Changes of Platelets, Serum Lactic Dehydrogenase, 
γ-Glutamyltranspeptidase, 
Choline Esterase and Creatine Phosphokinase Levels in Patients with Cushing’s Syndrome

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Changes of Platelets, Serum Lactic Dehydrogenase, γ-Glutamyltranspeptidase, Choline Esterase and Creatine Phosphokinase Levels in Patients with Cushing’s Syndrome. Tohoku J. exp. Med., 1984, 142 (2), 195–200 — In order to identify non-endocrine laboratory tests of diagnostic value in Cushing’s syndrome, we measured platelet counts and serum myogenic and hepatic enzyme levels in 10 patients with Cushing’s syndrome and compared the findings with those of 15 obese patients without Cushing’s syndrome. Patients with Cushing’s syndrome had increased numbers of platelets, moderately elevated serum lactic dehydrogenase and γ-glutamyltranspeptidase levels, and significantly lower creatine phosphokinase and choline esterase activities compared with those of obese control patients. We concluded that when several of these abnormal values were seen in obese patients the levels of suspicion for Cushing’s syndrome should be high.

Cushing’s syndrome; platelet counts; myogenic enzymes; hepatic enzymes

Diagnostic difficulties are sometimes encountered when physicians examine patients who may have Cushing’s syndrome. There are many obese, hairy women with menstrual abnormalities, hypertension and diabetes who do not produce excessive amounts of glucocorticoids. Various endocrinological examinations need to be done in the investigation of these patients but most of these tests are time-consuming and expensive.

One might expect to find certain non-endocrinological abnormal laboratory tests in patients with Cushing’s syndrome. While hematological changes such as lymphocytopenia and eosinopenia are frequently observed in Cushing’s syndrome, little is known about the numbers of platelets in the disease, despite the use of glucocorticoid therapy for various thrombocytopenic disorders. Also, glucocorti-
coids induce myopathy and osteoporosis. These disorders might be accompanied by changes in serum enzymes. In addition, obese patients without Cushing’s syndrome often have fatty liver and alteration of serum hepatic enzyme levels.

Because of these clinical observations, we measured platelets and serum myogenic and hepatic enzyme levels, and alkaline phosphatase in patients with Cushing’s syndrome and compared them with those of obese patients without Cushing’s syndrome. These tests are now easily available using automated equipments. Our purpose was to obtain some discriminatory data in the office or the bed side who need further endocrinological examinations for Cushing’s syndrome.

Materials and Methods

Ten patients with Cushing’s syndrome and 15 obese patients were studied. The diagnosis in all patients was corroborated by the endocrinological examinations including 17-hydroxycorticosteroids, 17-ketosteroids, diurnal rhythms of plasma cortisol, dexamethasone suppression and a metyrapone test. Seven of the patients with Cushing’s syndrome had bilateral adrenocortical hyperplasia, two had unilateral adenoma and the remaining one had multiple nodular hyperplasia. All diagnoses of Cushing’s were verified by surgery. All of the patients with Cushing’s syndrome were women. Their ages ranged from 28 to 62 years (mean 43). Four of the patients had less severe physical signs of Cushing’s syndrome such as generalized obesity, absence of a moon face and no wide purple striae. The remaining 6 cases had fully developed signs of the disease. There were 15 obese control patients without Cushing’s syndrome. Ten were women and five were men. Their mean age was 42 years. Nine had uncomplicated obesity and three had diabetes mellitus and three hypertension in addition to obesity. The body weight of all the control patients was more than 15% above their ideal weight. Over weight ranged from 15 to 60% with mean of 34%.

Blood samples were taken at the time of hospital visits or in the morning following admission, usually 8:30 to 10:30 a.m. Platelet counts were performed using a Coulter Counter, Model-S. Serum glutamic oxalacetic transaminase (GOT), glutamic pyruvic transaminase (GPT), alkaline phosphatase (AIP), leucine aminopeptidase (LAP) and lactic dehydrogenase (LDH) levels were determined with a Technicon SMAC. γ-Glutamyltranspeptidase (γ-GTP) and choline esterase (ChE) activities were measured with a Technicon AA-II. Creatine phosphokinase (CPK) and aldolase levels were measured with an LKB 2086, Mark-II and γ-hydroxybutyric acid dehydrogenase (HBD) with a RaBA-super type autoanalyzer.

All data were expressed as mean ± standard deviation. Differences were evaluated using Student’s t test and were considered significant when the p value was less than 0.05.

Results

Platelet counts (Fig. 1). There was a significant increase in the number of platelets in patients with Cushing’s syndrome as compared with control obese patients (36.3± 8.0 vs. 25.5±5.9×10^4/mm³ ; p < 0.01). However, the values in patients with less severe physical signs of Cushing’s syndrome overlapped with those of control obese patients.

Myogenic enzyme levels (Fig. 1). Serum CPK levels in Cushing’s syndrome and in obese control were 36 ± 13 and 77 ± 34 u/liter, respectively. The difference
between the groups was significant \((p < 0.001)\). In seven of the ten patients with Cushing's syndrome, the CPK level was lower than the normal range. Three of four patients with less severe signs remained in low values. There were no significant differences in aldolase or HBD levels between the Cushing's and non-Cushing's groups. On the other hand, elevated LDH activity was found in half of the Cushing's syndrome patients including less severe cases. The mean serum LDH level in Cushing's syndrome was 256 ± 79 compared with a value of 182 ± 34 u/liter for the control obese patients \((p < 0.02)\).

To determine whether the low CPK levels in Cushing's syndrome were due to an inhibitory effect of cortisol on the CPK assay system, stepwise increases in concentrations of cortisol, from 5 to 80 \(\mu\)g/100 ml per sample, were made in sera obtained from a patient with hypothyroidism and from a normal subject and then measured. No changes in estimated values of CPK were found. In addition, differences in CPK levels were not correlated with the concentrations of serum potassium in patients with Cushing's syndrome (range 2.5 to 5.4 mEq/liter).

Hepatic enzyme levels (Fig. 2). Both GOT and GPT levels were high in some patients with Cushing's syndrome, but most of them were in the normal range and there was no significant difference between the groups. One patient with Cushing's syndrome had a high AIP, but this patient also had gall stones. Excluding this patient, serum AIP levels in both groups were in the normal range.
The major findings of the present study were the observations that most patients with Cushing's syndrome had increased platelets, moderately elevated serum LDH and \( \gamma \)-GTP levels and low CPK and ChE activities as compared with those of obese patients without Cushing's syndrome. Previous papers of Cushing's syndrome have not pointed out these abnormalities except for LDH as features of endogenous hypercortisolism.

Although patients with Cushing's syndrome sometimes have echymoses, platelet counts are not performed routinely in patients with Cushing's syndrome. According to Soffer et al. (1961), platelet counts were abnormal (slightly reduced) in 3 of 33 patients. In contrast, Krieger (1982) in his recent monograph, reported that the platelet counts were often increased in this disease. In the past, platelet counts on a series of patients were done manually and by different technicians. Our data were obtained using a single machine with reproducible performance. The cause of the discrepancy in the earlier reports might be accounted for by the different procedures. Although we had no adequate explanation about the fact

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gamma\text{-GPT values in both groups had wide ranges. The mean value in Cushing's syndrome was } 157 \pm 121 \text{ compared with } 55 \pm 23 \text{ u/liter for control obese patients } (p < 0.05). \text{ Although the ChE levels were close to the normal range in both groups, in Cushing's syndrome the levels were significantly lower than those of control subjects } (378 \pm 84 \text{ vs. } 583 \pm 68 \text{ u/liter}; \ p < 0.001). \text{ Here again, we confirmed that the results of the ChE assay were not altered by cortisol in an in vitro experiment similar to that performed for the CPK determination. No significant difference in serum LAP levels was found between the groups.}
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that the high platelet counts were confined to the patients with the fully developed signs of Cushing's syndrome, length of duration of the illness might be the cause. We found that there were no significant relationships between the numbers of platelets and of red blood cells. The platelets were related to the numbers of leukocyte, but statistically not significant. In addition, it seemed unlikely that increment of platelet counts observed in this study might be enough to produce clinical manifestations other than echymoses which already pointed out. In any way, a significant increase in platelets has discriminatory value in the investigation of patients suspected of having Cushing's syndrome.

Patients with Cushing's syndrome frequently complain of fatigue and muscle weakness. This clinical state has been termed steroid myopathy. The exact cause of the myopathy is unknown. Changes in glucose, lipids, protein and electrolyte metabolism might contribute to this myopathy. We expected an elevated CPK level in serum from patients with Cushing's syndrome similar to that seen in the myopathy associated with hypokalemia and myxedema. However, it was found that serum CPK was significantly low in approximately 70% of the sera from Cushing's syndrome patients. Hinderks and Frohlich (1979) reported that CPK levels were low in many patients treated with glucocorticoid. They speculated that the reduced CPK might be due to a membrane stabilizing effect of the steroid. We found few papers reporting serum myogenic enzymes in Cushing's syndrome. Takaishi et al. (1977) found that serum CPK was elevated in 2 and normal in 3 patients with Cushing's syndrome. We knew of no reason for the difference between their findings and ours. However, we found that the steroid did not interfere with the CPK assay system as shown in additional study and there was no relationship between CPK levels and concentrations of serum potassium. Our findings suggested that the steroid myopathy had somewhat different aspects from other types of myopathy. Further studies including muscle biopsy should be necessary. Takaishi et al. (1977) also pointed out an elevated serum LDH activity in 16 of 20 patients with Cushing's syndrome (80%). In contrast, 50 percent of our patients had increased levels of this enzyme.

Osteoporosis and pathological fractures are other manifestations of Cushing's syndrome. We found no significant difference in serum AIP levels between Cushing's syndrome and control obese patients. Unfortunately, we did not examine the isoenzyme pattern of AIP.

Truncal obesity is a characteristic feature of Cushing's syndrome. However, Ross and Linch (1982) reported that 55% of their patients had generalized obesity and pointed out the distribution of obesity was not a reliable indicator of the disease. Fatty livers are found in obese patients very frequently. This can result in abnormal hepatic enzyme levels such as elevated GOT, GPT, \( \gamma \)-GTP and ChE. In the present study, elevated GOT and GPT were not consistent findings, but unexpectedly low levels of ChE were observed. Soffer et al. (1961) reported
that 6 patients with Cushing's syndrome had no abnormalities on histological examinations of the liver, while in 4 patients a moderate fatty infiltration was found and additional 3 patients had extensive fatty infiltrations. However, these findings were obtained from autopsied materials and antemortem examinations may not show the same fatty changes of the liver as postmortem studies. Alpers and Sabesin (1982) observed that, associated with glucocorticoid administration, fatty livers developed only after high doses of the steroid. Although we did not understand the basis for the low ChE activity in our patients, physicians would do well to examine the value of serum ChE when Cushing's syndrome is suspected.

Yoshiba et al. (1980) studied 19 patients treated with glucocorticoid and observed that 10 of them (52.6%) had an increased γ-GTP without any elevation of AlP. We found the same pattern of this enzyme in Cushing's syndrome. High AlP levels were found in only one of our patients and this patient had gall stones, while 66.6% of our patients had elevated γ-GTP levels. Yoshiba et al. (1980) postulated that the increased γ-GTP resulted from enzyme induction by the steroid hormone rather than cholestasis in view of the normal AlP levels.

In summary, the increased numbers of platelets, elevated LDH and γ-GTP, and lowered CPK and ChE levels in serum should be added to the table of abnormal laboratory data of Cushing's syndrome. Moreover, when several of these findings are present in an obese patient the level of suspicion for Cushing's syndrome should be high.

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References