LIMITATIONS IN THE USE OF $\gamma$-GLUTAMYL TRANSFERASE ESTIMATIONS IN ALCOHOL-DEPENDENT SUBJECTS

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Abstract — This paper studies a cohort of randomly selected attenders at a district alcohol treatment service and examines the relationship between clinical assessments and laboratory markers currently in use in the unit. It measures in particular the rate of change of serial $\gamma$-glutamyl transferase (GGT) during abstinence throughout an alcohol treatment programme in alcohol-dependent subjects. The results show that GGT is less often elevated in alcohol-dependent patients than was previously thought. Its predictive value changes little with respect to the age of the subject and length of drinking history. Measurement of GGT adds little to the diagnostic sensitivity of careful history taking. In the alcohol-dependent population, GGT estimation is of little value and a normal GGT does not exclude chronic alcohol dependence.

INTRODUCTION

Serum $\gamma$-glutamyl transferase (GGT) levels are commonly estimated in patients known or suspected of recent excessive alcohol intake. In alcohol treatment units, this estimation is often performed as part of the routine assessment procedure and sometimes repeated in an attempt to confirm either improvement in liver function or compliance with abstinence. There have been few publications examining the effectiveness of GGT estimations either singly, or more particularly, serially, in assessing these clinically important matters in patients with established alcohol dependence. This article aims to examine in what fashion GGT co-varies with various indicators of alcohol abuse, such as other liver function tests or mean corpuscular volume (MCV), and whether this is of clinical relevance.

Some of these issues have been addressed by various authors. For example, serum GGT has been found to be raised in a proportion of 'alcoholics' (variously defined or undefined) estimated as between 50 and 85% approximately (Rosalki, 1984). It has been further established that raised GGT values in alcoholics will generally return towards the normal range with abstinence, within approximately 5 weeks (Rosalki and Rau, 1972). Persistent elevation may be observed in those with cirrhosis (Levy et al., 1975). The fall in GGT has been found to be exponential in some (Lamy et al., 1974), but in those with levels less than five times the upper limit of normal, the fall may be delayed (Wadstein and Skude, 1979).

Clearly to be of practical clinical value, the relationships between the rate of reduction in GGT over time, alcohol intake, alcohol history, and other indicators must be better understood. Work on more recently introduced indicators of excessive alcohol consumption, such as carbohydrate-deficient transferrin (CDT), has compared $\gamma$-GGT against CDT and indicators such as liver function tests and MCV (Stibler et al., 1988; Kwoh-Gain et al., 1990). This work has, incidentally, provided a little more information concerning the behaviour of serial GGT estimations in alcoholics and some efforts have been made to link this with measures of alcohol intake.

We decided not to measure CDT, as a telephone survey of 15 hospital biochemistry laboratories (including university hospitals) in West Central Scotland revealed that none offered the test. Analysis of CDT levels is complex (Renner and Kanitz, 1997), and, although the diagnostic specificity is good, its sensitivity may not be as good as was originally believed (Arndt et al., 1997). Increased levels of CDT have been found
in the absence of alcohol abuse in patients with cardiac, lung and pancreatic pathology, and in patients with primary biliary cirrhosis.

Since, when assessing biochemical markers, most clinicians in the field of alcohol treatment currently rely on GGT alone or in conjunction with MCV, there appears to be a need for closer examination of the relationships between these routinely available markers as they are used in clinical practice. It is usually assumed (Rosalki, 1984) that raised GGT will detect a certain proportion of patients who have been drinking recently, and that MCV combined with a good clinical history will further increase sensitivity (Rosalki, 1984). In dealing with populations of drinkers who are mainly alcohol-dependent, to be useful, laboratory tests must provide information beyond the confirmation of recent abuse of alcohol, helpful though this finding may be in certain cases.

The present study therefore aimed to examine the relationship between clinical assessments and laboratory markers currently used in our Unit, and to measure particularly the rate of change of serial GGT and other measures during abstinence throughout a treatment programme in alcohol-dependent subjects. A systematic appraisal of some defining clinical characteristics of the population under study was required. This has usually been absent in studies which have concentrated on biochemical and haematological measures alone.

**SUBJECTS AND METHODS**

**Subjects**

The study was carried out on 45 alcohol-dependent patients attending our alcohol treatment service. All patients had been assessed by a psychiatrist in the clinic as requiring admission for treatment. The patients were divided into groups depending on their index GGT level.

**Methods**

A battery of measures was performed on a randomly selected cohort of patients presenting for assessment at an alcohol problems Unit in a district with a high prevalence of alcohol misuse and dependence. The group comprised subjects reaching the stage of initial physical examination and routine laboratory testing which was taken as the entry point to the study proper. Demographic and initial clinical assessment data were recorded to establish, in the first instance, whether the cohort was representative of patients attending the Unit.

The initial assessment consisted of: (1) demographic information; (2) clinical history, including typical weekly consumption of alcohol in units at the time of presentation; (3) short form alcohol-dependence data questionnaire (SADD) (Raistrick et al., 1983), this is a standardized severity of dependence questionnaire; (4) an alcohol problems questionnaire (Drummond, 1990); (5) laboratory investigations consisting of GGT, liver-function tests, and full blood count; (6) history of abuse of any other prescribed or illicit drugs; (7) previous attendance at the Unit; (8) duration in years of excessive drinking. Patients taking medicines known to cause disturbances in liver-function tests, such as neuroleptics, antidepressants and anticonvulsants, were excluded.

Following the above initial assessment, laboratory tests were performed at weekly intervals for the following 4 weeks or until the patient defaulted. Frequent checks for compliance with a regime of total abstinence were performed; all patients were either attending daily during the treatment programme or as in-patients. Checks included breath-alcohol sampling on entry to the programme and random spot checks thereafter.

Sequential GGT values were tabulated along with the other variables and analysed initially to examine: (1) level of abnormally raised initial value; (2) rate of reduction over 4 weeks; and (3) significant co-variance with any other variables.

**RESULTS**

A total of 45 patients entered the study, 40 were male and five female. The mean age of subjects was 43.6 years. The age range was 26 to 63 years. All had been alcohol-dependent for many years. None had biopsy-confirmed cirrhosis. The mean duration of drinking for each group and their age of onset of dependence are shown in Table 1. Subjects were subdivided into four groups according to initial GGT in order to demonstrate differences between groups with a high or low initial GGT value. Forty-three completed 2 out of 4 weeks and 15 defaulted before final measure-
Table 1. Mean age of onset and duration of alcohol dependence

<table>
<thead>
<tr>
<th>Subgroup by index</th>
<th>Mean duration of dependence (years)</th>
<th>Mean age of onset of dependence (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>y-GGT (IU/l)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–35 (n = 12)</td>
<td>17.1 (1.2)</td>
<td>21.8 (2.3)</td>
</tr>
<tr>
<td>36–50 (n = 10)</td>
<td>21.4 (3.2)</td>
<td>23.4 (5.4)</td>
</tr>
<tr>
<td>51–99 (n = 13)</td>
<td>19.2 (2.7)</td>
<td>24.3 (3.3)</td>
</tr>
<tr>
<td>&gt;100 (n = 10)</td>
<td>17.3 (3.0)</td>
<td>28.3 (3.3)</td>
</tr>
<tr>
<td>All patients (n = 45)</td>
<td>19.0 (1.7)</td>
<td>24.1 (1.3)</td>
</tr>
</tbody>
</table>

Values in parentheses are SEM. GGT denotes γ-glutamyl transferase.

Table 2. Severity of alcohol dependence and index GGT

<table>
<thead>
<tr>
<th>Subgroup by index GGT (IU/l)</th>
<th>Mean index GGT (IU/l)</th>
<th>Mean no. of previous admissions</th>
<th>Mean weekly alcohol intake (U/week)</th>
<th>Mean score on SADD</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–35 (n = 12)</td>
<td>24.3 (1.8)</td>
<td>0.8</td>
<td>152 (92)</td>
<td>30.4 (8.1)</td>
</tr>
<tr>
<td>36–50 (n = 10)</td>
<td>43.6 (1.6)</td>
<td>4.1</td>
<td>190 (71)</td>
<td>34.6 (2.7)</td>
</tr>
<tr>
<td>51–99 (n = 13)</td>
<td>71.8 (3.4)</td>
<td>2.1</td>
<td>215 (74)</td>
<td>27.7 (9.6)</td>
</tr>
<tr>
<td>&gt;100 (n = 10)</td>
<td>322.1 (70.7)</td>
<td>4.7</td>
<td>215 (80)</td>
<td>29.3 (6.1)</td>
</tr>
<tr>
<td>All patients (n = 45)</td>
<td>108.5 (23.0)</td>
<td>3.0</td>
<td>189 (80)</td>
<td>30.3 (7.6)</td>
</tr>
</tbody>
</table>

Values are means with SEM shown in parentheses. Abbreviations used: GGT, γ-glutamyl transferase; SADD, short form alcohol-dependence data questionnaire.

ment. Of those with index GGT 0–35 IU/l (n = 12), 10 completed week 2, nine week 3, and eight week 4. Of those in the group with index GGT 36–50 IU/l (n = 10), all completed week 2, eight completed week 3, and seven completed week 4. Of the group with index GGT in the range 51–99 IU/l (n = 13), 13 completed week 2, 10 completed week 3, and eight completed week 4. Those with the highest index γ-GGT 100+ IU/l (n = 10), eight completed week 2, eight completed week 3, and six completed week 4. There was no significant difference in default rates between the groups. Thus, 66% of patients completed the 4-week programme, typical of attenders at this Unit.

The mean weekly alcohol intake and mean previous attendances of subjects at entry to the study are displayed in Table 2, these findings are also typical of attenders at the Unit. There was a non-significant trend for the age of onset (Table 1), number of previous attendances and increased number of units per week (Table 2) to be increased in groups with higher initial GGT. It will be seen that the group as a whole had a high mean intake of alcohol, placing them firmly within an alcohol-dependent category, however defined.

Table 2 also illustrates mean index measure-ments of dependence for the four subgroups (as measured by SADD and laboratory GGT). Interestingly, there was no statistically significant relationship in our subjects between index GGT value and SADD score. A literature search revealed no other reference to this relationship. Only 49% of patients had GGT levels above the

Fig. 1. Change in mean γ-glutamyl transferase (GGT) with time.

The mean GGT values of the entire cohort of 45 alcohol-dependent patients over a 4-week period of abstinence are shown. Week 1 is index value. Laboratory range for GGT in normal subjects is ≤50 IU/l in males and ≤38 IU/l in females. Males and females were analysed together.
GGT IN ALCOHOL DEPENDENCE

300

GGT (iu/l)

200

Mean GGT 1 (Week 1)

100

GGT1 100*

GGT1 51-99

GGT1 36-50

GGT1 0-35

Mean GGT 2 (Week 2)

Mean GGT 3 (Week 3)

Mean GGT 4 (Week 4)

Sub-Group by initial GGT

Fig. 2. Decline in mean γ-glutamyl transferase (GGT) with time by subgroup.

The figure shows the decline in mean GGT for four subgroups of alcohol-dependent patients over a period of 4 weeks of abstinence. Subgroups are defined by index (week 1) GGT level. These are 0–35 IU/l, 36–50 IU/l, 51–99 IU/l, and >100 IU/l respectively. Values shown are mean values of GGT for each subgroup of patients for each week of the study. Laboratory range for GGT in normal subjects is ≤50 IU/l in males and ≤38 IU/l in females. Males and females were analysed together.

cut-off for our laboratory, despite their undoubtedly high alcohol intake prior to attending the Unit. MCV was raised in only 13%, whereas 10% of subjects had MCV and GGT both raised.

Figure 1 illustrates the rate of change in mean GGT values for the whole cohort over the duration of the study. When grouped into the four categories based on initial (index) values, the changes over time were as shown in Fig. 2. This illustrates the general trend of reduction towards normal values, except for the group with very high initial GGT values. As would be expected, there was a close association between grossly elevated initial levels of GGT and disturbance of liver function, as indicated by elevated alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase (data not shown).

There was no demonstrable association between any of the other parameters measured and GGT, either on index or subsequent estimations.

DISCUSSION

We have shown that, in a cohort of subjects randomly selected from attendees at a district alcohol treatment service and representative of the ‘typical’ patient coming under our care, GGT estimations, performed serially over 4 weeks, decline in value in a reasonably predictable fashion given total abstinence. However, 51% of subjects did have normal initial GGT levels at admission. Some of these latter subjects showed an initial rise, as previously reported (Teschke et al., 1977; Wadstein and Skude, 1979), possibly resulting from an effect on hepatic GGT synthesis or release of improved nutrition with abstinence on admission. Our results, however, suggest that careful assessment of alcohol intake, in this population, does not help in predicting either dependence as measured by SADD or the likelihood of raised GGT levels.

Results for males and females were analysed together despite the fact that reference ranges for males (less than 50 IU/l) and females (less than 38 IU/l) show a modest difference, since in all female cases the level of GGT was well above 50 IU/l. Furthermore, in view of the relatively small numbers in the study, results for both sexes were combined. Mean values for females in this study were higher, which is a typical finding (Rosalki, 1984).

When adjusted for age and length of drinking
history, little change was seen in predictive values of GGT. We would contend that this study provided information of relevance to those involved in treating alcohol-dependent patients. GGT levels were elevated in only 49%, contrary to the contentions of several authors who suggest a corresponding figure of 70% (Rosalki, 1984). Consideration of GGT, even combined with MCV, adds little to the diagnostic sensitivity of a clinical history. In subjects where GGT is elevated, our findings suggest that the rate of decline of GGT is best compared with the index value when grouped as in Fig. 2. In other words, maintenance of abstinence over a period of weeks can be reasonably assumed if GGT follows this pattern. Any rise in value after the first week can, by inference, be taken as evidence of continued drinking and this may be of clinical relevance.

In general terms, the practice of GGT estimation in this alcohol-dependent population must be regarded as of limited value, within the constraints outlined above. In particular a normal GGT indicates nothing of value and is far less important than clinical history. This is of course of particular relevance in other settings where alcohol abuse is suspected such as in general medical and surgical patients.

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REFERENCES


