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NOTE

The occurrence of neonatal acute respiratory disorders in 21-hydroxylase deficiency

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Abstract. Patients with 21-hydroxyase deficiency (21-OHD) usually do not present clinical symptoms other than female ambiguous genitalia and skin pigmentation at birth. However, we have found a case of neonatal transient tachypnea with spontaneous pneumomediastinum in a neonate with 21-OHD at birth. The purpose of this study was to investigate the occurrence of neonatal respiratory disorders in 21-OHD patients. From April 1989 to March 2009, 478,337 Japanese newborns were screened for congenital adrenal hyperplasia in Niigata prefecture. Among these newborns, 26 patients were diagnosed as having 21-OHD. We investigated the presence of neonatal respiratory disorders based on the retrospective medical records of 24 full-term patients with 21-OHD. Three of the 24 patients (12.5%) had neonatal acute respiratory disorders. Neonatal transient tachypnea developed in all patients with only oxygenation for two or three days after birth. Chest X-rays showed spontaneous pneumothorax or pneumomediastinum in two patients. In conclusion, 21-OHD patients may present with acute respiratory disorders, especially transient tachypnea with spontaneous pneumothorax, at birth. In cases of delivering mothers having other children with 21-OHD, newborns require attention regarding neonatal respiratory disorders if a prenatal diagnosis has not been performed.

Key words: 21-hydroxylase deficiency, Congenital adrenal hyperplasia, Neonatal respiratory disorders, Pneumothorax

CONGENITAL adrenal hyperplasia (CAH) is one of the most common inherited metabolic diseases and is characterized by impaired activity of one of the enzymes required for cortisol biosynthesis. Steroid 21-hydroxylase deficiency (21-OHD) is an autosomal recessive disorder that accounts for 90–95% of CAH cases [1]. A nationwide newborn screening program for CAH due to 21-OHD has been carried out in Japan since 1989 [2]. Most female patients are discovered because of ambiguous genitalia and skin pigmentation. On the other hand, male patients are discovered due to salt wasting symptoms such as vomiting, and poor weight gain one week after birth. Alternatively, they can be discovered by newborn screening due to having high levels of 17-hydroxyprogesterone (17-OHP) while being asymptomatic. Symptoms other than ambiguous genitalia and skin pigmentation usually do not present at birth. However, we have found a case of neonatal transient tachypnea with spontaneous pneumomediastinum in a full-term newborn with 21-OHD at birth. The purpose of this study was to investigate the occurrence of neonatal acute respiratory disorders (NARD) patients with 21-OHD.

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Patients and Methods

Patient

The patient (Case 3 in Table 1) was the second child of Japanese non-consanguineous parents. His elder brother was followed as having 21-OHD (salt wasting form) in our hospital. He was found to be homozygous for the Q318X mutation of the *CYP21A2* gene. His mother conceived the second child, but a prenatal diag-

Table 1 21-hydroxylase deficiency with neonatal acute respiratory disorders

	Case 1	Case 2	Case 3
CAH clinical forms	SW	SV	SW
Gestational age	41 weeks	38 weeks	41 weeks
Sex	Female	Female	Male
Apgar score at 1 min	8	9	8
Age at onset	at birth	at birth	at birth
Respiratory symptoms	tachypnea, expiratory grunting	tachypnea	tachypnea, retraction
Chest X ray	normal	pneumothorax	pneumomediastinum
Primary respiratory disorders	transient tachypnea	transient tachypnea	transient tachypnea
Treatment	oxygen	oxygen	oxygen
Recovery day	1 day	3 days	2 days

CAH, congenital adrenal hyperplasia; SW, salt-wasting form; SV, simple virilizing form

nosis was not performed. The patient was born at 41 weeks of gestation by uncomplicated vaginal delivery with a birth weight of 2906 g (-1.1 SD) and his Apgar scores were 8 at 1 minute. The patient did not require use of the positive pressure in the delivery room. At birth, skin pigmentation, tachypnea and retraction of the chest wall were evident, and he was admitted to the neonatal intensive care unit. A chest X-ray revealed pneumomediastinum (Fig. 1), and he was treated with 30% oxygen supplementation at neonatal incubator. In the next 2 days, his respiratory status improved, and his pneumomediastinum was also spontaneously resolved. Endocrine investigation revealed high levels of 17-OHP on filter paper (90 ng/mL; references <2), and he was also diagnosed as having 21-OHD and started hydrocortisone replacement at 3 days of age. His electrolytes were within normal range. He has had no further respiratory symptoms.

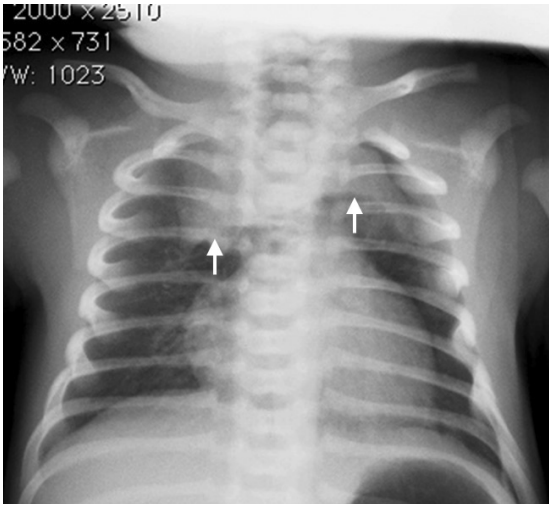

Fig. 1 Pneumomediastinum at chest X-ray
The arrows indicate a thymus lifted by free air, and a so-called angel wing sign.

Subjects and Methods

From April 1989 to March 2009 there were 478,337 Japanese newborns screened for congenital adrenal hyperplasia in Niigata prefecture. Among these newborns, 242 were positively screened patients. On further endocrinological examinations, 26 patients (an incidence of about 1 in 18,000) were diagnosed as having 21-OHD during that period. The salt-wasting form (SW) was diagnosed in 18 patients (11 males), the simple virilizing form (SV) in 7 patients (5 males), and the non-classical form in 1 patient. The primary endocrinologists (K.N., T.A., Y.A., T.K.) based their diagnoses of the SW and SV forms on the presence or absence of electrolyte abnormalities and hormonal data. All patients, except two born at 33 and 36 weeks of gestation, were term infants. We investigated the presence of NARD based on the retrospective medical records of 24 full-term patients with 21-OHD. NARD was defined as patients having at least one of the following respiratory abnormalities: tachypnea, central cyanosis in room air, retraction of the chest wall, nasal alar breathing, expiratory grunting or respiratory sound abnormality, with oxygen demand or neonatal incubator care during their first 3 days of age. This definition was entirely based on clinical observation irrespective of the etiology of respiratory disorders. Neonates who received assisted mechanical ventilation immediately after birth due to insufficient breathing before show-

ing clinical signs were also included. This research obtained the approval of the Niigata University School of Medicine Ethical Review Board.

Results

Three of the 24 patients (12.5%) had NARD. Neonatal transient tachypnea developed in all three patients; two of those patients had spontaneous pneumothorax or pneumomediastinum. No patients showed respiratory distress syndrome, meconium aspiration syndrome and pulmonary infection. Clinical features of the three patients are summarized in Table 1. Two patients had the SW form of 21-OHD and one patient had the SV form. All three patients presented with NARD at birth or soon thereafter. All patients recovered within a few days with only oxygenation support before hydrocortisone replacement therapy.

Discussion

As a complication in patients with 21-OHD at birth, 3 of the 24 full-term patients (12.5%) presented with NARD. Two patients (8.3%) showed spontaneous pneumothorax and pneumomediastnum. There are no previous reports about NARD in 21-OHD patients or any types of CAH. However, full-term infants with congenital adrenal hypoplasia have been reported to have developed NARD [3, 4]. In the general population, the incidence of NARD is 1.08% [5], and 2.8% [6] in all live-born infants. Rubaltelli *et al* [6] also reported that the incidence of NARD was 0.61% at a gestational age of 36 weeks or more. Also, the incidence of symptomatic spontaneous pneumothorax has been reported to be 0.08% of live births in another clinical report [7]. One limitation of this study is that we do not have data for the incidence of NARD in our regional area. However, it seems that there are many NARD and spontaneous pneumothorax in the term infant with 21-OHD patients in comparison with the past report.

Previous studies have shown that endogenous glucocorticoids play an important role in the development of the lungs and in lung repair [8, 9]. Very preterm infants who developed bronchopulmonary dysplasia have a blunted response to the ACTH stimulation test in the first week of life [8]. This provides evidence that these infants are less capable of releasing cortisol in response to stress, resulting in a relative adrenal insufficiency [8]. 21-OHD patients have a relative endogenous glucocorticoid deficiency due to the insufficient synthesis of glucocorticoid. Furthermore an increase of the placental estrogens produced from excessive DHEA-S derived from a 21-OHD fetus leads to increased conversion of active cortisol to inactive cortisone through the acceleration of 11β-hydroxysteroid dehydrogenase activity [10]. Therefore we supposed that neonates with 21-OHD have delayed pulmonary maturation compared with normal neonates. Furthermore, insufficient endogenous glucocorticoid production for the serious stressful situation of delivery may lead to transient tachypnea and result in air leak syndrome. If glucocorticoid deficiency is a main factor, similar symptoms should appear in patients with congenital lipoid CAH, which is a severe form of CAH. However, no such case has been reported. Only StAR knockout mice showed signs of either respiratory distress or volume depletion after birth and eventually died [11]. An increase of the placental estrogens produced from excessive DHEA-S may be a main factor, but the precise mechanism is not understood. Further consideration is necessary regarding the association between 21-OHD and NARD.

Regarding treatment, NARD was not serious and was resolved with only a few days of oxygenation therapy before beginning hydrocortisone replacement therapy for 21-OHD. This showed that the relative glucocorticoid deficiency during the stressful situation of delivery was transitory. However, the reason for the mild clinical phenotype of NARD in 21-OHD patients is unknown. Further extensive study is necessary to investigate whether there is a significant occurrence, and clinical phenotype of NARD among 21-OHD patients at birth.

In conclusion, 21-OHD patients may present with NARD, especially transient tachypnea with spontaneous air leak syndrome, at birth. In the cases of delivering mothers having other children with 21-OHD, newborns require careful attention regarding neonatal respiratory disorders if a prenatal diagnosis has not been performed.

Conflict of Interest

The authors declare no conflict of interest.

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