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RHINOLOGY

Blood markers of alcohol use in epistaxis patients

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Abstract Epistaxis and alcohol overconsumption are frequently encountered in patients admitted to emergency wards. The aim of the study was to analyze indirect markers of alcohol overconsumption in epistaxis patients and evaluate its role as a risk factor. In a cohort of 510 epistaxis patients indirect markers of alcohol overuse were measured including the mean corpuscular volume (MCV), gamma glutamyltransferase (GGT), aspartate aminotransferase and alanine aminotransferase. The results were compared to the normal findings in literature. Pathologic mean levels of GGT were found in epistaxis patients. Almost 5% had macrocytosis and MCV correlated positively with liver enzyme levels. Platelet counts were negatively correlated with both corpuscular volumes and liver enzymes. Indirect markers of alcohol overconsumption were found to be elevated in epistaxis patients. These results suggest that a subgroup of epistaxis patients overconsumes alcoholic beverages supporting the idea of alcohol abuse being a risk factor in epistaxis. Questioning about drinking habits should be employed and help offered to affected patients.

Keywords Epistaxis · Alcohol · Blood · MCV · GGT · Transaminase

Background

Epistaxis is the most common emergency in rhinology and accounts for almost 600 consultations at the University Hospital of Zurich per year [1]. Although the diagnosis rarely poses a difficulty, its treatment can be quite troublesome and patients often inquire about preventive measures that could be taken. The identification of risk factors in epistaxis therefore is essential and different causatives could be identified including antiaggregational drugs, anticoagulants and seasonal weather changes [1, 2]. The misuse of alcohol has been noticed in up to 25% of individuals admitted to an emergency ward [3]. Alcohol has not been studied extensively in epistaxis. A prolonged bleeding time in epistaxis patients with regular alcohol use was observed, even at low levels of intake [4].

We therefore decided to take a closer look at a possible influence of alcohol in epistaxis. It is very difficult to correctly assess alcohol intake in an emergency situation by a patient's history and measurement of blood-alcohol levels not only raises ethical concerns but also does not reflect long-term use. We therefore decided to use the routine blood testing that has been collected during a prospective epistaxis cohort study to measure indirect markers of alcohol intake [5]. The mean corpuscular volume (MCV) has been associated with alcohol overuse [6]. Chronic alcohol use was shown to be one of the major causes of macrocytosis (MCV $>$ 100 fl) [7]. Sensitivity and specificity for MCV $>$ 93 fl measurements predicting regular heavy drinking were reported to be as high as 73 and 96.7%, respectively [8]. Furthermore, it has been shown that gamma glutamyltransferase (GGT) and aspartate aminotransferase/alanine aminotransferase (AST/ALT) were reasonable markers for ethanol consumption when combined with measurements of MCV [9].

It was the goal of this study to examine blood markers of chronic alcohol use in a large cohort of epistaxis patients and to compare it to results from large screenings in the general population.

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Materials and methods

Patients

Patients presenting at the ENT department of the University Hospital of Zurich for the reason of non-traumatic epistaxis were included in this study between March 2007 and April 2008. Data collection was performed with the permission of the local ethical committee and review board.

Neither the intake of anticoagulants such as warfarin nor the use of antiaggregational medication such as acetylsalicylic acid or clopidogrel were considered exclusion criteria as they were evenly distributed among patients with elevated indirect markers of alcohol overuse and those with normal values. Furthermore, the exclusion of these patients would have lead to a selection of a certain patient subpopulation, which was not the aim of this study as we wanted to analyze a representative study group. The parameters used in this study and the corresponding norm-values can be found in Table 1. None of the patients that presented repeatedly had pathologic MCV levels at any visit. The source of bleeding, treatments and complications were also noted and have been published previously [1].

To classify a patient as having macrocytosis, the cut-off value of 100 fl was used. For the comparison with a normal population, the proportions provided in the literature were used. According to Cohen et al. [10] AST/ALT ratios of above 2 are almost indicative and >1.5 strongly suggestive for alcoholic damage of the liver. Therefore, the AST/ALT ratios were calculated for all patients.

Table 1 Normal values of blood markers

Parameter	Normal value (female)	Normal value (male)
Hb (g/dl)[a]	11.7–15.3	13.4–17.0
MCV (fl)[a]	80–100	80–100
MCH (pg)[a]	26–34	26–34
MCHC (%)[a]	31–36	31–36
Thrombocyte count (10^3/µl)[a]	143–400	143–400
GGT (U/l)	5–36	8–61
aP (U/l)	<104	<129 (older than 18 years)
		<390 (younger than 18 years)
AST (U/l)	10–35	10–50
ALT (U/l)	10–35	10–50
INR	0.8–1.2	0.8–1.2
PTT (s)	25–40	25–40

Hb hemoglobin, *MCV* mean corpuscular volume, *MCH* mean corpuscular hemoglobin, *MCHC* mean corpuscular hemoglobin concentration, *GGT* gamma glutamyltransferase, *aP* alkaline phosphatase, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *INR* international normalized ratio, *PPT* partial thromboplastin time

[a] Automated blood count

Statistics

Comparison of categorical data was done by the Chi-square test or Fischer's exact test. As the data showed a normal distribution, Student's t test analyzed differences in cell counts between groups and the Pearson coefficient was used in correlation analyses. The significance level alpha was set to 0.05.

Results

The original study population consisted of 591 bleeding events in 571 patients [1]. Bleeding sources were evenly distributed between both sides. In-hospital stay was required in 17%. One hundred ninety-eight (34%) reported using ASA therapy, 107 (18%) were on a coumarin treatment and 3% used clopidogrel. Anterior epistaxis was present in 399 events (68%), whereas 180 (31%) had a posterior bleeding source. Local cautery was applied in a total of 493 (84%). Packing with either a Rapid Rhino pack or using a Foley catheter was performed in 151 (26%) of events. Surgical therapy was performed by endonasal closure of the branches of the sphenopalatine artery by endoscopic surgery in 35 (6%) and 5 (1%) individuals needed an additional external approach to the ethmoidal vessels. Complications were observed in 3% of all patients.

Five hundred and fifty-seven peripheral venous blood samples were obtained during the first emergency visit in a total of 537 patients. Two hundred thirty-six (44%) female and 301 (56%) male patients with a mean age of 66.0 years (min 12 years, max 97 years) were enrolled. Twenty-seven samples could not be used for all analyses as their blood sampling was incomplete.

Samples from 510 patients could therefore be used entirely for the present study. The mean values and standard error of the mean of the measured blood counts as well as liver parameters can be found in Table 2. The only parameter that was found to be abnormal in both sex-groups was GGT, while MCV levels were within normal range and distribution. However, looking at macrocytosis in the studied population, 24 patients (4.7%) revealed pathologic values of >100 fl. Comparing these with the cumulative macrocytosis values from literature (480/16,488; 2.9%) consisting of 1.7% [11], 2.4% [12], 3.0% [7], 3.7% (cut off 98.5 fl) [13] we observed a significantly higher incidence ($p = 0.03$). Twelve of the 24 patients (50%) had a bleeding source located posteriorly and

Table 2 Mean values of blood markers

	Male	SEM male	Female	SEM female
Hb (g/dl)[a]	13.68	0.12	12.75	0.11
MCV (fl)[a]	90.27	0.40	89.40	0.37
MCH (pg)[a]	31.47	0.15	30.84	0.14
MCHC (%)[a]	34.86	0.08	34.48	0.09
Tc-count (10^3/µl)[a]	242.1	5.24	284.1	6.07
GGT (U/l)	74.11+	8.56	45.78+	6.07
aP (U/l)	83.96	8.56	83.07	2.61
AST (U/l)	33.39	1.36	29.23	0.99
ALT (U/l)	30.26	1.37	22.92	0.92
INR	1.33+	0.05	1.35+	0.06
PPT (s)	29.97	0.36	30.31	0.48

Hb hemoglobin, *MCV* mean corpuscular volume, *MCH* mean corpuscular hemoglobin, *MCHC* mean corpuscular hemoglobin concentration, *GGT* gamma glutamyltransferase, *aP* alkaline phosphatase, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *INR* international normalized ratio, *PPT* partial thromboplastin time, *SEM* standard error of the mean, + above reference level

[a] Automated blood count

required posterior packing for the treatment. On the other hand, 12 of 153 patients with posterior epistaxis had MCVs above 100 fl, whereas only 12 of 353 of anterior bleeders suffered from macrocytosis $p = 0.04$. Of the 24 patients identified of having macrocytosis the MCH was 104.5 ± 0.7 fl. 18 of the 24 (75%) individuals had pathologic GGT levels and the AST/ALT ratio was above 1.5 in 12 (50%) and above 2 in 5 (21%), indicating an alcohol-caused liver dysfunction in this group. No differences in the proportions of antiaggregational or anticoagulative medications used nor in the mean values of INR or PTT were found in the group with a macrocytosis.

Further analyses were performed regarding MCV and the levels of the liver parameters like GGT, alkaline phosphatase (aP), AST and ALT. GGT, AST and ALT positively correlate with the MCV highly significantly, whereas alkaline phosphatase (aP) does not ($p = 0.54$). $n = 488$ (MCV/GGT), $n = 463$ (MCV/aP), $n = 497$ (MCV/AST), $n = 494$ (MCV/ALT) (Fig. 1). These correlations further strengthen the hypothesis that macrocytosis is associated with liver dysfunction and potentially with ethanol intake. GGT were compared in epistaxis patients having a MCV > 100 fl ($n = 24$) or < 100 fl ($n = 465$) showing significantly higher levels in the group with macrocytosis (Fig. 2a).

To further assess influencing factors (besides drug-derived platelet dysfunction and decreased coagulation by vitamin K antagonists) we looked at platelet counts. A borderline difference was found between the two groups with ($n = 24$) and without ($n = 488$) macrocytosis (227,400 ± 17,300 vs. 262,700 ± 19,900 cells/Ul, $p = 0.08$, Fig. 2b). Finally looking at the connection between the platelet count, the MCV and liver parameters including GGT, AST and ALT, we again found a significant, but negative correlation of the thrombocyte number and the different measurements with the exception of aP ($p = 0.14$). $n = 512$ (Tc-count/MCV), $n = 488$ (Tc-count/GGT), $n = 497$ (Tc-count/AST), $n = 494$ (Tc-count/ALT) (Fig. 3).

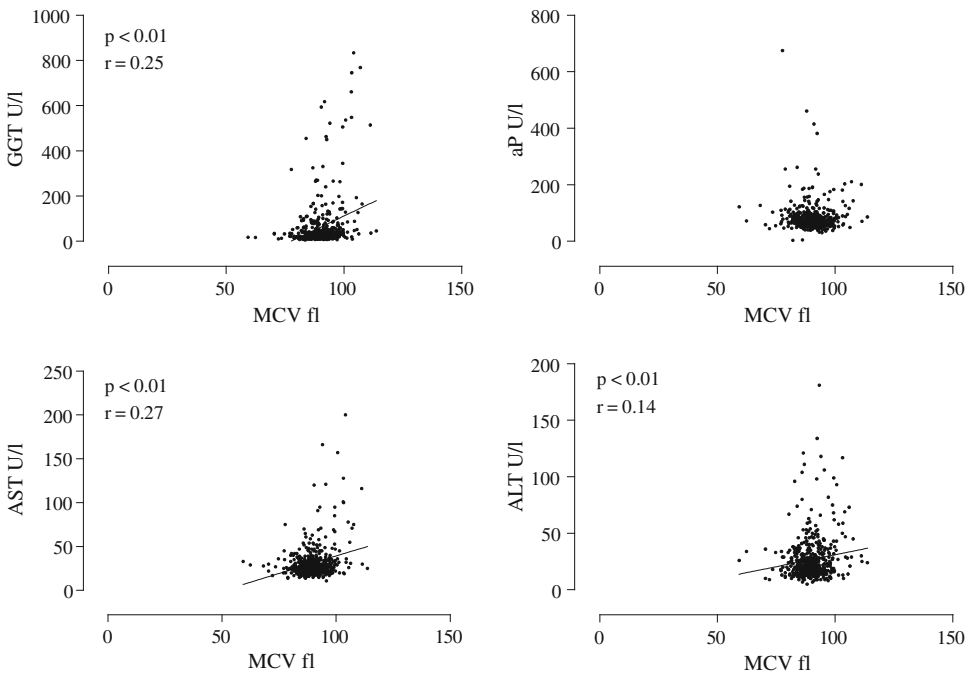

Fig. 1 Mean corpuscular volume (*MCV*) positively correlates with liver enzymes in epistaxis patients *p* and *r* values from Pearson's correlation are provided, where significant

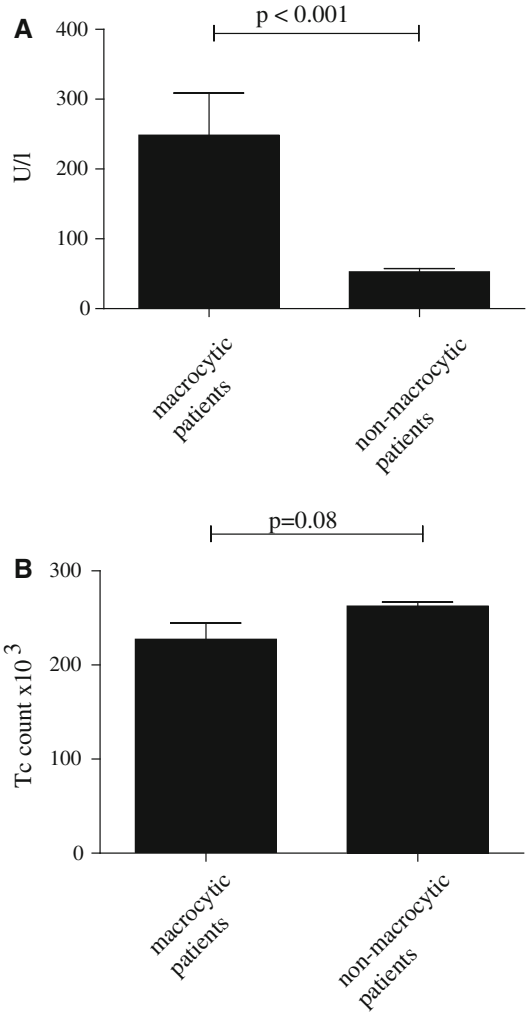

Fig. 2 GGT is elevated and platelet count is lower in epistaxis patients with macrocytosis results from Student's *t* test provided

Discussion

In the current study we investigated indirect markers of alcohol overconsumption in epistaxis patients including GGT levels and MCV. We observed a subgroup with macrocytosis within our cohort of epistaxis patients. Mean GGT levels were elevated in the whole study population and liver enzymes positively correlated with MCV, while platelet counts showed a decrease. All measured parameters suggest that a subgroup of patients suffer from alcohol overconsumption, supporting the idea of alcohol as a risk factor in epistaxis [4, 14–16].

GGT is supposed to be the first liver enzyme to be elevated in alcohol-induced liver damage [17]. Alcohol causes a wide array of adverse effects on blood cell formation by not yet clearly identified modes of action [18]. There, however, is a dose dependence of ethanol consumption and red blood indices [19].

The MCV has been reported to be a reasonable marker for chronic alcohol use especially in conjunction with liver parameters such as GGT [5]. We have identified a significant number of patients showing high levels of these markers in a non-selected group of epistaxis patients. MCV and other indicators have been reported to have a low sensitivity therefore we might have underestimated the number of patients with excessive drinking habits. However, specificity of these tests is higher and therefore the likelihood of a positively tested patient to truly overconsume alcohol is increasing [8]. We therefore consider MCV elevation in conjunction with rising levels of hepatic enzymes in the blood to be indirect markers of excessive drinking.

Besides the problem when performing a retrospective study (although using prospectively collected data), there of course are other factors that need to be considered: we were unable to address the patient's history concerning drinking habits. Different questionnaires have been developed to correctly assess alcohol overconsumption but their sensitivity and specificity when used alone are comparable to laboratory testings [20]. In an emergency situation the use of long questionnaires might not be the optimal way of screening [3].

In addition to alcohol overconsumption, there are other factors that may lead to a rise in liver enzymes and the corpuscular volume. Macrocytosis may be caused by many different disorders and agents such as medication, hypothyroidism and vitamin B12 deficiency [21]. The same is true for liver enzymes where different disorders and medications may cause a rise in levels [22]. A biliary cause can almost be excluded because of missing correlation of MCV and thrombocytes with alkaline phosphatase levels [23]. According to the found AST/ALT ratios an ethylic cause of the liver distress is highly likely.

Posterior bleedings were overrepresented (50%) in the group with elevated indirect markers of alcohol overuse, in comparison to the general epistaxis cohort, where posterior bleedings were reported to be only 31% [1]. Posterior bleeding usually led to more invasive treatments than anteriorly located ones and therefore poses a greater burden on the patient. Alcohol is already known to interfere with coagulation, thrombocyte function and fibrinolysis [24, 25]. Despite the fact that coagulopathies, thrombocyte dysfunction and alcohol lead to epistaxis, they were shown to be associated with posterior and severe bleedings [1, 14]. In our work posterior epistaxis was significantly associated with macrocytosis which is similar to the association of posterior and heavy bleedings in patients with aspirin intake [1]. We postulate that macrocytosis as a marker of alcohol overuse in epistaxis patients points to those individuals with an alcohol-induced hemostatic disorder, leading to more severe bleedings.

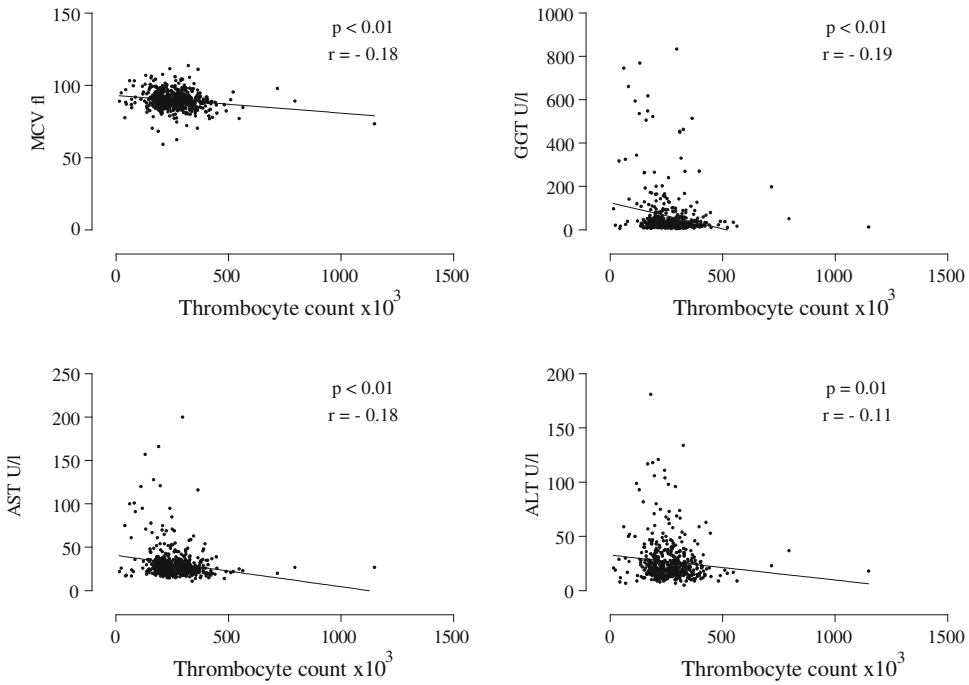

Fig. 3 Platelet counts negatively correlate with MCV and liver enzymes in epistaxis patients: *p* and *r* values from Pearson's correlation are provided, where significant

In conclusion, we observed that epistaxis patients suffer from macrocytosis in a larger proportion than found in the general population. Along with an increase of the erythrocyte volume an increase in other parameters suggestive of chronic alcohol intake could be shown. These findings support the idea that alcohol plays a role as a risk factor especially in posterior epistaxis. The results of this study justify further direct investigations of alcohol consumption in this patient cohort. Questioning about drinking habits should be employed in everyday practice when treating epistaxis patients and appropriate help needs to be offered to the affected patients.

Conflict of interest None.

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