Alcohol-induced Cushingoid Syndrome

A. G. H. SMALS, MD, *Division of Endocrinology, University of Nijmegen;*
K. T. NJO, MD, *Department of Medicine, Bethesda Hospital, Hoogeveen;*
J. M. KNOBEN, MD, *Department of Medicine, St Anna Hospital, Geldrop;*
C. M. RULAND, MD, *Department of Medicine, St Canisius Hospital, Nijmegen;*
P. W. C. KLOPPENBORG, MD, *Division of Endocrinology, University of Nijmegen, The Netherlands.*

Alcohol abuse has long been known to affect endocrine organs, including the pituitary adrenocortical system (Farmer and Fahre, 1975; Merry and Marks, 1973; Dillon, 1973). Hypercorticism which mimics Cushing's syndrome has been described by us and other authors (Smals *et al.*, 1976; Paton, 1976; Rees *et al.*, 1977). After our first report on three patients, we observed three more individuals with an alcohol-induced Cushingoid syndrome. This report summarises the data on six patients in whom clinical and biochemical findings could have led to a false diagnosis of Cushing's syndrome.

CASE REPORTS

Patient 1. A 39-year-old alcoholic woman was admitted to hospital with clinical and biochemical features (Table 1) strongly suggesting Cushing's syndrome (moon face, periocular pigmentation, truncal obesity, overt muscle wasting of arms and legs) and elevated serum GOT levels. Soon after admission the features of Cushing's syndrome disappeared with a parallel fall of the elevated plasma cortisol and serum transaminase levels.

Table 1. Biochemical data of 6 patients with alcohol induced Cushingoid syndrome.

Patient	Age (Yrs)	Sex	Plasma Cortisol (μg/100 ml) Basal 8 a.m.	4 p.m.	Dexameth 8 a.m.	Serum GOT (U/L)	Glucose intolerance
1	39	F	60	36	14	30	+
2	54	M	80	81	34	38	+
3	30	M	37	15	14	60	+
4	39	M	38	42	3	75	–
5	59	M	26	26	2	24	+
6	36	F	26	24	3	27	+
mean ± SD			44.5 ± 21.0	37.0 ± 23.4		42.0 ± 20.0	
range			26-80	15-81			
normal range			14-25	5-14	>4	<15	

Patient 2. A 54-year-old chronic alcoholic man was admitted for evaluation of impaired liver function, hypertension, vertebral wedging, glucose intolerance, Cushingoid appearance and biochemical abnormalities (Table 1) consistent with a diagnosis of Cushing's syndrome. In the hospital all features of Cushing's syndrome faded as the plasma cortisol and serum transaminase levels fell.

Patient 3. A 30-year-old chronic alcoholic man was admitted with biochemical (Table 1) and clinical features strongly suggesting a diagnosis of Cushing's syndrome (hypertension, plethora, moon face, purple abdominal striae and elevated serum GOT levels).

In hospital the clinical signs of Cushing's syndrome disappeared as the elevated plasma cortisol and serum transaminase levels returned to normal.

Patient 4. A 39-year-old alcoholic man was admitted for evaluation of his hypertension, muscle wasting and weakness, central obesity, elevated plasma cortisol levels without circadian rhythm and elevated serum GOT levels. Soon after admission the clinical and biochemical features (Table 1) of Cushing's syndrome disappeared.

Patient 5. A 59-year-old alcoholic man was admitted for evaluation of his increasing fatigue, hypertension, central obesity, muscle wasting, glucose intolerance and slightly elevated plasma cortisol level without circadian rhythm (Table 1). Serum GOT levels were elevated. In the hospital most biochemical and clinical abnormalities gradually disappeared.

Patient 6. A 36-year-old chronic alcoholic woman was admitted with biochemical (Table 1) and clinical features consistent with a diagnosis of Cushing's syndrome (facial mooning, central obesity and muscle wasting of arms and legs) and elevated GOT level.

The clinical and biochemical features of Cushing's syndrome progressively faded as the serum GOT level returned to normal.

MATERIALS AND METHODS

Basal 8 a.m. plasma cortisol and serum transaminase levels were measured on the first day after admission to hospital in 6 patients with alcohol-induced Cushingoid syndrome, 9 chronic alcoholics with elevated serum GOT levels without clinical signs of Cushing's syndrome, 19 non-alcoholic patients with a variety of liver pathology and elevated serum GOT levels and 10 control individuals. In the 6 patients with alcohol-induced Cushingoid syndrome the diurnal variation of plasma cortisol was measured and the effect of 2 mg of dexamethasone, given at 11 p.m., noted.

RESULTS

Table 1 summarises the biochemical data of the 6 chronic alcoholics with Cushingoid syndrome. Basal 8 a.m. and 4 p.m. plasma cortisol levels were elevated in all patients; the diurnal change of cortisol was absent in 4 and diminished in 2 patients. Overnight dexamethasone administration inadequately suppressed plasma cortisol levels in 3 of the 6 patients. In 10 chronic alcoholic subjects without clinical signs of Cushing's syndrome (Table 2) the mean 8 a.m. plasma cortisol level was significantly higher than in 10 control individuals ($p < 0.01$).

Table 2. Plasma cortisol and serum GOT levels in Cushingoid and non-Cushingoid alcoholics, patients with non-alcoholic liver disease and elevated SGOT levels, and controls.

	No. of patients	8 a.m. plasma cortisol (μg/100 ml)		SGOT (U/L)	
		mean ± SD	range	mean ± SD	range
I Cushingoid alcoholics	6	44.5 ± 21.0	26-80	42 ± 20	24-75
II Non-Cushingoid alcoholics	10	27.4 ± 7.6	18-47	39 ± 28	15-99
III patients with non-alcoholic liver disease	19	16.6 ± 6.9	9-32	32 ± 18	16-76
IV Controls	10	18.1 ± 3.9	11-25	<15	

In three of these non-Cushingoid alcoholics, overnight dexamethasone administration adequately suppressed plasma cortisol levels to a mean value of 2.6 ± 0.5 μg/100 ml. Serum GOT levels were elevated in all Cushingoid and non-Cushingoid alcoholic patients ($p > 0.1$). In the non-Cushingoid alcoholics no correlation was found between initial basal plasma cortisol levels and serum GOT values ($p > 0.1$).

In 19 non-alcoholic patients with a variety of liver pathology and elevated GOT levels the mean plasma cortisol level did not differ significantly from the mean value in the 10 control subjects ($p > 0.1$), but was significantly lower ($p < 0.001$) than in the non-Cushingoid alcoholics with liver impairment. The mean basal serum GOT levels in the Cushingoid and non-Cushingoid alcoholics did not differ significantly from the values in the non-alcoholic liver disease patients ($p > 0.1$). In these patients there was no significant correlation between basal plasma cortisol and serum GOT levels ($p > 0.1$).

In the alcoholic patients with a Cushingoid syndrome, plasma cortisol and serum transaminase levels were measured serially in the hospital and after discharge. A significant positive correlation was found between these multiple and individual series ($p < 0.05 - < 0.01$).

DISCUSSION

Clinical and biochemical findings more or less strongly suggesting Cushing's syndrome were found in 6 subjects (4 men and 2 women) with proven alcohol abuse. All had moon faces and plethora; hypertension and central obesity were evident in 5, muscle-wasting in 4, easy bruising in 2 and osteoporosis and striae lividae each in 1 patient. All patients had slightly or markedly elevated plasma cortisol levels with either complete lack (4) or blunting (2) of the diurnal rhythm. In 3 of the patients dexamethasone suppressibility of plasma cortisol was initially inadequate, in 3 others normal suppression was achieved. These data indicate that symptoms and signs of Cushing's syndrome in alcoholic patients can occur in the presence or absence of normal suppressibility of adrenal glucocorticoid function. In 5 of the patients, temporarily impaired glucose tolerance was an outstanding feature. All patients had elevated serum GOT levels. None of them had hyperlipidaemia which is known to interfere with the cortisol assay (Rees *et al.*, 1977).

Most of the abnormalities compatible with Cushing's syndrome disappeared soon after admission to hospital and abstinence from alcohol. This amelioration ran almost parallel with the return to normal of impaired liver function tests, suggesting a common cause or interrelationship. The elevated plasma cortisol levels and glucose intolerance returned to normal by the time serum transaminase levels had become normal. Excess alcohol ingestion was considered to be responsible for both the liver impairment and hyperactivity of the adrenal cortex, which finally resulted in a Cushingoid appearance. Alcohol withdrawal after admission might explain the recovery of most of the biochemical and clinical abnormalities consistent with hypercortisolism. Hypercortisolism was also found in chronic alcoholics without clinical features of Cushing's syndrome with slightly to moderately elevated serum GOT levels but not in non-alcoholic patients with a variety of liver diseases and similarly elevated serum transaminase levels. This finding excludes a straightforward causal relationship between impaired liver function and hypercortisolism in alcoholics. Until recently, well-documented reports on alcohol-induced Cushingoid syndrome were scarce. Dillon (1973) mentioned the strong resemblance of some chronic alcoholics to patients with Cushing's syndrome. Merry and Marks (1973) also stated that signs and symptoms similar to those observed in Cushing's syndrome were not infrequent in chronic alcoholics, some of whom had biochemical evidence of increased adrenocortical activity. Paton (1976) mentioned 8 alcoholics (5 men and 3 women) with features of Cushing's syndrome. All had histological evidence of alcoholic hepatitis or cirrhosis. In most but not all of these patients signs of Cushing's syndrome disappeared in hospital. Very recently Rees *et al.* (1977) reported 4 patients with alcohol-induced Cushingoid syndrome (2 men and 2 women). Biochemical and clinical features suggestive of Cushing's syndrome (plethoric face, easy bruising, truncal obesity) were present in 2 patients, whereas 2 others had only biochemical

abnormalities. Plasma cortisol levels were elevated in all patients and inadequately suppressed by dexamethasone in one of the patients tested. In 2 of the patients the circadian rhythm of corticotrophin secretion was absent. The clinical and biochemical abnormalities compatible with Cushing's syndrome disappeared after admission to hospital and with the return of normal liver function.

Including the patients of the present study 18 patients with alcohol-induced pseudo-Cushing's syndrome have been reported in recent literature. Alcohol abuse therefore has to be considered in the differential diagnosis of Cushing's syndrome.

The mechanism by which alcohol induces elevated plasma cortisol levels and a Cushingoid syndrome is still not fully explored. Ethanol could induce pituitary-dependent hypersecretion of ACTH, or impaired cortisol metabolism by the liver might contribute to hypercortisolism in alcoholics. Enhanced pituitary ACTH seems likely from findings of adrenal hyperplasia after alcohol administration in intact animals, and its absence in hypophysectomised rats or mice (Forbes and Duncan, 1951; Ellis, 1966; Mendelson, 1970). In this context Jenkins and Connolly (1968) did not find increases in plasma cortisol after ethanol infusion in patients with pituitary adenomas, in contrast to their findings in healthy men and women. Rees *et al.* (1977) measured plasma ACTH levels in three of their patients but, apart from a deranged circadian rhythm in two of them, levels were in the normal range. More studies will be necessary to define the role of ACTH in mediating alcohol-induced Cushingoid syndrome. Apart from enhanced ACTH secretion as a possible cause of hypercorticism, impaired cortisol metabolism by the liver might be a contributing factor. Although the striking parallelism between the degrees of liver function impairment and the hypercorticism is in favour of this hypothesis, several points contradict it. McCann and Fulton (1975) found lowered cortisol values in patients with chronic liver disease including alcoholic cirrhosis. Mendelson (1970) failed to demonstrate alterations in liver function in alcoholic subjects showing significant plasma cortisol increases in response to excess alcohol ingestion. Furthermore we, in this study, could not demonstrate any correlation between the serum GOT levels and plasma cortisol concentrations either in non-alcoholic patients with impaired liver function or in alcoholics without a Cushingoid appearance. Although serum GOT levels did not differ significantly between these two groups, the mean plasma cortisol level was significantly higher in the latter. Therefore, liver damage itself cannot account for the hypercorticism in chronic alcoholics. Rather, the impairment of the liver function and the hypercorticism have to be considered as consequences of the same causative agent, i.e., alcohol abuse.

Whatever the cause of the hypercorticism, biochemical and clinical findings in chronic alcoholics can strongly resemble those in Cushing's syndrome and lead to a false diagnosis. Awareness of this fact may save the alcoholic patient from unnecessary medical, surgical or radiotherapeutic intervention. The reason why

some alcoholics evince signs of adrenal overactivity and develop the Cushingoid appearance and others do not remains to be elucidated.

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THE PORCELAIN DOCTOR

'This learned and pleasing gentleman' said Boswell of Dr Martin Wall. Educated at Winchester and New College, Oxford, and trained at Bart's, Martin Wall eventually became Professor of Clinical Medicine at Oxford in 1785. Three years later he was Harveian Orator at the College and also elected to the Fellowship of the Royal Society. A fair achievement for anyone, but who now remembers Martin the professor when all lovers of fine porcelain remember his father, Dr John Wall? Recently the Royal Worcester Porcelain Company celebrated the bicentenary of its foundation by Dr John and his apothecary. After his death his collected writings were published by his son, who added a biographical note.

John Wall was the son of 'an opulent tradesman of Powich'. He was educated at a local grammar school and then graduated from Merton College, Oxford. He was a man of many parts; 'an early and unremitting attachment to the Art of painting engaged almost every moment of his leisure hours'. He combined this talent with a love of ceramics but it was 'his distinguished skill in chemistry and his assiduous researches . . . to discover materials proper for the imitation of the china ware' that led to the establishment of the porcelain industry in the city of Worcester. His medical works included a tract on the waters of Malvern that helped to popularise the spa and a letter read before the College of Physicians on 13th November, 1772. This letter was addressed to Dr Heberden and recorded the first case of angina to come to autopsy. Despite all this achievement his son wrote that 'the activity of his mind . . . was curbed and restrained by repeated attacks of a disorder which at last put a period to his life'. Any guess as to diagnosis?