

## PITUITARY-ADRENAL FUNCTIONING IN MALE ALCOHOLICS \*

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*Serum adrenocorticotrophic hormone (ACTH) and cortisol were assayed in 38 males alcoholics and 24 male control subjects using radioimmunoassay (RIA) techniques. Biochemical parameters of hepatic function, depressive symptoms and severity of withdrawal were also assessed. Thirteen percent and eleven percent of the patients and elevated serum ACTH and Cortisol levels respectively. Evidence of advance liver disease was scant and significant symptoms of depression was observed in only 14% of the patients. By and large withdrawal symptoms were mild. Two patients have clinical features suggestive of pseudo Cushing's syndrome without hypercortisolaemia*

**A**bnormal hypothalamic-pituitary-adrenal (H-P-A) functions are commonly seen following chronic use of ethanol. Elevated serum adrenocortico trophic hormone (ACTH) and cortisol were reported among patients with alcoholism (Elias *et al.*, 1982; Valimaki *et al.*, 1984). Higher urinary levels of metabolites of glucocorticoids (Cronholm *et al.*, 1985), and positive dexamethasone suppression test (DST) i.e. Cortisol nonsuppression were also observed (Delporte *et al.*, 1985). Clinical features resembling Cushing's syndrome without elevation of ACTH and cortisol values were reported. These were rapidly reversible and hence called pseudo Cushing's syndrome (Morgan, 1982; Noth and Walter, 1984). Some authors, however, reported normal H-P-A functioning in alcoholism (Hasselbalch *et al.*, 1982; Arkwright, 1982).

Several other factors besides excess alcohol use were implicated. Depressive mood changes commonly observed in alcoholism, stress as manifested by alcohol withdrawal states could also cause H-P-A activation (de Fuente 1983; Van Thiel, 1983 and Schuckit, 1986).

These reports are mostly from the west. Data on Indian patients are non-existent, which could very well be different. This is evident through variable incidence of alcohol induced

liver damage in several countries (Mendenhall, 1987).

We present here our observation on Serum ACTH and cortisol among patients with alcoholism. Cross-Sectional examination of mood, severity of withdrawal symptoms and liver function were also done.

### MATERIAL AND METHODS

**T**he patients (N=38) were adult males (age 16 to 60 years) satisfying DSM-III (APA, 1980) criteria of alcohol dependence, undergoing treatment at National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore. The exclusion criteria were:

- i) Presence of concurrent psychiatric disorders (e.g. Schizophrenia, major affective disorder as per DSM-III criteria).
- ii) dependence of other drugs and abuse
- iii) presence of diabetes mellitus
- iv) concomitant use of steroids, thyroid and antithyroid preparations and drug like salicylates and dicumarol.

The control group (N = 24) consisted of non-patients healthy adult males age 16 to 60 years. All the subjects were included in the study with informed consent. The followings were assessed within 48-72 hrs of last alcohol intake.

1. A semistructured interview schedule was used to collect information on demographic data, details of alcohol use (age of initiation, duration of daily use, duration of dependence, average of daily consumption and date of last use).

2. A physical examination checklist was used to collect information on physical State.

3. Clinical rating of alcohol withdrawal features was done by applying DSM-III criteria of alcohol withdrawal on a four point scale (0-3) (APA, 1980).

4. Cross-sectional, mood was assessed by Hamilton Depression Scale (HDS) (Hamilton, 1967) between 8 AM to 9 AM.

5. Venous blood sample (1st sample) was collected from the patients between 8 AM to 9 AM in fasting state for hormonal and liver function tests within 48-72 hours of last use of alcohol.

The withdrawal symptoms were controlled by chlordiazepoxide 60 -80 mg p.o. per day over a period of two weeks along with oral/parenteral vitamin supplements. Liver biopsy (needle) was done after assessment of coagulogram. Blood samples were again collected after four weeks of stay in hospital (2nd sample) for repeat investigations of Hormone(s) and liver function profile following 10-14 days of stoppage of chlordiazepoxide. During this period patients were strictly abstinent. Withdrawal symptoms and mood were reassessed during this period.

Hepatic function tests involving serum bilirubin, total protein, albumin, aspartate aminotransferase (AST) alanine aminotransferase (ALT) and alkaline phosphatase (ALP) were analysed in Hitachi 705 autoanalyser. Serum gammaglutamyltranspeptidase (GGT) was assayed by the method of Szaaz (1969). Hormone assays were carried out by employing radioimmunoassay (RIA) technique. RIA kits from Diagnostic Products Corporation U.S.A. (for ACTH) and Leeco Diagnostics Incorporated, Michigan, USA (for cortisol) were used.

Radiometric quantification was carried out by using Compugamma, LKB, Wallac. The liver biopsy specimens were stained with haemotoxylin, eosin, reticulin, PSA for glycogen and Masson's trichrome for the collagen.

## RESULTS

The clinical data on patients showed that their mean age was around 35 years ( $34.5 \pm 7.7$ ). The control group was younger (mean age 28 years). Most of the patients started drinking around the age of 20 years ( $21.7 \pm 6.1$ ). It was apparent that there was a great variability in the years of daily drinking ( $8.6 \pm 7.7$ ) as well as in the duration (years) of dependence ( $2.7 \pm 3.7$ ) as assessed by the appearance of withdrawal symptoms. The average daily consumption in the previous month was around 142 gms of ethanol ( $141.8 \pm 60.5$ ). The patients consumed ethanol, for most of the days ( $27.4 \pm 6.6$ ) in the month prior to the inclusion in the study.

The withdrawal severity rating score after 48-72 hours of last drink, was around 7 ( $7.7 \pm 1.9$ ) which is about 35% of the maximum score of 20 possible on the scale. This indicated a mild degree of withdrawal, and this was completely reversible ( $0.4 \pm 0.8$ ) by four weeks.

Analysis of scores on Hamilton Depression Scale (HDS) shows that only 14% of the patients had score above 16 ( $18.8 \pm 2.2$ ) indicating 'major depression'. In contrast 40% of the patients had no depression (score 7) and 46% had 'minor depression' (score 8-15). The mean score noted on the first week declined significantly ( $p < .01$ ) by the fourth week.

difference between the patients and controls, and were within laboratory normal limits (Table I). However, it was seen that 13% and 11% of the patients had elevated ACTH and cortisol values (above normal laboratory range) respectively.

Biochemical parameters indicating liver function (Table II) showed that value of serum

**Table-1 : Serum hormones levels of control group and patients \* (intake)**

Hormonal Parameters	Laboratory reference value	Patients (N=38)	Control (N=24)	't'	p
Adrenocorticotrophic hormone (ACTH)	18-59 Pg/ml	$31.8 \pm 21.7$	$42.9 \pm 36.2$	-1.28	NS
Cortisol	5-25 $\mu$ g/ml	$16 \pm 8.4$	$14.8 \pm 8.8$	0.74	NS

\* *t* tests were applied.

**Table-2 : Hepatic function of control group and patients \* (intake).**

Parameters of liver function	Laboratory reference values	Patients (N=38)	Control (N=24)	t	p
Total Protein	6.8-8.6 gm%	$7.1 \pm 1.5$	$7.5 \pm 0.7$	1.17	NS
Albumin	3.6-4.4 gm%	$4.2 \pm 0.4$	$4.5 \pm 0.5$	2.21	<0.05
Bilirubin	0.8-1 mg%	$1.3 \pm 1.4$	$0.8 \pm 0.4$	-2.54	<0.05
Aspartate Amino transferase (AST)	0-30 IU/L	$80.6 \pm 85.4$	$27.2 \pm 16.7$	-3.75	<0.01**
Alanine Aminotransferase (ALT)	0-30 IU/L	$51 \pm 81.5$	$28.1 \pm 32.7$	-1.55	NS
Alkaline Phosphatase	35-110 IU/L	$100.8 \pm 46.4$	$68.3 \pm 20.3$	-3.13	<0.05
Gammaglutayml trans peptidase (GGT)	7-32 IU/L	$139.8 \pm 142.7$	$51.1 \pm 20.1$	-3.77	<0.01**

\* *t* test was applied

\*\* Modified 't' test was used.

First blood sample was collected within 2 days ( $2.6 \pm 0.9$ ) of last drink. Serum level of ACTH and cortisol did not show any significant

AST ( $p < 0.01$ ) and GGT ( $p < 0.01$ ) were significantly elevated among the patient during first week. Other value of hepatic function in-

cluding ALT were comparable. Marked variability of the values of AST and GGT was seen.

ACTH and cortisol levels in patients following four weeks of abstinence (2nd sample) were not significantly different from the values obtained during intake (1st sample). However, significant improvement i.e. decline of the values of AST ( $p < 0.05$ ) and ALP ( $p < 0.05$ ) and GGT ( $p < 0.01$ ) were noticed after four weeks of abstinence when seen against the values obtained earlier (1st sample), Table II.

Liver biopsy findings were available on eleven patients only due to various difficulties. The results showed that one person had fatty liver, seven had alcoholic hepatitis and only one person had precirrhosis. None had classical findings showing cirrhosis.

Physical examination revealed that two patients had Cushingoid feature eg. periorbital puffiness, central obesity, fine silky hair and buffalo hump. Both had, however, normal plasma cortisol level.

## DISCUSSION

The subjects for this study were selected using DSM III criteria which is an acceptable clinical definition of alcoholism.

The values of serum ACTH and cortisol were elevated among 13% and 11% of patients. These observations were compatible with previous reports. Serum ACTH was high in 37.5% and plasma cortisol in 6% of alcoholics (Valimaki *et al.*, 1984).

Apparently the data on endocrinal parameters were normal among majority of our sample. Possible reasons could be several. Most clinically relevant forms of alcohol related health damage are related to drinking pattern

i.e. amount of consumption, duration of use and heavy use. It takes year or decades for organ damage to develop. This is obvious from data on liver damage. A healthy subject with a daily intake of 210 gm of ethanol for 20 years would develop cirrhosis (Lelbach, 1974). In a Veterans Administration Study even clinically mild alcoholic hepatitis developed following consumption of 234 gm of ethanol for 22 years (Mendenhall, 1987). Most of our patients were drinking 142 gm of ethanol per day daily for  $8.6 \pm 7.7$  years. Per capita consumption of 100% ethanol in Karnataka, where the subjects belonged, was 4.8 lit/annum (The Excise Commissioner, 1988). In contrast it was 15.1 lit/annum in USA (DHAS, 1987). Thus we were dealing with a population with lower level of consumption as against western subjects. Ethanol exerts harm only when drinking exceeds certain amount over a significantly long period.

Pseudo Cushing's syndrome was frequent in patients with alcoholic cirrhosis (Van Thiel *et al.*, 1983). Decline of biochemical parameters of hepatic functions by fourth week of abstinence would indicate a reversible alcoholic liver disease in the present sample. So also was the histopathological report where low prevalence of precirrhosis or cirrhosis was seen. Hence evidence of advanced liver disease was scant in our sample.

It was also suggested that alcohol related health damage could be different in patients attending psychiatric hospitals than those attending general hospitals (Obnishi and Okuda, 1985). It was seen that patients attending psychiatric hospitals had lesser degree of alcohol related health damage as evidenced by higher incidence of alcoholic hepatitis (hepatitis B negative) rather than cirrhosis.

Fourteen percent of the patients had HDS score above 16. This was inspite of the fact that concurrent diagnosis of depressive disorders was an exclusion criteria. Major depres-

sion as per HDS criteria is not synonymous with clinical concept of Major depression. Our findings would suggest that these subjects during alcohol withdrawal experienced sufficient number of depressive symptoms though shortlasting. HPA dysfunction was common in patients with alcoholism and major depression (DelaFuente *et al.*, 1983). Low prevalence of 'depressive illness' in our sample might explain normal HPA function.

The severity of withdrawal state also effects cortisol secretion. Our patients had mild degree of withdrawal features (mean  $7.8 \pm 1.9$ , maximum possible score 20). This is less likely to bring about significant change in serum cortisol levels.

Reversibility of serum hormone levels following abstinence was not obvious as most of the values at intake (1st sample) were within laboratory normal range. Reversibility of liver function tests seen in this study is in keeping with earlier reports (Eckhardt *et al.*, 1984).

We found Cushingoid features in two patients. In absence of hypercortisolaemia the findings were difficult to interpret. Similar observation were made by Hasselbalch *et al.* (1982).

To conclude we want to propose that increment in secretion of ACTH and cortisol is seen in a subgroup of patients with alcoholism. These changes are likely to be independent of liver disease as majority of our patients did not have advanced liver disease. Affective changes, severe withdrawal state and cirrhosis of liver possibly have additive effects.

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