The Chlorpropamide Alcohol Flush

Lack of Specificity for Familial Non-insulin Dependent Diabetes

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Summary. A facial flush provoked by alcohol in chlorpropamide treated diabetics has been described as a genetic marker for a dominantly inherited type of non-insulin dependent diabetes. In this study a chlorpropamide alcohol flush was observed in 16.9% of control subjects ($n = 154$), 23.3% of insulin dependent diabetics ($n = 437$) and 16.5% of patients with non-insulin dependent diabetes ($n = 145$). Among the non-insulin dependent diabetics no difference in the frequency of the chlorpropamide alcohol flush was found between those with and without a family history of diabetes. Specificity was not improved by skin temperature measurement or additional placebo tests. According to these data the chlorpropamide alcohol flush does not seem to be specific for non-insulin dependent diabetes and hypotheses about the aetiology of this type of diabetes based on the chlorpropamide alcohol flush should be regarded with caution.

Key words: Chlorpropamide alcohol flush, non-insulin dependent diabetes, insulin dependent diabetes, MODY, genetics, HLA-types.

Leslie and Pyke [1] have reported a facial flush reaction provoked by small amounts of alcohol in patients given chlorpropamide. The authors suggest this chlorpropamide alcohol flush (CPAF) as genetic marker for a special type of non-insulin dependent diabetes (NIDDM) with autosomal dominant inheritance [2], including the so called MODY and comprising about 20% of all diabetics. The test was positive in 31% of NIDDM without, and 81% of NIDDM with a family history of diabetes but only in 10% of normal subjects and 10% of insulin depend-

ent diabetics (IDDM). Within the diabetic families the flush reaction followed the transmission of NIDDM, and a positive flush test in non diabetic family members was regarded as a risk factor. Furthermore, the CPAF has given rise to hypotheses about the aetiology of NIDDM [3, 4].

Following this line defined groups of diabetics have been investigated to check the association of CPAF with special types of diabetes. In a second part of the study specificity and reproducibility of CPAF were tested using objective test evaluation by facial skin temperature measurements.

Subjects and Methods

CPAF-tests were performed as described by Leslie and Pyke [1]. The subjects received 250 mg (one tablet) of chlorpropamide 12 h and 36 h before administration of 20 ml of dry sherry (18% alcohol). Tests were performed 1 to 2 h after the last meal, usually after breakfast. One hour after sherry ingestion the subjects, who did not know what reaction was expected, were asked to answer a questionnaire with a list of several possible reactions among which "hot feeling in the face" (in German: "Hitzeempfindungen im Gesicht") was regarded as positive. In accordance with Leslie and Pyke [1] a visible flush was not regarded as a prerequisite for a positive test but only the patients' subjective description. Placebo tests were not performed in this series.

The control subjects were either students and young teachers ($n = 101$) or non diabetic relatives of patients with IDDM ($n = 53$). Patients with IDDM (ketosis prone, insulin treatment within half a year after diagnosis) were recruited from 5 different studies each of which was performed independently by one investigator:

- A: patients from a diabetic clinic ($n = 54$),
- B: patients with age at onset < 25 years from a summer camp for juvenile diabetics ($n = 47$),
- C: patients from an earlier study on HLA association [5] ($n = 90$),
- D: female patients with IDDM from an earlier study on the diabetes risk for their children [6] ($n = 198$),
- E: subjects with IDDM with an age at onset ≥ 25 years ($n = 48$).

No special selection was performed in all these groups other than that stated above. The consent of the patients was required, however, and was obtained in about 75% of all requested. From patients with IDDM who turned out to be CPAF-positive HLA antigens were determined if the individuals agreed to a venepuncture ($n = 49$).

Fourteen patients from 5 different families had typical MODY (Tattersall syndrome [7, 8]) with early onset, lack of ketoacidosis, lack of diabetic complications, and with family members with a similar type of diabetes. In three of these families, including the family shown in Figure 1, all affected members had a low renal threshold for glucose, as was described by Tattersall in two of his three original families [7], including the Mason-family reported to be CPAF-positive [4].

Patients with NIDDM and age at onset between 25 and 75 years were grouped into those without ($n = 69$) and with ($n = 62$) a family history of NIDDM (at least one first degree relative).

In a second series on 21 controls, 8 previously flush positive subjects with IDDM, 4 MODY's, and 10 NIDDM patients with a positive family history additional tests with placebo as well as with chlorpropamide were performed. In eight of these patients either

Table 1. Percentage of CPAF-positive subjects (subjective evaluation by questionnaire) amongst groups of normal individuals, insulin-dependent diabetics (IDDM), Tattersall Syndrome (MODY) (7, 8), and non-insulin-dependent diabetics (NIDDM). For explanation of groups A–E see Methods

		n	% positive
I	Normal individuals	154	16.9
II	IDDM		
	A	54	25.9
	B	47	23.4
	C	90	18.9
	D	198	23.2
	E	48	29.2
	Sum	437	23.3
III	MODY	14	28.6
IV	NIDDM (other than MODY)		
	a) without family history	69	13.0
	b) with family history	62	17.7
	Sum	131	15.3

Fig. 1. Pedigree of a family with typical MODY (Tattersall syndrome). Age at onset of diabetes is given for all affected members. Patients in whom CPAF-tests were performed are indicated by an asterisk. All tests were negative

the placebo test or the chlorpropamide test was performed twice. Facial skin temperature was measured continuously with a small temperature sensor probe fixed with adhesive tape over the cheeks, and a Technoterm 5500 digital thermometer (Testoterm KG, Lenzkirch, Germany). Room temperature was kept constant at 20 °C and the sherry was only given after acclimatisation and at least 20 min. of constant skin temperature. An increase of facial skin temperature of 1.2 °C or more within 30 min after sherry was arbitrarily regarded as a positive reaction (1.1 °C or more were regarded positive by Leslie et al. [3]).

Results

The percentage of positive tests among the various groups of subjects is given in Table 1. Within the group of normal controls there was no significant difference between the relatives of patients with IDDM (18.9% positive) and the others (15.8%). One family with a clearcut Tattersall syndrome (= Mason type diabetes [2, 4]) is shown in Figure 1. All 7 members of this family in whom the test was performed were CPAF negative. The frequencies of the diabetes associated HLA-types B8 (44.9%), B15 (28.6%) and B8 + B15 (8.2%) among the 49 CPAF-positive IDDM subjects were significantly higher than in normal controls and about equal that in IDDM in general (44.5, 22.4 and 5.4 resp. [5]).

The results of the skin temperature measurements are given in Tables 2 and 3. In most but not all cases an increase of skin temperature correlated with the patients report of a positive flush. In the subjects in whom the tests with skin temperature measurement were performed more than once the reproducibility was limited (Table 4).

Discussion

Test performance and evaluation in the present study were similar to previous descriptions [1, 2, 4, 9]. It was the person's subjective description that determined whether the appropriate response had occurred. Placebo tests seemed not to be essential since only one out of 193 individuals were reported by Leslie and Pyke [1] to react positively to placebo. These authors, who initially had also used 20 ml of sherry [9] later used 40 ml [1, 2] but only in very rare cases was a difference in response observed (personal communication).

The results of the present study, however, differ in various aspects from those by Leslie and Pyke [1, 2]. In the present study the frequency of CPAF is higher among normal controls and IDDM and lower among patients with NIDDM. In addition, no difference was observed between non-insulin dependent

Table 2. Basal facial skin temperature (°C) and increment after alcohol (20 ml of sherry) following pretreatment with placebo or chlorpropamide. + = facial flush according to subjective assessment (questionnaire), - = no subjective flush reaction. Other abbreviations as Table 1

Diagnosis			Previous subjective test result	Placebo			Chlorpropamide		
				basal	incr.	subj.	basal	incr.	subj.
I	Normal individuals	1	+	34.1	1.1	—	32.4	1.9	+
		2	+	32.0	0.3	—	31.5	0.8	—
		3	+	32.0	1.0	—	32.1	0.7	—
		4	+	31.5	1.3	+	31.7	1.1	—
		5	+	30.6	2.4	+	32.1	2.9	+
		6	—	32.8	1.5	+	33.0	1.3	+
		7	—	33.4	0.7	—	33.4	−0.3	—
		8	—	31.6	1.5	+	31.3	1.3	+
		9	—	34.5	0.6	—	34.1	0.5	—
		10	—	31.7	0.4	—	32.8	0.5	—
		11	—	33.8	0.6	+	33.6	1.1	+
		12	—	33.5	0.7	—	33.6	0.2	—
		13	—	32.4	1.5	—	33.1	0.4	—
		14	—	33.2	0.6	—	35.0	0.6	—
		15	+	33.3	1.0	—	33.5	0.3	—
		16	—	34.2	0.2	—	32.0	0.4	—
		17	+	29.5	1.6	+	30.0	1.2	+
		18	+	34.0	0.9	—	32.9	1.6	+
		19	+	31.0	1.9	+	30.8	3.5	+
		20	no pretest	34.5	0.6	—	33.0	1.4	+
		21	no pretest	32.1	1.3	—	32.9	0.5	—
			Mean		32.7 ± 0.3	1.0 ± 0.1		32.6 ± 0.3	1.0 ± 0.2
II	IDDM	1	+	30.2	4.7	+	32.7	2.4	+
		2	+	34.3	0.7	—	33.4	1.6	+
		3	+	32.7	1.8	+	33.5	1.6	+
		4	+	31.8	0.8	—	31.0	0.6	—
		5	+	33.5	0.2	—	32.7	0.2	—
		6	+	34.2	0.1	—	33.4	0.2	—
		7	+	32.1	0.5	—	32.4	0.6	—
		8	+	32.6	0.9	—	34.0	0.4	—
		9		32.7 ± 0.5	1.2 ± 0.5		32.9 ± 0.3	1.7 ± 0.3	
	Mean								
III	MODY	1	+	31.5	1.4	+	32.4	1.7	+
		2	+	32.8	1.1	+	32.9	2.1	+
		3	+	33.6	1.3	+	32.8	1.8	+
		4	—	33.4	1.8	+	31.5	1.1	—
		Mean		32.8 ± 0.5	1.4 ± 0.2		32.4 ± 0.3	1.7 ± 0.2	
IV	NIDDM with positive family history	1	—	32.4	0.7	—	30.4	1.9	—
		2	—	31.0	1.8	+	30.3	1.7	+
		3	—	32.9	−0.2	—	29.3	0.6	—
		4	—	29.3	0.0	—	28.5	0.8	—
		5	—	33.9	0.6	+	33.7	0.9	+
		6	—	30.5	1.0	—	31.5	1.1	—
		7	—	31.6	1.6	—	31.6	2.0	—
		8	—	32.9	0.5	—	31.0	3.0	+
		9	—	31.6	2.4	+	30.9	2.7	+
		10	—	32.2	1.1	—	33.6	0.1	—
		Mean		31.8 ± 0.4	1.0 ± 0.3		31.1 ± 0.5	1.5 ± 0.3	
Total mean			32.5 ± 0.2	1.1 ± 0.1		32.3 ± 0.2	1.2 ± 0.1		

Table 3. Skin temperature rise after 20 ml of sherry following pretreatment with placebo (Pl) or chlorpropamide (Chl) in 21 normal and 22 diabetic subjects. + = increment of $\geq 1.2^\circ\text{C}$, - = lower or no increment. Other abbreviations as Table 1

	n	Pl-/ Chl-	Pl+/ Chl-	Pl+/ Chl+	Pl-/ Chl+
I Normal individuals	21	10	3	5	3
II IDDM	8	5	0	2	1
III MODY	4	0	1	2	1
IV NIDDM with positive family history	10	5	0	3	2
Sum	43	20	4	12	7

diabetes with and without a family history of diabetes. The differences between the various groups of the present study are not statistically significant. CPAF therefore seems not to be specific for any special type of diabetes mellitus. This lack of association with NIDDM was also described in a small series (14 normals, 19 diabetics) by other authors [10]. The same HLA-distribution among CPAF-positive and

negative patients with IDDM suggests that there is no aetiological difference between these two groups.

Although in most cases a clear assignment as CPAF positive or negative was possible on the basis of subjective test evaluation the reaction is not of an all or none character and it is difficult to define the prerequisites for a positive diagnosis. The reproducibility is limited, as could be observed with repetitive testing of skin temperature increments. The basal skin temperature and thereby the increment [11] may depend on several other influences such as environmental temperature, emotional factors, smoking before the test or further unknown variables. The flush reaction is not specific for a pretreatment with chlorpropamide but we have not performed enough placebo tests to assess whether chlorpropamide increases the sensitivity to small amounts of alcohol in many individuals. Since the subjects tested in the second part of our study were recruited after their subjective flush result was known the results obtained by skin temperature measurements cannot yield true incidence figures.

No plausible explanation can be provided for the differences between the results by Leslie and Pyke

Table 4. Skin temperature measurement ($^\circ\text{C}$) during 30 min after alcohol (20 ml of sherry) and pretreatment with placebo (Pl) or chlorpropamide (Chl) in eight individuals with more than two tests. m, male; f, female. Other abbreviations as Table 1

Diagnosis	Present age	Sex	Test	Flush according to questionnaire	Basal	10'	20'	30'	Peak increment
Normal	71	f	Chl	+	28.6	29.5	30.3	31.2	2.6
			Chl	+	32.1	32.7	34.2	35.0	2.9
			Pl	+	30.6	30.7	31.6	33.0	2.4
Normal	26	f	Chl	+	33.0	33.4	34.4	34.4	1.4
			Pl	-	31.1	31.7	31.6	31.8	0.7
			Chl	-	30.7	31.0	31.1	31.3	0.6
IDDM	19	f	Pl	-	35.4	35.1	35.3	35.2	0.1
			Pl	-	34.3	34.8	34.9	34.5	0.6
			Chl	+	33.4	34.5	35.0	34.6	1.6
IDDM	28	f	Chl	+	34.2	35.1	35.2	35.4	1.2
			Pl	+	32.7	33.3	34.3	34.5	1.8
			Chl	+	33.5	34.4	35.1	34.9	1.6
NIDDM	65	f	Pl	+	32.7	33.8	34.6	35.2	2.5
			Pl	+	33.8	34.9	35.3	34.9	1.5
			Chl	+	33.7	35.1	35.2	34.8	1.5
MODY	22	f	Pl	-	34.0	34.2	34.3	34.2	0.3
			Pl	+	33.6	34.7	34.7	34.5	1.1
			Chl	+	32.8	33.4	34.2	34.6	1.8
MODY	38	m	Pl	+	32.8	33.3	33.5	33.9	1.1
			Chl	+	34.5	35.2	35.3	35.2	0.8
			Chl	+	32.9	34.4	34.2	34.8	1.9
MODY	40	f	Pl	+	30.9	31.1	31.6	31.9	1.0
			Pl	+	31.5	32.0	32.6	32.9	1.4
			Chl	+	32.4	33.0	34.1	34.0	1.6

and our study. Further studies from other authors are needed to clarify whether there is an association of CPAF with a genetic type of NIDDM which we might have missed in our study. We conclude that the test is not suitable for individual diagnosis or for application in genetic counselling.

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