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Adrenal Cortisol Response to One Microgram Adrenocorticotropin Stimulation Test in Children with Type – 1 Diabetes Mellitus

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***Abstract*- Objective:** The study was done with the purpose of evaluating the adrenal cortical response to 1 microgram ACTH stimulation test in children with type-1 diabetes and compared with that of controls.

Design: Case – control study. 28 children with type – 1 diabetes attending the outpatient department of endocrinology department, M.S.Ramaiah Medical College and Teaching Hospital and 20 age and sex matched controls from Happy Home Orphange, KGF were infused with 1µg ACTH.

Methods: Cortisol levels were estimated using radio immunoassay technique, before and 30 minute after 1 µg ACTH infusion.

Results: The cortisol levels significantly increased in normal as well as children with type – 1 diabetes. But the increase was not found to be the same in both the groups. The effect of ACTH in increasing cortisol levels is much more in normal as compared to children with type-1 diabetes.

Conclusion: The results suggest a blunted adrenal cortisol response to ACTH in children with type-1 diabetes, which might influence the control of the disease and play a role in the development of its chronic complications.

***Index Terms*-** ACTH stimulation test, type-1 diabetes

I. INTRODUCTION

Diabetes mellitus is a disease that has many facets among which is its influence on the hypothalamo pituitary – adrenal axis. Conflicting results have been reported on adrenal steroid secretions in patients with type – 1 diabetes mellitus (1). Studies done on human and animal models with type-1 DM showed controversial results with majority showing hypercortisolism (2-8) and some showing hypocortisolism (9-12). Hence the present study was undertaken to evaluate adrenal cortisol in children with type – 1 DM.

Moreover, in the present study, the more sensitive 1 µg ACTH stimulation test was administered to detect even mild adrenal suppression.

II. SUBJECTS AND METHODS

Subjects and protocol:

A consecutive series of 28 children with type-1 diabetes attending Endocrinology OPD, M.S. Ramaiah Medical Teaching Hospital were studied. The study was approved by the institutional ethical committee. A written consent was obtained from the cases and controls as well as from their parents. The parents were also thoroughly assured that a meager dose of 1µg of synacthen absolutely had no side effects on the children. All patients had a complete physical examination. The duration of diabetes since diagnosis, current diabetic medications, weight, height and any recent weight loss or severe hypoglycemia requiring inpatient admission during the past year were recorded. All patients were in good physical health and none had required hospital admission for poor glycemic control during the previous year or had any hypoglycemic episode during the 24 – 48 hours preceding the test. No patient showed evidence of renal, hepatic, thyroid, cardiac or adrenal disease.

22 normal children were recruited through volunteer office of happy home orphanage. They were age and sex matched with the diabetic patients. All controls were physically well and medication free and had a normal physical examination. The cases and controls were asked to report in a fasting state and blood sample was drawn for measurement of plasma glucose and cortisol at 9.00am. Thereafter 1 microgram tetracosactrin (synacthen) was injected as a bolus. Blood samples were again drawn 30 minutes later for estimation of cortisol. The blood samples were stored at -20°C, later they were subjected for quantitative determination of cortisol levels using the Gamma Coat Cortisol Radio Immuno Assay Kit.

III. ACTH PREPARATION

0.25mg ampoule of synacthen was diluted in 100ml of normal saline. 0.4ml containing 1 microgram of synacthen was injected.

IV. ASSAY PROCEDURE

Serum cortisol concentrations were determined using the Gamma coat 125 cortisol radioimmuno assay kit. The procedure is based on the competitive binding principles.

V. STATISTICAL ANALYSIS

The data obtained was analyzed using paired student t test.

VI. RESULTS

Normal children consisted of 13 females and 7 males. Children with type – 1 diabetes consisted of 21 females and 7 males. Diabetics had a mean age of 10.39± 3.45 years compared with a mean age of 10.85± 2.92 for controls. The duration of diabetes was 2-3 years. Patients had mean fasting plasma glucose levels of 110.5±9.35 mg/dl as compared with 66.95± 7.8 mg/dl in controls. In the diabetics, mean plasma glycated haemoglobin levels at the time of study were 8.0% (SD 1.0%).

The results of the study showed a blunted response to 1 microgram ACTH stimulation test in children with type – 1 diabetes (effect size being 1.61) as compared to normal children (effect size being 2.61).

Study Design: A Case –control study

Table 1
Basic characteristics

Basic Characteristics	Normal (Mean ± SD)	Type 1 DM (Mean ± SD)	Significance
Age in years	10.85	10.39	P=0.633
Sex	Male=7 (35.0%) Female=13 (65.0%)	Male=7 (25.0%) Female=21 (75.0%)	P=0.452
Inference	Samples are age and sex matched (P>0.05)		

Table 2

Cortisol levels (Microgram/dl)	Male (Mean ± SD)	Female (Mean ± SD)	Overall
Normal Children			
Basal	5.77±1.38	6.92±2.47	6.52±2.19
ACTH	12.29±0.95	14.85±3.89	13.95±3.38
Significance By student t	11.320**	7.367**	7.430**
Effect size	5.50	2.78	2.61
Type 1 Diabetics Children			
Basal	16.60±3.78	17.44±7.64	16.90±6.89
ACTH	27.60±9.94	34.24±12.81	32.75±12.05
Significance	3.687**	5.836**	7.000**
Effect size	1.46	1.59	1.61

VII. DISCUSSION

The study was undertaken to determine whether abnormalities of adrenal function occur in children with type – 1 diabetes mellitus. This was evaluated using the most sensitive 1 microgram ACTH stimulation test.

Adrenal function can be assessed by various methods e.g. by measuring serum cortisol or 24 hr. excretion of cortisol and its metabolites in urine with gas chromatography – mass spectroscopy (3). More recently, the corticotrophin releasing hormone test was also used to assess the function of the hypothalamic – pituitary – adrenal axis (14). Adrenal response in a stressful situation is mainly assessed by the insulin tolerance test (ITT) and the synthetic adrenocorticotrophic hormone (ACTH) (synacthen) stimulation test (15). However, ITT has been linked to deaths in children as a result of the insulin – induced hypoglycemia or its treatment (16). In contrast, the dosage of ACTH used in the standard (0.25 mg) synacthen test (SST) produces supraphysiological ACTH levels that are never found in response to a real – life stress situation. In recent years, the low dose (1 microgram) synacthen test (LDST) has been used as a more physiological stimulus to the adrenal gland (17), that is more sensitive than the standard synacthen test (0.25 mg) in detecting mild adrenal suppression (18, 19). Therefore, in the present study, we administered the low dose synacthen test – 1 µg ACTH stimulation test to detect adrenal abnormalities.

Studies done on adrenal function in patients with type – 1 diabetes mellitus shows highly conflicting results as evidenced by the following examples.

VIII. STUDIES SUGGESTING HYPERACTIVITY OF HPA AXIS

- Results of a study done on patients with diabetic neuropathy showed specific and persistent increase in the activity of the HPA axis (20).
- Study conducted among diabetic outpatients showed significantly elevated 9 A.M plasma levels of cortisol as well as significantly elevated plasma levels of cortisol and adrenocorticotropic hormone at both 4 PM before and 4 PM after dexamethasone (6).
- Diabetic patients with moderate – to – severe retinopathy had significantly higher postdexamethasone plasma levels of adrenocorticotropic hormone than patients with minimal or no retinopathy (8).
- A review article examined some of the evidence indicating hyperactivation of HPA axis in patients with diabetes. They concluded that hyperactivation is associated with increased expression of hypothalamic corticotrophin – releasing hormone (CRH) MRNA and hippocampal mineralocorticoid receptor (MR) MRNA (21).

IX. STUDIES INDICATING HYPOCORTISOLISM

- In an animal study, diabetic, insulin – treated diabetic and nondiabetic rats underwent a hyperinsulinemic – hypoglycemic glucose clamp to evaluate central

mechanisms of HPA axis and counter regulatory responses to insulin – induced hypoglycemia. Increases in plasma ACTH, corticosterone and epinephrine were significantly lower in diabetic rats versus controls (22).

- In another study, counter regulatory hormone secretion during a 3 hr. hypoglycemic hyper insulinemic clamp were measured in well controlled, poorly controlled IDDM subjects. They concluded that ACTH, cortisol and epinephrine responses during hypoglycemia area reduced in IDDM patients in strict glycemic control (23).

In comparison to the results of the above stated studies, the results of our study revealed significantly increased cortisol levels to the test in both the control and the study groups. But there appears to be a blunted response, effect size being 1.61 in children with type – 1 diabetes as compared to normal children, the effect size being 2.61. The most likely mechanism which can explain the results of our study is the mechanism cited in the study of Brendan T et al (23). Strict glycemic control of insulin dependent diabetes mellitus significantly reduces the incidence of diabetic complications (24, 25). This benefit of improved glycemic control is achieved at the expense of a 3 – fold increase in the incidence of severe hypoglycemic events (24, 26). Numerous studies of IDDM subjects in strict glycemic control have shown that these patients exhibit altered catecholamine, cortisol and GH responses to hypoglycemia (27 – 34). These subjects also exhibit reduced symptom perception of hypoglycemia, and require lower glucose levels to activate counter regulatory hormones (34 – 39). Exposure to recurrent hypoglycemia is the most common mechanism by which these alterations occur in subjects with IDDM, as similar defects can be detected in subjects with insulinomas (40 – 42) and can be induced in subjects with IDDM and in normal volunteers exposed to recurrent hypoglycemia. (43 – 49). These defects in counter regulation can be largely reversed by avoidance of hypoglycemia (50 – 55). The exact mechanism by which hypoglycemia induces these alterations in counter regulation remains uncertain. The most likely mechanism for these adaptations is a central adaptation to recurrent hypoglycemia that maintains cerebral glucose utilization during hypoglycemia, resulting in decreased activation of the cerebral glucose sensors. Thus, there is less activation of the hypothalamic – pituitary adrenal axis and sympatho adrenal medullary system with resultant reduction in the counter regulatory hormone response to hypoglycemia (56 – 59).

In conclusion, this study has shown mild adrenal cortical suppression to short synacthen test in children with type-1 diabetes. The exact mechanism underlying these alterations remains uncertain. A better understanding of these mechanisms may be important in developing new treatment modalities for patients with diabetes mellitus.

X. Limitations of the Study

Follow up study of the same patients is required to study the response of the adrenal gland in these patients.

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