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Patient Report

Two preterm infants with late onset circulatory collapse induced by levothyroxine sodium

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Systemic hypotension in the postnatal period is associated with increasing mortality of preterm infants. Although several clinical aspects of developmental cardiovascular physiology explain some mechanisms of this phenomenon, the precise mechanism has not yet been elucidated.[1] Adrenal insufficiency is believed to be one of the causes of vasopressor-resistant hypotension occurring in the immediate postnatal period.[2,3] Two current randomized studies indicate that prophylactic therapy with glucocorticoids is effective for systemic hypotension in the early postnatal period[4,5] and this adrenal insufficiency is thought to be physiologically transient with recovery in the first week of life.[3]

In spite of these reports, some very-low-birthweight infants (VLBWI) manifest systemic hypotension two to four weeks after birth without any obvious causes such as infection, patent ductus arteriosus (PDA) or hypovolemia.[6,7] In such late-onset circulatory collapse, the mechanisms are not documented precisely yet. Empirical treatment with glucocorticoids is often performed[6] and recently it was reported that adrenal insufficiency might also have some role in the development of late-onset circulatory collapse.[7]

Here, we report two patients with late onset circulatory collapse immediately after administration of levothyroxine sodium (L-T4) for hypothyroidism. Although the hypotension was resistant to volume expansion therapy, inotropic agents and vasopressors, the glucocorticoid therapy improved blood pressure efficiently.

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Abbreviations: L-T4, levothyroxine sodium; TSH, thyroid stimulating hormone; VLBWI, very-low-birthweight infants; PDA, patent ductus arteriosus; HDC, hydrocortisone.

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Case Report

Case 1

Case 1 was a female infant born after 28 weeks 0 days of gestation, with a birthweight of 1076 g. Apgar scores were 7 and 9 at 1 and 5 min after birth, respectively. During pregnancy, no risk factors for congenital hypothyroidism were identified. Immediately after birth, the infant was treated in our neonatal intensive care unit (NICU). She was treated with the usual treatment for a VLBW infant including oxygen therapy without mechanical ventilation, infusion therapy, inotropic agent administration (5 μg/kg/min of dopamine), and antibiotics. Tube feeding of breast milk was started three days after birth. Except for continuous oxygen therapy (inspiratory oxygen fraction 0.25–0.3), all other interventions were ceased. We initiated erythromycin administration 13 days after birth, considering the possibility of chronic lung disease.

At the age of 11 days, her thyroid stimulating hormone (TSH) level was within the normal range on the neonatal mass-screening. However at the age of 26 days, she presented hypothyroidism (TSH: 83.41 μU/mL, free thyroxine [fT4]: 0.59 ng/dL) (Table 1) on the routine screening of our NICU. We then started L-T4 administration (6 μg/kg/day) by tube-feeding. After twelve hours of L-T4 treatment, she experienced apnea-bradycardia attacks, and sudden onset of hypotension, oliguria and hyponatremia (Na: 118 mEq/L; K: 5.82 mEq/L) (Table 2).

We immediately started intensive therapy with oxygen supplied by nasal-continuous positive airway pressure, infusion therapy, inotropic agents and diuretics. In spite of these therapies, she did not show sufficient improvement. Any underlying causes such as infections, PDA or hypovolemia were not documented. Considering the clinical course and the results of the examination, we suspected adrenal insufficiency and started hydrocortisone administration (HDC, 5 mg/kg/dose) via intravenous injection (Fig. 1a). Immediately after the HDC treatment, the patient's blood pressure and respiratory condition improved and the electrolytes imbalance was corrected.

Table 1 Endocrinological data of the two patients on neonatal mass screening. In both cases, TSH increased compared to the first result and the levels of fT4 were below the normal range

		Case 1		Case 2	
		Day 11	Day 26	Day 17	Day 19
TSH	(μU/mL)	10.29	83.41	75.2	311.9
fT4	(ng/dL)		0.59		0.04
17-OHP	(ng/ml)	0.36		24.01	

fT4, free thyroxine; 17-OHP, 17-hydroxyprogesterone; TSH, thyroid stimulating hormone.

Thereafter, her clinical course was satisfactory without any abnormal findings on brain magnetic resonance imaging, including the pituitary gland. At present, she is one and a half years old, and thus far, no abnormality has been observed in her development or growth. The thyroid function is within the normal range (TSH: 2.09 μU/mL, fT4: 1.62 ng/dL, fT3: 4.60 pg/mL) by administration of L-T4 (25 μg/day).

Case 2

Case 2 was a female infant born after 24 weeks and 5 days of gestation. Her birthweight was 774 g and Apgar scores were 6 and 8 at 1 and 5 min after birth, respectively. During pregnancy, no risk factors for congenital hypothyroidism were identified. Immediately after her birth, she was admitted to our NICU. We treated her with our routine intensive therapy regimen including mechanical ventilation with surfactant therapy, infusion therapy, antibiotics and glucose insulin therapy. Indomethacin was also given for her PDA due to prematurity. The clinical course was satisfactory and she was allowed to have breast milk 5 days after birth. In spite of her stable clinical condition, oxygen administration was necessary (inspiratory oxygen fraction 0.4–0.5 on mechanical ventilation). We suspected chronic lung disease, and started erythromycin administration at 10 days after birth. Except for these treatments, we were able to cease other therapies.

At the age of 17 days her TSH level was elevated (TSH: 75.2 μU/mL) on the neonatal mass-screening (Table 1). We re-examined her thyroid function 19 days after birth. The level of TSH was remarkably elevated (TSH: 311.9 μU/mL, fT4: 0.04 ng/dL) (Table 1) and L-T4 administration (8 μg/kg/day) was started.

Twenty-four hours after the initiation of L-T4, she developed hypotension, oliguria, hyponatremia and hyperkalemia (Na: 117 mEq/L; K: 7.58 mEq/L) (Table 2). We treated her with oxygen (inspiratory fraction 0.7–1.0 supported mechanical ventilation), infusion therapy, cardiotropic agents (dopamine and dobutamine: =<13 μg/kg/min) and diuretics. In spite of these therapies, her clinical condition did not show any remarkable improvement. We could not detect any underlying causes of the circulatory collapse. As in case 1, we suspected adrenal insufficiency, and initiated hydrocortisone administration (5 mg/kg/dose). Her clinical condition remarkably improved and all signs and symptoms disappeared (Fig. 1b). At present, she is six months old and has normal development and growth. The thyroid function is within the normal range (TSH: 3.20 μU/mL, fT4: 1.25 ng/dL, fT3: 3.56 pg/mL) by administration of L-T4 (6 μg/kg/day).

In both cases, any signs and symptoms that indicate hypothyroidism were not observed before the L-T4 treatment. Glucocorticoids were not given to the mothers during pregnancy or the patients before the onset of the circulatory collapse. There were no exposures to excess iodine such as repeated topical treatment of povidone-iodine antiseptic solutions.

Discussion

We should consider some clinical points from our experience. First, late onset circulatory collapse due to adrenal insufficiency should be considered even in patients who have not shown any signs or symptoms of adrenal insufficiency in their first two weeks of life. Second, thyroid hormone replacement therapy precipitates adrenal insufficiency and when initiating the treatment, we should take great care to monitor closely for the development of adrenal insufficiency.

Hypothyroidism often masks adrenal insufficiency, and L-T4 supplementation precipitates the adrenal insufficiency.[8] It is believed that thyroxin increases the clearance of cortisol,[9] and in

Table 2 Clinical data before and after the onset of circulatory collapse. In addition to hypotension and hyponatremia, metabolic acidosis and hyperkalemia were also observed

		Case 1		Case 2	
		Day 28	Day 29	Day 19	Day 21
CRP	(mg/dL)	<0.3	<0.3	<0.3	<0.3
WBC	(/μL)	–	–	22 810	23 400
pH		7.375	7.299	7.300	7.204
pCO_2	(Torr)	45.6	39.2	44.6	53.2
HCO_3^-	(mmol/L)	26.1	18.8	21.5	20.5
BE	(mmol/L)	0.4	−7.0	−4.9	−7.9
Na	(mEq/L)	133	118	127	117
K	(mEq/L)	5.68	5.82	4.88	7.58
Urine Volume	(mL/kg/hr)	3.0	0.08	2.0	0.00
FiO_2		0.24	0.26	0.60	1.0

BE, base excess; CRP, C-reactive protein; FiO_2, fraction of inspired oxygen; HCO_3^-, bicarbonate; pCO_2, carbon dioxide partial pressure; WBC, white blood cells.

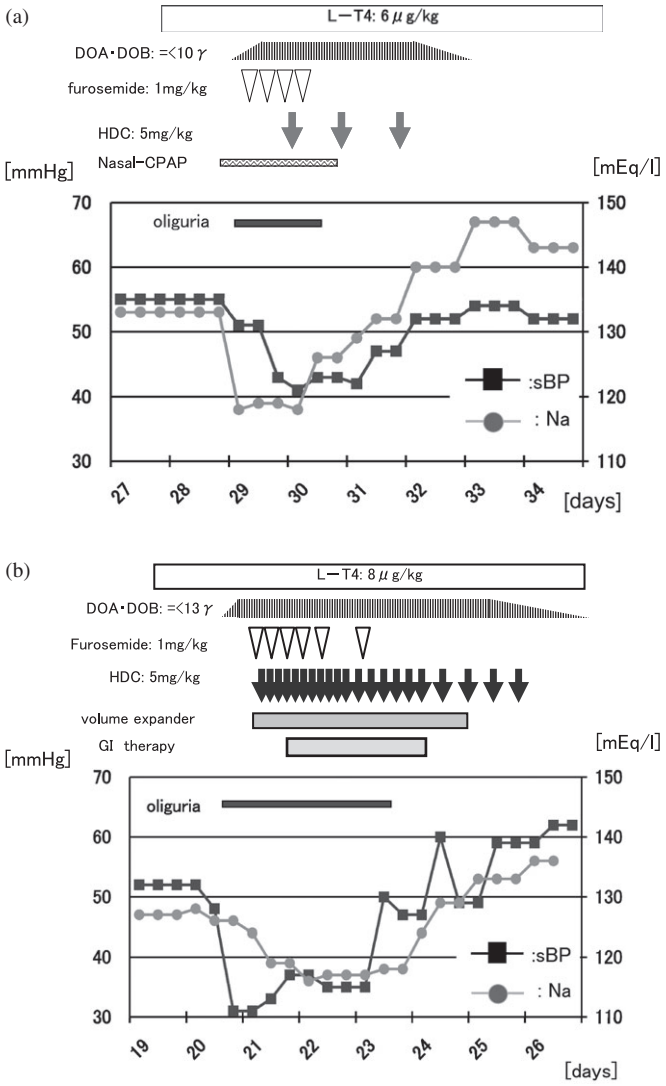

Fig. 1 The clinical courses of (a) Case 1 and (b) Case 2. Immediately after the initiation of levothyroxine sodium (L-T4), hypotension and hyponatremia appeared. These clinical symptoms and signs were promptly corrected with hydrocortisone (HDC) treatment. CPAP, continuous positive airway pressure; DOA, dopamine; DOB, dobutamine; GI, glucose insulin infusion; sBP, systolic blood pressure.

order to avoid adrenal crisis, glucocorticoid administration prior to thyroxin administration is recommended in patients suspected to have both hypothyroidism and adrenal insufficiency. Although we could not obtain precise endocrinological data of our patients during circulatory collapse due to severe illness, the clinical courses strongly suggest that the sudden onset of systemic hypotension in both patients was caused by adrenal insufficiency precipitated by administration of L-T4.

In preterm infants, physiological transient adrenal insufficiency is documented in the immediate postnatal period.[3,10] This adrenal insufficiency may recover during in the second week of their life[3] and is thought to be one of the major factors responsible for hypotension in the early postnatal period. Adrenal shock is vasopressor-resistant and two recent randomized control studies recommend glucocorticoid therapy for the treatment of refractory or pressor-resistant hypotension in their first week of life.[4,5] In general, transient adrenal insufficiency is thought to be caused by immature function of the hypothalamus-pituitary-adrenal axis.[2,3]

In comparison with early-onset hypotension, less attention has been paid to late-onset systemic hypotension. A recent Japanese nationwide surveillance reported that about 4% of VLBWI were treated with glucocorticoid because of late-onset systemic hypotension.[6] Although there are no apparent endocrinological data that indicate adrenal insufficiency,[7] some authors have suggested that transient adrenal insufficiency could be prolonged and might occasionally result in late-onset vasopressor-resistant systemic hypotension.[3,10] These data suggest that late-onset circulatory systemic hypotension induced by adrenal insufficiency is more common than previously believed. From our experience, we should consider adrenal insufficiency as the cause of systemic hypotension in preterm infants at any period, especially those who do not show any signs or symptoms of adrenal insufficiency during the first two weeks of life.

It is a difficult problem how to predict and prevent this kind of circulatory collapse precipitated by L-T4 administration. Prophylactic treatment with glucocorticoid could be one option to prevent adrenal insufficiency prompted by L-T4 administration. However, in the prophylactic treatment, the side-effects of glucocorticoid should be considered. Besides the usual side-effects of glucocorticoid, we should consider the particulars of preterm infants, e.g. the effect on neurological development, growth and other serious complications such as intestinal perforation. Facile treatment with glucocorticoids is still cautioned by the recent reports.[11,12] In contrast to the immediate postnatal period, adrenal insufficiency is estimated to be relatively uncommon in the late postnatal period.[7] Therefore, prophylactic treatment during the late postnatal period will likely result in the treatment of patients with normal adrenal function.

Here we have reported two preterm infants with late onset of circulatory collapse induced by L-T4 administration for the treatment of hypothyroidism. When initiating L-T4, we should consider the possibility of subclinical adrenal insufficiency. Adrenal insufficiency has a sudden onset and does not have any specific signs or symptoms. Therefore careful observation is necessary. The mechanisms and the effective treatment are not yet determined and further research including prospective clinical trials are necessary in order to determine the best method for preventing and treating adrenal insufficiency in the late postnatal period.

References

1 Noori S, Friedlich P, Seri I. *Fetal and Neonatal Physiology*, 3rd edn. Saunders, Philadelphia, 2003.
2 Helbock HJ, Insoft RM, Conte FA. Glucocorticoid-responsive hypotension in extremely low birth weight newborns. *Pediatrics* 1993; **92**: 715–7.
3 Ng PC, Lee CH, Lam CW *et al.* Transient adrenocortical insufficiency of prematurity and systemic hypotension in very low birthweight infants. *Arch. Dis. Child. Fetal Neonatal Ed.* 2004; **89**: F119–26.
4 Efird MM, Heerens AT, Gordon PV, Bose CL, Young DA. A randomized-controlled trial of prophylactic hydrocortisone supple-

mentation for the prevention of hypotension in extremely low birth weight infants. *J. Perinatol.* 2005; **25**: 119–24.
5 Ng PC, Lee CH, Bnur FL *et al.* A double-blind, randomized, controlled study of a ″stress dose″ of hydrocortisone for rescue treatment of refractory hypotension in preterm infants. *Pediatrics* 2006; **117**: 367–75.
6 Kusuda S, Fujimura M, Sakuma I *et al.* Morbidity and mortality of infants with very low birth weight in Japan: center variation. *Pediatrics* 2006; **118**, e1130–8.
7 Masumoto K, Kusuda S, Aoyagi H *et al.* Comparison of serum cortisol concentrations in preterm infants with or without late-onset circulatory collapse due to adrenal insufficiency of prematurity. *Pediatr. Res.* 2008; **63**, 686–90.
8 Fonseca V, Brown R, Hochhauser D, Ginsburg J, Havard CW. Acute adrenal crisis precipitated by thyroxine. *Br. Med. J. (Clin. Res. Ed.)* 1986; **292**: 1185–6.
9 Martin MM, Mintz DH. Effect of altered thyroid function upon adrenocortical acth and methopyrapone (su-4885) responsiveness in man. *J. Clin. Endocrinol. Metab.* 1965; **25**: 20–7.
10 Watterberg KL, Gerdes JS, Cook KL. Impaired glucocorticoid synthesis in premature infants developing chronic lung disease. *Pediatr. Res.* 2001; **50**: 190–5.
11 Stark AR, Carlo WA, Tyson JE *et al.* Adverse effects of early dexamethasone in extremely-low-birth-weight infants. National Institute of Child Health and Human Development Neonatal Research Network. *N. Engl. J. Med.* 2001; **344**: 95–101.
12 Yeh TF, Lin YJ, Lin HC *et al.* Outcomes at school age after postnatal dexamethasone therapy for lung disease of prematurity. *N. Engl. J. Med.* 2004; **350**: 1304–13.