Relative adrenal insufficiency in adult-onset cerebral X-linked adrenoleukodystrophy

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Practical Implications

Even in patients with advanced ACALD and infection with normal serum cortisol levels, consider the risk of relative adrenal insufficiency and administer steroids immediately when hyponatremia or hypoglycemia develops.

A 48-year-old man with adrenoleukodystrophy was admitted because of heavy sweating, sputum, and high fever. Brain MRI showed extensive cerebral white matter demyelination (figure, A). The patient was previously diagnosed with adult-onset cerebral X-linked adrenoleukodystrophy (ACALD) with *ABCD1* gene mutation at age 46 years. Laboratory findings on admission showed inflammatory changes (white blood cell count 12,400/ μ L, C-reactive protein 2.1 mg/dL), hypotonic hyponatremia (Na 118 mEq/L, Osm 255 mOsm), hyperkalemia (K 5.6 mEq/L), and hypoglycemia (75 mg/dL). The serum cortisol level was higher than normal (cortisol 35.2 μ g/dL). Chest CT showed mild consolidation in the right lower lobe (figure, B).

Although a hormone stimulation test had not been conducted in the past, the patient never showed clinical symptoms of adrenal insufficiency, electrolyte disturbance, or hypoglycemia. Laboratory tests showed hypotonic hyponatremia with hyperkalemia and hypoglycemia, which we attributed to relative adrenal insufficiency induced by infection. We started antibiotics and hydrocortisone 300 mg/d, and the pneumonia and hypotonic hyponatremia with hyperkalemia and hypoglycemia improved. We decreased the dose of hydrocortisone to 50 mg/d, but hyponatremia and severe hypoglycemia soon recurred. We restarted hydrocortisone and fludrocortisone, and the hyponatremia and hypoglycemia dramatically improved. To evaluate adrenal function in advanced ACALD with mild infection, we conducted an adrenocorticotropin hormone (ACTH) stimulation test and corticotropin-releasing hormone (CRH) stimulation test (figure, C and D) in the patient with mild pneumonia. These tests showed 2 findings. First, in both stimulation tests, the baseline values of ACTH and cortisol before stimulation were higher than the normal ranges (figure, C and D). Second, the ACTH increased after CRH injection, but the cortisol did not change and was consistently higher than normal (figure, D). These findings suggest that the demand for cortisol is extremely high in advanced ACALD with infection, but cortisol secretion might be limited.

DISCUSSION

Hormone stimulation tests in a patient with advanced ACALD and mild infection are rare. X-linked adrenoleukodystrophy (X-ALD) is an inborn error of metabolism caused by mutations in the *ABCD1* gene. Very-long-chain fatty acids accumulate in all tissues, resulting in disorders of nervous system white matter, axons, adrenal cortex, and testis.^{1,2} X-ALD in males has 6 phenotypes: childhood cerebral, adolescent, adult cerebral, adrenomyeloneuropathy, Addison only, and asymptomatic.² Clinical expression varies widely according to phenotype.² The incidence of adrenal insufficiency also varies according to phenotype. One study showed adrenocortical dysfunction was diagnosed in 76% of ALD males, 77% of cerebral phenotypes, and 73% of adrenomyeloneuropathy. In 35 of the 70 patients with adrenomyeloneuropathy,

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Figure MRI, CT, and hormone stimulation tests in a patient with advanced ACALD associated with infection

(A) Axial T2-weighted image shows extensive cerebral white matter demyelination. (B) Noncontrast chest CT scan shows mild consolidation in the right lower lobe of the lung. ACTH stimulation test (C), and CRH stimulation test (D) in a patient with advanced ACALD associated with mild infection. In both stimulation tests, the baseline values of ACTH and cortisol before stimulation are higher than the normal values (C, D). The ACTH is increased by CRH injection, but the cortisol level does not respond to ACTH and is consistently higher than the normal range (D). ACALD = adult-onset cerebral X-linked adrenoleukodystrophy; ACTH = adrenocorticotropic hormone; CRH = corticotropin-releasing hormone.

adrenocortical insufficiency was diagnosed before X-ALD, and in 33 patients, dysfunction was diagnosed after X-ALD.³ Adrenal hormone replacement therapy is mandatory and effective. Generally, glucocorticoid is used and not all patients require mineralocorticoid replacement.⁴

Hormone stimulation tests are rarely performed in ACALD. The results in advanced ACALD associated with infection are especially rare. Our study had 2 main findings. First, the baseline serum cortisol level before ACTH or CRH stimulation was 30 to 40 µg/dL, which was higher than the normal range. One study reported a relation between the severity of infection and the baseline values of serum cortisol in non-ALD patients; the median baseline values of serum cortisol in sepsis, severe sepsis, and septic shock were 28.61, 34.23, and 39.21 µg/dL, respectively.⁵ These findings suggest the demands for cortisol in advanced ACALD associated with even mild infection are as high as those in non-ALD patients with sepsis or septic shock.

Second, the ACTH level increased up to 295 pg/mL after the CRH injection, but the cortisol level did not respond to ACTH and remained around 43 µg/dL, which is as high as in non-ALD patients with septic shock. CRH stimulation tests in non-ALD patients with severe sepsis showed that the peak ACTH level after CRH injection did not exceed 90 pg/mL.⁶ Moreover, the baseline serum cortisol level can be higher than 65 µg/dL if the adrenal function is normal in non-ALD patients with severe sepsis.⁷ These findings suggest that the demand for cortisol is quite high in advanced ACALD even in the presence of mild infection, but cortisol secretion is limited. Because pituitary function is normal, ACTH increases remarkably.

Our study revealed that the demand for cortisol is extremely high in advanced ACALD, even under mild infection. Because cortisol secretion is limited, however, patients with advanced

ACALD are at risk of relative adrenal insufficiency. Even if patients with advanced ACALD and infection have normal serum cortisol levels, we should consider the risk of relative adrenal insufficiency and administer steroids immediately when hyponatremia or hypoglycemia develops.

REFERENCES

1. Engelen M, Kemp S, Poll-The BT. X-linked adrenoleukodystrophy: pathogenesis and treatment. *Curr Neurol Neurosci Rep* 2014;14:486.
2. Moser HW. Adrenoleukodystrophy: phenotype, genetics, pathogenesis and therapy. *Brain* 1997;120:1485–1508.
3. van Geel BM, Bezman L, Loes DJ, Moser HW, Raymond GV. Evolution of phenotypes in adult male patients with X-linked adrenoleukodystrophy. *Ann Neurol* 2001;49:186–194.
4. Berger J, Pujol A, Aubourg P, Forss-Petter S. Current and future pharmacological treatment strategies in X-linked adrenoleukodystrophy. *Brain Pathol* 2010;20:845–856.
5. Zhang Q, Dong G, Zhao X, Wang M, Li CS. Prognostic significance of hypothalamic-pituitary-adrenal axis hormones in early sepsis: a study performed in the emergency department. *Intensive Care Med* 2014;40:1499–1508.
6. Schroeder S, Wichers M, Klingmüller D, et al. The hypothalamic-pituitary-adrenal axis of patients with severe sepsis: altered response to corticotropin-releasing hormone. *Crit Care Med* 2001;29:310–316.
7. Burry L, Little A, Hallett D, Mehta S. Detection of critical illness-related corticosteroid insufficiency using 1 µg adrenocorticotrophic hormone test. *Shock* 2013;39:144–148.

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