RECURRENT DETOXIFICATIONS ARE ASSOCIATED WITH CRAVING IN PATIENTS CLASSIFIED AS TYPE 1 ACCORDING TO LESCH’S TYPOLOGY

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Abstract — Aims: Recurrent detoxifications have been suggested to be associated with elevated alcohol craving. The aim of this investigation was to study the influence of preceding detoxifications on craving in patients with alcoholism classified according to Lesch’s typology. Methods: We examined 192 patients (154 men, 38 women) after admission for detoxification treatment. Craving was assessed using the Obsessive Compulsive Drinking Scale, and patients were classified into one of the four subgroups of Lesch’s typology. The number of preceding detoxifications was assessed with a structured interview. Results: Lesch’s typology type 4 patients showed significantly higher craving scores than type 1–3 patients (Mann–Whitney U-Test; \( P < 0.05 \)). With respect to the influence of recurrent detoxifications, we found a significant correlation between the number of preceding detoxifications and the extent of craving for the whole population (Spearman’s rho \( r = 0.241, P = 0.001, N = 192 \)), particularly for patients of Lesch’s type 1 (Spearman’s rho \( r = 0.534, P = 0.001, N = 37 \)). No significant association was found for patients of the other subgroups (Lesch’s type 2–4). Conclusion: The influence of recurrent detoxifications on craving is especially important in patients with Lesch’s type 1. Our results underline the importance of the kindling effect particularly in this group of patients, possibly mediated by an increase of glutamatergic neurotransmission. Furthermore, our results emphasize the need to classify patients with alcohol-dependency in addiction research.

INTRODUCTION

Recent studies show the impact of craving on alcohol relapse (Geerlings and Lesch, 1999; Bottlender and Soyka, 2004) and the efficacy of pharmacological therapy (Kiefer et al., 2003b; Kiefer and Wiedemann, 2004). Intensive research about factors influencing craving has been conducted up to now. In this context, recurrent detoxifications have been shown to elevate alcohol craving (Malcolm et al., 2000), whereas other studies found contradictory results (Duka et al., 2002). Furthermore, various investigations showed that detoxification experiences have kindling effects on the risk of alcohol-related seizures (Lechtenberg and Worner, 1991; Becker and Hale, 1993; Booth and Blow, 1993; Moak and Anton, 1996; Worner, 1996).

However, most of the previous studies did not include a subgroup typology of alcoholism. Lesch’s typology is a well-established classification taking into account social, mental, and somatic factors (Lesch et al., 1990; Lesch and Walter, 1996). The typology differentiates four subtypes: type 1 (model of allergy) is characterized as patients with heavy alcohol detoxifications, who tend to use alcohol to weaken detoxification symptoms. Patients of type 2 (model of anxiety or conflict) use alcohol as self-medication because of anxiolytic effects. An affective disorder is the main characteristic of type 3 (alcohol as an antidepressant). Type 4 patients (alcohol as adaptation) show pre-morbid cerebral defects, behavioural disorders and a high social burden. The decision tree developed in 1990 helps to classify patients according to Lesch’s typology at admission. If it is not possible to determine an appropriate medical history, a period of 5 days is allowed to pass before classification into the referring type. The Lesch’s typology has been applied in various studies (Kiefer and Barocka, 1999; Lesch et al., 2001; Sperling et al., 2000; Bleich et al., 2004).

Identifying neurobiological and social factors that influence alcohol craving may help to identify subgroups of patients for a more differentiated pharmacological and psychotherapeutic treatment. This study was undertaken to analyse the effect of recurrent detoxifications on craving, differentiating subtypes of alcoholism according to Lesch’s typology.

SUBJECTS AND METHODS

The investigation was part of the FARS (Franconian Alcoholism Research Studies), a large prospective research project about neurobiological factors in alcoholism (Hillemacher et al., 2004, 2005; Bleich et al., 2005). The study was approved by the Ethics committee of the local medical faculty and was performed between October 2002 and March 2003 in the detoxification unit of the Clinic for addiction and psychotherapeutic medicine (Klinikum am Europakanal, Erlangen, Germany). Written informed consent was obtained from all 192 consecutively recruited patients (154 men, 38 women, mean age 43.7, SD 8.8 years, range 22–67 years) who were included in the study on the day of admission. As inclusion criteria we defined suffering from alcohol-dependency according to the International Classification of Diseases (ICD-10). Furthermore, only patients with an active drinking pattern (non-abstinent) or those with an early abstinence (stopped drinking <72 h before admission) were included. Patients with a concomitant psychiatric disorder other than abuse or dependence on substances, diagnosis of liver cirrhosis, renal or pancreatic dysfunction, malnutrition or patients taking vitamin supplements were excluded from the study (Bleich et al., 2005). In all cases, patients were detoxified using clomethiazole and carbamazepine as an individual symptom-triggered treatment. Other detoxification medication was not used excepting vitamins, potassium,
or magnesium. During the detoxification period, abstinence was monitored by carbohydrate-deficient transferrin (CDT) (Helander et al., 2001), breath alcohol, and urine analysis.

The extent of craving was assessed with the Obsessive Compulsive Drinking Scale (OCDS) (Anton et al., 1995, 1996) on the day of admission before starting detoxification treatment, distinguishing between the total score, the obsessive and the compulsive subscale.

In addition, patients were initially classified according to Lesch’s typology into one of the four subgroups (groups 1–4). Allocation to types 1–4 was done using a computer program according to the decision tree (Lesch et al., 1990). Furthermore, in a structured interview personal and sociodemographic data were recorded (Wetterling et al., 1999), such as known mental or somatic illnesses, daily intake of alcohol, and age of onset of alcohol-dependency. The information of preceding detoxifications (including not medically supervised detoxifications) was recorded in the same structured interview. Additionally, we analysed the hospital records to verify the information given by the patients as many patients had been admitted to the same detoxification unit before. Analogously we assessed the number of preceding seizures during alcohol detoxification and the number of alcohol deliriums.

### Statistical analysis

None of the utilized variables was normally distributed (using the Kolmogorov–Smirnov test). Therefore, we used non-parametric methods (Spearman’s rho, Mann–Whitney U-test and Kruskal–Wallis test) to analyse data employing SPSS™ for Windows 11.5 (SPSS Inc., Chicago, IL). The significance level was defined as α < 0.05.

#### Table 1. Frequency of different variables in dependence of Lesch’s typology

<table>
<thead>
<tr>
<th>Lesch’s type</th>
<th>Mean ± SD</th>
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<tbody>
<tr>
<td></td>
<td>OCDS total</td>
</tr>
<tr>
<td>Lesch’s type 1 (N = 37)</td>
<td>17.4 ± 7.3</td>
</tr>
<tr>
<td>Lesch’s type 2 (N = 94)</td>
<td>21.0 ± 7.2</td>
</tr>
<tr>
<td>Lesch’s type 3 (N = 38)</td>
<td>19.0 ± 7.9</td>
</tr>
<tr>
<td>Lesch’s type 4 (N = 23)</td>
<td>24.3 ± 6.9</td>
</tr>
<tr>
<td>Whole population (N = 192)</td>
<td>20.3 ± 7.6</td>
</tr>
</tbody>
</table>

*Significant differences between the different Lesch’s types, tested with Kruskal–Wallis test for independent samples (OCDS total score chi-squared = 12.2, P = 0.007; OCDS compulsive subscale chi-squared = 17.4, P = 0.001; number of detoxifications chi-squared = 9.7, P = 0.021).

#### Table 2. Correlation analysis in dependence of Lesch’s typology

<table>
<thead>
<tr>
<th>Lesch’s type</th>
<th>OCDS total score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lesch’s type 1 (N = 37)</td>
</tr>
<tr>
<td>Age</td>
<td>r = -0.244, n.s.</td>
</tr>
<tr>
<td>Age of onset</td>
<td>r = -0.299, n.s.</td>
</tr>
<tr>
<td>Number of preceding detoxifications</td>
<td>r = 0.534, P = 0.001</td>
</tr>
<tr>
<td>Daily intake</td>
<td>r = 0.496, P = 0.003</td>
</tr>
</tbody>
</table>

r, Spearman’s rho; n.s., not significant.
results were observed for the other types. Details are summarized in the Results section.

and patients with two or more previous detoxifications (Fig. 1). We found significant differences regarding the extent of craving for the two groups only in patients with Lesch’s type 1 (Mann–Whitney U-test: OCDS total score: \( Z = -3.3, P = 0.001 \); OCDS obsessive subscale: \( Z = -2.1, P = 0.40 \); OCDS compulsive subscale: \( Z = -3.6, P < 0.001 \)), not for any of the other subgroups.

To compare these results with findings of other investigations, we also analysed data without classifying patients according to Lesch’s typology. In the whole patients sample the number of recurrent detoxifications was significantly correlated with the extent of craving (OCDS total score: \( r = 0.241, P = 0.001 \); OCDS compulsive subscore: \( r = 0.356, P < 0.001 \)). Also we compared patients with less than two and subjects with two or more detoxifications (Mann–Whitney U-test: OCDS total score: \( Z = -2.7, P = 0.008 \); OCDS compulsive subscale: \( Z = -4.0, P < 0.001 \)).

**DISCUSSION**

In our study, patients of Lesch’s type 4 showed highest craving scores during alcohol detoxification, significantly higher than patients of the three other groups. This result may be explained by the typical prenatal cerebral damage and behavioural disorders that characterize this type of patient according to Lesch’s typology. Therefore, it is not surprising to find the highest craving scores in this subgroup, which tends to increase vulnerability for alcohol dependence (Lesch and Walter, 1996; Sperling et al., 2000).

In previous studies a significant association between craving scores and recurrent detoxifications has been described (Malcolm et al., 2000). The present results are in line with these prior findings, taking into account that we found a significant correlation between both items for the whole study population, but especially for patients classified as type 1 according to Lesch’s typology and particularly for compulsive craving. These findings are consistent with previously described characteristics of this subgroup. Type 1 patients are characterized as patients suffering from marked symptoms during detoxification and using alcohol especially to dilute detoxification symptoms. In other subgroups, previous experience of recurrent detoxifications seems to have no or only little influence on craving. The previously described findings of an association between recurrent detoxification and obsessive-compulsive craving may be owing to the lack of classification into subgroups (Malcolm et al., 2000). Our results for the whole study population are probably explained by the high correlation in Lesch’s type 1 patients. Hence, our results underline the importance of classifying alcoholics using a specific typology in addiction research.

In another study, no association between number of detoxifications and craving was found (Duka et al., 2002). One reason for the conflicting results may be the use of a different craving scale that does not consider obsessive and compulsive aspects of craving. Also patients in this previous study underwent a specific psychotherapeutic programme that may have influenced cognitive processes with respect to alcohol craving.

Furthermore, our findings support the kindling hypothesis in alcohol craving, at least in patients classified as type 1 according to Lesch’s typology. Recent investigations have shown that repeated detoxifications increase excitatory amino acids like glutamate (Dahchour and De Witte, 2003b; De Witte, 2004). In various studies, the importance of the glutamate system in alcohol craving has been described as crucial, especially for craving during detoxification (Kiefer et al., 2003a; De Witte, 2004). An imbalance between excitatory (particularly glutamate) and inhibitory amino acids (particularly GABA) is involved in both alcohol craving and kindling after recurrent detoxifications (Dahchour and De Witte, 2003b; De Witte, 2004), which may be the link between both pathologies and may help explain our findings.

The association between the number of detoxifications and craving in Lesch’s type 1 patients may also be explained by higher relapse rates in these patients as a consequence of craving. From our point of view this inverse interpretation is not probable as in our sample patients of Lesch’s type 1 not only suffered from relatively low craving (compared to patients of the other subgroups) but also from significantly fewer detoxifications. This strengthens our interpretation that previous detoxifications may be a specific risk factor for elevated craving in Lesch’s type 1 patients. However, a contrary association cannot be ruled out with our study design.

In this context it is interesting that the efficacy of acamprosate in the prevention of relapse has particularly been shown in patients with Lesch’s type 1 (Lesch and Walter, 1996; Lesch et al., 2001). These findings are in line with the described mechanism of acamprosate, involving a reduction of excitatory amino acids, particularly glutamate, which are increased after repeated alcohol detoxifications (Dahchour and De Witte, 2000, 2003a). In conclusion, our results support the prior findings about a kindling effect on craving after recurrent detoxifications. This strengthens our interpretation that previous detoxifications may be a specific risk factor for elevated craving in Lesch’s type 1 patients. However, a contrary association cannot be ruled out with our study design.

Further research is necessary to confirm our results, to
elucidate the pathophysiological pathways of kindling in alcohol craving and to investigate clinical implications.

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