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HYPOTHALAMO-PITUITARY RESPONSE BEFORE AND AFTER SURGICAL STRESS (SPLENECTOMY) IN THALASSEMIC PATIENTS

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- **ABSTRACT**

Background/Objective: Multiple endocrinopathy is a common manifestation in thalassemia. Although the response of the stress hormones to induced hypoglycemia has been studied in these patients, the impact of surgical stress is not yet determined.
Methods: The hypothalamo-pituitary-adrenal axis of 27 thalassemic patients (TP), [4-15 years old (y.)] admitted for splenectomy,was evaluated before and after surgical stress during 1996-8.Blood samples for measurement of ACTH , cortisol, growth hormone (GH), thyroid stimulating hormone (TSH) and prolactin (PRL) were taken a day before and also approximately two hours after surgical insult. For comparison,22 non-thalassemic patients (NTP) (3.5-14 y.) admitted for elective laparotomy,were selected as the control group .
Results: The cortisol response after surgical stress was significantly higher than baseline in both the TP (17.4 ? 6.3 vs 30.81 ? 11.49 g/ dl; P<0.00l) and the NTP (20.65 ? 9.1 vs 36.87 ? 11.08 g/ dl; P<0.001). NTP showed a significant elevation of ACTH upon surgical stress (P<0.001), while the difference between pre- and post-stress ACTH was not statistically significant in TP (P=0.123). However, the ACTH concentration before operation in TP. was significantly higher than that of NTP (P<0.042) with no remarkable difference after surgical stress between the two groups (P=0.261). GH increased significantly after operation in TP and NTP (P< 0.016 and <0.05, respectively). A significant change in TSH (P< 0.03) and PRL (P< 0.004) was also observed in TP after operation.
Conclusion: The hypothalamo-pituitary as well as the pituitary-adrenal axes are usually intact and responsive in TP. It is concluded that, the remarkable increase in ACTH concentration before operation may be due to a decreased adrenal reserve. Thus, the possibility of primary partial adrenal insufficiency, particularly under stress situations, should be considered in every thalassemic patient.

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Key Words • Thalassemia • surgery • pituitary-adrenal system • adrenal glands • cortisol

Introduction

Endocrinopathy in thalassemia major is a well-known phenomenon. [1-14] Although all endocrine glands will ultimately be involved by hemosiderosis in thalassemic patients (TP), the hypofunction of some may not be clinically evident until late in the disease process.[1-7] This is especially true since the routine life-long administration of desferrioxamine (desferal), started from early childhood, is added to the medical management of these patients.[1,3-5,8] Nevertheless, the response in stressful situations, particularly when the disease is advanced, may not be optimal.[2,7,9-11] Although the degree of cortisol and ACTH response as well as other stress hormones such as growth hormone (GH) and thyroid stimulating hormone (TSH) in thalassemia has been studied by several investigators following induced hypoglycemia, [2,4,8-11] the impact of a physical or natural stress, such as operation or trauma, has not yet been assessed.

In this article, the pituitary-adrenal axis and hypothalamo-pituitary function of TP under non-stressful conditions, and also upon surgical insult in a pediatric population is evaluated and the results are compared with a non-thalassemic patients (NTP) group.

Materials and Methods

The study was conducted during 1996-8 on 32 TP who, because of their increased blood transfusion requirement, were candidates for splenectomy. All patients had been on a low transfusion regimen since before their 4th-5th year of age to maintain their hemoglobin between 9 and 10 gr%. The majority of

these patients had also received desferrioxamine (desferal) regularly (according to the protocol in our center: subcutaneously nocturnally 5-6 times per week and also after each transfusion). Blood samples for determination of cortisol, ACTH, GH, TSH and prolactin (PRL) were taken in the morning, the day before operation and then about two hours after the beginning of operation. The sera were kept in a sub-freezing temperature (-10 to -4 ? C). For comparison, thirty age and sex-matched NTP undergoing laparotomy without any evidence of chronic disease, malnutrition, or malignancy were selected as the control group. The timing of blood sample collections in this group was similar to that of the study group. Blood samples taken at an inappropriate time deviating from the protocol, or patients who developed major intra-operative complications before sampling were excluded from the study.

Both cortisol and ACTH were measured by double antibody technique. Measurement of GH, TSH and PRL were performed by RIA, immunoradiometric assay (IRMA) and RIA, respectively.

Student t test and matched-paired t-test were used for statistical analysis.

Results

Following the exclusion of a few patients from both groups for erroneous timing of blood sampling, 27 (19 M, 8 F) TP and 22 (13 M, 9 F) NTP were included in the study. The age range of TP was 4-15 years (mean: 8.96) and that of NTP 3.5-14 years (mean: 7.95).

The cortisol response about two hours after surgical insult was significantly greater than baseline for both the TP (17.4 ? 6.3 vs 30.81 ? 11.49 ug/dl; P< 0.001) and controls (20.65 ? 9.13 vs 36.87 ? 11.08 ? g/dl; P< 0.001). There were no statistically significant differences between pre-surgical stress cortisol values in TP and controls (Table 1). The same was true for post-surgical stress cortisol levels.

Although the ACTH level was elevated after surgical stress in TP, by 1.79-fold (mean:104.15 vs 186.8 pg/ml), on the average the difference was not statistically significant compared to its pre-operative value (104.15 ? 60.74 vs 186.8 ? 246.24 pg/ml; P=0.123). On the other hand, NTP showed a significant elevation of ACTH upon surgical stress (72.5 ? 39.5 vs 129.09 ? 67.9 pg/ml; P< 0.001). However, the ACTH concentration before operation in TP was significantly higher than that of NTP (104.15 ? 60.74 vs 72.5 ? 39.5 pg/ml; P<0.042), while no significant difference was present following surgical insult between the two groups (186.8 ? 246.24 vs 129.09 ? 67.9; pg/ml; P= 0.261) (Table 1).

GH increased significantly after operation in TP and NTP [2.64?3.46 vs 7.67 ? 9.65 ng/ml; (P<0.016) ; 1.98 ? 2.26 vs 4.2 ? 4.58 ng/ml; (P<0.05) respectively]. A remarkable change in TSH [(2.48? 1.85 vs 4.28 ? 3.71 mIU/L; (P<0.03)] and PRL [265.4 ? 297.7 vs 502.4? 274.3 mIU/L; (P <0.004)] was also observed in TP after surgery. Although TSH and PRL raised post-operatively in NTP, the difference was not significant (Table 2).

Serum ferritin levels in 8 of 13 young TP (4-8 y.) was less than 2000 ng/ml (<1000 in one), and 2000-3000 in the remaining five, while in the 14 older patients (9-15 y.) it was less than 2000 in 5 (<1000 in 1), 2000-3000 in 7 and more than 3000 ng/ml in the oldest two (13 and 15 y.) patients.

Discussion

Regular blood transfusion in TP to maintain an adequate hemoglobin level, and also the addition of the iron chelating agent (desferal) to the regimen, have caused an improved clinical picture and life span in thalassemic patients. [1,3-5] As a result, the majority of patients whose short lives were once threatened,

and usually terminated, by cardiac failure[1,4] or overwhelming post-splenectomy infection,[15] are now able to survive long enough to face a variety of endocrine problems.[1-14,16-20]

Although reduced growth and delayed or absent pubertal development are the most frequent and clinically apparent endocrine complications, almost all other endocrine organs will ultimately be affected to some extent, with or without clinical symptoms.[1,3,5,9,14] The pituitary-adrenal axis is usually relatively normal in most TP,[1,4-8,14,16,21] or only partially deficient in some[9,11,17,18] during adolescence as well as early adulthood. Interestingly, iron deposition in the adrenal glands occurs mostly in zona glomerulosa, which is the site for mineralocorticoid production.[2,4,7] Therefore, infrequent involvement of the zona fasciculata (the site for cortisol synthesis) may partly explain the less common chance of primary adrenal insufficiency in thalassemia major compared to other endocrine deficiencies. Nevertheless, it seems that the adrenal reserve in thalassemia is inversely related to the age of the patient, the volume of blood transfusion and, thus, the degree of iron load and infiltration in the gland.[2,8-13,16-19] Pituitary and/or hypothalamic dysfunction may also be age-related.[5,22] Therefore, the majority of TP are also expected to have normal hypothalamo-pituitary function before adolescence.

The results in the present series may indicate that the adrenal glands function normally in TP, as shown by adequate baseline cortisol levels and a significant rise in response to surgical stress, quite similar to those obtained in NTP (Table 1). However, the underlying cause of the significantly increased level of ACTH before operation is presumably decreased adrenal reserve. Therefore, apparently acceptable cortisol levels before and also after surgical insult are at the expense of increased ACTH concentrations, causing maximal stimulation of the adrenal glands in this group of patients. This finding may be consistent with primary partial (or early) adrenal insufficiency. Obviously, an already high pre operative ACTH concentration along with acceptable pituitary response after stress almost excludes the possibility of pituitary-hypothalamic hypofunction. Moreover, a profound ACTH response observed in some of our patients after surgical stress and also a significant increase in other stress hormones (GH and TSH) may be explained on the basis of the triggering effect of operation upon an already hyperplastic pituitary gland. Similarly, McIntosh has also found basal morning ACTH to be 3-4 times above the normal value in a group of prepubertal thalassemic patients who had not only a normal resting cortisol level, but also a good response to adrenal stimulation in the majority of cases.[11] He has, thereby concluded that high ACTH in these cases is to compensate a decreased adrenal reserves. However, some investigators have reported pituitary involvement[9,12,23,24] or a more profound decline in ACTH reserve compared to that of cortisol[2] . Others have found no evidence for pituitary insufficiency.[6,13,14,16-18,21,25] correlating with our results. Bashir et al. have also reported hypo-adrenalism in patients with hemoglobinopathies including thalassemia.[20] The decrease in cortisol level in that study was most severe in sickle cell trait and least in alpha 2-thalassemia (25% and 57% of the mean cortisol levels of the normal subjects respectively).[20] Nevertheless, a relatively normal or elevated cortisol level in some patients may be secondary to its diminished degradation in the affected liver.[2] The mean TSH and PRL concentrations increased proportionately in our patients. This can be explained on the basis of increased TRH in a responsive hypothalamus secondarily enhancing not only TSH but also PRL secretion. This latter phenomenon is due to sensitivity and responsiveness of the PRL center to the stimulus effect of TRH.[26,27]

The role of the chelating agent for a better clinical picture is as important as maintaining high hemoglobin. It has been claimed that there is a correlation between the serum ferritin level, the age of the patient and the possibility of endocrine deficiencies.[3-5,12,28,29] Older patients in the present series also had, on average, higher ferritin levels. The manifestations of endocrinopathy can be prevented or postponed in well-chelated and transfused patients.[3,4] Furthermore, not only does intensive chelating

therapy preserve the integrity of ACTH-cortisol axis,[8] or hypothalamo-pituitary function but it may even reverse the initial signs of iron intoxication and some endocrinopathies.[3,23] Therefore, the pituitary ACTH reserve and also the capacity of the adrenal glands to show a normal cortisol response upon ACTH stimulation can be protected by long-term chelation therapy starting from early childhood.[8]

In conclusion, the hypothalamo pituitary as well as the pituitary-adrenal axes are almost intact and normally responsive in the majority of thalassemic patients. However, despite a significant rise in cortisol level following surgical insult, the possibility of primary partial adrenal insufficiency, due to the remarkably elevated preoperative ACTH level with less than expected cortisol concentration, should also be considered in these patients. This is especially true in relatively older patients with high ferritin levels, as the chances of acquiring this particular problem increases with age and iron load. For this reason, in older thalassemic patients, especially those undergoing a major operation, or in whom an unexplained hypotension develops following a stressful situation, such as trauma, infection or surgery, the administration of steroids may be justified.

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