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Biological markers of alcoholism

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Abstract

Biological markers are biochemical or physiological characteristics which may help to classify a person according to the presence or absence of some disease or risk of disease, either with respect to their current status or future susceptibility. Many biological markers related to alcoholism have been described; this review suggests a classification of them and indicates areas where they are well-established and other areas where further investigation may be useful. [Whitfield JB. Biological markers of alcoholism. *Drug Alcohol Rev* 1991; 10: 127–135]

Key words: ethyl alcohol; alcohol abuse; diagnosis; biological marker.

Introduction

There has been much research and discussion recently about biological markers, a concept which extends beyond the field of alcohol. There is a need for a conceptual framework as a starting-point for thinking about biological markers in alcoholism: within such a framework it should be possible to identify areas of knowledge and achievement, and areas of current research. There will probably be some areas which will turn out to have been little more than speculation, but even if the speculation turns out to be unfounded it is still worthwhile if it leads to testable hypotheses.

In addition, the marker concept has a number of potential practical consequences in the drug and alcohol area which go beyond scientific and technical questions: as successful markers are identified they should be integrated into clinical practice and in some cases this will raise social or ethical problems.

There are a number of questions which need to be considered.

(1) What are biological markers, and how can they be useful?
(2) What markers for alcoholism or hazardous alcohol consumption exist, and how good are they?
(3) How can they best be used and interpreted, within the limitations of current knowledge?
(4) What is likely to be available in the future?

A marker is something which helps in classification, in assigning a person to one out of two or more possible categories. This is the role of diagnostic tests of all kinds, but the biological marker concept can extend beyond diagnosis of a current condition. It can also be used in relation to the risk of something happening in the future. To give an analogy, there are laboratory tests which can help in the diagnosis of myocardial infarction and there are others which can give a prediction—however imperfect—of whether a person will have a myocardial infarction in the future.

Biological markers may, therefore, be diagnostic tests, or risk factors for future disease. One dimension is shown in Table 1; the distinction

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between those markers which relate to the current state of a person and those which relate to a person's susceptibility to problems in the future. These two groups have been referred to as 'state markers' and 'trait markers', although it is occasionally difficult to be sure which category of marker we are dealing with.

Most trait markers described so far have been based on quantitative measurements, like the state markers, but one ultimate aim is to proceed to the definition of genetic markers at the DNA level. Because there genetic effects on many aspects of alcoholism [1–4] there are reasonable prospects of being able to define DNA markers for each.

The other point to be remembered is that the different markers may reflect different aspects of the whole condition of alcoholism. This is the other dimension of Table 1, and biological markers may reflect physical complications of alcohol abuse, or the psychiatric aspects, or the quantity of alcohol consumed. Obviously, these three areas are, in practice, strongly related. Many people will have abnormalities in each area and so it may be difficult to determine exactly what a test is a marker of, but we should keep the distinction in mind.

It will be noted that only two out of the six cells in Table 1 can be confidently marked as explored territory, but the other four offer interesting possibilities for the future.

Currently available markers

The markers which are presently widely available are mainly markers of alcohol intake, or possibly of organ damage secondary to harmful alcohol use—the third and first of the categories shown in Table 1. They are not markers of 'alcoholism' and correlate better with results of questionnaires asking about consumption than with those assessing dependence.

The first line in Table 1 relates to markers of physical disease as a consequence of alcohol abuse. The state markers here are the conventional markers of organ damage or function; the liver function tests, tests reflecting pancreatic, endocrine, muscular consequences of alcohol and tests of vitamin status, for example. More specific tests, relating to such events as collagen metabolism in the liver as part of the process of fibrosis, have been proposed [5,6], but do not appear to be sufficiently discriminating to be clinically useful. Trait markers, reflecting susceptibility to damage from alcohol, have been proposed, but the pattern so far has generally been of a positive report followed by a number of negative ones. Nevertheless, there are reasons to believe that differences in disease susceptibility exist [1] and it would be useful to find markers for them, both for clinical and scientific reasons.

Table 1. *Biological markers in alcoholism: a classification scheme and the availability of markers of each type*

	State markers	Trait markers
Physical disease	+	?
Dependence	?	?
Hazardous intake	+	?

The next class of markers are those which reflect alcohol intake. The ones which are most widely available for clinical use are plasma gamma-glutamyl transferase (GGT) and erythrocyte mean cell volume (MCV). The fact that they are affected by the level of alcohol intake, even within the comparatively normal population, has been known for about 15 years [7–9]. However, both these tests are rather insensitive (i.e. not abnormal in all heavy drinkers) [10] and they may, especially in hospital patients, be non-specific (i.e. abnormal in people with other diseases who are not heavy drinkers).

In numerous studies conducted in health-screening clinics or in community samples [e.g. 11–13], the sensitivity of GGT and MCV is such that about 35–45% of men taking an average of eight or more drinks a day have a result above the 95th percentile for non-drinkers, or for those taking no more than two drinks once a week. A number of literature reports have confused the issue by estimating sensitivity using cut-off points which do not give 95% specificity. Another reason for variation in reported sensitivity is variation in the type of patients or subjects studied: the proportion of patients showing abnormality, for any marker, is likely to vary with severity of the condition and, therefore, any realistic comparison of tests should be based on results obtained from analysis of the same samples.

However, the response of GGT to alcohol is not uniform across all age groups. Several reports show

that sensitivity is lower in men aged less than 30, but in young subjects who do have elevated levels the absolute values are higher [14,15]. It also seems, for some reason, to be less sensitive to alcohol consumption in women [Figure 1], even though it is generally accepted that women can sustain damage from lower alcohol intakes than men.

Although quite a lot is known about the response of GGT and MCV to alcohol, the mechanisms by which alcohol affects them are still uncertain. In the absence of such knowledge, the question arises about whether any conclusion can be drawn about the significance of a raised GGT, knowing that only about half of admitted hazardous drinkers have abnormal GGTs.

The interpretation of a raised GGT depends on whether it is considered a marker for damage or for some protective mechanism. There are a number of indications that it does, in fact, indicate damage; from comparison of liver biopsy results in alcoholics with high or normal GGTs [16,17], from the strong association between GGT and AST values in heavy drinkers [18], and from epidemiological studies [19].

Table 2 shows some results from a study conducted in Malmo on normal middle-aged men [19]. Some 8000 men were screened for lifestyle and biochemical factors, and some 200 deaths occurred in the follow-up period, from all causes. Analysis of the results revealed that a high GGT was the most significant risk factor for death in this cohort; much higher than cholesterol, for example.

Therefore, it looks as if a high GGT is an indication that something is seriously wrong. However, a contrary view has been expressed, and it is based on the probable physiological role of GGT. It is possible that GGT acts to maintain a supply of glutathione precursors to cells, including in some circumstances the hepatocyte [20]. If so, increased levels of GGT in the liver could help to maintain appropriate glutathione reserves and to protect against oxidative stress.

Other state markers

Over the last 5–10 years two other promising markers of alcohol use have been identified; desialylated or carbohydrate-deficient transferrin [21–26] and protein-acetaldehyde adducts. Neither of these have quite progressed past the research stage, but CDT at least should become more generally available within the next couple of years.

According to literature reports, CDT is more sensitive and more specific than GGT. However, it is also more expensive and labour-intensive to measure. In our own rather limited experience CDT was abnormal less frequently than GGT in

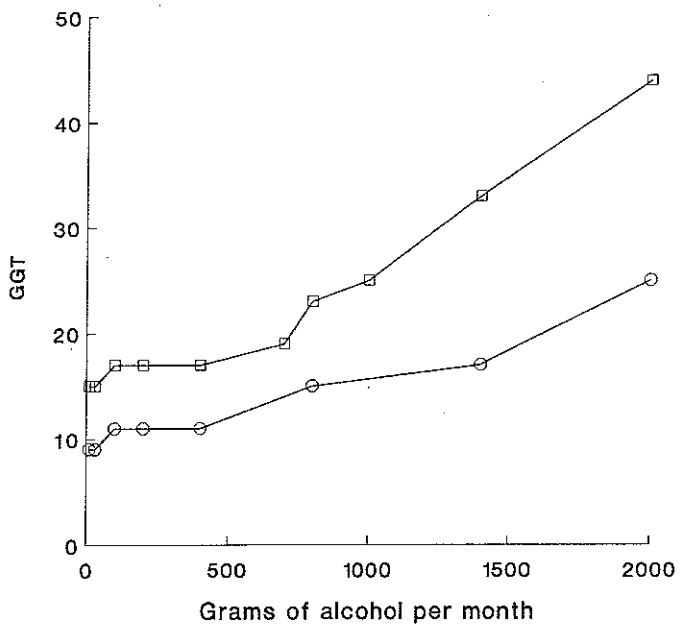

Figure 1. *Effect of estimated monthly alcohol consumption on median GGT values in men (⊟) and women (⊖). Data from [14].*

patients admitted to a detoxication unit, but in subjects recruited to an early intervention study (who merely consumed alcohol in potentially harmful amounts) the CDT was more sensitive than either GGT or MCV. It is possible that CDT is more of an intake marker than GGT, because consumption of 60 g of alcohol daily for a few weeks can increase the CDT [22], but does not increase GGT in normal subjects.

The other state marker that has been discussed recently is acetaldehyde-protein adducts [27,28]. It is proposed that these are formed by a two-stage reaction between acetaldehyde and either plasma or liver cell proteins. This reaction can certainly be carried out *in vitro*, with the production of modified proteins, and antibodies can be raised against these *in vitro*-modified proteins which are directed specifically against the acetaldehyde residue. However, the question (as with so many theories about the role of acetaldehyde) is how far similar reactions occur *in vivo*. The concentration of acetaldehyde in the circulation of normal subjects after alcohol is less, possibly much less, than 1 μmol/l and formation of acetaldehyde adducts in the plasma may be negligible.

However, the situation may be different in habitual heavy drinkers or alcoholics, especially if their liver cells are damaged in ways which lead to release of their contents into the circulation. Such people will not only form larger amounts of acetaldehyde from ethanol, but they have lower concentrations of ALDH [29]. Therefore, higher concentrations of acetaldehyde in the circulation may lead to formation of adducts with plasma proteins or with haemoglobin. Alternatively or additionally, there is evidence for a specific protein in the liver which preferentially combines with acetaldehyde, at least in rats [30], and acetaldehyde adducts with this protein could appear in the circulation in the presence of liver damage. There is some evidence that the appearance of adducts in the circulation is associated with a raised plasma AST, a classic indicator of hepatocyte injury [31].

Acetaldehyde-protein adducts may be useful as a marker, although perhaps not as a pure consumption marker, and they may play a pathological role in immunologically-mediated liver damage. However, there are still unanswered questions about these adducts.

Uses of state markers of intake

All these state markers of consumption suffer from the problem that alcohol intake is a continuous variable, and there is uncertainty about the safe limit of alcohol intake for any particular person. Even when a test appears to be good at distinguishing between non-drinkers and people known to be taking excessive amounts of alcohol, it may perform much less well when applied to the entire population.

There are three main ways in which state markers may be used. First, to monitor progress, either in alcoholics or hazardous drinkers [32]. Secondly, as screening tests; although not all those with an alcohol problem will be detected, people with high levels may need further evaluation of their alcohol intake and some form of intervention programme. The effectiveness of such an approach has been demonstrated in Sweden [32,33]. Thirdly, the markers may be used to validate self-reports of changes in alcohol intake for research purposes [34].

Markers related to dependence

The third category of markers are those which are indicators of psychological attributes or psychiatric states. The one which has been most thorougly investigated is platelet monoamine oxidase activity (MAO), which has been shown in many papers [35–38] to be lower in alcoholics than controls. This seems to be a trait marker, because the low values can persist over a considerable period of abstinence from alcohol [39,40]. It is probably not specific for alcoholism; low values have been found in other mental illnesses and in healthy subjects with personalities which may be described as reckless, impulsive or sensation-seeking [41–43].

Interestingly, a low platelet MAO seems to be a marker for familial alcoholism [44,45], characterized in the Cloninger typology [46] as Type 2 (male-type, early onset). However, although one paper [47] has reported a specific association, there are still a number of obstacles to accepting a low platelet MAO as a risk factor for Type 2 alcoholism. No prospective studies appear to have been carried out, so it might be a secondary result of alcohol use. Cloninger's typology has not been universally accepted, for a number of reasons [48,49]. The gene for MAO is on the X

Table 2. *Risk factors for death in middle-aged men (modified from ref. 19), in decreasing order of significance. For factors not shown, $p > 0.05$*

All causes (218 deaths)	Alcohol-related (55 deaths)	
GGT	GGT	Equal
Smoking category	Mm-MAST score	Equal
Systolic blood pressure	Creatinine	Equal
Mm-MAST score	Cholesterol	
Triglycerides		
Creatinine		

chromosome, which does not fit easily with the generally accepted autosomal pattern of inheritance for alcoholism [50,51]. There is even uncertainty about how MAO should best be measured, with some dispute about whether the total or alcohol-inhibited activity is the most appropriate [52, 53].

Less information is available about adenylate cyclase, another proposed marker of dependence. Variation in this enzyme could affect a key step in the transduction of signals across cell membranes, so it is a theoretically attractive possibility, but only a few papers have appeared [53–56]. If adenylate cyclase is less stimulated by alcohol in some people, probably because of genetic variation in its structure, then such people would take more alcohol to achieve a desired effect. In time there would be adaptation to constant stimulation by alcohol and removal of alcohol would lead to biochemical effects experienced as withdrawal.

Table 3. *Association between dopamine D_2 receptor A1 allele and alcoholism (from ref. 57)*

	A1 absent	A1 present
Non-alcoholic ($n=35$)	28	7
Alcoholic ($n=35$)	11	24

Chi-square = 14.8, $p < 0.001$.

Other components of neurotransmission, especially receptors, offer possibilities for genetic variation to affect the response to alcohol. Such variation might lead to either excessive consumption or dependence. There has recently been a report that variation in the gene for the dopamine D2 receptor is associated with alcoholism [57]. A summary of the results for control and alcoholic groups is shown in Table 3. However, confirmation of this report is required, and even then it is intesting to calculate that at any reasonable estimate of the prevalence of alcoholism, the majority of people with the A1 allele would not be alcoholics.

Alcohol-metabolizing enzymes

A lot of attention has been given over the years to possible interaction between alcohol-metabolizing enzymes (ADH and ALDH) and alcoholism [58–63]. These enzymes could potentially affect the incidence of physical disease caused by alcohol, or dependence, or consumption. That is, they could be trait markers in any of the three categories in Table 1.

The best known example is the way variation in ALDH can affect alcohol use [61–63] within Asian populations. A considerable proportion of Japanese—around half—have a form of mitochondrial aldehyde dehydrogenase which is inactive. This is inherited as an autosomal dominant condition and results in high circulating acetaldehyde concentrations after alcohol is taken. The ALDH-deficient subjects experience the 'alcohol flush reaction', which generally results in them avoiding alcohol, and the incidence of alcoholism is low among the deficient subjects. The ALDH deficiency with the alcohol flush reaction is also found in other Asian groups, although less commonly than among Japanese, and in some native populations in South America. In South America, however, it appears that another mutation is responsible [64].

Acute reactions to small amounts of alcohol, due to cytoplasmic ALDH deficiencies, have been described in a small number of Europeans [65]. It remains to be determined how common this phenomenon is and whether the deficiency has a significant effect on alcohol use in those affected.

Lesser degrees of variation in ALDH activity could, in theory, exist and determine circulating acetaldehyde concentrations after alcohol. This could affect the proposed formation of psychoactive substances from reaction of acetaldehyde

Table 4. *Biological markers in alcoholism, 1990: a selection of established and proposed markers*

	State markers	Trait markers
Physical disease	Organ function tests, e.g. AST, ALT, albumin; amylase, lipase; creatine kinase; measures of liver fibrosis, e.g. laminin, procollagen; measures of vitamin status, e.g. transketolase activity and TPP effect	Proposed involvement of HLA and PI systems; abnormal forms of transketolase; inactive forms of ALDH
Dependence	None known	Monoamine oxidase, adenylate cyclase; dopamine receptor; low-activity forms of ALDH
Hazardous intake	GGT, MCV, urate, HDL-cholesterol, carbohydrate-deficient transferrin, acetaldehyde-protein adducts, hexosaminidase	Inactive forms of ALDH as a protective factor

with neurotransmitters [66] and, hence, play a role in the development of dependence.

In addition, variation in ALDH and acetaldehyde concentrations could determine whether organ damage occurs in subjects taking large amounts of alcohol: the increased formation of acetaldehyde-protein adducts in partially ALDH-deficient subjects could lead to immunologically-mediated liver or other organ damage.

Finally, variation in ADH activity could have similar effects. A subject with fast alcohol metabolism should produce acetaldehyde more quickly and attain a higher steady-state concentration of acetaldehyde than a slow metabolizer of alcohol, and some or all of the effects proposed for ALDH could occur as a consequence of ADH variation.

However, most of these ideas about effects of variation in alcohol-metabolizing enzymes are speculative so far. Although these possibilities have been discussed for some time, acceptable methods for typing ADH and ALDH from human subjects have only recently become available and we shall have to wait for substantiation or rejection of these theories.

Conclusion

State markers for alcohol consumption are reasonably well established, but their usefulness is limited by lack of sensitivity or by lack of technically simple methods. Research on factors affecting GGT levels, in particular, may allow us to make better interpretations of readily available results. There seems a definite need for better markers of alcohol-related organ damage.

The trait markers offer fascinating possibilities for the future, but much work will be needed before their validity and reliability are established. If genetic markers for alcoholism can be discovered, either by pedigree analysis or by investigation of candidate genes, this will have both scientific and clinical implications.

On the scientific front, a genetic marker or markers should help to establish which biochemical processes are involved in alcoholism. The clinical or community use of genetic markers, however, would require the resolution of a number of other issues. Screening for drug use and genetic screening for susceptibility to disease, are both sensitive issues. In combination they would be likely to arouse considerable, and justifiable, concern.

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