Successful pregnancy in a woman with rare compound heterozygoticity for congenital adrenal hyperplasia; Case report

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Summary

Pregnancy rates in women with congenital adrenal hyperplasia – even when adequately treated – are reported to be low. We hereby describe our recent experience with the pregnancy of a patient who had congenital adrenal hyperplasia due to a rare combination of P30L/I172N mutations in the CYP21 (21-hydroxylase) gene.

Key words: Pregnancy; Congenital adrenal hyperplasia; Mutation analysis.

Introduction

Congenital adrenal hyperplasia (CAH), and particularly its non-classical (NC) form, is increasingly diagnosed as a cause of amenorrhea in girls and if untreated leads to various degrees of hirsutism, resembling polycystic ovary syndrome. Pregnancy rates in women with CAH – even when they are adequately treated – are reported to be low. We hereby describe our recent experience with the pregnancy of a patient who had CAH due to a rare combination of mutations in the CYP21 (21-hydroxylase) gene.

Case report

A 24-year-old woman was referred for endocrine evaluation when pregnancy was confirmed (5th week of gestation).

Her past medical history included absence of menses by age 16. On physical examination her height was 154 cm (5th percentile) and weight was 49 kg. The body habitus was unequivocally female with no virilization. Mild hirsutism was noted in the cheeks, chest and lumbar region. Breast buds were noted at Tanner stage 1 and normal female genitalia with no clitoromegaly were found. The karyotype was normal female XX. Baseline serum 17-hydroxyprogesterone was elevated at 60 nmol/l (normal < 3.0 nmol/l). After an above-normal elevation with synthetic corticotropin (Synacthen test) the diagnosis of NC-CAH, apparently caused by 21-hydroxylase deficiency, was established and was treated with low-dose daily dexamethasone (DEX) thereafter. Menses appeared soon.

At age 23 she became pregnant but her pregnancy was terminated by spontaneous abortion at eight weeks of gestation. Dilatation and curettage precipitated an addisonian crisis (with corticotropin at 369 pg/ml [normal: 9-52 pg/ml] and cortisol at 174 nmol/ml [normal: 138-690 nmol/ml]) despite previously adequate oral DEX therapy.

Following the current referral we sought to further clarify the nature of the patient's CAH. DNA was extracted from peripheral leukocytes of the patient and her husband. Genomic DNA was digested with restriction enzymes and after electophoresis and hybridization, allele-specific PCR was used to evaluate the following mutations of the CYP21 gene: P30L, I_2splice, 8bpdelE_3, I172N, cluster E_6, V281L, Q318X, R356W and P453S. The patient was a compound heterozygote with a P30L /I172N genotype, while her husband showed no mutations.

Although prenatal sex determination disclosed the fetus to be male, treatment with a replacement dose of DEX was continued in order to avoid possible adrenal insufficiency during her pregnancy. Clinical and ultrasound follow-up of the fetus during pregnancy was normal. A healthy baby boy was born after an uneventful normal delivery.

Discussion

CAH is one of the most frequent inborn errors of metabolism and is most often due to derangement of the CYP21 gene on chromosome 6p21.3 (which leads to variable degrees of defective corticosteroid synthesis). CAH is inherited as an autosomal recessive disease [1]. Currently the different forms of CAH are classified according to the clinical expression of the disease as the salt-wasting form (SW), the simple virilizing form (SV), and the NC-CAH form.

Our patient had clinically apparent NC-CAH with no manifestations of virilization. The mutations found in her were in codons 30 (P30L; where proline is substituted for leucine) and 172 (I172N; where isoleucine has been substituted for asparagine) [2-4]. This specific genotype is rare, accounting for only one of 32 cases and two of 25 cases of native Greek females with SV and NC variants of CAH [5]. To the best of our knowledge there are no reports of pregnancy and subsequent outcome in women with this variant.

Greeks have been shown to have a higher frequency of P30L mutations in the CYP21 gene, in both SV- and NC-CAH phenotypes [5] Analogous findings have been reported in Germans by Krone *et al.* [6]. The discrepancy between genotype and phenotype with CYP21 mutations is more marked for SV- and NC-CAH phenotypes, while

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genotyping for CYP21 mutations is more reliable than clinical classification for SW genotypes [7]

Virilization in newborns due to CAH can be prevented effectively with prenatal administration of DEX to the mother (at doses between 0.5 and 2 mg/day) and is successful in 75% of treated cases in eliminating or reducing the masculinization of the affected female's external genitalia [8-11]. DEX treatment should only be considered in families with a previous child with a virilizing form of the disease and has to be started at six to seven weeks of gestation. Consequently, DEX has to initially be given "blindly" to all mothers at risk until the diagnosis of an affected female can be ascertained by analysis of DNA from a chorionic villous biopsy, (which cannot be performed until the 10th week of pregnancy). Thus, as CAH is inherited as an autosomal recessive disease and only affected girls benefit from the treatment, seven out of eight fetuses are treated unnecessarily. Possible adverse effects of large doses DEX on the brain and kidneys have been shown in experimental animals during the second trimester, while human studies are lacking. Of course, since in our case only the mother was affected and the offspring was male there was no danger of CAH in the fetus but DEX was nevertheless continued given the previous addisonian crisis of the patient.

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