Clinical Case Report

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Late-onset transient adrenal insufficiency in preterm twins with twin-to-twin transfusion syndrome

A case report

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Abstract

Rationale: Late-onset transient adrenal insufficiency with circulatory collapse is a rare condition that occurs in preterm infants. Although the incidence of late-onset transient adrenal insufficiency in preterm infants has been reported in Japan, reports from Western countries are lacking. In addition, no study has investigated the effect of twin-to-twin transfusion syndrome (TTTS) in monozygotic twins.

Patient concerns: A pair of extremely low birth weight twins presented with TTTS.

Diagnoses: Both twins developed late-onset adrenal insufficiency with oliguria, hypotension, hyponatremia, and pulmonary edema at a postnatal age of 24 days and 51 days, respectively.

Intervention: Temporary administration of intravenous hydrocortisone was initiated.

Outcomes: Their symptoms improved dramatically and they survived the event without any neurologic sequelae after 3 years of follow-up.

Lessons: Late-onset circulatory collapse may occur, especially in extremely preterm infants, even at 2 months after birth. Hydrocortisone therapy is an effective treatment to rescue circulatory collapse caused by adrenal insufficiency in preterm infants and may not affect long-term neuromotor and cognitive outcomes.

Abbreviations: ELBW = extremely low birth weight, GA = gestational age, HPA = hypothalamic-pituitary-adrenal, IVH = intraventricular hemorrhage, NEC = necrotizing enterocolitis, PDA = patent ductus arteriosus, PMA = postmenstrual age, PNA = postnatal age, RDS = respiratory distress syndrome, TTTS = twin-to-twin transfusion syndrome.

Keywords: hydrocortisone, hypotension, late-onset, preterm, transient adrenal insufficiency

1. Introduction

Transient adrenal insufficiency and the resulting devastating circulatory collapse has been reported in preterm infants.[1,2] Transient adrenal insufficiency has been observed in preterm infants within the first week of life and also at around 2 to 8 weeks. Two distinct groups of glucocorticoid-responsive transient adrenal insufficiency in preterm infants have thus been classified: early-onset and late-onset types.[3] The early-onset type occurs within the first week of life,[4] while the late-onset type occurs after the first week of life.[3,5–7]

In this study, we report late-onset adrenal insufficiency in a pair of extremely low birth weight (ELBW) monozygotic preterm twins with novel findings to any previously published case. These female monochorionic twins shared a common placenta with discordant body weights and suffered from twin-to-twin transfusion syndrome (TTTS). They were born to a healthy 28-year-old Taiwanese mother (G1P1). The mother received regular prenatal examinations at a local obstetrics hospital with an unremarkable course.

2. Case report

Ethical approval was granted for this case report by the Institutional Review Board of the E-Da hospital.

2.1. Case 1

Twin A had a gestational age of 24 weeks 2 days and a birth body weight of 552 g. She was born at home with spontaneous umbilical cord fracture. According to her mother, almost no amniotic fluid was noted at birth. Twin A suffered from general cyanosis, hypothermia, and weak spontaneous breathing with subcostal retraction on admission. She was the donor of TTTS because of oligohydramnios and smaller body weight than her sister. A chest X-ray revealed respiratory distress syndrome,

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Table 1

The characteristics of the twins.

Twin	GA	BW, g	Sex	Apgar at 1/5 min	CAM	PIH	Prenatal dexamethasone	Events before LCC onset	PMA/PNA at LCC onset	Data at LCC onset: Plasma ACTH, pg/mL	Data at LCC onset: Serum cortisol, μg/dL
A	24+2	552	F	unknown	No	No	No	RDS grade II-III, IVH grade II-III, PDA with heart failure, NEC grade I	27+5/24	43.06 pg/mL	1.3
B	24+4	750	F	3/6	No	No	6 mg	RDS grade II-III, IVH grade II, PDA with heart failure, NEC grade I, Pneumonia	31+6/51	Not measure	<1.0

ACTH = adrenocorticotropic hormone, CAM = chorioamnionitis, GA = gestational age, in wks + d, HC = intravenous hydrocortisone, IVH = intraventricular hemorrhage, LCC = late-onset of circulatory collapse, NEC = necrotizing enterocolitis, PDA = patent ductus arteriosus, PIH = pregnancy-induced hypertension, PMA = postmenstrual age, in wks + d, PNA = postnatal age, in d, RDS = respiratory distress syndrome.

grade II-III. Initial brain sonography revealed intraventricular hemorrhage (IVH), grade II-III with bilateral periventricular echogenicity. Patent ductus arteriosus (PDA) ligation was performed on day 12 after birth due to congestive heart failure and acute renal failure, after which her hemodynamic condition stabilized and we tapered down the use of dopamine.

However, intermittent hyponatremia and oliguria were still observed in the later life. Hypotension, pulmonary edema, increased oxygen demand, and metabolic acidosis were found when she was around 24 days old. We increased the dosage of dopamine, then added epinephrine and milrinone, but without success. Adrenal insufficiency with hypocortisolemia (1.3 μg/dL) was diagnosed after excluding other possible etiologies. We therefore initiated intravenous hydrocortisone therapy from a postmenstrual age (PMA) of 28 weeks 6 days, with an initial dose of 2.5 mg/kg/dose, every 12 hours. After hydrocortisone was given 2 hours, her blood pressure rapidly increased, accompanying with improved oliguria and hyponatremia. We then changed the frequency to every 6 hours for fewer fluctuations in urine output and blood pressure. The inotropic agent was discontinued at a PMA of 30 weeks 6 days, while hydrocortisone was tapered off successfully after 39 days of treatment (PMA of 34 weeks 2 days). The total dose of hydrocortisone was 39.9 mg (42.5 mg/kg) throughout the hospitalization course.

2.2. Case 2

Twin B, the recipient of TTTS, was delivered vaginally 2 days after twin A with a gestational age of 24 weeks 4 days and a birth body weight of 750 g. Four doses of antenatal steroids with dexamethasone were given to her mother. Prenatal sonography revealed polyhydramnios. Immediate resuscitation was performed due to respiratory failure, low APGAR score (3′–>6′), and hypotension. A chest x-ray revealed respiratory distress syndrome, grade II-III. Brain sonography revealed bilateral grade II IVH, and cardiac sonography showed PDA, with a medium-sized atrial septal defect, type II. Progressive heart failure with enlarged PDA was noted, so PDA ligation was arranged at a postnatal age of 10 days. Her vital signs improved after the surgery and we discontinued the inotropic agent.

Nevertheless, hypotension and oliguria were developed around a PMA of 28 weeks. Inotropic agents were prescribed but lack of response. She showed similar signs of adrenal insufficiency with her twin A sister, included hypotension, oliguria, pulmonary edema, and hyponatremia with a low serum cortisol concentration (<1.0 μg/dL). Therefore, intravenous hydrocortisone was administered at a PMA of 32 weeks 1 day, which resulted in a dramatic improvement in her blood pressure. Occasional rebound of hypotension and oliguria were observed when trying to taper down the hydrocortisone dosage. In total, twin B received 35.3 mg (23.7 mg/kg) of intravenous hydrocortisone over 22 days. The characteristics and treatment results of both twins are summarized in Tables 1 and 2.

3. Discussion

Late-onset transient adrenal insufficiency is a rare condition that occurs in preterm infants. It has been reported particularly in Japanese studies in recent years, but not in studies from Western countries. To the best of our knowledge, this is the first reported case of monozygotic twins with twin-to-twin transfusion who suffered late-onset adrenal insufficiency.

In this report, the pair of twins with ELBW and TTTS suffered from hypotension, oliguria, hyponatremia, pulmonary edema, and hypocortisolemia after a postnatal age of 3 weeks. They both had bilateral grade II IVH initially but did not develop periventricular leukomalacia, which is a common complication of late-onset adrenal insufficiency[5,6] in later life. Their neuromotor and cognitive function were also normal after 3 years of observation, which is compatible with the study of Nakanishi et al.[6] They also had common morbidities of prematurity, including respiratory distress syndrome, PDA, IVH, necrotizing enterocolitis, retinopathy of prematurity, and chronic lung disease compared with other cases in relevant studies.[4,7]

Table 2

Hydrocortisone therapy and outcomes of the twins.

Twin	PMA/PNA at LCC onset	Resolve age of LCC (PMA/PNA)	PDA ligation time (PMA/PNA)	Inotropic agents during LCC, duration	Duration of HC therapy for LCC	Initial HC dose, mg/kg/d	Recovery time after first HC dose, h	Total HC dose after diagnosis of LCC	PMA/PNA at discharge	Outcomes at 3-y follow-up
A	27+5/24	34+2/70	26+0/12	Dopamine, 22 d	39 d	2.5	4~6	39.9 mg (42.5 g/kg)	44+3/141	CKD, stage III, no PVL
B	31+6/51	35+1/74	26+0/10	Dopamine, 6 d	22 d	2.3	4~6	35.3 mg (23.7 mg/kg)	40+3/111	CKD, stage III, no PVL

CKD = chronic kidney disease, GA = gestational age, in wks + d, HC = intravenous hydrocortisone, LCC = late onset of circulatory collapse, PDA = patent ductus arteriosus, PMA = postmenstrual age, in wks + d, PNA = postnatal age, in d, PVL = periventricular leukomalacia.

However, stage III chronic kidney disease was diagnosed in both twins after 3 years follow-up, which has not been reported in previous studies.[3,4,7] This may have been due to TTTS and early acute kidney injury events.

Bourchier and Weston[4] defined the early onset of adrenal insufficiency in preterm infants as that occurring within the first week of life, with no disruption of clinically significant left to right shunt PDA. The underlying pathophysiology is related to the immaturity and maladaptation of the hypothalamic-pituitary-adrenal (HPA) axis to immediate postnatal life.[3,7–9] Ng et al[9] reported that early-onset adrenal insufficiency in premature infants is transient, and that most recover by day 14 of postnatal life. The late-onset circulatory collapse in preterm infants is thought to be due to a "relatively" low cortisol concentration status. This means that even though the cortisol level is within normal range according to the gestational age, it is inadequate to cope with stress in critically ill preterm infants.[7]

Although adrenal insufficiency of prematurity is usually transient and may recover following maturation of the adrenal glands and HPA axis within several weeks,[7–10] it requires emergency management due to potentially devastating circulatory collapse and the resulting risk of IVH, periventricular malacia, and poor neurodevelopmental outcomes.[4] The prompt administration of glucocorticoid supplements[11,12] instead of volume expansion or inotropic agents is suggested because this population has been shown to be refractory to such therapy.[7]

In the current study, late-onset adrenal insufficiency occurred at least 1 week after PDA ligation surgery in both twins. We treated hypotension if the mean arterial blood pressure in mm Hg was lower than the gestational age in weeks.[13] Both twins received inotropic support for the initial treatment of hypotension, but without success. Relative adrenal insufficiency was diagnosed later because of low plasma cortisol levels. They received an initial hydrocortisone dosage of 2.5 and 2.3 mg/kg/day, respectively, for a duration of 39 and 22 days, respectively. This result is compatible with a study from Japan, which also reported that preterm infants with late-onset adrenal insufficiency had a wide range in the duration of hydrocortisone therapy from 5 to 67 days (mean 23.8 days).[3] The mean blood pressure and urine output dramatically improved within a few hours after the administration of hydrocortisone, and remained mostly stable when we shortened the interval between hydrocortisone treatment to 6 hours with a lower dose, and even when the inotropic agents were tapered off in the following days. This outcome is similar to the other reports that treated refractory hypotensive neonates with corticosteroids.[11,12]

In conclusion, late-onset adrenal insufficiency occurs in the first few weeks of life cause acute circulatory failure in prematurity. Clinicians should be aware of unusually late-onset hypotension in an extremely preterm infant, even as long as 2 months after birth. Hydrocortisone therapy is an effective treatment to rescue circulation collapse and may not affect long-term neuromotor and cognitive outcomes. Nevertheless, chronic kidney disease was diagnosed in our twins in contrast to other studies on preterm twins or infants with transient adrenal insufficiency, which may have been a complication of TTTS and early acute kidney injury. Observational studies with a longer follow-up period are needed to delineate this new clinical entity and identify the long-term impact of hydrocortisone therapy on mental and physical development.

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