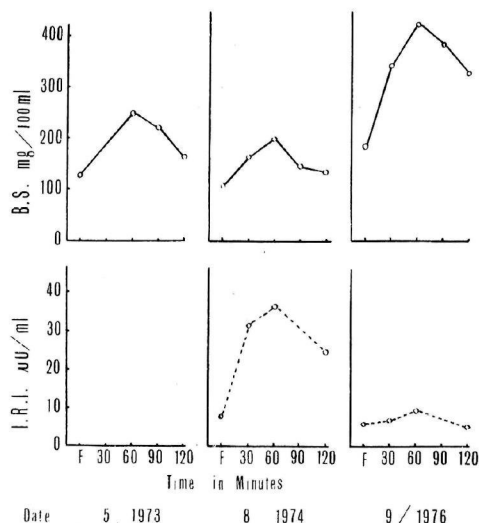


Fig. 3 Initial and follow-up glucose tolerance test of 13 years old girl

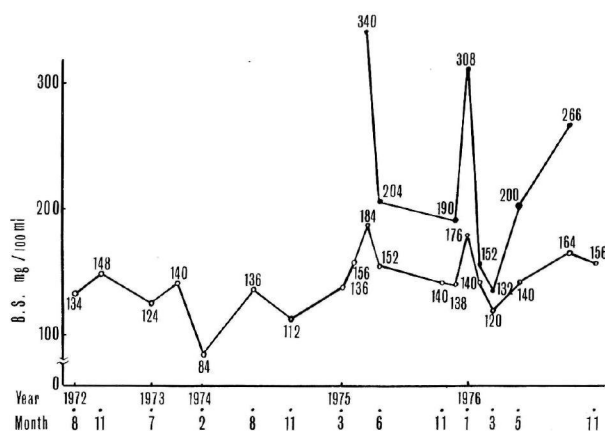


Fig. 4 Initial and follow-up fasting blood sugar and blood sugar two hours after meal of 12 years old boy

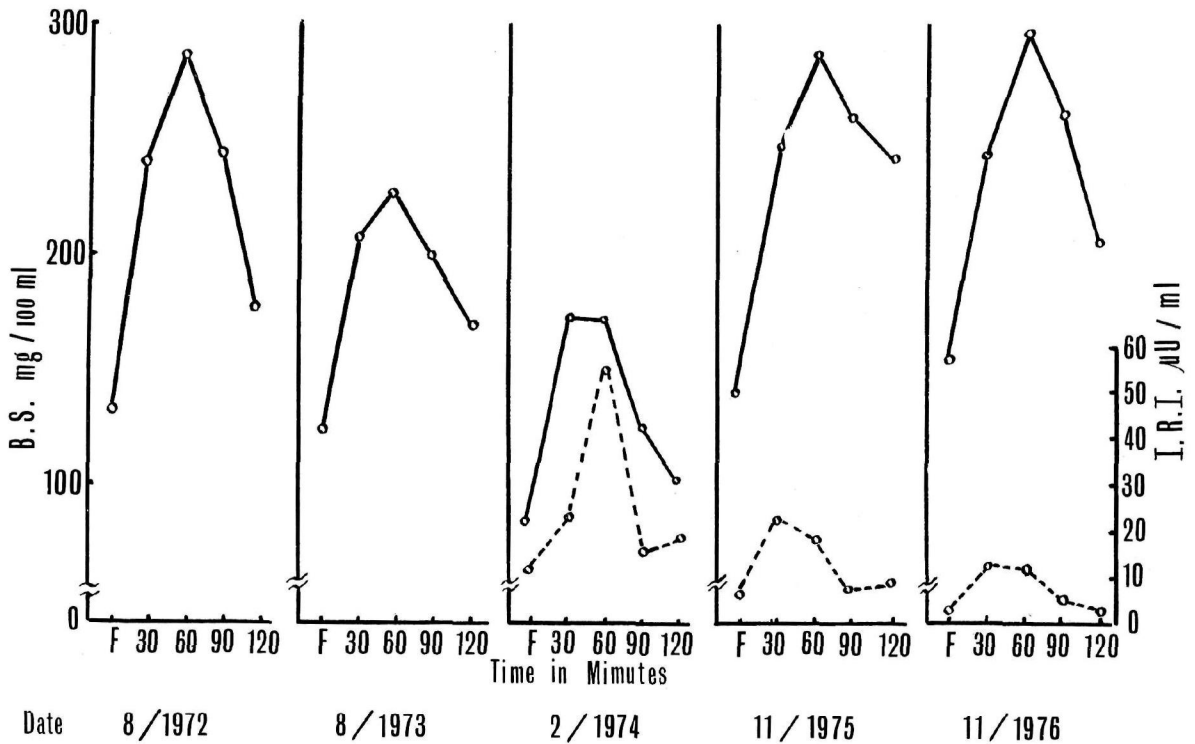


Fig. 5 Initial and follow-up glucose tolerance test of 12 years old boy

Discussion

It has generally been assumed that diabetes in children can rarely be recognized at an early stage, since the first manifestation of overt childhood diabetes are frequently of sudden or explosive onset. In 1960, Fajans and Conn reported that asymptomatic, latent, or chemical diabetes can be recognized in children and young adults by the finding of either mildly or grossly abnormal carbohydrate tolerance, and that such patients may exhibit the nonprogressive course of maturity-onset type of diabetes. But Fajans et al reported that among 15 patients, aged 9 to 12, three cases progressed from chemical diabetes to insulin-dependent diabetes. The age at diagnosis were respectively, 14, 11 and 17 years, and the initial fasting blood sugar levels were 99, 106 and 77 mg/100ml, respectively. The initial glucose tolerance tests of these 3 Patients did not differ from those of the whole group. The time interval between the diagnosis of asymptomatic diabetes and the progression to insulin-dependent diabetes was $4\frac{1}{2}$ months, 2 years, and 2 years, respectively. These 3 patients had been treated with diet, phenformin, and tolbutamide, respectively. In 1972, Rosenbloom reported the follow-up study on 198 cases of chemical childhood diabetes, including his 25 patients as shown in Table 2. Among 198 cases, 21 cases progressed to insulin-dependent diabetes during one to seventeen years of observation. The progression rate was found to be 12.6 %. In our follow-up study, the progression rate was 20%. Our three cases did not suffer from any virus infections, prior to the progression of overt diabetes. The time interval between the diagnosis of chemical diabetes and the progression to insulin-dependent diabetes was 2 years and 3 months, one year and 9 months, and 3 years and 4 months, respectively. The initial glucose

tolerance tests our cases did not differ from other chemical diabetics. The initial patterns of the insulin secretion in these 2 cases were the same as those of the other chemical diabetes. The insulin secretion and the insulinogenic index decreased gradually and progressed from chemical diabetes to insulin-dependent diabetes. Therefore, it is impossible to foresee the progression to insulin-dependent diabetes from the pattern of insulin secretion in the stage of chemical diabetes. Recently, Tattersall and Fajans reported that hereditary background will be different between juvenili-onset diabetes (JOD) and maturity-onset type diabetes in young people (MODY). If it is true, does the childhood diabetes developed from MODY to JOD essentially belong to JOD or MODY? It is presumed that there are 4 stages in the course of diabetes mellitus, i.e., prediabetes, latent chemical diabetes, chemical diabetes, and overt diabetes (Cammerini-Dávalos). Presuming the onset of diabetes is due to both the hereditary background and environmental factors, by the proportion of both factors, 4 types of diabetes will be found clinically and some cases remain in the state of chemical diabetes for life, and the other cases progress from chemical diabetes to overt diabetes. Therefore, there is no difference essentially as for diabetes between them. Of course, about 10 - 20% of childhood diabetes will be affected due to viral infection, but now it is believed that the liability of virus infection will be determined by the special typing of human leucocyte antigen (HLA) and HLA typing is transmitted through the generations. Therefore, it is presumed that to be susceptible to a virus infection will be due to the hereditary background of HLA. Therefore, at this stage of our hereditary study on childhood diabetes, it is concluded that there are two different types, chemical and overt diabetes, as a phenotype, and the heterogeneity will be the main cause of this phenomena. But at the stage of chemical diabetes, it is impossible to foresee which case does progress to overt diabetes, even if by determination of insulin level during glucose tolerance test, i.e., it is unknown to clarify the heterogeneity between chemical diabetes and overt diabetes at the stage of chemical diabetes. Therefore, in the future, it is necessary to find the proper means for the problem through the follow-up study on childhood diabetes.

Table 2. Progression of chemical diabetes in children

	Number followed	Number developing overt diabetes mellitus
EHRlich	6	6
PIDES	7	1
COLLE	12	1
PANLSEN	14	0
DRASH	14	0
BALSAM	19	0
FAJAN	21	4
ROSENBLOOM	25	1
JACKSON	80	8
Total	198	21

Summary

Out of 15 chemical childhood diabetics, 12 cases were diagnosed by the urinary examination of diabetes in school, and 3 cases were found by the family examination of diabetes. Three cases progressed from chemical diabetes to overt diabetes (insulin-dependent diabetes). The age at diagnosis were respectively, 11, 14 and 13 years, and initial fasting blood sugar levels were 98, 108 and 132mg/100ml, respectively. The time interval between the diagnosis of chemical diabetes and the progression to insulin-dependent diabetes was 2 years and 3 months, one year and 9 months, and 3 years and 4 months. The initial patterns of the insulin secretion in these 2 cases were the same as those of the other chemical diabetes. The insulin secretion and the insulinogenic index gradually decreased, and progressed to overt diabetes. Three girls were not affected by virus infection. At the stage of chemical diabetes, it is impossible to foresee which case does progress to overt diabetes.

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