

Case Report

Two Subjects with Congenital Adrenal Hyperplasia due to 21-OH Hydroxylase Deficiency and Type 1 Diabetes Mellitus: Is there a Genetic Connection?

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Abbreviations

T1DM: Type 1 Diabetes Mellitus; 21-OH CAH: Congenital Adrenal Hyperplasia Due To 21-Hydroxylase Deficiency

Case Presentation

Patient 1

Patient 1 is a female diagnosed with 21-OH CAH prenatally *via* genetic amniocentesis. Her older brother had been diagnosed at age 5 years as part of endocrinological work-up for precocious puberty. Familial disease causing mutations in the *CYP21A2* gene were known (p.I172N and p.Q318X). Parental testing identified that the p.Q318X mutation was maternally inherited and the p.I172N mutation was paternally inherited, which determined that these mutations exist in a trans configuration in the patient. Patient 1 had been medically managed on standard doses of hydrocortisone and fludrocortisone with good compliance. There was no family history of T1DM or other autoimmune diseases.

At age 11 years, on routine endocrinology laboratory screening, patient 1 was noted to have blood glucose level of 596 and bicarbonate level of 18, along with a prior three to four week history of polydipsia, polyphagia, and polyuria. She was admitted to CHOC Children's Hospital in Orange, California for further treatment and evaluation, and was diagnosed with T1DM. Currently, her T1DM is managed with insulin lispro *via* an Omnipod pump and manual glucose monitoring. Genetic susceptibility testing for T1DM was completed *via* the Barbara Davis Center. HLA genotyping revealed multiple alleles that are high risk for T1DM including DQA1-B-0201, DQB1-B-0202, and DQB1-A-0302. In addition, she has DQA1-A-0301 and DRB1-A 0401 that were paternally inherited, which in combination predisposes her to T1DM. Unfortunately, she does not have any protective alleles for T1DM.

Patient 2

Patient 2 is a male diagnosed with 21-OH CAH between 1-2

Abstract

Type 1 diabetes mellitus (T1DM) and congenital adrenal hyperplasia due to 21-hydroxylase deficiency (21-OH CAH) are relatively common conditions, but there are only a few reported cases in the literature of T1DM in association with 21-OH CAH. T1DM and 21-OH CAH have neighboring genetic loci, but the conditions generally occur independently of each other.

This report presents two patients evaluated through pediatric endocrine clinic secondary to their concurrent diagnosis of 21-OH CAH and T1DM.

Keywords: Type 1 diabetes mellitus; Congenital adrenal hyperplasia; Genetics; Genetic susceptibility testing

weeks of age due to positive newborn screening. Subsequent genetic testing revealed that he is homozygous for p. R356W mutation in the *CYP21A2* gene. Parental carrier testing was not completed since he is homozygous in this region for this specific mutation, as it suggests that both parents are obligate carriers of this condition. His CAH has been managed with standard doses of hydrocortisone and fludrocortisone with good patient compliance. Family history is pertinent for T1DM in a half-brother and grandmother, and hyperthyroidism in another male sibling.

At that time, blood glucose level was 710, bicarbonate level was 27, and he had minimal ketonuria. He was started on an insulin drip by the outside emergency department given the degree of hyperglycemia and was initially transferred to the CHOC Children's Hospital PICU for further treatment and evaluation. He was quickly transitioned to subcutaneous insulin after pediatric endocrinology was consulted, and was diagnosed with T1DM during that admission. His T1DM is currently managed with insulin lispro *via* a Medtronic pump and blood glucose monitoring with a Dexcom sensor. Genetic susceptibility testing for T1DM was completed *via* the Barbara Davis Center. HLA genotyping revealed multiple alleles that are high risk for T1DM including DQA1-*0505 and DQB1-*0301, which were maternally inherited. Interestingly, the patient's father, who does not have T1DM, has multiple high-risk alleles for T1DM, including DRB1-*0401, DQA1-*0301, and DQB1-*0302. The patient does not have any protective alleles for T1DM.

Discussion/Conclusion

T1DM and CAH are both relatively common conditions. Although T1DM is a multifactorial disease, there is a strong genetic component with the major susceptibility locus mapping to the HLA class II genes at chromosome 6p21.3 [1,2]. In particular, HLA- DQA1, DQB1, and DRB1 genes, located on chromosome 6p21.32, are implicated in T1DM [3,4]. CAH is a Mendelian condition known to be inherited in an autosomal recessive manner. CAH due to 21-hydroxylase deficiency (21-OH CAH; MIM #201910) is associated with biallelic

mutations in the *CYP21A2* gene (MIM *613815), at chromosome 6p21.33 [5-7]. The location of the *CYP21A2* gene is in close proximity to the HLA B and HLA DR loci. [8]. A few specific mutations in the *CYP21A2* gene are proposed to arise from an exchange of genetic material between the *CYP21A2* gene and a pseudogene located near to it, *CYP21A1*, which is essentially a nonfunctioning gene that is very similar genetically to the functional *CYP21A2* gene [9,10].

Although T1DM and 21-OH CAH have neighboring genetic loci, both conditions are expected to occur independently of each other. There are few reports in the literature of pediatric patients with 21-OH CAH discovered during infancy, who are also diagnosed with T1DM later in childhood [11]. In general, patients with 21-OH CAH are at an increased risk for diseases associated with metabolic syndrome (i.e. cardiovascular disease and type 2 diabetes mellitus) and hypertension [11,12]. When on glucocorticoid replacement therapy, the dose needed is usually supraphysiologic and can lead to abnormalities in lipid and glucose metabolism, along with increased body mass index, body fat mass, insulin levels, leptin levels and blood pressure [13,14]. There is currently no established connection between 21-OH CAH and T1DM.

T1DM is considered a multifactorial autoimmune disease and therefore can be associated with a variety of other similar conditions, most notably celiac disease, Addison's disease, vitiligo, autoimmune thyroid disease, autoimmune gastritis, and pernicious anemia [15]. Patients with T1DM and failure of other endocrine glands secondary to immune-mediated destruction of those endocrine tissues are known to have polyglandular autoimmune syndrome [16]. 21-OH CAH is a Mendelian genetic condition, and is not considered an autoimmune disease; therefore, there is not the same natural association with T1DM as other autoimmune endocrinopathies.

The relationship between T1DM and various HLA genotypes have been very well studied [3]. Although there is a link between 21-OH CAH and HLA-BW47, its connection to other HLA genotypes has not been as well established [17,18]. A study by Manfras et al. (1993) found the *CYP21* gene was associated with HLA-A3, BW47, C6, DR7, DR53, and DQ2 in their population of 21 families with at least one or two children with the severe form of 21-OHCAH [19]. Interestingly, the DR7 haplotypes have been noted to be protective against T1DM [20]. None of the other haplotypes noted in that study are known to be associated with T1DM. A study by Sobel et al. (1983) conducted a decade earlier also found an association between 21-OH CAH and HLA-A, B, C, DR, MT, and MB [18]. More recently, a study from Iran found an increased frequency of HLA-B18 and HLA-B21 in children with 21-OH CAH [21]. Neither of these genotypes has been observed to have an association with T1DM. A study of HLA haplotypes in a Croatian population also suggests that there may be different HLA haplotypes associated with different 21-OH CAH mutations [22]. From the data currently available, neither patient 1 nor patient 2 have HLA genotypes that overlap with the known HLA types associated with 21-OH CAH.

For the two cases presented, it is more likely that the diagnosis of T1DM is completely independent to their prior diagnosis of 21-OH CAH. Previously published studies have not found overlap between the locations of each condition-associated HLA genotypes that would allow the accurate conclusion that patients with 21-OH CAH could

have a predisposition to develop T1DM in later childhood. It is an interesting observation that the susceptibility genes for T1DM and the gene for 21-OH CAH are at neighboring loci on chromosome 6p21.3 and the observations in two of our pediatric patients who presented with both conditions, indicating that there may be a relationship between the two conditions that ought to be further explored. Further studies of larger populations with CAH and T1DM would be helpful in further establishing this, but difficult given the paucity of such patients.

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