Low Plasma Levels of Adrenocorticotropic Hormone in Patients with Acute Influenza

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Plasma levels of adrenocorticotropic hormone (ACTH) and cortisol were measured in young adults with influenza virus type A (H3N2) infection for whom cultures were positive and in comparable controls without symptoms or other evidence of illness. The mean plasma ACTH level ± SE in 19 patients with acute influenza was 13.5 ± 2.1 pg/mL compared with 23 ± 3.2 pg/mL in 11 controls ($P = .02$). Mean plasma ACTH levels ± SE had risen to 21 ± 4.1 pg/mL in specimens obtained from patients during convalescence. The mean plasma cortisol level ± SE in patients with acute influenza was 13.7 ± 1.4 μg/dL compared with 10.8 ± 1.0 μg/dL in controls ($P = $ not significant). ACTH levels in individual controls were relatively higher than their cortisol levels, but ACTH levels in patients tended to be lower than cortisol levels in paired specimens. These findings suggest that influenza virus type A infection may have an inhibitory effect on the production or release of ACTH.

Influenza is a common viral illness that continues to be a serious threat to health worldwide, being associated with 10,000 to 40,000 excess deaths and >150,000 excess hospitalizations annually during epidemics in the United States [1–3]. Although the excess deaths due to influenza occur primarily in aged and chronically ill persons, there is a threat to the health of younger persons as well [4]. Influenza occurs in pandemics in an unpredictable fashion; however, a significant number of cases occur each year.

Before cortisol became available for clinical use in 1950, influenza A was often fatal in persons with primary adrenocortical deficiency (Addison’s disease) [5]. Later, death was prevented when patients with Addison’s disease were cautioned that upon developing symptoms of influenza they should immediately increase their dosage of cortisol during the illness.

In recent years, evidence has accumulated that the hypothalamic-pituitary-adrenal (HPA) axis is an important component of the body’s response to infection, its stimulation being one of the events that initiates an immune response [6]. Therefore, a study was undertaken to determine plasma levels of adrenocorticotropic hormone (ACTH) and cortisol in young adults with acute influenza A who presented to the Department of Student Health at the University of Virginia (Charlottesville) during the months of January to March 1994 and January to March 1995 to determine these levels in healthy controls studied during the same time.

Methods

Young adults aged 18–25 years who presented to the Department of Student Health at the University of Virginia during the winters of 1994–1995 and 1995–1996 because of symptoms of acute influenza were recruited for the study. The duration of illness ranged from 1 to 3 days. Eleven university students (eight males and three females; average age, 23 years) of comparable age who did not have respiratory symptoms or a history of another acute illness within the preceding month were studied as healthy controls.

Nasal wash specimens were collected during the acute illness for culture of influenza virus in MDCK cells [7]. Blood samples were drawn from patients during the acute illness and 1 week later for determination of plasma ACTH and cortisol levels. A single blood specimen was drawn from controls for determination of ACTH and cortisol levels. Blood specimens from patients were drawn between 10:00 a.m. and 3:30 p.m. (mean ± SE, 12:52 p.m. ± 30 minutes). Blood specimens from controls were drawn between 10:30 a.m. and 3:00 p.m. (mean ± SE, 12:45 p.m. ± 35 minutes).

Serum ACTH concentrations were measured in duplicate by a chemoluminescence assay (Nichols Institute, San Juan Capistrano, CA). The sensitivity of the assay was 0.5 pg/mL (0.11 pmol/L). The interassay coefficients of variation (CV) were 6.8% and 7.4% at 34 pg/mL (7.5 pmol/L) and 328 pg/mL (72 pmol/L), respectively. Serum cortisol concentrations were measured by a fluorescence polarization immunoassay with use of the TDx analyzer (Abbott Diagnostics, North Chicago, IL). The analytical sensitivity of the assay was 0.45...
μg/dL (12 nmol/L), and the functional sensitivity (intraassay CV, <20%) was 3 μg/dL (83 nmol/L). Levels of <3 μg/dL (83 nmol/L) were reported as <3 μg/dL (83 nmol/L). The mean interassay CV were 14.0%, 5.7%, and 4.7% at 3 μg/dL (91 nmol/L), 21.9 μg/dL (604 nmol/L), and 36.3 μg/dL (1,002 nmol/L), respectively.

Results
Twenty-six patients with influenza consented to participate in the study. Influenza virus type A (H3N2) was isolated from 19 patients (11 males and eight females; average age, 21 years), 11 in January–March 1994 and eight in January–March 1995.

The initial mean plasma ACTH level ± SE in the 19 patients (13.5 ± 2.1 pg/mL) was significantly lower than that in the 11 controls (23 ± 3.2 pg/mL) (P = .02; t test) (figure 1). The mean plasma cortisol level ± SE in the patients (13.7 ± 1.4 μg/dL) was not significantly higher than that in the controls (10.8 ± 1.0 μg/dL). However, there was a greater difference between the cortisol levels in the patients. In convalescent-phase specimens from patients, the mean plasma ACTH level ± SE was 21 ± 4.1 pg/ml (P = .1, compared with values in acute-phase samples), and the mean plasma cortisol level was 13.3 ± 1.4 μg/dL.

The ACTH levels in all controls were relatively higher than their corresponding cortisol levels, but the ACTH levels in eight of the patients were relatively lower than their cortisol levels, findings consistent with an inhibitory effect on the production or release of ACTH (figure 2).

Discussion
Infections have been shown to be associated with increased plasma concentrations of cortisol and ACTH [8]. The mean magnitude of change in cortisol concentrations was 3.6-fold in children with a variety of febrile illnesses [9] and fivefold in those with pneumonia and meningitis. The nature of some of these infections was not well defined, but presumably, most were due to bacteria.

There is limited prior evidence that this response may not occur in cases of influenza. Mickerson [10] reported that four patients with influenza had decreased urinary excretion of steroids that increased following administration of corticotropin (ACTH). In the current study of young adults with acute influenza virus type A infection, the mean plasma cortisol level was not elevated. The plasma ACTH level in patients was low relative to that in healthy controls. One week later, the mean plasma ACTH level in patients had risen to a level comparable with that in the healthy controls. Thus, there was no evidence of activation of the HPA axis by influenza. Instead, the pattern observed suggests that influenza virus infection may interfere with the host’s response via the HPA axis by inhibiting the production or release of ACTH.

What is known about the CNS in patients with influenza is that somnolence and lethargy are commonly seen in severe cases, but encephalitis, which is clinically recognized, is unusual [11]. Influenza virus has been isolated from brain tissue [12], and viral antigen has been found in ependymal cells [13] in fatal cases. In addition, influenza virus has been recovered from CSF in cases of encephalopathy [14, 15]. Although direct viral invasion of the CNS cannot be excluded, cytokine release from infected areas in the airway or elsewhere is another, and possibly more likely, explanation for the findings. Cytokines are now believed to have an important role in the pathogenesis of acute respiratory infections.

Regardless of the mechanism, if influenza does have a suppressive effect on the HPA axis, it is of interest and may be relevant in understanding some aspects of the pathogenesis of influenza. Studies of the possible effect of other viral infections on the HPA axis would also be of interest.
References