CARBOHYDRATE-DEFICIENT TRANSFERRIN AS A SCREENING MARKER FOR DRINKING IN A GENERAL HOSPITAL POPULATION

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Abstract — We investigated the usefulness of the laboratory marker of alcohol consumption carbohydrate-deficient transferrin (CDT) in 101 consecutively admitted patients in a surgical and internal medical ward of a hospital in a rural wine-growing area. Four major aspects were considered: the influence of liver disease, the method of expression of CDT values (relative % vs absolute units/l), level and pattern of alcohol consumption and comparison with γ-glutamyl transferase (GGT). The results show that %CDT is a more valuable discriminating marker of high alcohol consumption than absolute CDT values and its usefulness in this respect is independent of changes in serum total transferrin levels, as in liver disease. Sensitivity and specificity of %CDT were 70 and 98% respectively, compared with 65 and 83% respectively for GGT.

INTRODUCTION

Psychiatry needs a more precise alcoholism diagnosis with more therapeutic potential than the presently used diagnostic criteria (Lesch et al., 1990, 1993). The same applies for detection of high alcohol intake. Specificity studies for state markers are needed, in order to allow a differentiation to be made between a temporarily high alcohol intake, short-term excessive drinking and a chronic intoxicating drinking pattern. In addition to psychiatrists, general practitioners, surgeons, anaesthetists and internal medical specialists also need rapid, easy and reliable markers for high alcohol intake and for alcohol dependence detection. The necessity to use a screening marker in all other medical disciplines arises also because of the interactions between ethanol, methanol and the other congeners in alcoholic beverages and their metabolites with most administered drugs, including anaesthetics.

Serum transferrin is a glycoprotein (see Fig. 1) with a molecular mass of 80,000. It consists of a single polypeptide with two N-linked polysaccharide chains. The chains are branched with usually five ‘antennae’. Most of these antennae have terminal sialic acid residues. It is known that the fraction of transferrin variants carrying only one or two terminal sialic acid residues is elevated in serum from individuals with chronic high alcohol consumption. This fraction is named carbohydrate-deficient transferrin (CDT), which was introduced as a marker for alcohol intake. The available diagnostic criteria, however, are still too imprecise for realization of the full potential of this test, which may be an important factor in the divergent results.

The experiments whose results are described and discussed in this and the two accompanying papers were designed to investigate in detail the status of CDT as a marker for alcohol consumption in a variety of clinical settings. In the present paper, we examined the sensitivity and specificity of CDT in comparison with those of γ-glutamyl transferase (GGT) as screening markers for drinking in a general hospital population. We have chosen for this purpose an internal medical and a surgical ward in a hospital situated in a wine-producing area where 33% of all adult males and 2% of all adult females

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have a daily alcohol consumption of more than 60 g (Mader et al., 1981). It has previously been stated (Borg et al., 1992; Borg, 1993) that daily consumption of 60 g of alcohol for ten days increases CDT values (measured in mg/l), and it was therefore considered important to ascertain whether patients from our population would show similar changes. It was also considered important in the present work to ascertain the role of liver disease in the changes in CDT. Furthermore, because changes in the amount of total transferrin will influence the absolute CDT values, it was considered that measurement of the % CDT may yield more reliable data than that of absolute CDT values, contrary to the statements by Allen et al. (1994). The results of these investigations form the subject of the present paper.

PATIENTS AND METHODS

Patients and diagnoses

A total of 101 patients were consecutively, in the sequence of their admission, recruited into the study. They were examined somatically and neurologically. The diagnoses, which led to hospital admission, were divided into two groups: (a) those suggestive of alcohol abuse (e.g. liver diseases, pancreatitis, polyneuropathies); (b) those not directly related to alcohol consumption (e.g. hernia inguinalis, cancer, pneumonia etc.), though we were aware of the fact that in some of these diseases there may be indirect connections. During the admission period, other diseases were also detected, so that at discharge the primary diagnoses were completed and comorbidity established. According to this comorbidity, patients’ diagnoses were changed between the above-mentioned groups. As an example, a case of pneumonia had been the diagnosis leading to hospital admission, after which additional diseases, such as polyneuropathy and steatosis hepatitis, were found so that at discharge the number of alcohol-related diagnoses given had increased.

Each patient’s drinking pattern prior to admis-
CDT AS A MARKER OF ALCOHOL CONSUMPTION

Fig. 2. Detection of high alcohol consumption in presence or absence of liver disease by carbohydrate-deficient transferrin (CDT).

The results from 101 patients admitted at The Kittsee Hospital (a general hospital in Austria), departments of surgery and internal medicine, demonstrate that with Axis %CDT 70% of the patients consuming >60 g of alcohol on average daily basis were identified. Specificity is 98%.

Assay of CDT

In this study CDT was measured at %CDT, with a cut-off value of up to 2.4%. 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 following Axis %CDT method was used. Serum (75 μl) was mixed with 150 μl of a solution containing 125I-labelled anti-transferrin antibody Fab fragment and Fe(III) for iron saturation. The amount of transferrin in serum is in large excess of the amount of antibody added. The complexes formed between the isoforms of transferrin (i.e., those with different contents of sialic acid) and antibody were then separated by adding 100 μl of this mixture followed by 100 μl of a non-eluting buffer to a strong anionic exchange column (single use). This was performed in duplicate for each sample. Complexes between antibody and isoforms of transferrin containing di-, mono- and asialotransferrin were salt-eluted from the column by adding 3 ml of a chloride-containing buffer. The radioactivity in the eluted fraction was measured by gamma-counting (Packard Crystal counter). The relative amount of radioactivity (i.e.
labelled antibody) eluted corresponds to the relative amount of these isoforms of transferrin (%CDT) in a serum sample and %CDT was estimated from a standard curve established by the use of sera with known %CDT contents.

RESULTS

Of the 101 total admissions, 14 (13.9%) (13 male, 1 female) were admitted with an alcohol-related diagnosis. Another 18 patients (17.8%) were admitted with a non-alcohol-related diagnosis (17 male, 1 female), but subsequently received a definite alcohol-related diagnosis. Of the 101 patients, 15 (14.9%) showed elevated CDT levels, 4 of these had a non-alcohol-related diagnosis, 5 had alcohol-related diseases at admission and 6 started with a non-alcohol-related diagnosis, but received subsequently an additional alcohol-related diagnosis. According to their liver disease, their subjectively declared drinking habits and the drinking pattern assessed with the Lesch questionnaire, we classified our patients into four groups as follows: (1) <60 g of alcohol daily, without liver disease (n = 59); (2) <60 g of alcohol daily, with liver disease (n = 21); (3) >60 g of alcohol daily, without liver disease (n = 5); (4) >60 g of alcohol daily, with liver disease (n = 16). GGT, absolute CDT and %CDT values were measured in all four groups and their specificities and sensitivities were calculated. Out of the above 37 patients with liver disease, 5 had a liver disease not caused by alcohol intake.

Specificity and sensitivity of %CDT

From the data in Fig. 2, it can be deduced that the %CDT as a test has a sensitivity of 70% and specificity of 98%. Patients consuming <60 g of alcohol per day showed no elevated values of %CDT regardless of liver disease. A sensitivity of 70% suggests that one-third of all patients with liver disease show a %CDT value <2.5%.

Measuring absolute CDT units results in lower discriminative ability

Liver disease may lead to changes in total transferrin level and possibly reduce the discriminating ability of absolute CDT values. Figure 3
CDT AS A MARKER OF ALCOHOL CONSUMPTION

The GGT values from the patients at The Kittsee Hospital show that 50% of the non-drinking patients with liver disease had elevated GGT.

Fig. 4. Detection of high alcohol intake by γ-glutamyl transferase (GGT).

shows the results of measuring the CDT absolute values (mg/l). With a reference value of 45 mg/l, this method gave one false-positive result and a lower sensitivity for the lower alcohol consumption group. Thus the results in Figs 2 and 3 suggest that measuring %CDT yields higher specificity than absolute CDT, and that Axis %CDT analysis clearly separates patients with high and low alcohol consumption.

Comparison of GGT and %CDT as correlates of drinking behaviour

Figure 4 indicates that 13 individuals consuming <60g of alcohol per day showed false-positive GGT results. In this study group the sensitivity of GGT is 65% and the specificity 83%.

Correlation according to diagnosis

The patients from the Kittsee Hospital were separated into two different groups according to cause of admission and the comorbidity. Patients were clinically defined as 'subjects with an alcohol-related disease' and 'subjects with no connection with alcohol'. The distribution of patients in the two groups was about the same regardless of age or sex. Regarding CDT at a

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reference limit of 2.5%, the number of patients in the group of alcohol-related diseases was twofold higher than in the other group.

%CDT is independent of low total transferrin levels

As stated in the Introduction, low levels of total transferrin, which may occur in liver disease, could influence the results when measuring absolute CDT values. When selecting patients with total transferrin values <1700 mg/l, the %CDT results show a sensitivity and a specificity of 100%. As regards the alcohol consumption pattern, neither false-positive nor false-negative results were seen, though the difference between the two CDT measurement methods (absolute vs %CDT) was not significant (small sample number) (Figs 5 and 6). By contrast, in the group of patients with low total transferrin, GGT showed a sensitivity of 60% and a specificity of 75% (Fig. 7).

DISCUSSION

Reliable screening markers to diagnose objectively alcohol abuse are of great importance in current medicine (Schmidt and Rommelspacher, 1990; Rosman and Lieber, 1992). Progress has been made in this area by developing various methods for measuring CDT and its reliability as a marker of alcohol drinking, abuse and addiction (Stibler et al., 1979; Behrens et al., 1988; Stibler and Borg, 1988; Nystrom et al., 1992; Borg et al., 1992; Borg, 1993; Bell et al., 1993; Allen et al., 1994). For screening in a general hospital, %CDT has proved to be the most reliable marker of chronic alcohol consumption. The %CDT Axis method used in this study is not as time-consuming and cumbersome as previous methods developed for CDT measurements. This time-saving aspect is of great importance if %CDT analysis is going to be a part of routine laboratory testing (measurements take only minutes).

In the present study, a number of issues were addressed, namely relationships between CDT on the one hand and level of alcohol consumption and presence of liver disease on the other, the value of CDT measurement in comparison with that of another marker, GGT, and the expression of the CDT values (as a percentage or absolute amount). As regards the latter point, the results in Figs 2 and 3 suggest clearly the greater sensitivity of the %CDT. Furthermore, as the data in Figs 5 and 6 demonstrate, %CDT is superior to absolute values in detecting high alcohol intake in patients with low total transferrin levels (those with liver disease). The data in Figs 2 and 3 additionally demonstrate that the presence of liver disease does not influence the ability of CDT to detect high
alcohol consumption (>60 g of alcohol per day) when this marker is expressed as a percentage. However, because the group of patients with liver disease who consumed > 60 g of ethanol daily was small in number, further studies with larger numbers are required. A comparison of %CDT and GGT in the present work shows clearly that the latter has a lower specificity for detection of high alcohol intake (Fig. 7 vs Fig. 5 for %CDT) and gives false-positive results in those with low alcohol intake, because of the presence of liver disease (Fig. 4).

Among groups of patients with definite changes in total transferrin concentrations, as occurs in liver disease, hormone disturbances and pregnancy, the quantification of CDT as a percentage appears to be superior and preferable to that in absolute units (corresponding to HbA1c in the field of diabetes). Clearly, there may be an advantage with such a ratio measurement, which compensates for low transferrin production. However, the high ratio is not due to alcohol-induced causes, but to other causes. Studies investigating patients with different diseases leading to different rapidity of total transferrin changes (such as carcinoma, different forms of hepatitis etc.) are needed. Also it would be of importance to show in further studies the connection between CDT and total transferrin in different groups of patients. Regarding elevated levels of total transferrin due to oestrogens, Lof et al. (1994) reported a high specificity for CDT also in pregnant women, and O. M. Lesch et al. (in preparation) did not detect elevated %CDT values in non-alcohol consuming pregnant women, although false-positive values were noted with absolute CDT measurements.

The present results clearly demonstrate the value of CDT in detecting high alcohol intake in patients in a general hospital’s surgical and internal medical wards. A person’s subjective information about own alcohol consumption is often unreliable (Lesch, 1985; Litten and Allen, 1992), and because of the possible serious consequences of the interactions between alcohol and other drugs, it is clear that availability of a rapid and reliable laboratory test for detection of alcohol consumption is important for other medical specialities too, in particular anaesthesiology and also psychiatry, in view of epidemiological evidence that ~30% of patients with affective disorders (Goodwin et al., 1977; Kendler et al., 1992) and 10% of patients suffering from schizophrenia abuse alcohol before admission.

REFERENCES


