PAPERS AND ORIGINALS

Chlorpropamide-alcohol flushing: a dominantly inherited trait associated with diabetes

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Summary and conclusions

A simple test was devised to identify people susceptible to chlorpropamide-alcohol flushing (CPAF). Subjects were given a placebo tablet, followed by sherry 12 and 36 hours later. They then received a chlorpropamide tablet and sherry again after 12 and 36 hours. This single-dose challenge test was given to non-insulin-dependent diabetics, insulin-dependent diabetics, and normal subjects. CPAF was common in the non-insulin-dependent diabetics but rare in the other groups. When the test was used in identical twins and families of affected subjects CPAF appeared to be a dominantly inherited trait.

We conclude that facial flushing after alcohol in people taking chlorpropamide is related to non-insulin-dependent diabetes, especially when there is a strong family history of diabetes, but not to insulin-dependent diabetes. It is a dominantly inherited trait.

Introduction

Facial flushing after alcohol is a well-recognised complication of chlorpropamide treatment and occurs in about 33% of patients receiving chlorpropamide.[1] After observing chlorpropamide-alcohol flushing (CPAF) in a mother and her two daughters with diabetes we wondered whether the reaction had a genetic basis and was related to diabetes. We therefore investigated its nature, frequency, and familial pattern in the two main types—namely, insulin- and non-insulin-dependent diabetes. We use the term "insulin-dependent" diabetes in preference to "juvenile-onset" or type 1 diabetes since it is more accurate and precise; likewise we prefer "non-insulin-dependent" diabetes to "maturity-onset" or type 2 diabetes.

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Present series

CPAF may start as early as five minutes and usually within 20 minutes after a drink of alcohol and lasts for about 30-60 minutes. It always affects the face, and sometimes the neck and extensor surface of the arms; it is associated with a warm, tingling, or even burning sensation in the face, and occasionally lightheadedness. Breathlessness was reported during the flush by several patients who had no respiratory disease, four of whom also described wheezing. Patients were in no doubt that the flush had occurred and described it consistently without having been told what to expect. The flush may be observed and recorded photographically and thermographically.

Some people flush with alcohol alone, but this is uncommon and occurs only after large amounts have been drunk and not after the very small amounts needed to induce CPAF. Even when a sensitive method of measurement such as increased optical density in the ear lobe is used less than 10% of Caucasians flush after alcohol.[2] Unlike the menopausal flush CPAF is neither spontaneous nor commonly associated with sweating, and patients who have experienced both state that they are clearly different. In contrast to the disulfiram (Antabuse) reaction, which is exhibited by everyone who takes the drug, only a few patients are liable to CPAF, which is never accompanied by vomiting. The reaction is almost specific to chlorpropamide: out of 44 patients who flushed with chlorpropamide, only three flushed when changed to glipizide or glibenclamide, and clinically it is rare to find alcohol flushing in patients taking other sulphonylureas. Ten patients who gave a history of CPAF flushed when challenged with absolute alcohol. The flush is therefore not due to congeners.

It is highly unlikely that the flush is due to sensitisation by previous sulphonylurea treatment since subjects who had never received sulphonylureas flushed. Furthermore, patients report the alcohol flush from the onset of chlorpropamide treatment, and no one who has flushed has ever reported losing the reaction, which has been noted in some cases for 20 years. The age range is wide, patients aged 9-92 years having observed the reaction, which is not sex linked.

SINGLE-CHALLENGE TEST FOR CPAF

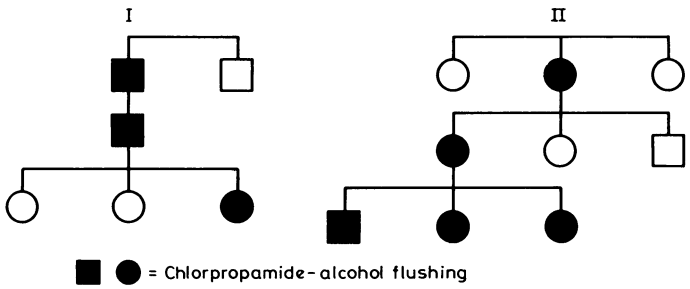
We gave patients a placebo specially prepared so as to be indistinguishable from chlorpropamide and then 40 ml of sherry 12 and 36 hours later. After 48 hours patients were given a tablet of

chlorpropamide 250 mg and 40 ml of sherry again 12 and 36 hours later. The placebo was always given first (though the patients did not know this) as some patients may show alcohol flushing for several days after a single tablet of chlorpropamide. Thirty-three out of 35 subjects who had a history of CPAF reacted positively to this test by flushing at 12 hours, but in two the flush was more noticeable 36 hours after chlorpropamide. Out of 193 patients, only one flushed after the placebo and she also flushed after chlorpropamide. Patients described their reaction to the test as being the same as that on chlorpropamide treatment. Six patients were tested on three separate occasions and had the same reaction on each.

We used this test for subsequent investigations. The patients were asked to describe any reaction to the drink, and the test was considered to be positive only if they reported a definite facial flush after chlorpropamide but not after the placebo. Since the placebo was always given first the test was single-blind, but it was the patient's description that determined whether the appropriate response had occurred.

INHERITANCE OF CPAF

To establish whether CPAF was inherited we tested the following groups. (1) Twelve pairs of identical twins, one or both of whom was diabetic: in each pair the twins gave the same reaction to the test. Of the six concordant pairs (both diabetic), four flushed and two did not; of the six discordant pairs (only one diabetic), two flushed and four did not. One set of concordant diabetic identical triplets was also tested, and all three flushed. (2) Parents of 13 affected subjects: in each case one parent flushed. (3) Twenty offspring of 12 affected subjects: of these, 12 flushed and eight did not. (4) Two families, who showed direct parent-to-child transmission of CPAF through three generations (figure).



Two families showing chlorpropamide-alcohol flushing through three generations.

CPAF AND DIABETES

To determine the relation between CPAF and diabetes we tested three groups of people: (1) 234 selected non-insulin-dependent diabetics; (2) 60 insulin-dependent diabetics, all of whom were young and in whom a definite need for insulin had been established; and (3) 60 normal subjects. Flushing was common among the non-insulin-dependent diabetics but rare in the other two groups: 119 (51%) non-insulin-dependent diabetics flushed compared with six (10%) insulin-dependent diabetics and six (10%) normal subjects. The normal subjects who flushed all gave normal results to glucose tolerance tests.

There was a striking difference in the incidence of CPAF among the non-insulin-dependent diabetics with and without a first-degree family history of diabetes (table). Out of 91 of these patients with a first-degree family history, 74 (81%) flushed; the numbers were similar for those with one or more than one affected relative. Of the remaining 143 without a first-degree family history, only 45 (31%) flushed. By contrast, the number of insulin-dependent diabetics who flushed did not differ according to the presence or absence of a family history of diabetes (table).

No (%) of non-insulin- and insulin-dependent diabetics with and without first-degree family histories of diabetes who showed chlorpropamide-alcohol flushing

	First-degree family history	
	Present	Absent
Non-insulin-dependent diabetics	74 (81%) (n=91)	45 (31%) (n=143)
Insulin-dependent diabetics	1 (7%) (n=14)	4 (9%) (n=46)

Discussion

Almost all the patients who had flushed with alcohol while receiving chlorpropamide flushed when challenged with a single tablet of chlorpropamide, 250 mg, and alcohol. They were in no doubt that they had flushed and did not do so with the placebo. Those who responded positively to the single-tablet challenge test did so again when it was repeated. As only two out of 35 patients with a clinical history of alcohol flushing when receiving chlorpropamide did not flush on this test we felt justified in using it in our studies.

CPAF is a real phenomenon that is distinct from other causes of flushing. Patients prone to the flush notice it consistently, and we have found no patient in whom the tendency to flush has disappeared. CPAF is not due to sensitisation, since it occurs in people who have never received sulphonylureas, and patients who show it describe it as having occurred from the onset of treatment.

The results obtained in identical twins strongly suggest that CPAF is inherited. In all 12 pairs tested both twins reacted similarly to the test, including the six pairs discordant for diabetes. The set of diabetic identical triplets all flushed. We believe that CPAF is a dominant trait for three reasons. Firstly, in every case in which we have been able to test the parents of affected subjects one has flushed; secondly, those who show CPAF have affected and normal offspring in about equal numbers; and thirdly, there is direct transmission from parent to child through three generations.

CPAF is associated with non-insulin-dependent but not insulin-dependent diabetes. There is considerable evidence that these two types of diabetes are genetically distinct—for example, insulin-dependent diabetes is associated with certain histocompatibility antigens, whereas non-insulin-dependent diabetes is not[3 4]; and most identical twins with non-insulin-dependent diabetes are concordant for diabetes, while many with insulin-dependent diabetes are discordant.[5] The association between CPAF and diabetes is confined to the non-insulin-dependent type, especially when there is a strong family history of the disease. This suggests that non-insulin-dependent diabetes may be a heterogeneous condition divisible into two groups—that is, flushers with a strong family history of diabetes and non-flushers without such a strong history. The percentage of non-insulin-dependent diabetics without a family history who flush (31%), however, is still greater than that in normal subjects. This might be at least partly because of difficulty in obtaining a full family history of such a mild disease as non-insulin-dependent diabetes.

The nature of the association between CPAF and diabetes is not clear; we do not even know whether the CPAF has any direct physiological connection with the mechanism of production of diabetes. By the Hardy-Weinberg principle the relative proportion of flushers and non-flushers should remain constant from one generation to another.[6] Since the incidence of non-flushers in our normal controls was 90%, we calculate the prevalence of the gene for CPAF to be 5%. This gene prevalence in a normal population is greater than the usually accepted prevalence of diabetes,[7] but mild diabetes may go unrecognised and its real prevalence may therefore be higher. Furthermore, our control group was small and the Hardy-Weinberg equilibrium disregards factors such as selection, mutation, and linkage disequilibrium, so the estimation of the prevalence of the gene is probably inaccurate.

We do not know whether all non-diabetics who flush will become diabetic. We calculate the relative risk[8 9] of someone with CPAF developing non-insulin-dependent diabetes as being 9, increasing to 38 if there is an affected first-degree

relative. The relative risk is simply the risk of someone with this trait as compared to someone without it becoming diabetic. The degree of risk applies only to Caucasians since we did not study other racial groups; there is some ethnic variation in the tendency to flush,[10] which in the case of flushing after alcohol alone probably has a genetic basis,[11] so the prevalence of CPAF may also be different in other populations.

In conclusion, we have devised a simple single-dose test for CPAF. CPAF is a dominantly inherited trait associated with non-insulin-dependent diabetes especially when there is a strong family history of the disease. CPAF is not associated with insulin-dependent diabetes, confirming the genetic difference between this and non-insulin-dependent diabetes.

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Chlorpropamide-alcohol flushing: a definition of its relation to non-insulin-dependent diabetes

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Summary and conclusions

The single-challenge test for chlorpropamide-alcohol flushing (CPAF) was used to study two groups of patients with non-insulin-dependent diabetes and a family history of the disease who were distinguished only by their age at diagnosis (under and over 30). Their relatives were also studied. The proportions of patients showing CPAF in both groups were similar, and the family histories suggested dominant inheritance. When offspring of diabetics in whom the disease was diagnosed early were studied CPAF seemed to precede the appearance of diabetes.

We conclude that the patients in both groups had the same, distinct syndrome, which is characterised by diabetes diagnosed at any age that is inherited as an autosomal dominant trait and associated with CPAF. This syndrome, which constitutes about one-fifth of all cases of non-insulin-dependent diabetes, may be detected with a single-challenge CPAF test before the onset of glucose intolerance. CPAF therefore acts as a genetic marker for the syndrome.

Introduction

As shown in the previous paper in this issue, facial flushing after alcohol in patients receiving chlorpropamide is a distinct entity inherited as an autosomal dominant trait. It is found commonly in non-insulin-dependent diabetics, particularly those with a family history of the disease, but only rarely in insulin-dependent diabetics and normal subjects. We have attempted to define the relation of chlorpropamide-alcohol flushing (CPAF) to diabetes by studying families of non-insulin-dependent diabetics with a family history of diabetes. Since CPAF is dominantly inherited we have also studied its occurrence in a type of diabetes thought to be inherited in the same fashion—that is, "Mason-type" diabetes[1] (named after the first family we observed), also called mild diabetes of young onset.[2 3] The evidence that this syndrome is dominantly inherited is, firstly, that in sibships of affected patients half the sibs are also affected; secondly, that nearly all affected subjects have an affected parent; and, thirdly, that several cases of inheritance through three consecutive generations have been seen.

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Subjects and methods

We used the single-challenge test for CPAF (described in our previous paper) to study two groups of non-insulin-dependent diabetics with a family history of the disease: the groups were divided according to age at diagnosis in the belief that patients diagnosed under the age of 30 correspond to those with Mason-type diabetes and are distinct from those diagnosed later. Group 1 comprised 15 propositi diagnosed before the age of 30, and 32 of their parents and sibs, of whom 18 were diabetic and 14 not. Group 2 comprised 37 propositi diagnosed after the age of 30 who had at least two affected first-degree relatives, and 42 of their parents and sibs, of whom 20 were diabetic and 22 not.

Results

All the 15 propositi and 16 of the 18 diabetic relatives in group 1 flushed, while only two of the 14 non-diabetic relatives did so. In group 2, 32 of the 37 propositi and 17 of the 20 diabetic relatives flushed, whereas none of the 22 non-diabetic relatives did so. Thus in group 1 a total of 31 of the 33 diabetics (94%) and two of the 14 normal subjects (14%) showed CPAF; in group 2 the proportions were 49 of the 57 diabetics (86%) and none of the non-diabetic relatives. These results show a strong association between CPAF and diabetes in both groups, the incidence of CPAF being similar in each. Since CPAF is an inherited trait this suggests that diabetes in these selected groups has a genetic basis. If this is so the clinical features of the diabetes will be the same, and we therefore examined the diabetics