

Primary adrenal insufficiency in patients with acquired immunodeficiency syndrome: report of four cases

Yi-Wen Huang¹, Ching-Chung Chang¹, Hsin-Yun Sun¹, Mao-Yuan Chen¹, Chien-Ching Hung^{1,2},
Shan-Chwen Chang¹

¹Department of Internal Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei; and ²Department of Parasitology, National Taiwan University College of Medicine, Taipei, Taiwan, ROC

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Adrenal insufficiency, though rare, is a well-known complication of acquired immunodeficiency syndrome (AIDS). Over the past 9 years at the National Taiwan University Hospital, 4 patients were diagnosed with primary adrenal insufficiency among 854 non-hemophiliac patients with human immunodeficiency virus infection, with an incidence of 0.19 per 100 patient-years (95% confidence interval, 0.17-0.21 per 100 patient-years). All of the 4 patients were severely immunosuppressed and had been diagnosed with at least 1 AIDS-defining opportunistic illness ever reported to produce adrenal insufficiency in AIDS patients. In 1 of the patients, fluconazole was considered contributory to the development of adrenal insufficiency after treatment at a daily dose of 800 mg for 68 days.

Key words: Acquired immunodeficiency syndrome, adrenal gland diseases, opportunistic infections, pneumocystis pneumonia

The adrenal gland is the endocrine organ most commonly involved at autopsy in patients who die of acquired immunodeficiency syndrome (AIDS) [1]. Estimated incidence of adrenal insufficiency is 5-8%, which is higher than the incidence in the general population [2]. Potential etiologies of human immunodeficiency virus (HIV)-related adrenal insufficiency include direct involvement by HIV, AIDS-associated opportunistic infections and neoplasms, hemorrhage, autoimmune diseases, adverse effects of drugs used to treat these disorders [3,4], and peripheral resistance to glucocorticoids [5].

Symptoms suggestive of adrenal insufficiency, such as weakness, weight loss, hyponatremia, and hyperkalemia are not uncommon in patients at advanced stage of HIV infection without adrenal insufficiency because of concurrent opportunistic diseases and treatment. Therefore, it may prove difficult to determine clinically whether adrenal insufficiencies are due to direct cytopathologic effects of HIV, AIDS-related conditions, or drugs [6].

Here, we describe 4 cases of primary adrenal insufficiency in patients at the advanced stage of HIV infection. The report suggests that early recognition of

adrenal insufficiency and initiation of potent anti-retroviral therapy to restore immunity are important in improving survival.

Subjects and Methods

Since June 1994, a prospective surveillance study was started at the National Taiwan University Hospital, a major referral center for management of HIV-related complications. A standardized protocol had been followed to investigate causes of any presenting symptoms of non-haemophiliac HIV-infected patients who were aged ≥ 15 years. The detailed study methods had been described before [7]. All of the enrolled patients were observed until September 2003, or the date when patients were lost to follow-up or died, whichever occurred first.

In patients presenting with symptoms, such as weakness, weight loss, hyponatremia, and hyperkalemia, that were not apparently attributable to opportunistic diseases diagnosed, blood specimens were obtained for determination of cortisol, thyroid function, and adrenocorticotropic hormone (ACTH).

Adrenal insufficiency syndrome was diagnosed when a patient presented with consistent symptomatology plus a serum cortisol level below the lower normal limit. Primary adrenal insufficiency was defined as inability

Corresponding author: Dr. Chien-Ching Hung, Department of Internal Medicine, National Taiwan University Hospital, 7 Chung-Shan South Road, Taipei, Taiwan, ROC.

of the adrenal glands to secrete sufficient quantities of hormone, not associated with inadequate ACTH formation or release.

Results

From June 1994 through June 2003, 854 non-hemophiliac HIV-infected patients aged ≥ 15 years were seen as inpatients or outpatients. The majority of them were at advanced stage of HIV infection: 69.1% being diagnosed with AIDS with a median CD4+ lymphocyte count of 64 cells/ μ L (range, 0-1202 cells/ μ L); and 45.5% with an initial CD4+ lymphocyte count lower than 50 cells/ μ L.

Four patients were diagnosed with adrenal insufficiency. Their clinical characteristics are shown in Table 1. All 4 patients had consistent symptoms and electrolyte imbalance suggestive of adrenal insufficiency. Primary adrenal insufficiency was confirmed by serum cortisol and ACTH levels except for the third patient with cryptococcosis, in whom no ACTH examination was performed. Fluconazole was considered contributory to development of adrenal insufficiency after he was treated for cryptococcosis at a daily dose of 800 mg for 68 days. His symptoms and abnormal laboratory results related to adrenal insufficiency resolved after switching fluconazole to amphotericin B and corticosteroid replacement therapy.

All of the 4 patients had had AIDS-defining opportunistic illnesses with a high plasma HIV RNA

viral load (PVL) by reverse transcription-polymerase chain reaction (Roche Amplicor, version 1.5, Branchburg, NJ, USA) and a depleted CD4+ lymphocyte count at presentation. Despite severe immunosuppression and life-threatening opportunistic diseases, the first 3 patients survived after achievement of viral suppression and immune restoration with highly active antiretroviral therapy (HAART) and treatment and subsequent maintenance therapy for opportunistic diseases. The fourth patient who was not compliant with HAART and other antimicrobial prophylaxis or treatment died of disseminated *Mycobacterium avium* complex (MAC) and cytomegalovirus (CMV) infection as described below.

Case Report

A 37-year-old homosexual man was admitted to the hospital because of fever, anorexia and diarrhea for 4 days. He had been diagnosed with AIDS for 8 years. Several combinations of antiretroviral therapy had been prescribed with poor virologic and immunologic responses due to poor compliance. The CD4+ lymphocyte count 2 weeks before this admission was 7 cells/ μ L and PVL was 158,000 copies/mL. Rescue antiretroviral therapy with stavudine (30 mg twice daily), didanosine (300 mg once daily), and zidovudine (200 mg twice daily) plus indinavir (800 mg twice daily) was started. The temperature was 37°C, pulse was 80 per minute, and the respiration rate was 20 per minute. The blood pressure was 110/70 mm Hg. On physical examination,

Table 1. Clinical characteristics of 4 human immunodeficiency virus-infected patients with primary adrenal insufficiency

Case no.	Age/ gender	Weight loss	Hypotension	Nausea and vomiting	Na ⁺ (mmol/L)	K ⁺ (mmol/L)	Cortisol (μ g/dL) ^a	ACTH (pg/mL) ^a	CD4+ (cells/ μ L)	PVL (copies/mL)	Active disease or concurrent drugs related to adrenal insufficiency
1	37/M	+	-	+	109	5.4	11.8	400	7	158,000	CMV disease; disseminated MAC infection
2	45/M	+	+	+	127	5.6	12.2	210	ND	ND	TB; PCP
3	35/M	+	-	+	135	6	3.79	ND	1	301,136	Cryptococcosis; fluconazole 800 mg once daily (68 days)
4	40/M	+	+	+	116	8.6	12.3	157	13	197,000	CMV retinitis, colitis, neuropathy, and myelopathy; disseminated MAC infection; invasive amebiasis

Abbreviations: ACTH = adrenocorticotropic hormone; CMV = cytomegalovirus; MAC = *Mycobacterium avium* complex; ND = not done; PCP = *Pneumocystis carinii* pneumonia; PVL = plasma human immunodeficiency virus-RNA viral load; TB = tuberculosis

^aNormal ranges: serum cortisol (am), 5-25 μ g/mL; ACTH, 10-65 pg/mL.

the patient was cachectic, lethargic and had marked muscle wasting. The skin had poor turgor and was diffusely darkly hyperpigmented with a few hyperpigmented macules on the lips. The lungs were clear, and the heart was normal. There was no gynecomastia. The abdomen was not tender and there was no organomegaly. Extremities were thin without edema or cyanosis. Genitalia were normal. Neurological examination was normal, except for lethargy. The white cell count was 2820/ μ L, with 83.6% neutrophils, 6.7% band forms, 4.7% monocytes, 4% eosinophils, and 1% basophils. The hemoglobin was 10.8 g/dL, and the platelet count 185,000/ μ L. The blood urea nitrogen was 11 mg/dL, serum creatinine 0.7 mg/dL, serum sodium 109 mmol/L, and potassium 5.4 mmol/L.

Persistent anorexia, nausea and vomiting were noted despite treatment with prokinetic agents. Upper gastrointestinal endoscopy revealed esophageal ulcer and biopsy disclosed CMV infection. Ganciclovir 250 mg twice daily was given intravenously. Bone marrow aspiration and biopsy were performed for prolonged fever of undetermined etiology. Cultures of the bone marrow specimen subsequently yielded MAC. Clarithromycin (500 mg twice daily), ethambutol (800 mg once daily) and ciprofloxacin (500 mg twice daily) were prescribed. On the ninth day of admission, fatigue, weakness, and asthenia were noted with personality changes. The sodium level was 109 mmol/L, and the potassium level 5.4 mmol/L. The plasma cortisol level at 8 am was 11.8 μ g/dL (normal range, 5-25 μ g/dL), and the plasma ACTH concentration at 8 am 400 pg/mL (normal range, 10-65 pg/mL). Primary adrenal insufficiency was diagnosed, which was further supported by ACTH stimulation test. The test was performed by administering cosyntropin 0.2 mg intramuscularly twice daily for 2 consecutive days. The plasma cortisol level on the third day of the test showed 16.3 μ g/dL and the plasma ACTH concentration was 106 pg/mL. Hydrocortisone 100 mg daily was given intravenously. His signs and symptoms improved gradually.

At discharge, he was taking prednisolone at a daily dose of 7.5 mg, which was gradually tapered over the subsequent 8 months. After initiation of rescue therapy, his PVL was suppressed to less than 400 copies/mL and CD4+ count rose to >100 cells/ μ L. After he had CD4+ count >100 cells/ μ L on 2 consecutive determinations with an interval of 12 weeks, maintenance therapy for disseminated MAC infection was discontinued.

Discussion

We reported 4 cases of adrenal insufficiency in patients at the advanced stage of HIV infection and with opportunistic infections. Adrenal insufficiency was a rare disease, accounting for 0.47% of the 854 patients cared at this hospital over the past 9 years, although most of the patients had AIDS and many opportunistic infections known to involve adrenal gland at autopsy [7]. Estimated incidence of adrenal insufficiency is 5-8%, which is higher than in the general population [2]. The apparent discrepancy between our cohort and others may be due to different methods of study. The study by Masharani and Schambelan [2] enrolled patients undergoing autopsy, which might have overestimated the incidence. However, the incidence of adrenal insufficiency in our study might have been underestimated because not every HIV-infected patient underwent investigations of adrenal function.

The functional reserve of adrenal gland may be immense and frank adrenal insufficiency only appears when the adrenal glands are more than 90% destroyed. In the early phase of gradual adrenal destruction, there may be no demonstrable abnormalities in the routine laboratory parameters, although adrenal reserve is decreased — that is, while basal steroid output may be normal, a subnormal increase occurs after stress. Adrenal stimulation with ACTH may facilitate in uncovering abnormalities in this stage of the disease, eliciting a subnormal increase of cortisol levels or no increase at all. In more advanced stages of adrenal destruction, serum sodium, chloride, and bicarbonate levels are reduced, and the serum potassium level is elevated.

In patients with AIDS, adrenal pathology most frequently results from infection by CMV [1]. Other less common causes of infection include *Mycobacterium tuberculosis* [8], *Cryptococcus neoformans*, *Toxoplasma gondii*, MAC, *Pneumocystis carinii*, and *Histoplasma capsulatum* [9,10]. Adrenal function could also be inhibited in AIDS patients as a result of polyclonal B-cell activation and the production of anti-adrenal cell antibodies [3].

It is important to remember that variety of medications, such as rifampin, phenytoin, ketoconazole, and opiates, may cause adrenal insufficiency. The development of adrenal insufficiency in 1 of our patients might have been related to use of a higher dose of fluconazole (800 mg daily) for treatment of cryptococcal meningitis. Gradon and Sepkowitz had reported a patient with fluconazole-associated acute adrenal insufficiency

[11]. Studies in rats have shown a suppressive effect in vitro of fluconazole on the adrenal P-450 system [12], but the concentration of fluconazole required to produce suppression of adrenal steroid production in this model was 2 orders of magnitude higher than the concentration of ketoconazole required to produce a similar effect. Therefore, patients being treated with a higher dose of fluconazole should be monitored for the onset of signs and symptoms of adrenal insufficiency.

Primary adrenal insufficiency was suggested by the clinical presentations of hyponatremia, hyperkalemia, and hyperpigmented skin and oral mucosa. This diagnosis will be established by the elevated plasma ACTH concentration and subnormal increase of cortisol levels in response to cosyntropin. Such clinical symptoms may be non-specific in HIV-infected patients, however. The disturbance of serum electrolytes may be caused by diseases other than adrenal insufficiency. In 1 study, hyponatremia was found in 31% of 96 patients with AIDS or AIDS-related complex [13]. Hyperkalemia may result from administration of trimethoprim-sulfamethoxazole in treating *P. carinii* pneumonia.

Adrenal insufficiency should be suspected in all HIV-infected patients presenting with fatigue, weakness, anorexia, nausea, vomiting, hyponatremia and hyperkalemia, especially in patients with prolonged HIV infection, severe immunosuppression and a history of previous opportunistic disease, i.e., CMV disease or mycobacterial infection. Previous reports showed that a Na:K ratio less than 30 could be a useful diagnostic tool in patients with adrenal insufficiency [14]. All of our patients had the same findings.

Adrenal insufficiency may be associated with a high mortality rate. In the literature, 14 cases of adrenal insufficiency were reported with detailed characteristics from 1984 to 1995 and 5 of them died, a mortality rate of 36%. The fatality may be caused by adrenal insufficiency and AIDS-associated diseases before introduction of HAART. In this report, 1 of the 4 patients died because of his failure to adhere to HAART and therefore, continued immunosuppression. The other 3 patients, despite the fact that they were at the advanced stage of HIV infection, had favorable clinical, immunological, and virological responses to HAART, and their immunity was restored with resolution of opportunistic infection for which prolonged maintenance therapy could be safely discontinued.

In conclusion, adrenal insufficiency, though rare, should be suspected in HIV-infected patients, especially in patients with severe immunosuppression and a history

of opportunistic diseases, who present with fatigue, weakness, anorexia, nausea, vomiting, hyponatremia, and hyperkalemia. With better management of opportunistic diseases and HIV infection and improved survival in HIV-infected patients, the diagnosis of adrenal insufficiency should be made earlier and the treatment initiated earlier.

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