증 례

지속된 황달로 내원한 21-수산화효소 결핍증 남아 증례

[1]한림대학교 의과대학 한림대학교성심병원 소아청소년과
[2]울산대학교 의과대학 서울아산병원 의학유전학센터

곽민욱[1] · 이예나[1] · 김구환[2] · 강민재[1]

A Male Neonate with Prolonged Jaundice Secondary to 21-hydroxylase Deficiency

Min Woog Kwag, MD[1], Yena Lee, MD, PhD[1],
Gu-Hwan Kim, PhD[2], Min Jae Kang, MD, PhD[1]

[1]Department of Pediatrics, Hallym University Sacred Heart Hospital, Hallym University College of Medicine, Anyang, Republic of Korea
[2]Medical Genetics Center, Asan Medical Center Children's Hospital, University of Ulsan College of Medicine, Seoul, Republic of Korea

Congenital adrenal hyperplasia (CAH) is a genetic disorder characterized by decreased cortisol secretion, with 21-hydroxylase deficiency being the most common type. It is uncommon for CAH to present primarily as cholestasis; therefore, when a patient presents with prolonged jaundice, it is difficult to suspect CAH immediately. In this report, we aim to share our experience with an exceptional case of 21-hydroxylase deficiency. A 28-day-old male visited the outpatient clinic due to prolonged jaundice and elevated 17α-hydroxyprogesterone (17-OHP) levels in the newborn screening test. Since he showed no other symptoms such as lethargy or vomiting, he underwent a routine blood test for jaundice and a retest of 17-OHP at the outpatient clinic. Two hours after the blood draw, he was found to have severe hyponatremia and hyperkalemia, so he was immediately admitted to the intensive care unit. After treatment with hydrocortisone, fludrocortisone, sodium chloride, and intravenous fluids, the cholestasis and electrolyte imbalances improved over time. He was diagnosed with 21-hydroxylase deficiency, salt-wasting type, which was confirmed by the ACTH stimulation test and genetic testing. It is important to make a prompt diagnosis of CAH to avoid missing critical timing. Therefore, CAH should not be overlooked, even if the patient does not exhibit typical symptoms.

Key words: Neonatal jaundice, Congenital adrenal hyperplasia, 21-hydroxylase deficiency

Introduction

Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder resulting from defects in the adrenal steroidogenesis pathway. Patients with CAH have impaired synthesis of mineralocorticoids and glucocorticoids. As a result, the excessive production of ACTH leads to secondary adrenal hyperplasia. The most common type of CAH is the 21-hydroxylase deficiency, accounting for 95% of cases[1]. This occurs due to pathogenic mutations in the *CYP21A2* gene

Corresponding: Min Jae Kang, MD, PhD
Department of Pediatrics, Hallym University College of Medicine, 1 Hallymdaehak-gil, Chuncheon-si, Gangwon-do, 24252, Korea
Tel: +82-31-380-3730, Fax: +82-31-380-1900
E-mail: mjkang@hallym.or.kr
ORCID: https://orcid.org/0000-0003-3080-0941

and can be further classified into salt-wasting (SW) or simple virilizing (SV) types, known as classic CAH.

CAH patients show diverse spectrums of phenotypes according to the severity of the enzyme defect in the synthesis of cortisol and aldosterone. Patients with 21-hydroxylase deficiency may present with hypotension, lethargy, vomiting, and hypoglycemia. Additionally, the levels of androgens remain high, leading to virilization in girls and precocious puberty in boys[1,2]. When early identification and treatment of 21-hydroxylase deficiency are not properly managed, patients with the SW type can experience life-threatening adrenal crises during the first weeks of life. Therefore, many countries have implemented a screening program for CAH in the newborn period[3].

21-hydroxylase deficiency is a well-known disease with a genotype-phenotype correlation[4,5]. Genetic testing helps to identify the type of 21-hydroxylase deficiency. Some mutations, such as V281L, deletion at exon 3 and exon 6, Q318X, and R356W, have a high genotype-phenotype concordance[5]. However, there are some mutations, such as P30L, I172N, and I2G, which do not have a good genotype-phenotype correlation, and genetic testing takes time to get the results. Therefore, clinical symptoms and newborn screening results are important clues to avoid missing the critical treatment window.

Here, we present a patient with prolonged jaundice and elevated 17-hydroxyprogesterone (17-OHP) in a newborn screening test (NST) at the outpatient clinic. Because he had no other symptoms related to adrenal crisis, we initially expected him to have SV-type 21-hydroxylase deficiency. However, he revealed typical laboratory features of SW-type, which was later confirmed by genetic testing.

Case report

A 28-day-old male neonate visited the outpatient clinic due to persistent jaundice and elevated 17-OHP levels in the NST. The baby was born by cesarean section from a healthy mother without any underlying disease, at GA 37^{+1} weeks, weighing 2.71 kg (10th-50 th percentile). The prenatal examination was normal, but premature placental abruption resulted in a cesarean section. There were no perinatal problems, and he was normally discharged after one week of nursery care as planned. He had no jaundice during the first week after birth. He was vigorous and had been fed with breast milk or formula every 2 to 3 hours. He had no symptoms of vomiting, and his stool color was normal, not acholic. There was no family history of metabolic, liver, or endocrine diseases, or any other genetic diseases.

On physical examination at the clinic, he weighed 2.95 kg (3rd percentile), which was at the borderline of underweight for his age, even though the baby had been fed well. His height was 49.5 cm (10th percentile), and his head circumference was 34.5 cm (10th-50th percentile). Generally, he showed normal activity and good muscle tone, but his skin color was slightly icteric. The external genitalia had a normal size and shape of the penis and both descended testes. There was mild hyperpigmentation on both scrotums and in the oral mucosa and gums. His blood pressure was 76/44 mmHg, which was in the normal range.

There were two laboratory sheets of NST of 17-OHP, performed in the first and second weeks after birth. In the follow-up test, 17-OHP levels had increased from 17.9 ng/mL to 57.99 ng/mL (cutoff level: 6 ng/mL). Because he didn't show any typical symptoms of adrenal crisis, we considered the possibility of SV-type and conducted a blood test at the outpatient clinic for routine chemistry, including bilirubin levels and the ACTH stimulation test.

Two hours after the blood draw, the laboratory results showed severe electrolyte imbalance with sodium at 114 mmol/L and potassium at 7.6 mmol/L. He was

immediately admitted to the neonatal intensive care unit (NICU). His white blood cell count was 14,100/uL, platelet count was 720,000/uL, BUN level was 39.2 mg/dL, and creatinine level was 0.60 mg/dL, all suggesting dehydration. The evaluation for jaundice showed total bilirubin (TB) of 2.45 mg/dL, direct bilirubin (DB) of 1.18 mg/dL, aspartate aminotransferase (AST) of 22 IU/L, alanine aminotransferase (ALT) of 13 IU/L, and gamma-glutamyl transferase (GGT) of 1,605 IU/L (reference range: AST 22-71 IU/L; ALT 10-40 IU/L; GGT 13-147 IU/L).

After admission to the NICU with consideration for the SW-type, he immediately received intravenous fluids with electrolytes and hydrocortisone to treat dehydration, electrolyte imbalance, and potential adrenal crisis. Before therapy, initial serum glucose level was 84 mg/dL, and during therapy, his random blood sugar level was maintained at or above 70 mg/dL. The ultrasound for the liver and adrenal gland showed no lesions in either organ, a normal biliary tract without any obstruction or atresia, and normal-sized adrenal glands (Fig. 1). The basal plasma levels of hormones showed ACTH of 359 pg/mL (reference range, 7.2-63.3 pg/mL), cortisol of 2.71 μg/dL (reference range, 2.47-11.9 μg/mL), and 17-OHP of 419.49 ng/mL (reference range, 0.59-3.44 ng/mL). The stimulated plasma levels of cortisol and 17-OHP at 60 minutes after ACTH stimulation were 3.45 μg/dL and 584.88 ng/mL, respectively. Therefore, he was diagnosed with classic 21-hydroxylase deficiency with SW-type. Thyroid function test, blood and urinary cultures, and urinalysis including osmolality and pH were all normal. Genetic testing was done to confirm the type of 21-hydroxylase deficiency and to provide genetic counseling for the family as he was the first child.

After 2 days of intensive treatment for adrenal crisis, serum electrolyte levels were normalized (Table 1), and he received oral hydrocortisone, fludrocortisone, and sodium. Serum levels of TB, DB, and GGT normalized

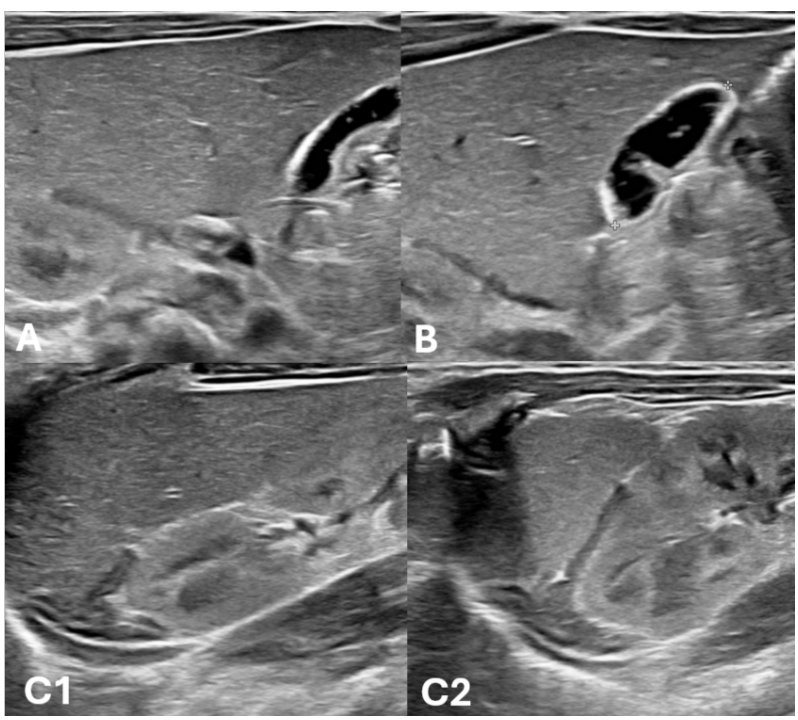

Fig. 1. Ultrasound images showed normal for liver (A), gallbladder without any biliary tract abnormality (B), and both adrenal gland (C1: Right, C2: Left).

spontaneously without any specific treatment like phototherapy or ursodeoxycholic acid (Table 1). Genetic testing of the *CYP21A2* gene revealed a compound heterozygote with a point mutation (c.1069C>T, p.Arg357Trp) in one allele and a large gene deletion from exon 1 to exon 7 in the other allele (Fig. 2), confirming the SW-type of 21-hydroxylase deficiency. On hospital day 9, he was discharged with normal skin color and without any symptoms related to adrenal crisis.

In his follow-up at the outpatient clinic after discharge, his serum bilirubin level was normalized and his 17-OHP level was controlled below 10 ng/mL (Fig. 3). At 2 months of age, his height was 57 cm (15th-25th percentile), his weight was 5.9 kg (50th-75th percentile), and his motor development was within the normal range.

Discussion

This case is a SW-type 21-hydroxylase deficiency presenting with prolonged jaundice without other fatal symptoms related to the SW crisis. Neonatal choles-

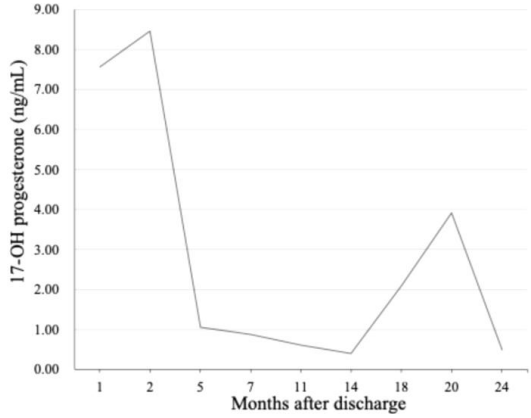

Fig. 3. Serum level of 17-hydroxyprogesterone after discharge at the outpatient clinic.

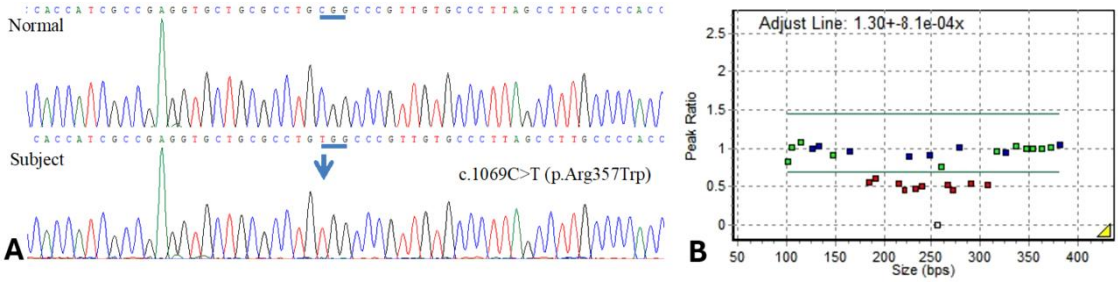

Fig. 2. Genetic testing for Sanger sequencing (A) and MLPA (B) for *CYP21A2* gene revealed a point mutation (p.R357W) and a large gene deletion from exon 1 to exon 7, which was consistent with a compound heterozygote.

Table 1. Laboratory changes in bilirubin, electrolytes, and ACTH levels over time after the start of treatment

	HD1	HD2	HD4	HD7	1 wk*	1 mo*	2 mo*	18 mo*	20 mo*	24 mo*
TB (mg/dL)	2.45	2.24	1.64	1.45	0.67	0.43	0.42	<0.20	0.29	<0.20
DB (mg/dL)	1.18	1.23	0.76	0.61	0.36	0.22	<0.20	<0.20	<0.20	<0.20
AST (IU/L)	22	24	39	28	37	40	38	51	31	32
ALT (IU/L)	13	12	40	23	23	27	26	20	14	14
GGT (IU/L)	1605	1455	1407	945	467	95	40	8	10	11
Sodium (mmol/L)	114	125	132	130	138	132	136	142	139	140
Potassium (mmol/L)	7.6	6.1	6.0	NA	5.7	6.3	4.8	4.2	5.1	4.5
ACTH (pg/mL)	359	NA	NA	NA	NA	NA	149	4.1	15.5	<3.0

Abbreviations: HD, hospital day; wk, week; mo, month; TB, total bilirubin; DB, direct bilirubin; NA, not available.
*Times after discharge

tasis refers to a state where conjugated hyperbilirubinemia persists in a newborn. When it lasts for more than 2 weeks, it is termed neonatal cholestasis[6] and its prevalence is approximately 1:2500[7]. The evaluation of neonatal cholestasis can be complex because various diseases such as biliary atresia, congenital panhypopituitarism, congenital adrenal hyperplasia, neonatal lupus, and pseudohypoaldosteronism must be differentiated. Although there are cases such as lipoid congenital adrenal hyperplasia presenting with cholestasis, classic 21-hydroxylase deficiency with cholestasis is quite rare.

The pathogenic mechanism of cholestasis in CAH is not clearly understood. It is postulated that hyperbilirubinemia in hypocortisolism results from diminished bile flow and/or excretion into the canaliculi, which can be caused by affected intrahepatic bile production, defects in bile transmembrane transport, or mechanical bile duct obstruction[8-10]. Studies on animal models also reported that cortisol decreases bile formation and flow in adrenalectomized rats[11]. Furthermore, the immaturity of the infantile liver can also lead to cholestasis. Interestingly, adrenal insufficiency with cholestasis occurs almost exclusively during the infantile period, and if hepatic manifestations persist after infancy, they usually present as hypertransaminasemia rather than cholestasis[12].

The p.R357W mutation is well known for causing SW type and is reported in 15.4% of cases in China and 17.6% in Japan[4,13]. The allele frequency of *CYP21A2* gene deletions is higher in Europe than in Asia, but it is also a common mutation, occurring in 10.8% of cases in China and 11.8% in Japan[13]. Among 230 patients with 21-hydroxylase deficiency in China, 3 patients had a compound heterozygote for p.R357W in one allele and deletion in the other allele, and all showed SW clinical symptoms. Among 93 patients with classic 21-hydroxylase deficiency in Croatia, 3 patients had the same genotype, and all exhibited SW clinical symptoms [13]. As the R357W mutation primarily results in the SW phenotype[4], it is very rare for classic CAH to present without SW symptoms when having two representative SW-genotype mutations.

Fortunately, the infant's condition was reversible with proper treatment. However, at the initial presentation, the patient had a severe salt losing with sodium dropping to as low as 114 mmol/L, and hyperkalemia was very severe at 7.6 mmol/L. It took time for the follow-up NST results to come out, and since the patient appeared healthy with no apparent symptoms, it was difficult to detect his condition. Since the adrenal crisis of CAH is preventable with appropriate administration of hydrocortisone and fludrocortisone, it is important to be aware of the clinical symptoms and laboratory features and refer the infant to an endocrinologist for early detection. Thanks to the free NST, which is fully covered by national insurance in South Korea, we could provide steroids immediately after detecting SW crisis lab results. If NST was not available initially, an adrenal crisis would be hard to diagnose in the first place when facing severe electrolyte imbalance.

In conclusion, classic 21-hydroxylase deficiency can rarely present as persistent unconjugated hyperbilirubinemia, complicating the initial diagnosis. If appropriately diagnosed, symptoms and critical imbalances can be rapidly resolved without sequelae. Therefore, it is important for primary healthcare providers to consider the possibility of CAH and make early referrals to prevent serious electrolyte imbalances such as SW crises, reduce morbidity, and prevent severe complications.

요 약

선천성 부신 과형성증, 21-수산화효소 결핍증은 부신 스테로이드 생성에 영향을 미치는 상염색체 열성 질환으로, 무기질코르티코이드와 글루코코르티코이드의 합성이 저하됩니다. 선천성 부신 과형성증은 저혈압, 무기력, 구토, 저혈당과 같은 증상을 유발할 수 있으며, 염분소실형

에서 심각한 경우 생명을 위협하는 부신 위기를 초래할 수 있습니다. 이 보고는 전형적인 부신 위기 증상 없이 지속되는 황달로 내원하여 염분소실형의 복합 이형접합체로 진단받은 드문 사례를 제시합니다. 선천성 부신 과형성증의 신속한 진단과 치료가 심각한 합병증을 예방하는 데 필요함을 강조하며, 신생아 선별검사와 철저한 임상 관찰의 중요성을 강조하는 바 입니다.

References

1) Speiser PW, Arlt W, Auchus RJ, Baskin LS, Conway GS, Merke DP, et al. Congenital Adrenal Hyperplasia Due to Steroid 21-Hydroxylase Deficiency: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2018;103:4043-88.
2) White PC, Curnow KM, Pascoe L. Disorders of steroid 11 beta-hydroxylase isozymes. Endocr Rev 1994;15:421-38.
3) Held PK, Bird IM, Heather NL. Newborn Screening for Congenital Adrenal Hyperplasia: Review of Factors Affecting Screening Accuracy. Int J Neonatal Screen 2020;6:67.
4) Wang R, Yu Y, Ye J, Han L, Qiu W, Zhang H, et al. 21-hydroxylase deficiency-induced congenital adrenal hyperplasia in 230 Chinese patients: Genotype-phenotype correlation and identification of nine novel mutations. Steroids 2016;108:47-55.
5) New MI, Abraham M, Gonzalez B, Dumic M, Razzaghy-Azar M, Chitayat D, et al. Genotype-phenotype correlation in 1,507 families with congenital adrenal hyperplasia owing to 21-hydroxylase deficiency. Proc Natl Acad Sci U S A 2013;110:2611-6.
6) Amy G Feldman, Ronald J Sokol. Neonatal Cholestasis. Neoreviews 2013;14:e63-e73.
7) Björn Fischler, Thierry Lamireau. Cholestasis in the newborn and infant. Clin Res Hepatol Gastroenterol 2014;38:263-7.
8) Cheung M, Bansal S, Aw MM, Buchanan CR, Mieli-Vergani G, Dhawan A. Liver failure in a neonate with congenital adrenal hyporesponsiveness. Eur J Pediatr 2003;162:558.
9) Khodadad A, Modaresi V, Kiani MA, Rabani A, Pakseresht B. A case of lipoid congenital adrenal hyperplasia presenting with cholestasis. Iran J Pediatr 2011;21:539-42.
10) Al-Hussaini A, Almutairi A, Mursi A, Alghofely M, Asery A. Isolated cortisol deficiency: a rare cause of neonatal cholestasis. Saudi J Gastroenterol 2012;18:339-41.
11) Bauman JW, Jr., Chang BS, Hall FR. The effects of adrenalectomy and hypophysectomy on bile flow in the rat. Acta Endocrinol (Copenh) 1966;52:404-8.
12) Gurakuqi GC, Stadlbauer V, Stepan V, Warnkross H, Trauner M. [Addison's disease as a rare cause of chronically elevated liver enzymes]. Z Gastroenterol 2006;44:179-83.
13) Dumic KK, Grubic Z, Yuen T, Wilson RC, Kusec V, Barisic I, et al. Molecular genetic analysis in 93 patients and 193 family members with classical congenital adrenal hyperplasia due to 21-hydroxylase deficiency in Croatia. J Steroid Biochem Mol Biol 2017;165:51-6.