ALCOHOL DEPENDENCE: IS CARBOHYDRATE-DEFICIENT TRANSFERRIN A MARKER FOR ALCOHOL INTAKE?

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Abstract — We investigated %CDT (carbohydrate-deficient transferrin) in 92 ethanol-intoxicated alcohol-dependent patients after consecutive admission to hospital and followed them for 28 days under controlled conditions. At admission, 63% (58 patients) showed elevated CDT (>2.5%) and 34 patients (37%) had normal CDT levels (<2.5%). No correlation of the %CDT values to alcohol-related disabilities, severity of the withdrawal syndrome, alcohol-drinking pattern before admission, or several other factors was found. The sensitivity of GGT (y-glutamyl transferase) was 58% for the same group of patients. Levels of %CDT decreased during the 28 days following abstinence, whereby we could separate four statistically different groups of 'CDT decrease'. In two of these groups, comprising most of the cases studied, normal %CDT levels were reached after 14 days of abstinence. Those patients with %CDT levels exceeding the upper normal level after 14 days of sobriety, showed a decrease during the following 14 days to levels of 2.55–2.61%.

INTRODUCTION

The iron-transporting protein transferrin consists of a polypeptide backbone to which several polysaccharide chains are linked. These polysaccharide chains are desialylated by alcohol consumption. This desialylated transferrin, carbohydrate-deficient transferrin (CDT), was introduced as a biochemical 'state marker' of heavy alcohol consumption by Stibler et al. (1979). Since then, many investigations of its usefulness as a marker of heavy alcohol consumption have been reported (see, e.g., Stibler and Borg, 1986; 1988; Stibler et al., 1986; Behrens et al., 1988; Kwok-Gain et al., 1990; Nystrom et al., 1992; Rosman and Lieber, 1992; Borg, 1993; Bell et al., 1993; Allen et al., 1994; Lof et al., 1994). Although these studies showed clearly that CDT generally reflects high alcohol intake, a number of questions remain unanswered; in particular, the precise relationships between levels of CDT and extent of alcohol intake, pattern and duration of consumption, and decline in CDT following abstinence. These aspects are of particular importance in assessing the suitability of CDT as a 'relapse', as well as 'state' marker of alcohol consumption (Schmidt and Rommelspacher, 1990; Rosman and Lieber, 1992).

In the preceding paper (Lesch et al., 1996a) we have demonstrated the usefulness of CDT as a marker of high alcohol consumption irrespective of changes in total transferrin levels or the presence of liver disease, and its superiority to y-glutamyl transferase (GGT) in a general hospital population. In the present paper, we report the results of experiments in which we investigated the value of CDT in alcohol-dependent patients in relation to: (1) GGT and blood ethanol concentration at admission; (2) extent and pattern of alcohol consumption before admission; (3) level and pattern of decline in CDT with duration of

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abstinence; (4) severity of withdrawal and other alcohol-related disabilities.

PATIENTS AND METHODS

Patients and design

Ninety-two male alcohol-dependent patients were investigated at the time of admission for detoxification and during a 4-week follow-up period. We only included patients who were diagnosed according to DSM-III-R as having 'Alcohol dependence, severe' (at least seven symptoms present) with no remission. Additionally, we applied a semi-structured questionnaire related to the typology of Lesch (1985), in order to classify the drinking pattern as well as the severity of somatic, psychic and social deterioration. The drinking pattern of the patients before admission was established with respect to amount, frequency and drinking rhythm. Sobriety control was checked daily by a breathalyser test.

Laboratory tests

Upon admission, in addition to the severity of alcohol intoxication, levels of the laboratory markers GGT, ALAT, ASAT, MCV, CDT, total transferrin and blood counts were determined. Both relative (%) and absolute (U/l) values of CDT were measured. For measurement of %CDT, U/l CDT and total transferrin, serum was frozen to −30 °C before analysis at the laboratories of Axis Biochemicals in Norway, in accordance with the procedure outlined in the preceding paper (Lesch et al., 1996a). The normal range was set at values of 0–2.4% in accordance with Behrens et al. (1988), Kwoh-Gain et al. (1990) and Axis's own experience. The %CDT was measured at admission (day 0) and on days 3, 7, 14, 21 and 28 after the start of abstinence (detoxification), and the numbers of patients tested on these days were 92, 91, 89, 90, 66 and 67 respectively. The smaller numbers at the later time intervals are due to drop-out, the rate of which was 29.35%, caused by earlier discharge or refusal to give blood. The %CDT was determined according to the Axis method, whereas absolute CDT values (U/l) were measured in 42 samples according to the Pharmacia method. An initial study comparing the two methods demonstrated a good correlation (see Lesch et al., 1996b).

Correlations

We attempted possible correlations between different patient-related factors and the %CDT values. For this purpose, the latter values were divided into the following categories: <2.5%, 2.5–3.5%, 3.6–4.5%, 4.6–5.5%, 5.6–10.5% and >10.5%, to enable more precise correlations to be made. For statistical evaluation, we applied the Pearson $\chi^2$-test.

The patient-related factors considered in these correlations were the following:

1. Diseases: liver diseases, severe chronic diseases (including psychiatric diseases) in the first and second degree relatives, disorders of the perinatal period, polyneuropathy, cardiac, pancreatic or gastrointestinal disease, epilepsy, cerebral dysfunctions, withdrawal syndromes, tolerance reduction, loss of control and loss of memory.

2. Drinking pattern: history, type of beverage preferred (beer, wine, strong drinks, mixtures), alcohol consumption before the age of 14 (two patients had regular alcohol consumption before the age of 8, and both had %CDT values of ~10.6%) and accidents under the influence of alcohol.

3. Psychological factors and life events: behavioural disorders during childhood, brain trauma (e.g. due to accidents), self-destructive or other aggressive behaviour, sleep disorders, sexual dysfunction, depression and suicide attempts.

4. Typology: according to Jellinek (1946) and Lesch (1985).

5. General factors: age, social status, profession, age of mother/father at the patient's birth, alcoholism in first or second degree relatives, order of nascence among siblings and tobacco consumption.

RESULTS

Results at admission

Of all the 92 alcoholic patients, 34 (37.0%) had CDT values of <2.5%. By contrast, 58 patients (63%) had elevated %CDT values, yielding a sensitivity in elevated CDT of 63.0% when identifying drinking alcohol-dependent patients. If a cut-off point of <2.0% CDT is adopted, the sensitivity rises to 78.3%, whereas a lowering of
the cut-off point to <1.5% CDT increases the sensitivity only moderately (to 84.8%). A cut-off point of 2.0% CDT therefore merits consideration.

**Distribution of patients according to %CDT values**

As stated above, of the 92 patients, 34 (37.0%) had CDT values <2.5%, whereas the remainder exhibited elevated values as follows: 9 (9.8%) had CDT values in the range of 2.5–3.5%, 7 (7.6%) had values of 3.6–4.5%, 6 (6.5%) had values of 4.6–5.5%, 22 (23.9%) had values of 5.6–10.5%, and 14 patients (15.2%) had levels of >10.6%.

**Comparison of %CDT with GGT and effect of liver disease**

The data in Fig. 1 show that 34 out of 82 patients exhibited no significant elevation in
γ-glutamyl transferase (GGT), despite having been drinking before the admission. Using 50 U/l GGT as a cut-off point, GGT shows a sensitivity of 58.5%.

We found (data not shown) no significant correlation between %CDT values and the severity of liver diseases. Thus fatty liver with liver enlargement and elevated values of alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT) and GGT were present in all the %CDT categories shown. Among patients with liver cirrhosis, high as well as low %CDT values were present.

**Relationship between %CDT values and alcohol intake**

Five patients with >2.5 promille of blood alcohol (>250 mg/dl) had CDT values lower than the cut-off limit of 2.5%. There was no correlation between the extent of acute alcohol intoxication, expressed as elevation of blood ethanol concentration, and elevation of %CDT
values (Fig. 2). Furthermore, there was no significant correlation between %CDT and the duration of pathological drinking or the increased level of alcohol consumption in grams (Fig. 3). As can be seen in Fig. 3, six patients drinking >400 g of alcohol daily had CDT levels >4.5%, whereas two patients had a CDT value of 2.5–3.5% and three patients had a CDT level of <2.5%.

No significant correlation was found with respect to different patterns of drinking during the 2 months before admission (Fig. 4) nor the severity of the withdrawal syndrome during the 48 h following admission (data not shown).

**Relationship between %CDT values and other factors**

The different categories of %CDT levels were compared with other parameters. These were: gastrointestinal disease, neuropathy, GGT at admission, genetic factors (alcohol dependence in first and second degree relatives) and clinical subgroups of alcoholism according to the typo-
logies of Lesch and Jellinek (Types I, II, III and IV and Gamma- and Delta-Type). None of these factors showed any correlation with %CDT values (data not shown).

Results during 28 days following admission
The mean %CDT values of all patients studied showed a gradual decline with time following detoxification. This was so despite the fact that, of the 92 patients tested on day 0, only 67 were available for testing on day 28. In the 65 patients from whom blood samples were obtained on all testing occasions, the mean %CDT results declined from a starting value of 6.03% on day 0 to values of 5.16, 3.14, 2.19, 1.80 and 1.56 on days 2, 7, 14, 21 and 28 respectively after admission (Fig. 5).

The distribution of the %CDT results in the individual 65 patients during treatment is shown in Fig. 6. Here, it is clear that %CDT values did not decrease constantly in all patients; they increased in some patients during the 28-day treatment period. It is however possible that these latter patients could have been drinking from time to time despite being inpatients and having undergone daily breath-alcohol testing, or alternatively the CDT assay may still have some imperfections.

In an analysis of variance, we identified four groups of patients with different decline patterns for CDT that showed statistically significant differences (test for homogeneity of variances: Cochran’s $C = 0.3563, P = 0.381$; Bartlett Box $F = 7.038, P = 0.000$; max. variance/min. variance $= 6.545$) (Fig. 7). One group ($n = 31$) started with a low %CDT (mean 2.13) at admission, which decreased to a slightly lower level (mean 1.01). The second group ($n = 25$) included patients admitted with a mean %CDT of 6.91% that declined by day 14 to <2.5%. A third group ($n = 7$) exhibited a mean %CDT value of 13.18 that fell by day 28 to values >2.5%. The fourth group ($n = 2$) started with much higher levels (>30% CDT), which declined to levels just above the cut-off point of 2.5%.

When comparing categories of CDT <2.5% and >2.5% on the 14th day of abstinence with the corresponding GGT values upon admission, it was found that in the elevated %CDT patients’ group, 17 had a high, whereas only 6 had a low, GGT value (no significant correlation).

DISCUSSION
In the present paper, a number of issues have been addressed experimentally, most of which are related to alcohol consumption itself, whereas others concerned the consequences of this consumption and also some other factors. As regards factors unrelated directly to alcohol consumption, we observed no correlation between changes in the
%CDT levels and GGT at admission, severity of liver disease, gastrointestinal disease, neuropathy, genetic factors and clinical classification of alcoholics according to the typologies of Lesch and Jellinek. Additionally, as regards GGT, the sensitivity of this marker in the present study was 58%, in comparison with a CDT sensitivity of 63% using a cut-off point of 2.5% for the latter, whereas in relation to genetics or particular sub-grouping of alcoholic patients, there is no evidence from our study that supports a link with CDT.

Our results have also demonstrated no correlation between %CDT values and extent of acute alcohol intoxication, i.e. elevation of blood ethanol concentration (Fig. 2), amounts of alcohol consumed before admission (Fig. 3), pattern of drinking during the 2 months preceding admission (Fig. 4) or the severity of the alcohol withdrawal syndrome.

Although the mean %CDT in the patient group as a whole declined to <2.5% by day 14 following abstinence (Fig. 5), the data in Fig. 6 show clearly that some patients did not show such a continuous decline with time after detoxification; some showed sporadic increases, the possible reason(s) for which remains to be established. On the basis of the decline in %CDT after abstinence, we were able to classify alcoholics into four categories with different patterns of decline (Fig. 7). It should however be pointed out here that the numbers of patients in the two categories in which CDT values were >2.5% even after 28 days of abstinence were small, and that such categories included those patients with the highest pre-detoxification %CDT values. These observations are of importance in relation to forensic aspects where a longer observation period may be necessary in subjects with the above characteristics. Of more interest is the fact that a sizeable proportion of our patients had %CDT values within the normal range, despite their high alcohol consumption (Fig. 2). The relevance or lack of it for elevation of serum CDT concentration. A possible explanation of these differences may be related to differences in pattern of drinking between the Nordic countries (episodic) and those of middle Europe (continuous daily; see, e.g. Mader et al., 1981).

According to the definition of Rosman and Lieber (1992), %CDT is a 'state marker'. According to their definition a 'relapse marker' is specific for acute alcohol intake, whereas a 'screening marker' demonstrates chronic alcohol consumption. As to these definitions, our results suggest that %CDT could be used as a 'screening marker', whereas its value as a 'relapse marker' requires further investigation.

REFERENCES
intake: a study with healthy subjects. Alcohol and Alcoholism 31, 265–271.