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Adrenal Insufficiency due to Total Primary Empty Sella Syndrome

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Abstract

A 64-year-old woman was transported suffering from persistent lower abdominal pain, vomiting, and low-grade fever. Magnetic resonance imaging revealed an empty sella (ES) and hormone tests revealed a disappearance of diurnal variation of cortisol, low cortisol and adrenocorticotropic hormone (ACTH) secretion especially in the morning, and poor ACTH-cortisol axis reaction, as well as normal hypothalamus-pituitary gland-thyroid or adrenal gland axis hormone reaction. The cause of ES remained unclear; however, based on a diagnosis as adrenal insufficiency due to inappropriate ACTH secretion caused by total primary ES syndrome, we started hydrocortisone (15 mg/day). Afterwards, she immediately became symptom-free and was discharged.

Keywords: Adrenal insufficiency; Cortisol; Adrenocorticotropic hormone; Empty sella syndrome

Introduction

"Empty sella" (ES) refers to the neuroradiological or pathological finding of an apparently ES turcica that contains no pituitary tissue [1]. An ES develops when cerebrospinal fluid (CSF) fills the sella turcica, compressing pituitary tissue until it lines the floor and walls of the sella, and when there is remodeling of the sella turcica and a flattening of the pituitary gland that results from subarachnoid space extension into an intra-seller position and a stretching of the pituitary stalk [2-6]. ES syndrome (ESS) refers to an anatomical and radiological condition, first described by Busch in 1951 [6]. ESS is complete or partial, depending on whether the sella turcica is completely or partially filled with CSF; this results in displacement of the pituitary gland, and therefore ESS is the pathological variant [6, 7]. In partial ESS, there is a pituitary gland thickness of 3 - 7 mm, with the sella filled less than 50% with CSF [6]. On the other hand, total ESS refers to when the pituitary gland thickness is less than 2 mm, and spinal fluid fills over half of the sella [6]. ESS patients have one or more pituitary hormone deficiencies [6].

Regarding pathophysiology and etiology, ESS is subdivided into two categories: primary ESS (PES) and secondary ESS (SES). PES occurs when there is increased CSF pressure alongside a defect in the diaphragma sellae . While there is no clear genetic association known to cause a predisposition to PES, it is likely that the incompetent diaphragma sellae was present at the patient's birth . The pathogenetic mechanisms of PES are not well established, but an

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ischemic atrophy of the adenohypophysis may be involved in the development of a PES with idiopathic chronic raised intracranial pressure, preventing the recovery of the gland volume after the intracranial pressure is restored to normal values . Restitution of ES may also be an indicator of ordinary intracranial pressure . This is rarely known to cause pituitary dysfunction . On the other hand, there is a reported case in which a diagnosis of PES with anterior pituitary dysfunction was made in the absence of any history of pituitary irradiation, pituitary adenoma, or surgery . SES can occur as a result of damage to the pituitary itself (e.g., pituitary apoplexy) or as a consequence of surgery, radiation treatment, immunotherapy or other novel forms of treatment, hemorrhage, autoimmune hypophysitis, neurosarcoidosis, or an infarction of the pituitary gland, and it may occur at any time during the patient's life . In addition, a relationship has been reported between infection with Hantaan virus and SES .

Case Report

A 64-year-old woman was transported suffering from persistent lower abdominal pain, vomiting, and low-grade fever. She had also been transported to our hospital 2 years ago due to the same complaint. Her medical history included total blindness when she was in her 30s, undergoing fibroid surgery when she was in her 40s, schizophrenia, type 2 diabetes mellitus without any complications, hypertension, and dyslipidemia. She was treated with risperidone, metformin, voglibose, candesartan, and pravastatin. The patient was unemployed and did not have any food or drug allergies. She had never experienced abnormal menstruation, including amenorrhea, and had a son. She had no family history of any immunodeficiency disorders or other congenital anomalies. She was independent for everyday activities, lived alone, and received food delivery services. On the other hand, she had sometimes complained about fatigue or abdominal pain, especially in the morning, according to her detailed history. This case report was approved by the Kanazawa Medical University Himi Municipal Hospital ethics committee and carried out in conformance with the principles of the Declaration of Helsinki.

She was 150 cm tall and weighed 57 kg, and she was obese, but without moon face, skin rashes, or striae. Her vital signs were abnormal, with a blood pressure of 104/58 mm Hg, a heart rate of 76 regular beats/min, a body temperature of 37.6 °C, oxygen saturation of 97% in ambient air, and a respiratory rate of 16/min; her Glasgow Coma Scale score was 15 (Eye (E) 4 Verbal (V) 5 Motor (M) 6) points. She complained of tenderness throughout the entire abdomen, and nothing else abnormal, including skin findings, was detected upon physical examination. A routine laboratory examination revealed increased values of white blood cells, lactate dehydrogenase, creatine kinase, and decreased values of blood urea nitrogen, sodium, and chloride. On the other hand, other values were normal, including complete blood count, biochemistry, casual blood glucose, ammonia, and urine tests . In addition, no dramatic hormone secretion abnormality was confirmed in spotting pituitary, thyroid, and adrenal gland hormone examinations. In an imaging examination, a cranial computed tomography (CT) scan revealed ES in the pituitary gland with a height of 1 mm . A magnetic resonance imaging (MRI) scan found CSF filling the sella turcica, and its intensity was the same as the cerebral ventricle (iso-intensity in T1-weighted image, and high intensity in T2-weighted image), in addition to the similar findings of the CT scan . On the other hand, chest and abdominal CT scans revealed normal findings. At this point, we suspected her diagnosis was ESS, which led to insufficient ACTH secretion and adrenal insufficiency. After she was hospitalized, we measured daily ACTH and cortisol secretion and performed two hormone load tests, namely an insulin tolerance test (ITT) and intravenous (IV) administration of Novolin R® 6 U (0.1 U/kg), and an anterior pituitary function test through combined IV administration of four hypothalamic releasing hormones: corticotropin-releasing hormone (CRH), thyrotropin-releasing hormone (TRH), luteinizing hormone-releasing hormone (LH-RH), and growth-hormone releasing factor (GRF). As a result, we confirmed a disappearance of diurnal variation of cortisol, low ACTH secretion in the morning, and poor ACTH-cortisol axis reaction as well as normal hypothalamus-pituitary-gland-thyroid or adrenal gland axis hormone reaction. More specifically, on the ITT, a hypoglycemic state occurred 30 min after insulin administration and continued until 90 min after; on the other hand, we could not regard this as single ACTH deficiency, because its secretion was confirmed. Other pituitary hormones had been secreted adequately by the hypothalamus upon release of hormone stimulation. On the other hand, her daily cortisol secretion to urine was 58.8 mg/dL/day and was within normal range.

Based on these results, we suspected the following pathology: CSF filled her sella turcica and caused insufficient pituitary hormone secretion. Then, she suffered from adrenal gland cortex function failure, and diurnal variation of cortisol vanished based on low ACTH secretion. On the other hand, cortisol secretion had been sustained at the very limit, and a time lag occurred between cortisol and ACTH secretion. The phenomenon was due to PES. Along the way, some kinds of stress had caused further ACTH hyposecretion, which led to her symptoms. Therefore, she only ever experienced hyponatremia due to temporary adrenal insufficiency when she experienced stress. Her gonadal hormone function had been maintained because she hadn't experienced amenorrhea, and she had given birth. The cause of her complete blindness was suspected to be due to compression of the optic nerve by ES. On the other hand, the cause of ES in this case remained unclear.

Although we could not get a definite diagnosis, we diagnosed it as adrenal insufficiency due to inappropriate ACTH secretion caused by PES. We concluded that it would be safer to treat her through corticosteroid replacement therapy, especially in the morning, because she would repeatedly suffer from adrenal insufficiency with high percentages under stress conditions. We started hydrocortisone (15 mg/day) from the 10th hospital day, and she immediately became symptom-free, and she was discharged on the 19th hospital day. On the other hand, we also expected to administer hydrocortisone (10 mg) to be taken in the event of stress, including similar symptoms, burn, or trauma.

Discussion

We present the first known case of adrenal insufficiency due to insufficient ACTH secretion caused by total PES.

ESS is considered to a relatively rare entity, but research reports that it is present in 5.5-20% of autopsies, and that it is also present in an estimated 12% of neuroimaging patients . Additionally, some reports note an even higher incidence in clinical practice, with estimates of up to 35% . ESS incidence peaks in the forties through sixties . However, the incidence of pediatric ES varies significantly by population surveyed, ranging from as little as 1.2% in children without endocrine symptoms to as much as 68% in children with known endocrinopathy [2].

Because endocrine function is ordinarily intact, patients with ESS typically have normal histories and physical exams . Clinical manifestations of ESS include headache (the most typical manifestation), hypopituitarism, CSF rhinorrhea, visual abnormalities and deterioration including impairment of the visual field, overweight/obesity, hypertension, irregular menses, primary amenorrhea, and multiple pregnancies, some of which may often be associated with intracranial hypertension In our case, recurrent manic-like episodes had been confirmed, and hyponatremia was seen upon her admission; therefore, we suspected adrenal cortical insufficiency as the cause.

In most cases, pituitary function is normal despite the pituitary gland's abnormal appearance of the pituitary gland, but in approximately 20% of cases, any or all pituitary hormone levels may be affected . Hyperprolactinemia and GH deficiency appear to be the two most common findings in ES: hyperprolactinemia is present in 10-17% of cases and may be due to a microprolactinoma or functional hyperprolactinemia, while GH deficiency is present in 4-60% of cases, but its clinical significance in adults is unclear . Gonadotropin deficiency is found in 2-32% of cases, while ACTH, thyroid-stimulating hormone (TSH), and antidiuretic hormone (ADH) deficiencies are less frequent, with incidences of approximately 1% each . Specifically, in some reports, authors advised following basic neuroendocrinological testing: fasting cortisol, free thyroxine (FT_4), estradiol or testosterone, insulin-like growth factor 1 (IGF-1), and prolactin . In addition, the following labs are necessary for pituitary function evaluation in any patient found to have ES: for the adrenal axis, early-morning fasting cortisol levels are a screening option for ACTH deficiency, and overtly low levels of cortisol (less than 3.0 µg/dL) are considered consistent with adrenal insufficiency .

Most patients with ES remain asymptomatic throughout their life and require no treatment; however, in cases where isolated ACTH deficiency develops, corticosteroid treatment should be enforced in order to avoid fatal consequences . Patients allergic to succinate ester can tolerate alternative ester-free corticosteroids[31]. Patients with hypopituitarism should be given hormone replacement therapy in time, and followed up afterwards, but chronic hyponatremia should always be corrected gradually, in order to avoid osmotic myelinolysis syndromes .

Conclusion

This case study has several limitations. First, this paper reviews a single case report and case series of ESS. Therefore, the actual situation of ESS may differ from the results of the literature review, due to reporting bias. Second, we did not measure hormone values during the patient's convalescent stage; therefore, we should have measured them and compared them with the values at time of admission for a detailed diagnosis. Third, metyrapone testing should be performed to assist in this diagnosis.

In conclusion, we have reported the first known case of adrenal insufficiency due to insufficient ACTH secretion caused by total PES. This case highlights the complex pathology, procedure of diagnosis, and treatment for ESS. On the other hand, further investigations are needed to clarify the precise pathogenesis of ESS.

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