Alcohol-induced Cushing syndrome
Hypercortisolism caused by alcohol abuse

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ABSTRACT

Background: Cushing's syndrome (CS), a rare syndrome caused by overexposure to glucocorticoids, is difficult to diagnose. The underlying causes of CS include pituitary and ectopic adrenocorticotropic hormone (ACTH) producing tumours and adrenal adenomas or hyperplasia. Alcoholism, however, can cause similar symptoms, giving rise to a so-called pseudo-Cushing state, which aggravates the differential diagnostic dilemmas of CS.

Aim: To document any specific clinical or biochemical features of alcohol-induced CS.

Methods: A Medline computer-aided search was performed to identify studies that have attempted to differentiate between alcohol-induced pseudo-Cushing and CS. Only original articles, not reviews, written in English were included. A total of 62 articles were included.

Results: Clinical and biochemical abnormalities mimicking increased hypothalamus-pituitary-adrenal (HPA) axis activity were found in the majority of the patients, although the severity of the changes varied widely. The most frequently occurring abnormalities were: insufficient suppression after low-dose dexamethasone or increased 24-hour urinary free cortisol (UFC). After alcohol withdrawal, cortisol decreased and dexamethasone-induced suppression of cortisol increased. No differences were noted between alcoholic and control subjects after an ACTH stimulation test, insulin tolerance test or metyrapone test. Differences were found after a naloxone test and hexarelin test. Studies using corticotropin-releasing hormone stimulation and tests after ethanol ingestion revealed inconclusive results.

Conclusion: There is no clear definition for the alcohol-induced pseudo-Cushing state, and hitherto studies fail to provide clues to differentiate between pseudo-Cushing and Cushing's syndrome. Only cessation of alcohol can normalise biochemical abnormalities and regress hypercortisolic symptoms.

KEYWORDS

Alcohol, cortisol, Cushing's syndrome

INTRODUCTION

Cushing's syndrome (CS) is an extremely rare clinical syndrome characterised by overexposure to glucocorticoids with an annual incidence of two to three per million. CS is caused by uncontrolled overexposure of the body, including the central nervous system, to corticosteroids. This results in a phenotype characterised by psychopathology (mainly depression), features of the metabolic syndrome (such as insulin resistance, hypertension, and abdominal fat accumulation), but also proximal muscle wasting, and easy bruising.4 This uncontrolled exposure to endogenous cortisol is caused by tumours, which overproduce corticotropin-releasing hormone (CRH, in very rare cases), adrenocorticotropic hormone (ACTH, by pituitary adenomas or ectopic tumours), or cortisol (by adrenal tumours). Cushing's syndrome is a fatal condition in the absence of adequate treatment. Although the severe classical phenotype is not difficult to diagnose, some frequently occurring illnesses such as depression, obesity, physical stress, and chronic alcoholism can induce a phenotype that largely overlaps with CS and is also accompanied with increased cortisol exposure, and as a consequence, is called a pseudo-Cushing state. The discrimination between CS and these frequently occurring pseudo-Cushing states is difficult because many symptoms of CS, such as overweight, depressed mood, hypertension and irregular menses, are also prevalent in pseudo-CS, and therefore, biochemical tests often provide equivocal results resulting in a low specificity.7 This review aims to focus on the diagnosis and therapy for alcohol-induced pseudo-Cushing's syndrome.
METHODS

A computer-aided search was performed in Medline using the search terms “alcohol AND hypercortisolism”, “alcohol AND cushing”, “alcoholic AND cortisol” and “alcoholic AND cushing”. Only articles written in English with an abstract were included. The search was performed on 9 September 2010 and resulted in a total of 423 articles. Based on title and abstracts, 352 were excluded; the remaining 71 articles were retrieved for further evaluation. One article was not available and another eight were excluded after complete evaluation, because they did not present original data or were not relevant for the aim of the present study. Finally, a total of 62 articles were included for detailed analysis.

RESULTS

Clinical presentation

Case reports were identified on patients who had symptoms compatible with CS, which eventually proved to be the result of alcoholic addiction, which illustrates that symptoms of the diseases resemble each other. Details on physical examination were reported in all 16 cases; 87.5% had a moon face, 60% hypertension, 81% muscle weakness or tiredness, 12.5% striae and 73% truncal obesity. In Cushing’s syndrome, moon face is reported in 82 to 90%, hypertension in 68 to 75%, weakness in 60 to 64%, and obesity in 95% of cases, respectively. Clinical symptoms were reported in 10 out of 16 cases: 90% had weight gain, 30% easy bruising, 30% sleepiness, 20% headache and only one person suffered from depression. In CS easy bruising is reported in 65%, whereas headache and sleepiness are not reported.

BIOCHEMICAL PRESENTATION

Circulating cortisol concentrations

In the case reports cortisol was elevated in 12 out of 13 patients, which normalised after alcohol abstinence in all patients. Twelve studies investigated plasma cortisol concentrations in alcoholic patients. Six studies found no differences with control subjects, while six other studies found elevated cortisol levels in alcoholics. A decrease in mean cortisol after abstinence (7-30 days) was seen in three other studies. Three studies measured cortisol during 24 hours and observed no differences in circadian rhythms in alcoholics compared with controls, although mean cortisol decreased in one study after approximately 30 days of abstinence. Coiro, et al. measured cortisol in ten women with alcohol-induced pseudo-Cushing and found a higher fasting cortisol at 8.30 am compared with controls. Frias et al. evaluated teenagers and adolescents during acute alcohol intoxication and found elevated cortisol levels, which was more pronounced in females. In the study by Bannan and colleagues, 20% of alcoholics were found to have hypercortisolism that appeared to be positively correlated to withdrawal symptoms. Stalder et al. detected higher cortisol in the hair of subjects who had recently stopped drinking alcohol compared with both controls and subjects who had a longer abstinence period.

Salivary cortisol

Salivary cortisol was measured in only two studies: The first (Adinoff et al.) reported higher salivary cortisol concentrations at daytime in intoxicated alcoholics and non-intoxicated withdrawal subjects than controls, whereas Beresford noted a higher salivary cortisol in heavy drinking than light drinking alcohol-dependent subjects at awaking and 30 minutes thereafter.

Urinary free cortisol (UFC) excretion

Five studies measured 24-hour UFC. Coiro et al. reported higher fasting mean cortisol than control subjects but no difference between pseudo-Cushing and Cushing patients. Stewart et al. and Wand et al. noted a higher mean 24-hour UFC in 28 alcoholics vs 32 controls. In contrast Rosman et al. reported a lower cortisol in alcoholic subjects, which was to be expected since all his subjects had proven cirrhosis or compelling clinical evidence for it. Willenbring observed normal urinary cortisol that decreased even further after three weeks of alcohol abstinence. Urinary cortisol or corticoids were elevated in three subjects presented in case reports, slightly elevated in two but not different compared with controls in seven subjects.

Dynamic tests to evaluate the HPA axis

Low-dose (1 mg) oral dexamethasone suppression: The dexamethasone suppression test (DST) can be used to demonstrate hypercortisolism. The Endocrine Society advises giving 1 mg dexamethasone orally at 11 pm and taking blood samples the next day at 8 am for determination of plasma cortisol, which should be suppressed to below 50 nmol/l to obtain a specificity greater than 95%. Nine studies took blood samples the next day at 8 am for cortisol levels, which was more pronounced in females. In the study by Bannan and colleagues, 20% of alcoholics were found to have hypercortisolism that appeared to be positively correlated to withdrawal symptoms.
after withdrawal with cortisol measurements at 3 pm. The longer the period of abstinence, the more patients had normalised suppression. In three case reports, abnormal dexamethasone suppression test in alcoholic patients normalised after abstinence.17,19,21 Many studies used Carroll's concept for psychiatric research to measure cortisol at 4 and 11 pm after a dexamethasone test.57 All 11 studies that measured cortisol at 4 pm noticed no suppression in some of the alcoholics, ranging from 6 to 63.3%. 27,48,50,53,54,58-62 Most patients were tested during alcohol withdrawal. Five studies measured cortisol at 11 pm; one of them found normal suppression,52 the others did not.27,50,53,61 Majumdar (1988) observed a non-suppressed cortisol at 4 pm in two out of 20 detoxicated alcoholics after a 2 mg DST.63 In six of 30 alcoholics who had just stopped drinking non-suppressed cortisol levels were found whereas after abstinence this number decreased to two. Rees also measured a high cortisol after a 2 mg DST in one out of two persons, which normalised after 16 days alcohol abstinence.21 Proto performed a DST with 2 mg dexamethasone a day for three days and noted normal suppression of cortisol in all six subjects.20 Hundt did a DST with 1.5 mg dexamethasone a day for three days and noted normal suppression of cortisol in all six subjects.25 Fink recruited ten alcoholic patients who were subjected to an intravenous DST with 1 mg/hour of dexamethasone for two hours with subsequent cortisol measurements at 1/2, 1.1 1/2 and 2 hours.65 Four patients showed abnormal cortisol values.

### Table 1. Studies reporting the results of a 1 mg dexamethasone suppression test

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Age (yrs)</th>
<th>Duration alcoholism (yrs)</th>
<th>Amount alcohol</th>
<th>Time since last drink</th>
<th>Cortisol &gt; 5 µg/dl after DST</th>
<th>Cortisol &gt; 5 µg/dl after abstinence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bailly 10</td>
<td>27-47</td>
<td>15.8</td>
<td>258</td>
<td>?</td>
<td>60%</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Coiro 2000 8</td>
<td>35.7</td>
<td>≥ 5</td>
<td>189.1 g/day</td>
<td>?</td>
<td>?</td>
<td>75%</td>
<td></td>
</tr>
<tr>
<td>Coiro 2004 10</td>
<td>31.7</td>
<td>≥ 5</td>
<td>240 g/wk</td>
<td>?</td>
<td>?</td>
<td>60%</td>
<td></td>
</tr>
<tr>
<td>Emsley 36</td>
<td>41-60</td>
<td>22/22</td>
<td>?</td>
<td>40/6 months</td>
<td>0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oszoy 30</td>
<td>43.03</td>
<td>21.83</td>
<td>330.4 g/day</td>
<td>≥ 4 weeks</td>
<td>22.22%</td>
<td>11.6%</td>
<td></td>
</tr>
<tr>
<td>Ravi 30</td>
<td>40</td>
<td>9.6</td>
<td>≥ 15 whiskey on ≥ 3 days</td>
<td>0</td>
<td>63.3%</td>
<td>11.1%</td>
<td></td>
</tr>
<tr>
<td>Rosman 17</td>
<td>31.53</td>
<td>10-30</td>
<td>?</td>
<td>?</td>
<td>12.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Swartz 1982 43</td>
<td>44.4/40.8 2.6/9.5</td>
<td>391/326 ml/day</td>
<td>?</td>
<td>≥ 2 weeks</td>
<td>?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Szucs 22</td>
<td>53</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

N = number of subjects, DST = dexamethasone suppression test. Emsley: 19 korsakoff and 17 non-amnesic alcoholists. Swartz: means were reported for non-suppressors and suppressors respectively.

### Other cortisol suppression tests

Many studies used Carroll's concept for psychiatric research to measure cortisol at 4 and 11 pm after a dexamethasone test.57 All 11 studies that measured cortisol at 4 pm noticed no suppression in some of the alcoholics, ranging from 6 to 63.3%. 27,48,50,53,54,58-62 Most patients were tested during alcohol withdrawal. Five studies measured cortisol at 11 pm; one of them found normal suppression,52 the others did not.27,50,53,61 Majumdar (1988) observed a non-suppressed cortisol at 4 pm in two out of 20 detoxicated alcoholics after a 2 mg DST.63 In six of 30 alcoholics who had just stopped drinking non-suppressed cortisol levels were found whereas after abstinence this number decreased to two. Rees also measured a high cortisol after a 2 mg DST in one out of two persons, which normalised after 16 days alcohol abstinence.21 Proto performed a DST with 2 mg dexamethasone a day for three days and noted normal suppression of cortisol in all six subjects.20 Hundt did a DST with 1.5 mg dexamethasone with measurements at 8 am and detected abnormal suppression in four out of 19 alcoholic patients (21%) during alcohol withdrawal.64 Fink recruited ten alcoholic patients who were subjected to an intravenous DST with 1 mg/hour of dexamethasone for two hours with subsequent cortisol measurements at 1/2, 1.1 1/2 and 2 hours.65 Four patients showed abnormal cortisol values.

### Combined suppression and stimulation tests

Three studies found no differences in cortisol between alcoholics and controls using the 250 µg ACTH stimulation test.29,47,55 One of these studies noticed that normal subjects had a cortisol response after a 0.25 µg ACTH stimulation test, which was absent in alcoholics.47 Another study observed that two out of 13 tested alcoholics did not meet criteria for normal responsiveness; however, four alcoholics had higher levels than normal subjects.46 A CRH test (100 µg or 1 µg/kg bolus) was performed in seven studies and three observed no differences in cortisol response in alcoholics and controls.25,30,50 although two of them found a blunted ACTH response.5,9 Two others observed a blunted cortisol response 22-47 and two noticed a higher cortisol.22,47 Two studies reported no differences in cortisol after an insulin tolerance test (ITT) between non-intoxicated alcoholics and controls,24,67 yet one noted a blunted ACTH response.67 ACTH was too high in the subject that underwent an ITT presented by Lamberts.19 Coiro 2000 performed a hexarelin test in 25 subjects and registered an increase in ACTH and cortisol in controls and subjects with Cushing, but not in alcoholics.51 Wand performed a metyrapone test in 14 alcoholics and 13 volunteers, and found similar decrements in cortisol in alcoholics and controls.47 Although the ACTH response and 11 deoxycortisol levels were much lower than in controls and thus 50% of alcoholics met criteria for adrenal insufficiency. Lamberts described a woman with a metyrapone test compatible with Cushing's syndrome.19 Inder infused 20 mg naloxone in nine alcoholics and nine controls and showed a blunted rise followed by a slower fall to normal values in alcoholics.47 The controls demonstrated positive correlations between basal cortisol and cortisol increment and ACTH increment, which were not present in the alcoholic subjects.

Nine studies measured cortisol response after alcohol intake. The studies all used different designs. Three of
them found no or a slight change in HPA hormones in alcoholics compared with controls, 55-68,69 three described a higher response69,70,71,72 and two others observed a lower response.73,74 One study noticed only changes in cortisol and ACTH in subjects who had gastrointestinal symptoms after drinking alcohol.75

The last two studies pointed towards an altered cortisol feedback mechanism in alcoholics. Lovallo measured cortisol after public speaking and detected no cortisol response in alcohol-dependent subjects, but did find this in controls.76

Coiro 2007 measured cortisol after an exercise test in alcoholics after four, six and eight weeks of abstinence.77 After four weeks abstinence, exercise induced no change in cortisol and ACTH in contrast to in controls; after eight weeks the difference between controls and alcoholic had disappeared.

### DISCUSSION

This review demonstrates that the clinical and biochemical features of the alcohol-induced pseudo-Cushing syndrome vary widely, and that no criteria are available to distinguish between CS and alcohol-induced CS. No stringent criteria were found for the definition of pseudo-Cushing syndrome. Different biochemical tests that evaluate different properties of the HPA axis yielded different results. In addition, standardisation of tests and test criteria varied widely precluding simple generalisations of test results. No laboratory tests yielded sufficient discriminatory power to detect alcohol-induced pseudo-Cushing syndrome. Signs and symptoms tend to normalise after cessation of alcoholism for at least a month. At end of the 1970s the first case reports appeared on patients with symptoms mimicking Cushing’s syndrome, caused by alcoholism.75,76 Tests that were characteristic for hypercortisolism normalised after cessation of alcohol abuse.

Plasma cortisol levels were higher in alcoholics in nine studies55,57,59,60-62 and normal in six other studies.22,24-27 This discrepancy can be explained by the different study designs: four of six studies that observed no differences in cortisol22,24-27 were done in subjects who had stopped drinking alcohol for at least ten days. In contrast, seven of nine studies that reported a higher cortisol used subjects who stopped drinking for less than one day.55,58,59-61,63-65 Consequently, the observed higher cortisol could either be provoked by alcohol or by the stress during the first days of abstinence.

Furthermore, blood samples of five out of six studies that observed no difference were taken between 8 and 9 am,22,24-27 while this was the case in only two out of nine studies that observed differences.(32,33) Other studies did not reveal time or took samples late in the morning, afternoon or night. Since cortisol secretion has a circadian rhythm, time of sampling has a great influence on cortisol level.

Inadequate suppression was measured in 0 to 75% of alcoholics67,68,69 during a 1 mg dexamethasone suppression test. However, the studies all used different designs. In the study that observed an appropriate suppression, tests were performed in subjects that were abstinent for at least 12 weeks.29 One study only stated that there was no difference in plasma cortisol between controls and alcoholics.31

After one month of abstinence more suppression was observed using a 1 mg dexamethasone suppression test.32,33 However, these three studies measured cortisol at three different moments and classified suppression as abnormal if at any of these moments suppression was abnormal. Also, they did not mention at which time the suppression was abnormal.

In conclusion, the literature does not provide any evidence for clinical symptoms or laboratory investigations suitable for diagnosing hypercortisolism caused by alcoholism. However, the number of patients studied was limited, different study designs, diverse definitions for alcoholism and pseudo-Cushing were used and tests were performed in various populations. Additionally, most studies were performed during alcoholic withdrawal, which is likely to induce stress and thus hypercortisolism.

Therefore, alcoholic patients diagnosed with CS should have repeat clinical and biochemical work-up after cessation of alcohol before subsequent (radiological) investigations can be performed.

### REFERENCES


Best treatment of alcohol-induced Cushing

The search did not find any articles about treatment of alcohol-induced Cushing’s syndrome. Nevertheless, case reports invariably demonstrated that resolution of symptoms and biochemical disturbances occurs after alcohol withdrawal.73,74

### BEST TREATMENT OF ALCOHOL-INDUCED CUSHING

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