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Letter to the Editor

Low-birth-weight infant with Antley-Bixler syndrome-like phenotype caused by POR mutation: a rare case report

Dear Editor,

Antley-Bixler syndrome (ABS) is a rare congenital disorder in which patients present with specific facial features and skeletal dysplasia[1]. A subgroup of patients with ABS-like phenotype (Antley-Bixler syndrome type 2) exhibit abnormal external congenital anomalies and steroid production disorder[2]. Recently, it has been found that the cause of these features is a loss-of-function mutation in the P450 oxidoreductase (POR) gene[3], which has significantly changed the disease concept. Herein, we report the case of an infant with ABS-like phenotype with extremely low birth weight who was diagnosed based on POR genetic analysis results.

The patient was the second girl of a pair of twins born via cesarean section at 34 weeks of gestation. She was admitted to our neonatal intensive care unit. The girl had intrauterine growth retardation with a birth weight of 1,018 g, and 1- and 5-min Apgar scores of 1 and 6 points, respectively. Her mother did not show any signs of virilization during pregnancy. Post-delivery, the coronal sutures on the patient's forehead were fused. The shape of her cranial skull exhibited a diamond shape because of increased head circumference with a small jaw. Hypoplasia was observed in the center of her face. In both the ears, closure of the ear canal, hypoplasia, and accessory ears were observed. Regarding the limbs, the humerus was fused; the patient exhibited spider-like fingers, and the second toes of both the feet were long. The vulva showed an enlarged clitoris and fusion of the labia minora. In addition, multiple joint contractures were observed (Figure 1). Postnatal blood examination did not show any notable abnormalities. Considering the low birth weight of the neonate, an endocrinological examination was performed; it revealed that 17-hydroxyprogesterone (17-OHP), cortisol, and adrenocorticotropic levels were all within the normal range. No abnormalities were detected on mass screening of inborn errors specific to the metabolism of the Japanese. The G-banding chromosome analysis revealed a normal female karyotype. The patient's clinical course often necessitated respiratory management with nasal continuous positive airway pressure because of respiratory disorders caused by the stenosis of the entire nasal cavity and subsidence of the tongue base. Oral intake was difficult because of micrognathia; thus, tube feeding was performed. Moreover, there were no signs of adrenal insufficiency, such as hypoglycemia, electrolyte abnormalities, and decreased blood pressure; therefore, no corticosteroid supplement was required at that time.

We suspected ABS on the basis of gross external malformations in the infant. We performed a urine steroid profile analysis and genetic testing after obtaining informed consent from the infant's parents. The urine steroid profile analysis revealed high levels of some urinary metabolites including pregnenolone, progesterone, 17-OHP, and 21-deoxycortisol. Conversely, dehydroepiandrosterone, androstenedione, and 11β-hydroxyandrostenedione levels were decreased; these results suggested a decreased activity of several P450 enzymes.

The genetic testing was focused on the POR gene. An analysis of the POR gene exons showed a guanine-to-adenine substitution in exon 11. Based on this base substitution, a missense mutation (R457H) in which the arginine at position 457 was replaced by histidine that was identified heterozygously; no R457H mutation was detected in the other allele (Figure 2).

Later, at 3 months after birth, the child was transferred to another general hospital. A few days later, she developed a fever and a blood test was performed, revealing the presence of marked hyponatremia (118 mEq/L). Since clinical adrenal insufficiency could not be ruled out, electrolyte replacement by infusion and corticosteroid replacement were per-

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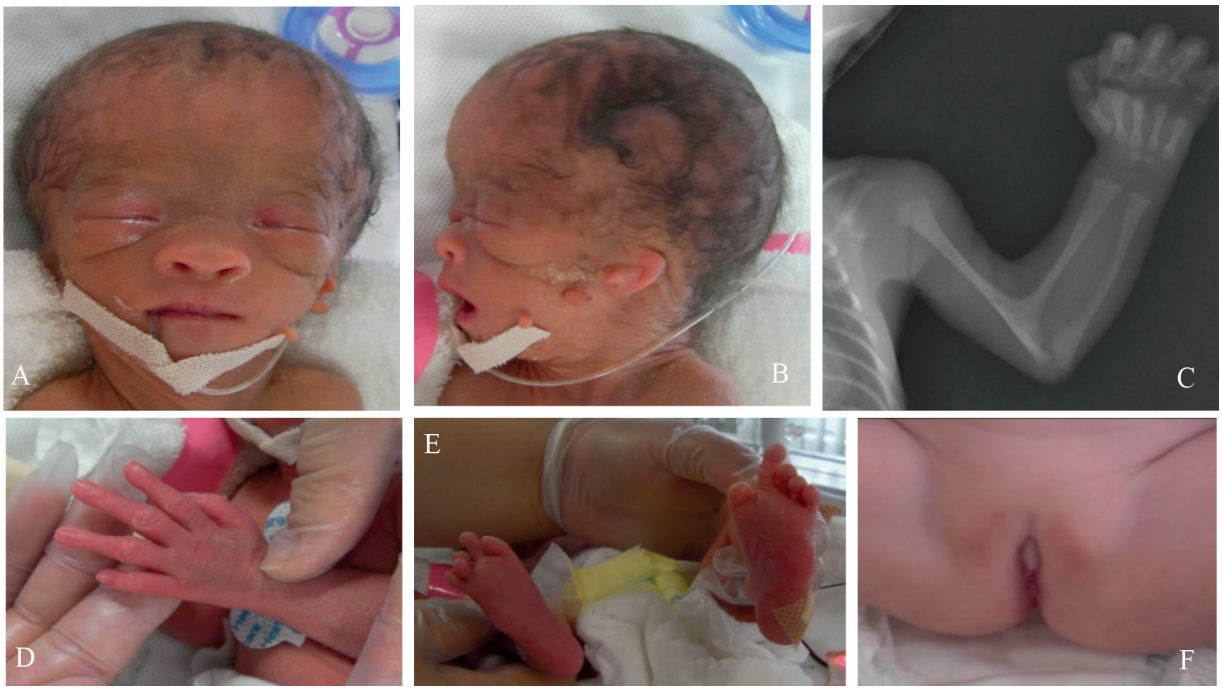

Figure 1. General appearance of the congenital external abnormalities of the patient. **A/B,** Diamond-shaped cranial skull anomaly caused by an increase in the circumference of the head and presence of a small jaw. **C,** A fusion anomaly of the humerus and joint contracture of the elbow were recognized in the left upper arm. **D,** Spider-like finger malformations. **E,** Long toes. **F,** Genital fusion abnormality.

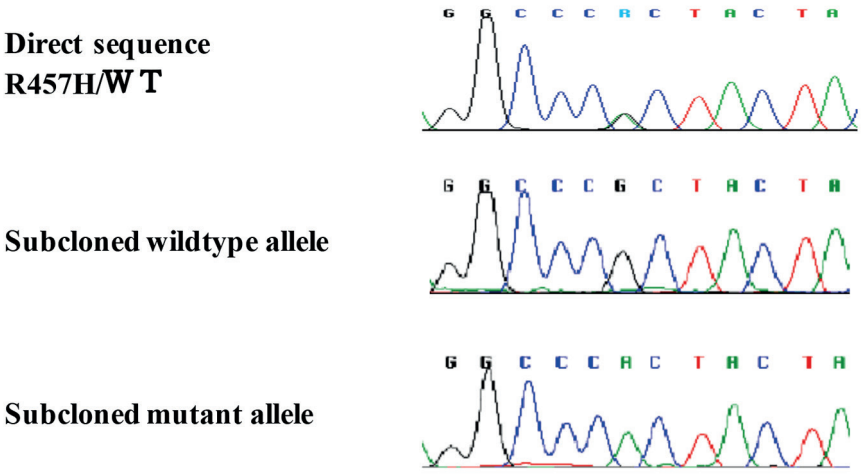

Figure 2. Genetic testing for the *POR* gene.

formed. First, as an initial treatment, hydrocortisone was intravenously injected at 10 mg/kg. Next, hydrocortisone was intravenously injected at 15 mg/kg/day in three divided doses over 2 days. Thereafter, her hyponatremia promptly improved. Currently, approximately 7 months after birth, she does not need corticosteroid supplementation, and her general condition is stable.

Herein, we reported a case of ABC-like phenotype, a rare autosomal recessive congenital malformation syndrome. ABS syndrome is characterized by early skull fusion, bone and joint symptoms in the limbs, and abnormalities in the external genitalia. According

to the causative gene-based classification, the type of ABS in which patients present with steroid production disorder and external genital abnormalities, i.e., ABS-like phenotype presence, is considered to be caused by POR gene mutation, whereas the type in which patients do not exhibit the above presentations is considered to be caused by FGFR2 gene mutation[4,5]; i.e., ABS and POR disorder (PORD) clinically overlap. The major cause of PORD is the loss of multiple POR-dependent enzyme activities because of POR gene loss-of-function mutations[6]. Therefore, the symptoms of bone dysgenesis, complex adrenal steroid profile production, and external genital abnormalities observed in the present case of ABS were deemed symptoms of PORD-overlapping ABS. In the treatment of PORD, respiratory management is critical in the neonatal period and hormone replacement therapy and rehabilitation are required during infancy. With the exception of severe cases, the life and intellectual prognoses range from moderate to good[7] and several cases of low-birth-weight infants have been reported. Occasionally, sudden death occurs in patients with PORD, possibly because of adrenal insufficiency[8]. Our patient also developed sudden hyponatremia associated with infection, but steroid replacement therapy promptly improved the symptoms. Such patients may suffer from adrenal insufficiency during several types of stress, such as infection and surgery; therefore, physicians should be aware of a risk of metabolic stress-like symptoms in the daily management of such ABS-like phenotype.

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Conflict of Interest

The Authors declare that they have no conflict of interests.

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