Metabolic Changes in Patients Severely Affected by Tetanus

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Metabolic changes in six severely affected tetanus patients suffering from characteristic labile hypertension (maximum systolic blood pressure greater than 200 mmHg, maximum diurnal change in systolic pressure greater than 100 mmHg) were investigated. Daily urinary excretion of urea nitrogen increased gradually from the onset of opisthotonus, reached a peak value (10.4 to 15.4 g/m²) in 8 to 20 days, and decreased subsequently. Average cumulative excretion in 30 days reached 239.6 ± 32.7 g/m². Urine catecholamine excretion was elevated in each patient and remained elevated during this period. Plasma cortisol and glucagon concentrations were not increased markedly except in a case complicated other systemic bacterial infection. Increased protein catabolism in these patients could not be explained by the metabolic effects of 'stressed hormones' alone, and neurologic factors must be considered.

SINCE LONG-TERM MECHANICAL respiratory support became available for tetanus patients, characteristic cardiovascular instability has been reported. In these patients alternating arterial hypertension and hypotension persist for approximately 2 weeks. In the early phases, sudden cardiac arrest is a common complication, while later complications include renal failure and respiratory infections, which contribute to death in these patients. Although many reports of this unique complication of severe tetanus exist, most are of sporadic cases. In addition, although its clinical features have been described as resulting from 'sympathetic nervous system overactivity,' only short periods of its clinical course have been investigated. We treated six cases of tetanus with typical circulatory instability from 1983 to 1988 and investigated the metabolic features from onset of opisthotonus to recovery. We demonstrate characteristic metabolic features in these tetanus patients.

Materials

Six patients severely affected by tetanus revealing unusually labile hypertension (maximum systolic blood pressure greater than 200 mmHg, maximum diurnal change in systolic pressure greater than 100 mmHg) were studied. Patients' past medical histories were unremarkable for hypertension and other metabolic diseases. Individual patient characteristics are shown in Table 1.

Methods

General Management

All patients were given human tetanus immunoglobulin (5000 IU) at admission and benzylpenicillin potassium (20 million U/day) was administered for 7 to 10 days. Sedation was achieved by intravenous administration of diazepam. Muscle paralysis was achieved by pancuronium bromide.

A ganglionic blocker and beta blocker were ineffective in controlling unstable blood pressure. In five of six patients, continuous spinal block using bupivacaine hydrochloride was needed during periods of severe circulatory instability. Although this was the most powerful way to stabilize labile hypertension, simultaneous catecholamine administration was necessary to counteract hypotension caused by the intrathecal local anesthetic. During the 10 to 24 hours after the onset of spinal block, 0.3 to 0.4 μg/Kg/min norepinephrine or epinephrine was needed. Doses of catecholamines could be decreased to 0.1–0.02 μg/Kg/min subsequently. One patient was treated by continuous infusion of barbiturate (thiamylal sodium) without spinal block.
Total parenteral nutrition was used in all patients. Steady nutritional supplementation was achieved within 5 days of admission. Patients received glucose (250 to 300 g/m²), 250 mL of a 10% lipid emulsion, amino acids (5.0 to 6.4 g/m²) with electrolytes, and other micronutrients continuously.

**Sample Analysis**

Twenty-four-hour urine specimens were collected in bottles containing 20 mL 6N hydrochloric acid for estimation of catecholamine excretion. Epinephrine and norepinephrine levels were determined by high-performance liquid chromatography using fluorometric detection. Blood samples for cortisol levels were measured in serum by radioimmunoassay. Blood samples for glucagon levels were taken in chilled tubes containing disodium salt of ethylenediaminetetraacetic acid and trasyloL to minimize proteolytic degradation. Plasma glucagon concentration was determined by radioimmunoassay.

The urea nitrogen content in 24-hour urine specimens was measured by routine examination in the central laboratory for clinical investigation in our hospital using specific enzyme methods.

**Results**

The daily urine urea nitrogen (UUN) excretion of six patients is plotted from the beginning of mechanical ventilation (Fig. 1). With the exception of one patient (case 4), UUN excretion progressively increased, reaching peak values in 8 to 15 days. In case 4 the peak UUN excretion was delayed to 20 days after the onset of mechanical ventilation. In this case the patient underwent surgical drainage of left-sided retroperitoneal abscess cavity on day 30. This patient did not have history of trauma, and Clostridium tetani was suspected to come from the colon. The
peak excretion values of these six cases ranged from 10.4 to 15.4 g/m² and cumulative 30-day excretion reached 239.6 ± 32.7 g/m².

Daily measurements of catabolic hormones were performed. Urine catecholamine excretion increased markedly in each patients (Fig. 2). The excretion of norepinephrine was increased markedly (Fig. 3). During periods of labile hypertension, some patients received continuous spinal block and small amount of catecholamine simultaneously. However urine catecholamine excretion remained increased in these patients after the cessation of continuous spinal block. In addition, in one patient (case 6) not receiving continuous spinal block, urine catecholamine excretion also was increased excessively.

Serum cortisol levels were measured in three of six patients. In contrast to urinary catecholamine increase, serum cortisol concentration was not increased. Serum cortisol levels remained in the normal range during the whole course, except in case 4, in which the patient suffered sepsis and needed surgery for a retroperitoneal abscess (Fig. 4).

Plasma glucagon concentrations also were measured in three cases. Glucagon levels did not increase excessively, except in case 4 (Fig. 5).

Discussion

One important observation of our study is the increased urinary nitrogen excretion in our patients. Urine urea nitrogen excretion increased from the onset of ventilation, reached a peak (at 8 to 20 days), and then decreased gradually, with levels remaining high for 1 month. These patterns are different from those of traumatized or postoperative patients. In traumatized and postoperative patients, the peak day comes earlier and the increase in UUN excretion is limited to a shorter period, barring complications.11

To investigate this catabolic response, three ‘stress’ hormones were measured in these patients. Urinary catecholamine excretion increased markedly. Increases in circulatory catecholamines were observed also in traumatized and postoperative patients. However these increased levels decreased within 1 day after injury.12 In our tetanus patients not only did urinary catecholamine excretion increase to the level of patients with pheochrom-
ocytoma but this increase was also sustained for 3 weeks or more without recurrent injury.

In contrast to the increases in catecholamine excretion, plasma cortisol levels were not elevated during the whole course. A mean plasma cortisol concentration of approximately 40 µg/dL was observed by Stoner following moderately severe injury. In our patients plasma cortisol concentrations did not exceed the upper border of morning levels found in normal subjects, except in case 4. As noted this was not considered to be a simple case of tetanus alone.

Plasma glucagon concentrations were not remarkably increased, except case 4. In cases of traumatized or surgically stressed patients, plasma glucagon levels are markedly elevated.

These results distinguish the endocrinologic features of tetanus patients from those of other stressed patients and raises questions about current theoretical constructs of the 'catabolic response.'

The first question regards the role of catecholamine in the post-traumatic metabolic course. Some have posited a theoretical link between catecholamine and other hormones in which catecholamines stimulate the supraoptic nuclei to the production of ACTH that leads to a secondary increase in cortisol production by the adrenal cortex. It has been speculated also that increased glucagon production is under the influence of catecholamines. In our patients, however, excessively secreted catecholamines did not induce elevations in plasma cortisol or glucagon, at any time. This suggests that increased catecholamine secretion does not necessarily trigger other 'stress' hormones.

A second question regards the relationship between protein catabolism and 'stressed' hormones. Studies of hormonal infusion have investigated the relationship of various hormones to nitrogen loss. Cortisol and glucagon have been considered to be the important hormones responsible for hormone mediated nitrogen loss.7-11 Bessey et al. emphasize synergistic interactions between the three 'stress hormones.' These studies suggest that nitrogen loss is in response to more than just catecholamine elevation. The duration and magnitude of nitrogen loss in our patients cannot be explained by a change in counter-regulatory hormones.

The plasma catecholamine level in explaining this unique metabolic change must be considered. In our patients the level of catecholamine was extremely elevated and is not comparable to the level of other states or hormonal infusion study. In addition we could speculate also about the influence of neurologic factor. The clinical features of these patients are essentially attributable to a derangement of function of neuron caused by tetanus toxin. Although it is difficult to estimate the effect of the neurologic factors on metabolic response quantitatively, results in our patients suggest that factors other than endocrinologic, possibly neurologic ones influenced protein catabolism. Case 4 was not a case of simple tetanus but rather was complicated by severe sepsis. The metabolic feature of this case may be explained by the additive effect of tetanus and general stress caused by infection.

The metabolic changes in our tetanus patients are different from those of other stress states. They are characterized by marked and sustained elevations in catecholamine secretion without increases in plasma cortisol or glucagon levels. In these patients UUN excretion is markedly increased for long periods of time. Increased protein catabolism was not be explained by the metabolic effect of 'stressed hormones' alone, but neurologic factors must be considered as well.

References