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Case Report

Encephalopathy After a High-Dose Dexamethasone Suppression Test in a Woman With X-Linked Ornithine Transcarbamylase Deficiency

Hyunho Seol, MD [1], Yoon Hee Hong, MD [2], Min Ji Jeon, MD, PhD [3,*]

[1] Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea
[2] Department of Neurology, Uijeongbu Eulji Medical Center, Eulji University School of Medicine, Uijeongbu, Republic of Korea
[3] Division of Endocrinology and Metabolism, Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

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ABSTRACT

Background/Objective: The high-dose dexamethasone suppression test is a common and usually benign endocrine procedure. We report a patient with ornithine transcarbamylase deficiency (OTCD) who developed hyperammonemic encephalopathy after a high-dose dexamethasone suppression test.

Case Report: A 46-year-old woman with a 1.3-cm right adrenal incidentaloma causing mild autonomous cortisol secretion underwent a high-dose dexamethasone suppression test for confirming adrenocorticotropic hormone independency. On the next day, she presented to the emergency room with confusion and somnolence. Her Glasgow Coma Scale score was 10 on arrival. The initial laboratory results showed ammonia, alanine transaminase, creatinine, and blood urea nitrogen levels of 289.51 (18.73-54.5) μg/dL, 21 (≤33) IU/L, 0.6 (0.6-1.1) mg/dL, and 13 (7-20) mg/dL, respectively. Electroencephalography showed triphasic morphology with no pathologies on brain imaging. Her husband told us that her brother and son had died in the neonatal period. On further review of medical records, we found that she was diagnosed as an OTCD carrier. We administered L-arginine, L-carnitine, rifaximin, and continuous renal replacement therapy. After 3 days, the serum ammonia level was 78.34 μg/dL with an increased Glasgow Coma Scale score of 15, and electroencephalography abnormalities disappeared.

Discussion: Liver diseases and urea cycle disorders are the leading causes of hyperammonemia. This causes encephalopathy and death if the ammonia levels are too high. X-linked OTCD urea cycle disorder affects men more severely as they have only the carrier X chromosome. Glucocorticoids can exacerbate this disorder because they increase protein substrates converted to ammonia.

Conclusion: This case reminds that it may be particularly important to have a complete medical history when administering glucocorticoids.

Introduction

Liver diseases and urea cycle disorders are the 2 leading causes of hyperammonemia, and hyperammonemia, at all ages, will induce encephalopathy. Ornithine transcarbamylase (OTC) is an enzyme that converts ornithine to citrulline in the urea cycle.[1] OTC deficiency (OTCD) is the commonly used term for the urea cycle disorders that result from X-linked mutations of the gene for OTC. OTCD causes hyperammonemia due to the impaired conversion of ammonia that is produced from protein catabolism.[2] Symptoms include lethargy, anorexia, vomiting, and altered mental status. In most male with OTCD, the diagnosis is made in the neonatal

Abbreviations: ACTH, adrenocorticotropic hormone; EEG, electroencephalography; OTC, ornithine transcarbamylase; OTCD, ornithine transcarbamylase deficiency.

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* Address correspondence to Dr Min Ji Jeon, Division of Endocrinology and Metabolism, Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea, 05505.
E-mail address: mj080332@amc.seoul.kr (M.J. Jeon).

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period.[1] In contrast, most women with X-linked mutations of the OTC gene do not develop overt OTCD hyperammonemic encephalopathy at all or not until later in life because they have 1 normal X-linked OTC gene. Glucocorticoids increase circulating protein substrates that are degraded to ammonia.[3,4] Several reports have described the development of ammonia-induced encephalopathy in patients with OTCD; however, these are relatively sparse. Here, we report the case of a patient with unsuspected OTCD who became disoriented after undergoing a high-dose dexamethasone suppression test.

Case Report

A 46-year-old woman who discovered a right adrenal incidentaloma during routine health checkup was referred to our endocrinology clinic to have an endocrine evaluation. There was no other particular medical history given by the patient, except for a benign thyroid nodule. Physical examination revealed no significant signs and symptoms suggestive of a functioning adrenal tumor, such as facial fullness, bruising, palpitation, and muscle wasting. The initial laboratory test results were as follows: (1) plasma metanephrine level, 0.02 (<0.1) μg/L; (2) 24-hour urine metanephrine level, 47.3 (52-341) μg; (3) plasma adrenocorticotropic hormone (ACTH) level, 36.9 (<60) pg/mL; (4) plasma cortisol level, 14.8 (5-25) μg/dL; (5) 24-hour urine cortisol level, 34 (20-90) μg; (6) renin activity level, 2 (0.68-1.36) ng/mL/hour; (7) plasma aldosterone level, 24.2 (3.57-24.0) ng/dL, and (8) plasma dehydroepiandrosterone sulfate level, 35.6 (31.2-263) μg/dL. Cortisol determinations were obtained on several occasions after administration of 1-mg dexamethasone the previous night and were always >1.8 μg/dL, confirming mild autonomous cortisol secretion (Table). Because the ACTH level fluctuated at high values, we decided to have the patient undergo the high-dose dexamethasone suppression test to confirm the ACTH independency. A high-dose dexamethasone suppression test was performed as follows: dexamethasone 2 mg was administered orally every 6 hours for 2 days.

On the next day, the patient was brought to the emergency room with rapidly progressing confusion and eventually somnolence. There was no history of toxic drug or alcohol exposure. Neurologic examination revealed a Glasgow Coma Scale score of 10. Laboratory testing revealed with serum ammonia, alanine transaminase, creatinine, and blood urea nitrogen levels of 289.51 (18.73-54.5) μg/dL, 21 (≤33) IU/L, 0.6 (0.6-1.1) mg/dL, and 13 (7-20) mg /dL, respectively. Brain magnetic resonance imaging and head angiography showed no remarkable finding. Electroencephalography (EEG) showed continuous generalized 2.5- to 3-Hz sharp-and-slow wave complexes with triphasic morphology (Fig. 1 *A*). In 6 hours of emergency room stay time, further history was obtained from the patient's husband who stated that the patient's brother had died in the neonatal period and, 15 years previously, she gave birth to a son who died as a neonate. After the patient delivered and her health care providers became aware of her son's diagnosis, she was also diagnosed as an OTCD carrier (Fig. 2). She had had no cognitive dysfunction for 15 years after OTCD diagnosis until after the recent dexamethasone suppression test.

On knowing hyperammonemia, she started low-protein enteral nutrition formula by a nasogastric tube. She was treated with the ammonia-lowering agents (L-arginine, L-carnitine, and rifaximin) and continuous renal replacement therapy. Three days after continuous renal replacement therapy with the use of 3 ammonia-lowering agents, her serum ammonia level decreased to 78.34 μg/dL, and her Glasgow Coma Scale score increased to 15 (Fig. 3). We then started administration of sodium benzoate and sodium phenylbutyrate.

Highlights

- Steroids can trigger ammonia toxicity in asymptomatic OTCD carriers
- OTCD should be considered in patients with adult-onset hyperammonemic encephalopathy
- Taking a patient's medical history is always essential for diagnosing a disease

Clinical Relevance

Although the high-dose dexamethasone suppression test is considered generally safe for differentiating Cushing syndrome, our case shows that it can trigger ammonia toxicity in ornithine transcarbamylase deficiency carriers. This case may help clinicians add ornithine transcarbamylase deficiency, which is the most prevalent urea cycle disorder, as a differential diagnosis for adult-onset hyperammonemic encephalopathy.

EEG findings improved because the continuous generalized 2.5- to 3-Hz sharp-and-slow wave complexes with triphasic morphology disappeared (Fig. 1 *B*). Her neurologic symptoms completely resolved. She was instructed to maintain a lifelong low-protein diet. For regular diet, total protein intake should be restricted not to over 30 g per day along with sodium phenylbutyrate and sodium benzoate granules. She was referred to the Department of Genetics and Genomic Sciences and was given genetic counseling. We are regularly following her up.

Discussion

Here, we describe the case of a previously healthy patient with OTCD who developed hyperammonemic encephalopathy after undergoing a high-dose dexamethasone suppression test for adrenal mass workup.

In several cases, hyperammonemic encephalopathy is accompanied by liver failure.[5] This case is unique in that despite the initial serum ammonia level being 289.51 μg/dL, the other laboratory findings revealed neither liver damage nor kidney injury. In this clinical situation, other rare causes of hyperammonemia, such as urea cycle disorder, should be considered. OTCD is the X-linked and most frequent urea cycle defect.[2] Although the high-dose dexamethasone suppression test is a common and usually benign endocrine procedure, it caused hyperammonemic encephalopathy in an OTCD carrier.

If these ammonia-lowering agents fail to reduce ammonia, hemodialysis is an important tool for correcting hyperammonemia. In addition, benzoate and phenylacetate are important treatments for patients with urea cycle defects. Benzoate conjugates with glycine, producing hippurate. Phenylacetate conjugates with glutamine, producing phenylacetylglutamine.[2,5] Phenylbutyrate is a prodrug of phenylacetate and lacks the odor of phenylacetate. Both the new products are water soluble and excretable; hence, sodium benzoate and sodium phenylacetate can be used to remove nitrogenous waste from the blood and increase the survival rate.[5,6]

Because the urea cycle functions as a biosynthetic pathway for arginine, arginine becomes an essential amino acid and should be administered to resume protein synthesis for patients with urea cycle enzyme deficiencies.[2]

In the hospital, glucocorticoids are one of the most commonly used drugs because they have an anti-inflammatory effect.

Table
Summary of the Adrenal Incidentaloma Workup Results

Serum ACTH levels measured before high-dose dexamethasone suppression test	Serum cortisol changes from overnight dexamethasone suppression test	Results of high-dose dexamethasone suppression test	
36.9 pg/mL	7.3 μg/dL	Serum cortisol	24-h urine cortisol
21.6 pg/mL	7.8 μg/dL	Baseline: 10 μg/dL	Baseline: 32.3 μg/day
31.1 pg/mL	2.9 μg/dL	After DXM: 4.5 μg/dL	After DXM: 14.1 μg/day
28.9 pg/mL	4.5 μg/dL		
51.6 pg/mL	4.6 μg/dL		

Abbreviations: ACTH = adrenocorticotropic hormone; DXM = dexamethasone.

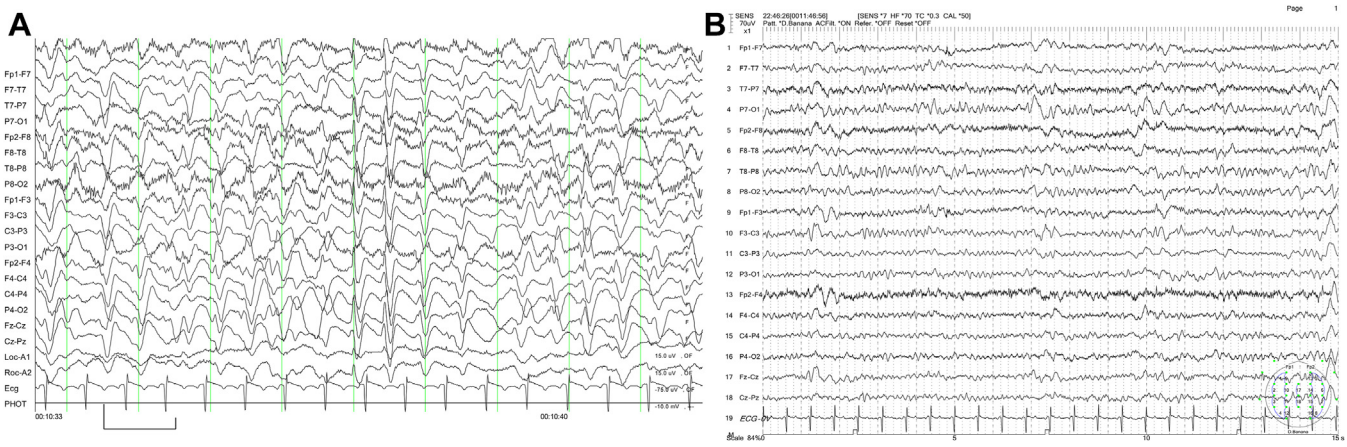

Fig. 1. Electroencephalography (EEG) change after continuous renal replacement therapy in a 46-year-old woman with hyperammonemia. *A*, EEG at the time of arrival. The continuous generalized 2.5- to 3-Hz sharp-and-slow wave complexes with triphasic morphology indicated the possibility of metabolic encephalopathy or nonconvulsive status epilepticus. *B*, EEG improvement after 3 days of continuous renal replacement therapy: the continuous sharp-and-slow wave complexes with triphasic morphology disappeared.

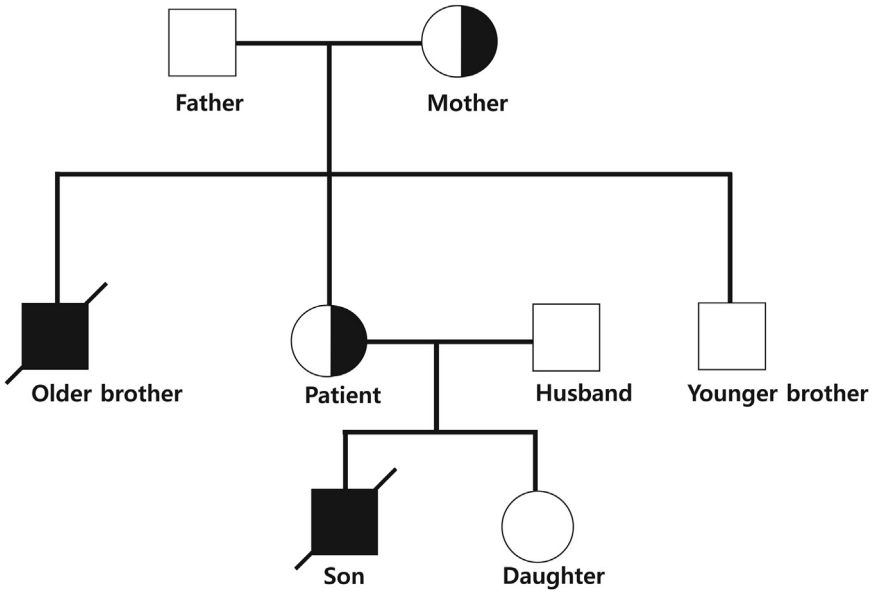

Fig. 2. Family tree of the patient. The patient and her mother were ornithine transcarbamylase deficiency mutation carriers. The genetic test revealed that the daughter was unaffected.

However, irrespective of the reason for glucocorticoid use, clinicians should be careful when administering high-dose glucocorticoids and consider the possibility of rare side effects, such as the present case. There is no clear glucocorticoid dose threshold that causes hyperammonemia in a patient with urea cycle defects. Another study has reported an OTCD carrier who developed a coma after receiving intravenous glucocorticoids for an asthma attack.[7] A small number of men with late-onset OTCD do exist. One report described a 56-year-old man with OTCD who developed a coma after receiving a glucocorticoid injection in his knee for

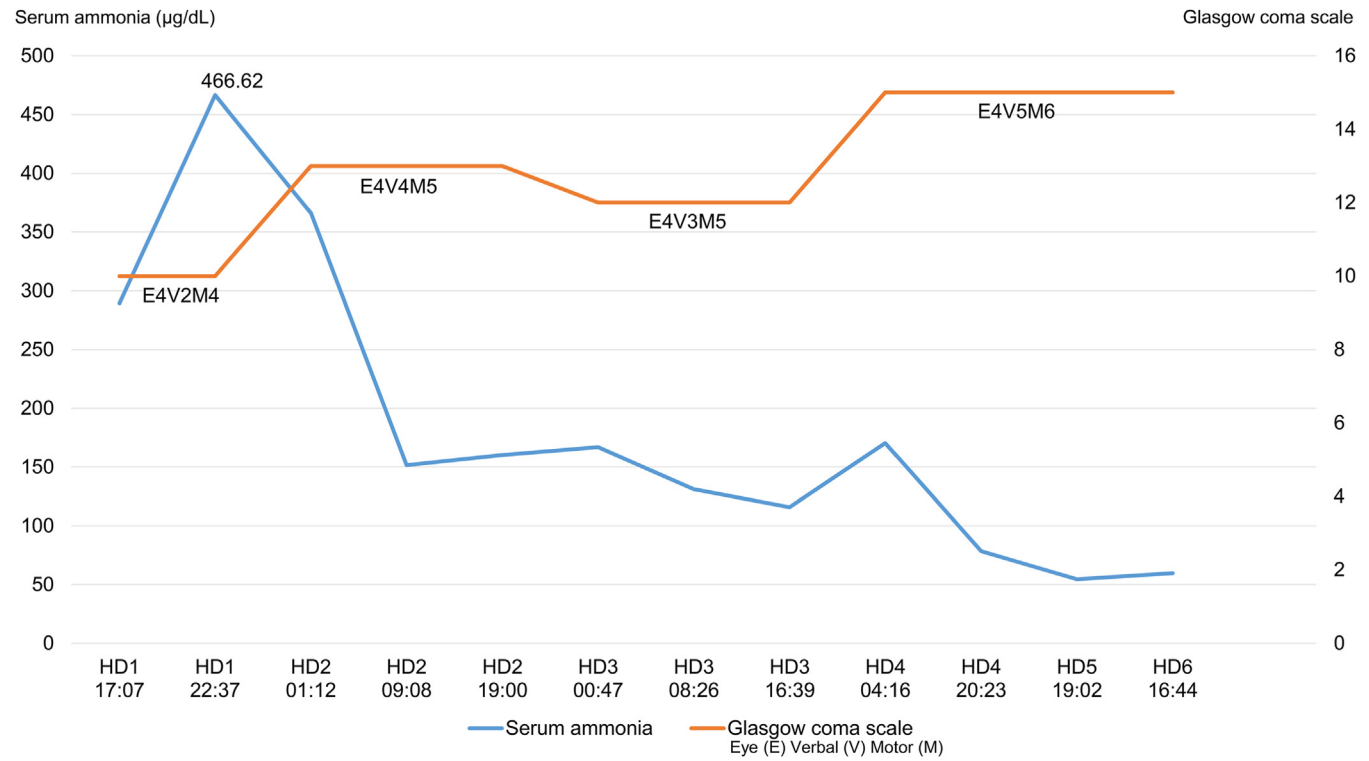

Fig. 3. Glasgow Coma Scale score improvement in relation to the serum ammonia level. Verbal and motor responses improved as the serum ammonia level drastically decreased immediately after continuous renal replacement therapy.

osteoarthritis.[8] In men with late-onset OTCD, several conditions, including the type of mutation, along with yet unknown factors, such as environment or other genes, are believed to affect the variable age of onset and severity of phenotype.[8,9]

Conclusion

The cortisol level after high-dose dexamethasone administration presented not enough cortisol suppression, which confirms ACTH independency and adrenal adenoma as a reason for cortisol excess (Table). Although unilateral adrenalectomy is the standard therapy for a cortisol-secreting adrenal adenoma, she followed up without surgery because postoperative glucocorticoid replacement is necessary after adrenalectomy, which is likely to cause a hyperammonemic encephalopathy again. This case is a reminder that it may be particularly important to have a complete medical history when administering high doses of potent glucocorticoids.

Disclosure

The authors have no conflicts of interest to disclose.

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