Assessment of adrenocortical function and autoantibodies in a baby born to a mother with autoimmune polyglandular syndrome Type 2

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ABSTRACT. We describe the case of a baby born to a mother with Addison’s disease in the context of Autoimmune Polyendocrine Syndrome Type 2. Adrenal cortex autoantibodies and steroid 21-hydroxylase autoantibodies were detectable in the sera of both mother and baby, suggesting the transplacental passage of these autoantibodies. Adrenal autoantibodies were present in the baby’s serum at delivery, at 3, 6 and till 34 months of age but no signs of clinical or subclinical adrenal insufficiency were found in the baby during the observation period. These data suggest that the presence of adrenal autoantibodies in serum alone is not a sufficient cause for the development of autoimmune adrenitis. (J. Endocrinol. Invest. 27: 618-621, 2004) ©2004, Editrice Kurtis

INTRODUCTION

The autoimmune form of adrenocortical insufficiency [Addison’s disease, (AD)] is more frequent in females than in males and the mean onset of the disease is 35 yr of age (1). Although a hypergonadotropic hypogonadism may be associated with AD, the affected females usually have normal gonadal function and may have normal pregnancies (2-6). Nevertheless, pregnancies among women with AD are not common due to several factors, one being concern about the wrong opinion about the adverse effects of substitutive corticosteroid therapy on the fetus. However, in AD the corticosteroid therapy during pregnancy is essential; furthermore, the dose of steroids often needs to be increased in order to prevent fetal damage resulting from inadequate maternal steroid levels (2, 4-6). Adrenal cortex autoantibodies (ACA) are serological markers of autoimmune AD (7). ACA are polyclonal IgGs reacting with the adrenal cortex cell cytoplasm in an immunofluorescence test (IFT) (7). The major adrenal autoantigen reactive with ACA has been identified as steroid 21-hydroxylase (21-OH) (8, 9). Therefore, autoantibodies (Abs) to 21-OH are serological markers of autoimmune AD as well and, it has been shown, they can inhibit 21-OH enzyme activity in vitro (10) although such an effect is not observed in vivo (11). A few cases of babies born to mothers with AD have been published and their metabolic condition and transplacental passage and changes in adrenal antibodies have been described (12-16). However, a long follow-up and detailed assessment of a possible pathogenic role of adrenal antibodies in such infants have not yet been reported and we now describe such an assessment.

Mother

The patient we describe developed Graves’ disease in April 1992 at 25 yr of age and was treated with methimazole for 6 months. After the treatment had been stopped she suffered a relapse of hyperthyroidism and developed ophthalmopathy. Ultrasound examination showed a diffuse goitre with the presence of isoechogenic nodules. Thyroid microsomal (TMHA) and thyroglobulin autoantibodies (TGHA) were positive by passive hemagglutination tests, however TSH receptor autoantibodies were not tested. Treatment with methimazole was started again but the patient showed a poor clinical response and worsening of her ophthalmopathy. Consequently, in July 1993, at 26 yr of age, a subtotal thyroidectomy was performed followed by thyroxine substitution therapy. Her oph-
thalamopathy did not improve after the operation nor after treatment with octreotide (0.05 mg im, five times a week for three months). Finally, in 1994 bilateral ocular decompression was carried out and this resulted in complete resolution of her eye disease. From April 1998 the patient developed progressive skin hyperpigmentation, asthenia and a weight loss of about 10 kg. In January 1999 (at 32 yr of age) she presented with classical symptoms of adrenal insufficiency including severe hypotension, vomiting and dizziness. On admission to our hospital’s Division of Endocrinology, she had low basal serum cortisol levels of <2ng/ml at 08:00 h and at 18:00 h (normal range of 60 to 285 ng/ml at 08:00 h and 40 to 150 ng/ml at 18:00 h) and elevated ACTH levels of 1200 pg/ml (normal range 5 to 60 pg/ml). Cortisol and ACTH were measured using an enzyme linked fluorescence assay (ELFA) technique. Oral glucose tolerance test and levels of HbA1c were within the normal range. A high titre (1:160) of ACA was detected by IFT using normal human adrenal tissue sections. High levels (3149 Units/ml) of autoantibodies to 21-OH were detected by immunoprecipitation assay (IPA) (RSR Ltd, Cardiff, CF23 8HE, UK) based on 125I-labelled 21-OH as described previously (17, 18). Autoantibodies to steroid 17α-hydroxylase (17α-OH) were detectable at 1.8 U/ml while autoantibodies to cytchrome P450 side chain cleavage enzyme (P450scs) and to steroid producing cells (StCA) were negative. 17α-OH Abs and P450scs Abs were measured by IPA based on 35S-labelled 17α-OH or 35S-labelled p450scs produced in an in vitro translation/transcription system (Promega UK Ltd, Southampton, SO16 7NS, UK) as reported before (18, 19) and StCA were detected by the indirect immunofluorescent technique on normal human gonadal tissue. The assays specificity and sensitivity of the above assays have been described in detail previously (17-19). In addition, low titres of islet cell antibodies (ICA) (10 JDF Units) and parietal cell antibodies were detected by IFT at this time. The patient was negative for TMHA, TGHA, TSH receptor, glutamic acid decarboxylase, IA-2, intrinsic factor, liver-kidney microsomal, nuclear, mitochondrial, and transglutaminase autoantibodies, as assessed by commercially available assay kits. The human leukocyte antigen (HLA) typing indicated that the patient had DRB1*04,*08, DQA1*0301, *04 and DQB1*0302, *04. Computerised tomography showed small adrenal glands and on the basis of these findings our patient was diagnosed with Autoimmune Polyglandular Syndrome (APS) Type 2 according to the Neufeld classification revised by Betterle et al. (1). Oral cortisone acetate treatment was started and currently she is on 3 daily doses of 50 mg of cortisone, 0.1 mg of fludrocortisone and 100 μg of L-thyroxine and remains well. In September 1999 the patient became pregnant (first pregnancy) but suffered spontaneous abortion at 24 weeks. On histological examination of the placenta multiple ischemic areas with hemorrhagic dissociation of maternal-fetal plate were found consistent with abruptio placentae. In addition, thrombosis of central umbilical cord vein was found but no visceral or somatic malformations were detected in the female fetus. FT₄ and TSH were in the normal range and the patient was negative for cardiolipin and β2-glycoprotein-IgG and IgM classes antibodies. In June 2000 the patient became pregnant again and delivered a healthy boy in March 2001 (see Baby section). The delivery was complicated by maternal post-partum hemorrhage but was managed successfully with standard procedures. Autoantibodies to steroidogenic enzymes and ACA were measured before and during both pregnancies and after delivery at different times as shown in Table 1. ACA were positive throughout the observation period but the titre fell from very high at diagnosis (1:160) to 1:16 at 6 months after giving birth. 21-OH Abs were very high at diagnosis (3149 U/ml) and remained positive during the follow-up although the levels fell to about 200 U/ml after delivery. Positivity, always at low titers, for 17α-OH Abs varied, being positive at diagnosis and before the 2nd pregnancy and at 6 months of the 2nd pregnancy but negative at all other times. Autoantibodies to P450scs were negative at diagnosis, became detectable at low titers during the 2nd pregnancy but undetectable at all other times. TGHA, TMHA and the TSH receptor autoantibodies remained negative during the observation period. Baby The baby boy was in breech presentation and was delivered at 38.6 weeks by caesarean section. His birth weight was 3500 g and the APGAR score was 8 at the first min. and 9 at 5 min. The baby was well, healthy and not breast fed. Because of the mother’s medical history, serum was collected for autoantibody and adrenal hormones tests on days 1, 90, 180 and 34 months after delivery. As shown in Table 2, ACA were positive on day 1 (titre 1:32), day 90 (titre 1:4) and weakly positive on day 180 and after 34 months. 21-OH Ab levels were 870, 21, 5.2 and 2.0 U/ml on day 1, 90, 180 and after 34 months, respectively. Autoantibodies to 17α-OH and P450scs were negative. The levels of ACTH and 17-OH progesterone were high at birth but in the normal range during the further period of observation. The cortisol levels were in the normal range at birth and during follow-up after delivery (Table 2). When assessed at 34 months of age, the baby was of a normal growth and development and did not show any signs of adrenal insufficiency.