LETTER TO THE EDITOR

Adrenocortical reserves in patients with Graves' disease

Ravinder Goswami and Narayana Kochupillai

*Department of Endocrinology and Metabolism, All India Institute of Medical Sciences, New Delhi 110029, India**(Correspondence should be addressed to N Kochupillai; Email: kochupillai@hotmail.com)*

Increased skin pigmentation, weight loss and bowel symptoms are the clinical features common to both thyrotoxicosis and primary adrenal insufficiency. In thyrotoxicosis, the cortisol production rate is increased but its rate of degradation is also increased. Continuing hyperactivity of the hypothalamus–pituitary–adrenal axis in thyrotoxicosis may result in exhaustion of adrenal cortisol reserves. Several investigators in the past have studied cortisol reserves in patients with thyrotoxicosis and have reported varied results. Possible causes of this variation included (1) different dose schedules and routes of adrenocorticotropin (ACTH) administration, and (2) the use of non-specific and indirect methods for the quantification of cortisol such as 17-hydroxycorticosteroid and the measurement of cortisol by fluorometric assay. In addition, the variable prevalence of coexisting adrenal autoimmunity in patients with Graves' disease can also result in differing study results.

We read, with interest, a study that recently appeared in this Journal (1) in which A Tsatsoulis and colleagues reported the results of low-dose ACTH stimulation in 10 patients with thyrotoxicosis. The mean peak and delta cortisol responses to ACTH were found to be significantly lower in thyrotoxicosis compared with the corresponding values when the same patients were euthyroid. A subnormal cortisol peak was reported in two severely toxic patients out of the 10 studied. No comment could be made regarding coexisting adrenal autoimmunity, because of heterogeneous etiology of thyrotoxicosis in the patients studied (six had Graves' disease and four had toxic nodular goiter).

In 1998 (2), we published similar information regarding thyrotoxicosis and adrenocortical reserves, using a standard-dose ACTH(1-24) stimulation test (Synthén, Ciba & Geigy, Switzerland, 250 µg i.v). Serum basal, 60 min post-ACTH, and delta cortisol responses were assessed in 22 patients with active Graves' disease, in 13 of them after carbimazole-controlled euthyroidism, and in 10 healthy controls. Estimation of serum cortisol was done using radioimmunoassay and adrenocortical autoantibodies, by indirect immunofluorescence. Adrenal gland size was measured using a 4-mm-thick computed tomography (CT) scan in 19/22 patients. The mean basal cortisol

value for Graves' disease patients in the hyperthyroid state was significantly lower than the values for patients in the euthyroid state and healthy controls (306 ± 103 , 410 ± 213 , 421 ± 146 nmol/l respectively; $P < 0.05$). In 5/22 patients (22%), the cortisol response to ACTH in patients in the hyperthyroid state was subnormal, unlike that in any of the controls. Patients with serum tri-iodothyronine (T_3) values of >400 ng/dl had lower one hour post ACTH cortisol response (560 ± 133 nmol/l) compared with those with $T_3 < 400$ ng/dl (724 ± 294 nmol/l) and significantly lower delta cortisol responses (213 ± 73 nmol/l vs 428 ± 265 nmol/l). In three of them, normalization of the cortisol response was observed in the euthyroid state. Although 3/22 patients had adrenocortical autoantibody positivity, none of them had an impaired cortisol response. In 13 of the 19 patients studied by CT, the adrenal glands showed diffuse enlargement of either thickness or anteroposterior width. In conclusion, our study had demonstrated several new facts about adrenal status in patients with Graves' disease. First, 22% of patients with Graves' disease have a subnormal cortisol response to ACTH. Secondly, abnormality of cortisol reserves is more pronounced in patients with severe thyrotoxicosis. An awareness of such information would help to alert physicians dealing with clinical thyrotoxicosis and would support the clinical practice of supplementing with steroids for life-threatening thyrotoxicosis. Thirdly, the presence of diffuse enlargement of the adrenal gland on imaging is an interesting observation and provides proof of hypothalamic–pituitary–adrenal overactivity in clinical thyrotoxicosis and that subnormal reserves are the consequence of exhausted adrenal cortisol reserves.

References

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