Biomarkers to Predict Alcohol Withdrawal Seizures – A Review of Current Literature

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Abstract: Alcohol withdrawal seizures are one major complication during detoxification treatment of alcohol dependent patients. Anticonvulsive pharmaceutical treatment can be administered but is associated with side-effects like nausea or hyponatriemia. Recent studies have identified different biomarkers that have been associated with the risk of alcohol withdrawal seizures. The aminoacid homocysteine as well as prolactin have been described to be associated with this individual seizure risk. Furthermore, markers of alcohol dependence like carbohydrate deficient transferrin (CDT) have been studied in this context. Also, genetic variants like the apolipoprotein E genotype have been found to be related to the history of withdrawal seizures. Knowledge and critical valuation of these recent findings on biomarkers may help to establish an assessment of the individual risk for withdrawal seizures and therefore may have important clinical implications.

Keywords: Alcohol withdrawal, seizures, CDT, homocysteine, prolactin, detoxcification, dependence, alcoholism.

INTRODUCTION

Alcohol withdrawal seizures are a common and severe complication of alcohol detoxification. Therefore, predicting the course of alcohol withdrawal and alcohol withdrawal seizures seems to be useful and tempting. Several recent studies have focused on biological parameters that may help to assess the individual risk for alcohol withdrawal seizures. This may help to establish an individualized pharmacological treatment to prevent alcohol withdrawal seizures in patients of high risk and to avoid unnecessary treatment in other.

Up to now the pathophysiological mechanisms in the genesis of alcohol withdrawal seizures are only partially revealed. Homocysteine, an excitatory amino acid, is evidentially elevated in non-abstinent alcoholics, with a steadily decrease during alcohol withdrawal [1-3]. Recent studies showed the impact of elevated homocysteine serum levels on alcohol withdrawal seizures: for first-onset [4] and for previous withdrawal seizures [5].

Also, elevated prolactin levels have been reported under chronic ethanol exposure [6-8]. Post-ictal prolactin elevation is a well known phenomenon in patients with epilepsia [9] but has also been described after alcohol-related seizures [10]. A recent study now found that patients with a history of alcohol withdrawal seizures show significantly elevated prolactin serum levels at admission (not post-ictal). Therefore, it has been suggested that prolactin may also serve as a (prae-ictal) marker assessing the individual risk for alcohol withdrawal seizures [11].

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Additionally, a recent investigation focused on the validity of carbohydrate deficient transferring as a diagnostic aid for alcohol withdrawal seizures [12]. Also, genetic variants like the apoE polymorphisms have been associated with elevated risk for alcohol withdrawal seizures in patients undergoing alcohol detoxification [13]. Aim of this review is to give an overview about the existing literature on these biological markers and their potential to predict the individual risk for alcohol withdrawal seizures in patients with alcohol dependence.

THE AMINOACID HOMOCYSTEINE

Homocysteine is a sulphur-containing amino acid which is produced as a potentially toxic intermediate product in the metabolism of the essential amino acid methionine. Several investigations in recent years described that alcohol consumption, particularly in actively drinking alcoholics, is closely associated with elevated plasma homocysteine levels [1-3]. Also, homocysteine serum levels show a high positive correlation with the blood alcohol concentration. It is important to mention that a single intoxication, also including large amounts of alcohol, does not lead to a pathological elevation of plasma homocysteine concentrations in healthy, not alcohol-dependent subjects [14]. Hence, regular and continuous alcohol consumption seem to be an important and necessary condition, since a significant increase in plasma homocysteine concentrations has been observed in social drinkers with daily consumption of smaller amounts of alcohol [15]. This association between alcohol consumption and raised plasma levels of homocysteine might account for different pathophysiologic consequences such as brain atrophy [16], cognition deficits during alcohol detoxification [17] and withdrawal seizures [4, 18]. A suggested association with alcohol craving could not be confirmed in a recent investigation [19]. As elevated plasma homocysteine concentrations are also linked to other neuropsychiatric disorders such as depression [20, 21],

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schizophrenia [22] and cognitive impairment [23], an impact of elevated homocysteine levels on frequent comorbidities in alcohol dependent patients can be assumed.

The exact pathophysiological mechanisms of hyperhomocysteinemia causing alcohol withdrawal seizures in patients undergoing alcohol detoxification are still not completely revealed. The most reliable hypothesis is that hyperhomocysteinemia due to chronic alcohol consumption leads to an up-regulation of the NMDA receptor system. However, ethanol acts as a NMDA receptor antagonist, blocking the up-regulation of the NMDA receptor system. Then, during detoxification, excitatory amino acids such as glutamate and homocysteine lead to an overstimulation of NMDA receptors, while the simultaneous removal of the inhibitory effect of ethanol intensifies this stimulation [1, 24]. Course measurements during an alcohol withdrawal treatment showed a continuous reduction in plasma homocysteine levels, which return to normal range after several days of alcohol withdrawal [2, 4, 5, 25].

Additonal evidence regarding the involvement of homocysteine in seizure activity has been brought from experimental studies. It has been shown that systemic infusion of homocysteine is able to generate tonic-clonic seizures in rats [26]. Other studies with NMDA and non-NMDA antagonists showed a protective effect against homocysteine-induced seizures [27, 28]. Conclusively, homocysteine seems to play a central role in a shared biochemical cascade, involving overstimulation of NMDA receptors, oxidative stress, activation of caspases, DNA damage and mitochondrial dysfunction, which are crucial in the pathogenesis of excitotoxicity leading to neuronal cell loss [24, 29, 30].

Clinically, recent studies brought evidence for an association between homocysteine plasma levels and the risk of alcohol withdrawal seizures. So, homocysteine levels have been shown to predict first-ons*et al*cohol withdrawal seizures in patients with alcoholism [4, 5, 18, 31]. In this context, different cut-off levels for homocysteine plasma levels have been proposed in the last years, while most define normal fasting plasma levels of total homocysteine between 5 and 15µmol/l. Moderately elevated homocysteine levels range between 16 and 30µmol/l, intermediately elevated homocysteine levels between 31 and 100 µmol/l, and severe hyperhomocysteinaemia is present at over 100µmol/l. Studies have shown that in populations without evidence of a nutritional deficit, a reference interval of between 4.9 and 11.7µmol/l may be more adequate [32]. However, these cut-off levels are of limited use in the prediction of alcohol withdrawal seizures in alcohol-dependent patients, as in this patients group homocysteine levels are usually highly elevated. For clinical guidance, a recent study has calculated predictive cut-off values for alcohol withdrawal seizures risk assessment, using homocysteine plasma levels. This study found the highest combined sensitivity and specificity to suffer from a first-ons*et al*cohol withdrawal seizure at a homocysteine plasma level of 23.9 µmol/l, while the authors describe that the negative predictive value (15.8 µmol/l) is probably of higher clinical relevance [31]. In patients above this cut-off value a prophylactic medication with an antiepileptic drug should be taken into account.

CARBOHYDRATE DEFICIENT TRANSFERRING AND OTHER ALCOHOL-RELATED MARKERS

The validity of carbohydrate deficient transferring (CDT) and other alcohol-related markers to predict alcohol withdrawal seizures was subject of a recent investigation [12]. In this study, CDT at a cut off value of 5.4% (%CDT) showed the best predictive validity (sensitivity 39%, specificity 88%). The other markers that were studied in this investigation (s-ethanol, GGT, ASAT and ALAT) showed less predictive values. The authors state that CDT alone can not be recommended as marker to provide useful predictive information regarding the individual seizure risk. Furthermore, in this study concomitant use of anticonvulsive drugs had an important impact on CDT concentrations which questions the described predictive qualities of CDT. Also, the authors discuss the many possible influencing factors on CDT concentration such as iron deficiency, elevated body mass index.

PROLACTIN AS A PREDICTOR OF WITHDRAWAL SEIZURES

Various studies described an elevation of prolactin serum levels after acute and chronic ethanol exposure [6-8], normalizing during abstinence [33, 34]. Recent investigations have linked changes of prolactin serum levels with craving for alcohol in specific subgroups of patients, particularly patients of Lesch´s type 2 of alcohol dependence and female patients [35, 36].

Elevated prolactin levels have also been discussed to be an important marker in differential diagnosis between pseudoepileptic *vs* epileptic seizures [9], being elevated after generalized epileptic seizures. While results about the clinical utility of prolactin measurement are contradicting [37-39] prolactin measurement is routinely used for differential diagnosis of seizures in many hospitals. Furthermore, previous studies found that prolactin is also elevated after generalized alcohol withdrawal seizures [10]. Prolactin is supposed to be associated with the dopaminergic system as dopamine inhibits the release of prolactin in the hypothalamus [40]. However, recent studies have linked prolactin with glutamatergic neurotransmission, especially with the NMDA-receptor system [41-44]. Thus, it is feasible that an elevation of prolactin serum levels above the normal-range may be a sign of disturbed glutamatergic neurotransmission. A recent investigation now assessed the possible predictive utility of prolactin serum levels for the individual risk for alcohol withdrawal seizures [11].

Findings of this study suggest that elevated prolactin serum levels could serve as a marker of increased risk of seizures during alcohol withdrawal. The authors suppose that prolactin is not directly involved in the pathophysiology of withdrawal seizures (in contrast to homocysteine) but may be a marker for a disturbance of the glutamatergic and dopaminergic system during alcohol withdrawal [11]. However, this first study showed evidence for an association between elevated prolactin serum levels and the individual risk for alcohol withdrawal seizures. Evidently, before establishing prolactin measurement in clinical practice further studies are necessary including larger samples and different populations.

Furthermore, a recent study investigated a combined assessment of homocysteine and prolactin [45]. The findings of this investigation show better predicting qualities for homocysteine than for prolactine while the combined assessment of both variables leads to an increase of the predictive value. However, the results also show that the combined assessment seems to be clinically unsatisfactory. The authors discuss this as a consequence of the shared pathophysiological pathway of both parameters.

GENETIC VARIANTS AND THEIR RISK FOR WITHDRAWAL SEIZURES

Genetic factors regarding the personal risk for alcohol withdrawal seizures have been described in various studies. Schaumann *et al*. described 1994 in a family-based study a relevant role of genetic predisposition in development of alcohol withdrawal seizures [46].

Recent studies focused on the pathophysiological role of the dopamine transporter gene (DAT gene) as a risk factor for alcohol withdrawal seizures [47]. Particularly, the 3' part of the dopamine transporter gene DAT1/SLC6A3 has recently been associated with an increased risk for alcohol withdrawal seizures [48].

Additionally, the methylenetetrahydrofolate reductase (MTHFR) C6777T polymorphism has received recent attention. This polymorphism is of high importance in the homocysteine metabolism [49]. In this study, Lutz *et al*. described results of 221 alcoholic patients. They found that the T-allele is associated with a history of alcohol withdrawal seizures, compared to patients with only mild withdrawal syndrome and healthy controls. The authors conclude that the MTHFR polymorphism may have an influence in the pathogenesis of alcohol withdrawal seizures [49].

Besides this, recent research has been attracting increasing attention concerning the pathophysiological role of the apolipoprotein E gene (ApoE gene) and its alleles (ApoE2, ApoE3, ApoE4) in different psychiatric and neurological disorders. The results of various studies show that the apolipoprotein E4 allele has to be regarded as a vulnerability factor for a higher incidence of neurodegenerative diseases as well as for a reduced capacity for neuronal regeneration. Recently, a significant relationship between the ApoE4 allele and hippocampal atrophy in females with alcoholism has been observed [50].

Regarding epileptic seizures, it has been observed that ApoE polymorphism is not associated with the development of major seizure disorders including temporal lobe epilepsy [51-53]. Nevertheless, studies reported an earlier onset of chronic temporal lobe epilepsy [54] as well as increased risk of late posttraumatic seizures [55] in patients carrying the ApoE4 genotype.

A recent study now focused on a possible association between apolipoprotein E polymorphism and the individual risk of alcohol withdrawal seizures in patients suffering from alcohol dependence [13]. Surprisingly, in this study it was not the ApoE4 gene variant which was associated with alcohol withdrawal seizures. Instead, the authors found a significant association with the ApoE3 allele. According to these results patients carrying the ApoE2 allele were unlikely to report a history of withdrawal seizures during the course of their disease. The authors state that these preliminary findings have to be interpreted carefully but they hint towards the possibility that in patients with diagnosis of alcohol dependence the ApoE2 genotype might have a protective effect concerning the risk of developing alcohol withdrawal seizures. A protective effect of the E2 allele has also been reported in other neurological disorders such as ischemic cerebrovascular diseases and vascular dementia [56], age at onset of amyotrophic lateral sclerosis [57] and episodic memory decline in older persons [58].

CONCLUSION AND CLINICAL IMPLICATION

Clinically, a serological assessment of the individual risk for alcohol withdrawal seizures is of high importance. In many patients it is difficult to estimate this risk by the often insufficient medical history given at admission as many patients are admitted acutely intoxicated or with severe

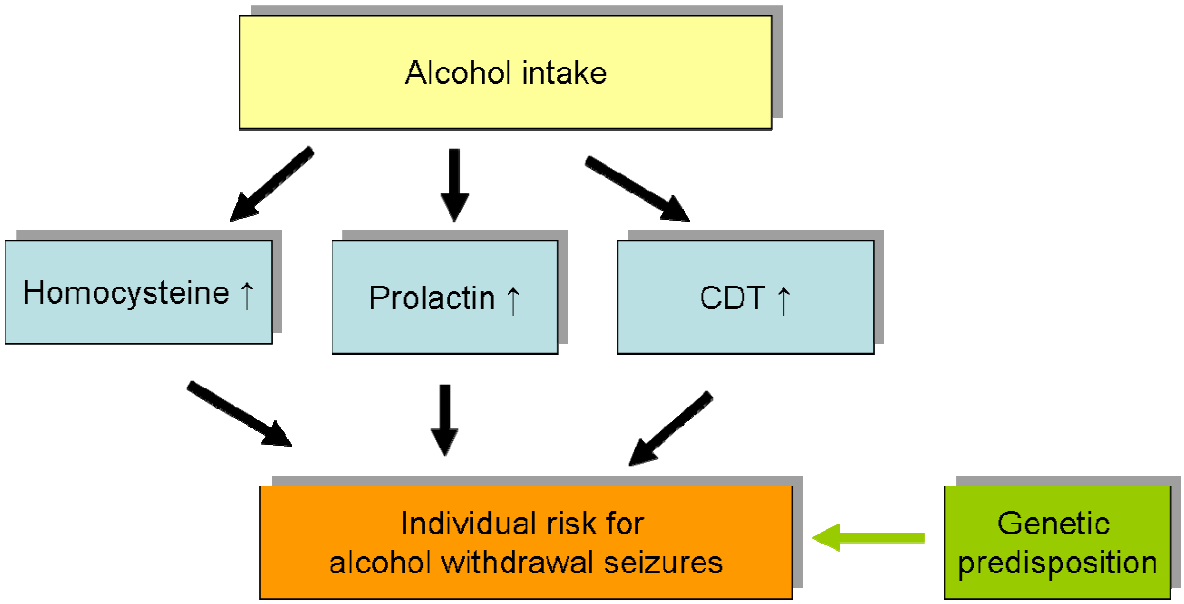

Fig. (1). Model of biomarkers to predict alcohol withdrawal seizures.

alcohol withdrawal syndrome. Recent investigations focused on different genetic and serological markers which in the future may help to establish a blood-based individual risk assessment. Such a risk assessment could lead to a personalized pharmacological treatment of alcohol withdrawal. The amino acid homocysteine seems to be of special interest in this context but its predictive values may be enhanced by other parameters like CDT, prolactin or an assessment of different genetic factors (Fig. **1**). However, there is still insufficient evidence to establish such a risk assessment for clinical use. At this time, best evidence has been shown for homocysteine with the described negative predictive value of 15.8µmol/l for decision regarding anticonvulsive therapy [31]. The present overview is limited by the absence of profound clinical studies in large populations to assess clinical evidence for the stated biomarkers. Another limitation is that most of the present findings are correlation in nature and lack evident pathophysiological models explaining a casual connection between biomarkers and alcohol withdrawal seizures. Therefore, further research is necessary and should 1) focus on the casual connections between these biomarkers and the genesis of alcohol withdrawal seizures in human and animal studies, 2) further investigate the clinical use of singular or combined assessment of these biomarkers and 3) evaluate, how these biomarkers fit with standard clinical assessment of risk including questionnaires like AUDIT [59].

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Received: March 27, 2009 Revised: August 21 2009 Accepted: September 10, 2009