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Case Report

Waterhouse-Friderichsen Syndrome and Central Diabetes Insipidus Due to *Escherichia coli* Meningitis

Shinsuke Mizuno,[1] Koji Yokoyama,[1] Takayuki Nukada,[1] and Shigeto Hara[1]

[1]Department of Pediatrics, Japanese Red Cross Society Wakayama Medical Center, Wakayama City, Wakayama, Japan

Correspondence: Shinsuke Mizuno, MD, Department of Pediatrics, Japanese Red Cross Society Wakayama Medical Center, 4-20 Komatsubara-dori, Wakayama-City, Wakayama 6408558, Japan. Email: 4t0121@gmail.com.

Abstract

Waterhouse-Friderichsen syndrome and central diabetes insipidus are uncommon but potentially fatal endocrine and metabolic diseases. Waterhouse-Friderichsen syndrome is defined as adrenal insufficiency caused by adrenal hemorrhage, which is typically bilateral and most frequently due to meningococcal infection. It is usually diagnosed by necropsy. Central diabetes insipidus in children is often caused by trauma, intracranial lesions, autoimmune diseases, and infections. In addition, it can be caused by mutations in the AVP-NPII gene, although this occurs typically later in childhood rather than in the neonatal period. This report describes a term infant who developed *Escherichia coli* meningitis, which resulted in septic shock and disseminated intravascular coagulation. Abdominal ultrasound led to an early diagnosis of bilateral adrenal hemorrhage and appropriate treatment with corticosteroids. Symptomatic central diabetes insipidus developed a few days after the onset of meningitis. Intravenous vasopressin was effective in resolving hemodynamic instability. In conclusion, sepsis and meningitis may have severely affected the endocrine system in this patient. Early diagnosis and appropriate treatment for both diseases may have resulted in better clinical outcomes for this patient.

Key Words: Waterhouse-Friderichsen syndrome, central diabetes insipidus, ultrasound, neonatal meningitis, *Escherichia coli*

Waterhouse-Friderichsen syndrome (WFS), a condition first described in 1911 [1, 2], is characterized by bilateral adrenal hemorrhage (AH) caused by overwhelming sepsis. WFS usually results from meningococcal disease, but it can also be caused by other etiologic agents [3, 4]. Although WFS is usually diagnosed by autopsy, advances in imaging modalities, including ultrasound (US), computed tomography, and magnetic resonance imaging, have enabled antenatal diagnosis [5]. Central diabetes insipidus (CDI) is an uncommon disease in neonates and can be a complication of central nervous system (CNS) infection [6]. Both WFS and CDI are potentially fatal endocrine and metabolic conditions. To our knowledge, few reports have described *Escherichia coli* (*E. coli*) meningitis as a cause of both WFS and CDI in neonates. The present report describes a full-term infant with WFS, and CDI caused by *E. coli* meningitis. Abdominal US allowed early diagnosis of WFS, leading to appropriate treatment. CDI in this patient was controlled by intravenous administration of vasopressin. Sepsis and meningitis can severely affect the endocrine system and result in WFS and CDI. Early detection and appropriate treatment of both diseases are essential to improve their outcomes. The study protocol was approved by the Institutional Review Board of the Japanese Red Cross Wakayama Medical Center (no. 982).

Case Presentation

An infant female was born via spontaneous vaginal delivery at a gestational age of 36 weeks and 0 days to a 17-year-old woman (gravida 2, para 1). The infant's birth weight was 2356 g and her Apgar scores were 9 at both 1 and 5 minutes. Meconium staining was not observed. The mother presented with preterm premature rupture of membranes at gestational age 35 weeks and 5 days, and upon admission the mother was prescribed intravenous ampicillin. Cultures of vaginal and stool samples of the mother at gestational age 34 weeks were positive for Group B *Streptococcus*, but negative for other organisms. The antenatal history of the mother was uneventful.

At birth, the infant displayed respiratory distress, requiring resuscitation with positive pressure ventilation. She was admitted to the neonatal intensive care unit, placed on a mechanical ventilator, and underwent work-up for sepsis, including blood cultures. Antibiotics were not administered, because the duration from rupture of membranes to her birth was less than 48 hours and her mother had no fever.

Sixteen hours after birth, the infant developed fever, convulsions, and drowsiness. She appeared to be pale, with cold extremities, cyanosis of the extremities, and poor capillary refill. She was febrile with a body temperature of 38.8 °C. Other vital signs included a pulse of 170 beats per minute, a blood pressure of 60/35 mmHg, a respiratory rate of 80 breaths per minute, and oxygen saturation of 87% on mechanical ventilation. Cardiovascular examination was normal, and her lungs were clear on auscultation. Her abdomen was soft, but not distended, and her muscle tone was slightly increased. There was no evidence of a skin rash or subcutaneous hemorrhage.

Diagnostic Assessment

Laboratory findings, including complete blood count and the results of coagulation tests and blood chemistry, are

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summarized in Table 1. Laboratory findings were consistent with disseminated intravascular coagulation. Cerebrospinal fluid (CSF) examination revealed a high cell count (8.15 × 109/L (8150/μL)) and a glucose concentration of 0.06 mmol/L (1 mg/dL). Gram staining of the CSF detected gram-negative rod organisms. Abdominal US performed because of suspected adrenal insufficiency showed bilateral AH (Fig. 1).

Three days after the onset of meningitis, she developed lethargy; her blood pressure decreased to 50/30 mmHg, and her urine output increased to 10 mL/kg per hour. Her urine had a specific gravity of 1.005 and an osmolality of 160 mOsm/kg H_2O (160 mmol/kg) (Fig. 2). Other significant laboratory abnormalities included a serum sodium concentration of 155 mmol/L (155 mEq/L), serum osmolality of 332 mOsm/kg H_2O (332 mmol/kg) (332 mmol/kg), and serum antidiuretic hormone level of 1.3 pg/mL (1.2 pmol/L).

Treatment/Outcome and Follow-Up

The patient was clinically diagnosed with early-onset neonatal meningitis and Waterhouse-Friderichsen Syndrome (WFS). Blood cultures obtained at admission and CSF cultures on DOL 1 were positive for *E. coli*. She was treated with appropriate antibiotics. Hydrocortisone (10 mg/kg/day) was added to her regimen to control pressure refractory hypotension and was continued based on the abdominal US finding. Within 24 hours, her blood pressure returned to the normal range without the need for vasoactive agents. After DOL 3, she required no further steroid therapy, with follow-up examinations showing a gradual regression of AH (Fig. 1). Blood and CSF cultures after 36 hours of treatment were both negative. Treatment with antibiotics was continued until DOL 22.

Table 1. Laboratory values associated with Waterhouse-Friderichsen syndrome on admission and after onset of meningitis

	Day 0	16-24 hours after birth	Day 2	Day 3
WBC ($\times 10^9$/L, 4.8-18.5)	2.8	3.1	6.4	15.1
Neut (%)	31.6	54.0	89.8	84.3
Eos (%)	2.8	9.0	1.7	1.6
Plt ($\times 10^9$/L, 280-910)	224	92	67	97
PT INR	—	2.05	1.47	1.04
APTT (s, 25-40)	—	67.3	46.5	33.0
D dimer (μg/mL, < 1)	—	9.87	4.09	2.95
CRP (mg/L, 0-14)	9.9	80.6	145.3	116.1
Na (mmol/L)	137	128	139	143
K (mmol/L)	4.5	6.1	3.6	4.0
Glu (mmol/L)	3.7	1.1	7.2	7.9
pH	7.49	6.51	7.43	7.41
HCO^{3-} (mmol/L)	25.5	14.6	28.6	24.3
BE (mmol/L)	2.7	−19.4	3.7	−0.2
Lac (mmol/L)	4.8	18.0	4.3	3.5

Abbreviations: APTT, activated partialthromboplastin time; BE, base excess; CRP, C-reactive protein; Glu, glucose; HCO3-, bicarbonate; K, potassium; Lac, lactate; Na, sodium; Plt, platelet; PT INR, prothrombin international normalized ratio; WBC, white blood cell.

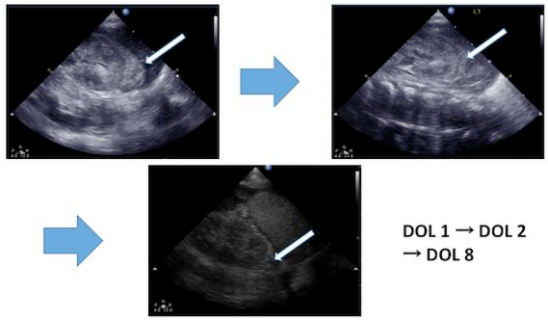

Figure 1. Abdominal ultrasound revealing adrenal hemorrhage (white arrow) on day of life 1 and its regression during admission.

The patient was also diagnosed with CDI, based on her low serum antidiuretic hormone levels and low urine osmolality. On DOL 4, CDI was treated with intravenous vasopressin (0.3 mU/kg/h). Two days later, her urine output decreased to 4 mL/kg/h and her urine osmolality improved to 213 mOsm/kg H_2O (213 mmol/kg). Her vasopressin dose was reduced as her urine output increased, and intravenous vasopressin was discontinued after DOL 12.

Cerebral magnetic resonance imaging, performed on DOLs 10 and 35, showed bilateral encephalomalacia, minor bleeding, and a splenial lesion, indicating mild encephalitis/encephalopathy with a reversible splenial lesion, but no signs of abscess, ventriculitis, or pituitary gland abnormality (Fig. 3). Initial testing for hypothalamic function was not assessed. However, progressive ACTH deficiency due to hypothalamic injury was a concern; thus, endocrine assessments were performed on DOL 35, which showed that serum concentrations of thyroid-stimulating hormone, thyroid hormone, and adrenocorticotropic hormone were normal, but her early morning cortisol level was low at 1.9 μg/dL (52.42 nmol/L). The corticotropin-releasing hormone stimulation test showed a normal adrenocorticotropic hormone response and no evidence of central adrenal insufficiency. Automated auditory brainstem response testing and electroencephalography showed no abnormalities. She was discharged on DOL 45 without respiratory assistance or a feeding tube.

Discussion

WFS and CDI are endocrine and metabolic emergencies that can have fatal outcomes. Early diagnosis and treatment are essential to improve patient prognosis [7, 8]. Both conditions, however, are very rare and are initially characterized by nonspecific manifestations, especially in neonates. Findings in the present patient showed that *E. coli* meningitis can cause WFS in neonates and early detection of AH by abdominal ultrasonography can improve the prognosis.

WFS is a serious adrenal condition, and appropriate treatment of AH may lead to better outcomes [7]. WFS is considered a complication of sepsis and sometimes accompanies disseminated intravascular coagulation, increasing adrenal blood flow and platelet aggregation in the adrenal vein, which can lead to AH. *Neisseria meningitides* is the most common causative pathogen, whereas only a few cases of WFS caused by *E. coli* have been reported [4]. WFS is usually diagnosed by necropsy, but recent advances in imaging modalities have allowed AH to be detected by US, computed tomography,

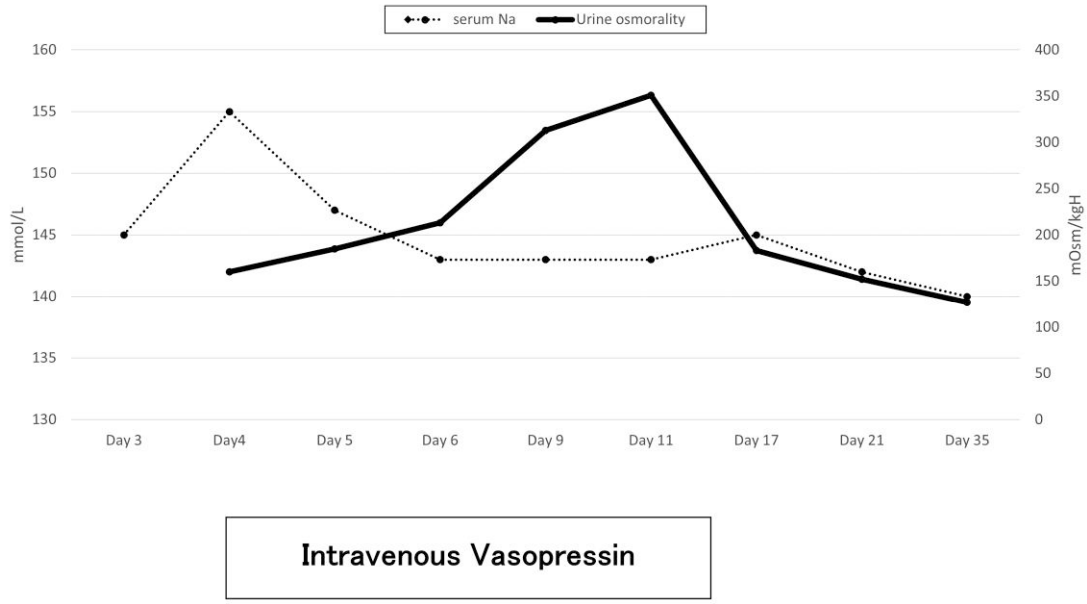

Figure 2. Laboratory changes associated with central diabetes insipidus throughout admission.

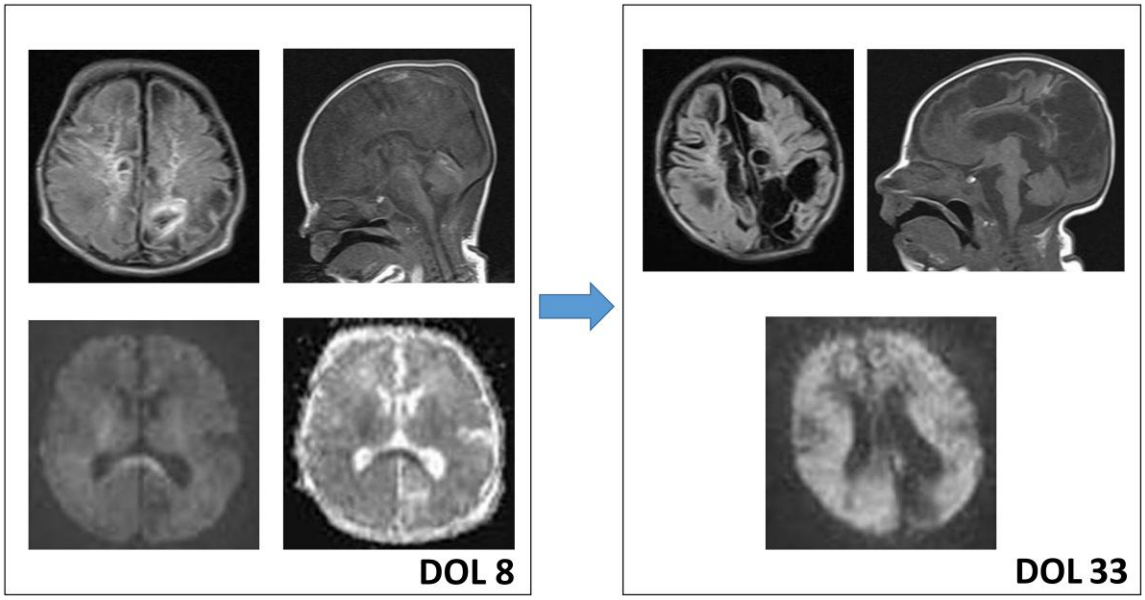

Figure 3. Brain magnetic resonance imaging showing bilateral encephalomalacia, minor bleeding, and changes characteristic of splenial lesions, indicating mild encephalitis/encephalopathy with a reversible splenial lesion but no sign of brain abscess, ventriculitis, or pituitary gland abnormality.

and magnetic resonance imaging [5]. The adrenal gland has a regenerative capacity, and neonatal AH is usually transient with complete resolution occurring spontaneously within 20 to 165 days. On the other hand, in the case of severe sepsis such as that leading to WFS, a lack of adrenocortical storage, immature hypothalamic-pituitary-adrenal axis function, cytokine-related suppression of ACTH, or cortisol synthesis may also contribute to the development of adrenal insufficiency. Once clinical conditions improve, hormone therapy should be suspended early to avoid impairment of the hypothalamic-pituitary-adrenal axis [9]. Abdominal US in the present patient revealed bilateral AH, with adrenal insufficiency diagnosed clinically based on laboratory data and an early response to glucocorticoid therapy. The present patient recovered from shock after a short course of hydrocortisone treatment, which allowed progressive treatment of hormone therapy after 3 days. Serial ultrasound scans showed that most lesions had regressed on DOL 8.

CDI in neonates is often caused by infections [8]. A review of CDI in neonates reported that only a few cases of CDI have been caused by *E. coli* infection [10]. Central nervous system infection results in generalized edema and inflammation of the posterior pituitary, followed by ischemia and infarction, leading to the disruption of AVP secretion [8, 10].

On the other hand, AVP secretion is normally inhibited by adrenal hormones through glucocorticoid receptors expressed on AVP neurons. When accompanied by adrenal insufficiency, AVP secretion by remaining arginine vasopressin neurons is stimulated in patients with CDI, resulting in decreased urine volume. This is called "masked DI," and glucocorticoid therapy in these patients could lead to increased urine volume.

In the neonatal intensive care unit settings, desmopressin can be administered intravenously, subcutaneously, and/or buccally, but only few studies of desmopressin therapy have been reported [8]. The present patient excreted large amounts of dilute urine and exhibited hypernatremia with hemodynamic instability on DOL 4. The 3-day lag between onset of meningitis and diagnosis of CDI could have been due to glucocorticoid treatment, which increases free water clearance and can unmask and/or exacerbate CDI by action via the activation of glucocorticoid receptors on AVP neurons. Intravenous vasopressin therapy was successful in this patient.

Learning Points

- WFS and CDI can occur as rare secondary complications of sepsis and meningitis following *E. coli* infection in neonates.
- Treatment with corticosteroids is appropriate when adrenal insufficiency is suspected.
- US may be useful for both early detection and follow-up evaluation.
- Early detection and appropriate treatment of both diseases are essential for improving outcomes.

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I certify that no other persons have made substantial contributions of the work. This study protocol was reviewed and approved by the Institutional Review Board of the Japanese Red Cross Wakayama Medical Center (No. 982).

Contributors

Shinsuke conceptualized the study, collected data, analyzed and interpreted data, drafted the initial manuscript, and critically reviewed and revised the manuscript. Koji, Takayuki, Yuka, and Shigeto collected data, drafted the initial manuscript, and reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Disclosures

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Informed Patient Consent for Publication

Signed informed consent obtained directly from the patient's relatives or guardians.

Data Availability Statement

The data that support the findings of this study are openly available.

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