BRIEF REPORT

Congenital Adrenal Hyperplasia with Non-functional Mutations in Both Alleles in a Clinically Unaffected Infant

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ABSTRACT

Background: Results in neonatal screening programs aiming at detection of congenital adrenal hyperplasia (CAH) can only report elevated levels of 17-hydroxy-progesterone (17-OHP), without being able to differentiate presence or absence of salt loss.

Aim: To predict presence or absence of salt loss in newborn infants with CAH.

Methods: The first specimen of suspected CAH in samples sent from People’s Democratic Republic of Laos (Lao PDR) was investigated for known mutations in CAH associated with salt loss.

Results: Molecular genetic diagnosis revealed mutations associated with loss of function in both alleles; however, the infant was clinically unaffected even without any corticosteroid substitution therapy.

Conclusions: Although molecular genetic methods can theoretically predict loss of function in CAH, our infant was clinically unaffected even without therapy at 6 years of age. We speculate that in CAH, remaining enzyme activity can be sufficiently high, despite the presence of loss of function mutations, which do not affect infants clinically.

KEYWORDS: congenital adrenal hyperplasia, 17-hydroxy-progesterone, neonatal screening, CYP21A2 gene, Laos
As part of the establishment of a newborn screening program in the People’s Democratic Republic of Laos, >11,000 samples of newly born infants were analyzed for thyrotropin-stimulating hormone and 17-hydroxy-progesterone (17-OHP) [1]. Although there were 269 retests because of altered predefined cut-off levels caused by early blood sampling, ultimately, there was only one single case of confirmed congenital adrenal hyperplasia (CAH) [1]. In a series of almost 500,000 infants tested for CAH in the Sapporo region of Japan, there were 26 confirmed cases of CAH, 20 of which had the salt wasting (SW) form of the disease [2]. CAH because of 21-hydroxylase deficiency is caused by mutations in the CYP21A2 gene and is often fatal in its classic forms if not treated with glucocorticoids [3]. A 17-OHP level >300 nmol/l indicates classic CAH, while 30–300 nmol/l usually can be found in non-classic CAH [3; 4]. In our patient, the initial 17-OHP level was measured at 577 nmol/l, which was suggestive of the classic form of CAH, with a high probability of being associated with SW. While we organized a confirmation sample to be taken from the infant, we also suggested treating the infant with glucocorticoids. Because there was no mineralocorticoid preparation available at that time at the largest delivery unit in the capital of Laos, Vientiane, in the Mother & Child Health Hospital, the local colleagues decided to treat the infant with dexamethasone. Because of non-compliance of the infant’s parents, dexamethasone treatment was discontinued after several days. Interestingly, the infant’s condition did not deteriorate following discontinuation of dexamethasone, and the child is well and healthy at now 6 years of age and is successfully attending regular school. To exclude confusion of blood samples, the identity of the source of all blood samples showing high levels of 17-OHP was tested and confirmed to be the same patient. To shed further light on these conflicting data, we proceeded to the molecular genetic investigation, which yielded a mutation at intron 2 (656 A/C→G). The latter is a known splicing mutation, which has a minor intrinsic activity and is common in Chinese patients [5]. The impression was that of a homozygous mutation or a compound heterozygous condition with a deletion on one allele and an I2 mutation on the other allele, both of which would be compatible with CAH. This infant fulfilled all laboratory criteria for CAH, but was clinically unaffected. For efficient clinical management of newborn infants with suspected CAH in resource-limited countries, it clearly would be desirable to be easily able to differentiate with simple methods in cases of CAH, whether there is SW. Although the sensitivity of newborn screening for the SW form of CAH is good, the positive predictive value is poor because of the high false-positive rate of the immunological assays for 17-OHP [6]. Despite the generally good genotype–phenotype concordance in CYP21A2 mutations [7], there are examples of rare mutations not covered by standard commercial testing, which ultimately explain familial cases of non-classical CAH [8]. Genotype–phenotype correlation may depend on geographic location. In a series from Portugal, genotype predicted phenotype successfully in 83.3% [7], whereas in Korean infants, the SW form of CAH had the best genotype–phenotype correlation [9]. Assuming a good genotype–phenotype correlation in our patient, at 17-OHP of 577 nmol/l, he would automatically be classified as classic CAH [3, 4]. Presumably, a vast majority of infants worldwide would receive treatment at this level of 17-OHP; low-resource countries like Laos can apparently be an exception. We speculate that an unknown percentage of infants with so-called obvious classic CAH may have sufficient intrinsic 21-hydroxylase activity; hence, they do not suffer from SW crisis and/or early neonatal death.

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REFERENCES