Autoantibodies to steroidogenic enzymes in patients with premature ovarian failure with and without Addison’s disease

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Abstract

Design: Adrenal cortex autoantibodies (ACA), steroid-producing cell autoantibodies (StCA) and autoantibodies (Abs) to steroidogenic enzymes in three groups of patients with premature ovarian failure (POF), 15 with autoimmune Addison’s disease (AD), 26 with non-adrenal autoimmune diseases and 31 with isolated POF, have been assessed.

Methods: ACA and StCA were measured using an immunofluorescence technique. Abs to 21-hydroxylase (21-OH), to 17α-hydroxylase (17α-OH) and to cytochrome P450 side-chain cleavage (P450scc) were measured using an immunoprecipitation assay.

Results: Seventy-three percent of patients with POF and AD were positive for StCA, 93% for 17α-OH and/or P450scc Abs, 93% for ACA and 100% for 21-OH Abs. Among patients with POF and non-adrenal autoimmune diseases, 8% were positive for StCA, 12% for 17α-OH and/or P450scc Abs, and 8% and 12% for ACA and 21-OH Abs respectively. StCA, 17α-OH and/or P450scc Abs were all found in 10% of patients with isolated POF and 13% had ACA and 21-OH Abs. All StCA-, 17α-OH- and/or P450scc Abs-positive patients were also positive for ACA and 21-OH Abs. Two patients with isolated POF who were ACA and 21-OH Ab positive developed AD 3 and 5 years after the onset of POF.

Conclusion: This study has shown that, when POF is associated with AD, StCA, 17α-OH and/or P450scc Abs are present in the majority of patients, while in the other two groups, these Abs are detectable in a much lower proportion of patients. Measurement of ACA/21-OH Abs in some patients with POF may be important in identifying patients at risk of developing overt AD.

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Introduction

Premature ovarian failure (POF) is a disorder characterized by the interruption of ovarian function after puberty and before the age of 40. The etiology of the disease varies in different patients; chromosomal abnormalities, defects of the gonadotropin receptors and/or post-receptor function (Savage’s syndrome), defects of gonadotropin secretion, enzymatic defects, irradiation, chemotherapy, infections and autoimmunity have been identified as being involved in the pathogenesis of POF (1). The prevalence of POF in the female population is about 1% (2) and autoimmune forms characterized by the presence of lymphocytic infiltration and/or circulating autoantibodies (Abs) recognizing ovarian autoantigens (3), are diagnosed in approximately 20% of POF patients (4). Idiopathic POF is frequently associated with other autoimmune diseases, such as thyroid diseases (9%), Addison’s disease (AD) (2%), rheumatoid arthritis (1%), vitiligo, type 1 diabetes mellitus, systemic lupus erythematosus, myasthenia gravis, Crohn’s disease and autoimmune polyglandular syndromes (APS) (5). Idiopathic POF not associated with autoimmune diseases is often referred to as isolated POF. The majority of patients with POF associated with autoimmune AD have steroid-producing cell Abs (StCA) (6). In contrast, StCA are found in 1–10% of patients with POF associated with other autoimmune diseases or patients with isolated POF (5, 6).

StCA are polyclonal immunoglobulins of the IgG class that react with cytoplasmic antigens common to adrenal cortex cells, Leydig cells of the testis, theca cells of the ovary and syncytiotrophoblasts of the placenta (7). The major autoantigen targets of StCA are steroid 17α-hydroxylase (17α-OH) and cytochrome P450 side-chain cleavage enzyme (P450scc) (8, 9). The presence of StCA in sera from patients with POF is associated with lymphocytic oophoritis (5, 6, 10).

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Adrenal cortex autoantibodies (ACA) are polyclonal immunoglobulins of the IgG class that react with the cytoplasm of adrenal cortex cells (11) and their major
specific target autoantigen has been identified to be the steroid 21-hydroxylase (21-OH) (9, 12, 13). ACA, when present, are markers of clinical, subclinical or potential AD (4, 9). The presence of ACA in patients with POF without clinical AD is rare and when present they are considered to be a marker of subclinical or potential AD in these patients (4, 9). There is a strong association between the presence of StCA and ACA irrespective of the clinical form of AD. Furthermore, StCA are not usually detected in the absence of ACA (4, 9).

In our study of a group of patients with POF, with or without AD, we have assessed the immunological profile of the patients in terms of the Abs response to major gonadal and adrenal autoantigens using the sensitive and specific detection methods that employ recombinant steroidogenic enzymes.

Materials and methods

Patient and control groups

Three groups of patients with POF have been studied. The first group comprised 15 patients with POF and AD (mean age 28.8 years); five patients in this group presented with APS type 1 (mean age 21.3 years), seven with APS type 2 (mean age 33.6 years) and three with APS type 4 (mean age 31.5 years). The second group comprised 26 patients with POF and various clinical autoimmune diseases other than AD (mean age 26.4 years); 16 presented with Hashimoto’s thyroiditis, four with type 1 diabetes mellitus, three with Graves’ disease, three with alopecia, one with systemic lupus erythematosus, one with myasthenia gravis, one with multiple sclerosis and one with coeliac disease. The third group comprised 31 patients with isolated POF (mean age 30.8 years) whose sera were sent to the Division of Endocrinology, University of Padua for testing.

All the patients had a hypergonadotropic hypogonadism with secondary amenorrhea or oligomenorrhea before the age of 40 years. Women with POF as a result of surgery, radiation or chemotherapy were not included in our study.

The diagnosis of various autoimmune diseases was based in each case on typical clinical signs and symptoms and/or positive result of Abs tests. Patients with APS type 1, APS type 2 and APS type 4 were classified according to the kit manufacturer’s instructions. Abs to other organ-specific and non-organ-specific autoantigens were detected using the classical indirect immunofluorescence test based on sections of human thyroid, stomach, pancreas, liver and kidney (18).

Autoantibodies

Serum samples from all the POF patients were tested for StCA, ACA, 17α-OH Abs, P450scce and 21-OH Abs.

StCA were detected by a complement-fixing indirect immunofluorescence technique, using normal human testis as previously reported (5). ACA were detected by the classical indirect immunofluorescence technique, using thin cryostatic sections of normal human adrenal glands, as previously reported (17). Results of StCA and ACA were reported as positive or negative compared with control sera (i.e. serum known to contain Abs and serum from a healthy blood donor) included in each experiment.

17α-OH Abs and P450scce Abs were detected using an immunoprecipitation assay (IPA) based on 35S-labeled respective autoantigens produced in an in vitro transcription/translation rabbit reticulocyte system (Promega Corporation, Southampton, Hants, UK) incorporating 35S-methionine (Amersham Pharmacia Biotech., Little Chalfont, Bucks, UK) as described previously (8). The Ab levels were expressed as arbitrarily defined units calculated from a calibration curve prepared using serial dilution of sera positive for 17α-OH Abs and P450scce Abs respectively (8).

21-OH Abs were detected using a diagnostic kit based on 125I-labeled recombinant human 21-OH produced in yeast (RSR Ltd, Cardiff, UK) as described previously (15). The results are expressed as arbitrary units according to the kit manufacturer’s instructions.

Cytogenetic analysis

The karyotype analysis was carried out in seven patients (one in the group of patients with POF and AD and six in the group of POF patients without AD) who were negative for StCA and all three of the steroidogenic enzyme Abs. The karyotype was determined using peripheral blood lymphocytes cultured according to the standard procedure: chromosome banding patterns were obtained by quinacrine-fluorescent Q banding. For each individual at least 11 prometaphases were investigated and two karyotypes over 550 per haploid set were analyzed (19).

Results

Patients with POF and AD

In all 15 patients with POF and autoimmune AD, the mean age at onset of POF was 28.8 years. In the five patients with POF and APS type 1, POF developed at a mean age of 21.3 years (in three patients AD appeared before and in two after POF). In the seven patients with APS type 2, POF developed at a mean age of 33.6 years (two patients developed AD and POF at the same time, in three POF preceded AD.
and in two AD appeared before POF). In the three patients with APS type 4, POF developed at a mean age of 31.5 years (one patient developed POF before AD and two developed AD first).

StCA were found in 11/15 (73%) of all patients with POF and AD (Table 1). All StCA-positive patients were also positive for 17α-OH and/or P450scc Abs. Three of four StCA-negative patients were positive for P450scc Abs and one of four was negative for both 17α-OH and P450scc Abs. ACA were found in 14/15 (93%) of patients and all these were also positive for 21-OH Abs (Table 1). The one ACA-negative patient was positive for 21-OH Abs but 17α-OH and P450scc Abs were not detectable. All the StCA-positive patients were positive for ACA and three patients were positive for ACA in the absence of StCA.

A detailed analysis of Abs in patients with POF and different forms of AD is summarized in Table 1. In patients with POF and APS type 1, StCA were positive in four of five patients (80%) and all four of five (80%) also had 17α-OH and/or P450scc Abs. ACA were detectable in five of five patients (100%) with POF and APS type 1 and the same patients were also positive for 21-OH Abs. Six of seven (86%) of patients with POF and APS type 2 (86%) were positive for StCA as well as for 17α-OH and/or P450scc Abs. One patient was negative for StCA but positive for P450scc Abs. ACA and 21-OH Abs were detected in seven of seven (100%) of these patients. Out of three patients with POF and APS type 4, StCA were detected in one patient who was also positive for P450scc Abs. The two StCA-negative patients were positive for P450scc Abs. ACA and 21-OH Abs were detected in seven of seven (100%) of these patients. Out of three patients with POF and APS type 4, StCA were detected in one patient who was also positive for P450scc Abs. The same patients that were StCA positive were also positive for 17α-OH Abs and/or P450scc Abs. The one ACA-negative patient was positive for 21-OH Abs alone. The patients that were StCA and/or 17α-OH Abs and P450scc Abs positive were also positive for ACA and/or 21-OH Abs (Table 2).

In the group of patients with isolated POF, StCA were found in three of 31 patients (10%) and the same patients were positive for 17α-OH and/or P450scc Abs. ACA and 21-OH Abs were present in four of 31 (13%) patients (Table 2). All patients who had detectable StCA and/or 17α-OH Abs and P450scc Abs were positive for ACA and 21-OH Abs.

Overall, out of 57 patients with POF without AD (groups 2 and 3), five patients (9%) were positive for StCA and six (11%) were positive for 17α-OH and/or P450scc Abs. The same patients that were StCA positive were also positive for 17α-OH and/or P450scc Abs. The same patients that were StCA and/or 17α-OH Abs and P450scc Abs positive were also positive for ACA and 21-OH Abs. The two StCA-negative patients were positive for P450scc Abs. ACA and 21-OH Abs were detected in seven of seven (100%) of these patients. Out of three patients with POF and APS type 4, StCA were detected in one patient who was also positive for P450scc Abs. The same patients that were StCA positive were also positive for 17α-OH Abs and/or P450scc Abs. Six of seven (11%) of patients were positive for ACA and seven of 57 (12%) for 21-OH Abs (Table 2). Levels of 17α-OH Abs and P450scc Abs ranged from 3.1 units/ml to 60.5 units/ml and 3.1 units/ml to 24 units/ml.

The patient with POF and AD who was negative for StCA and 17α-OH and/or P450scc Abs, but positive for ACA and 21-OH Abs, was found to have Turner’s syndrome on cytogenetic analysis.

**Patients with POF without AD**

The mean age at onset of POF among 26 patients who had POF associated with one or more autoimmune diseases other than AD was 26.4 years. Fifty-three percent of patients in this group presented with POF first and the associated autoimmune diseases developed later; the remaining patients (47%) developed POF after associated autoimmune diseases had presented. Among 31 patients who had isolated POF, the mean age at onset was 30.8 years.

Out of 26 patients with POF and autoimmune diseases other than AD, two (8%) were StCA positive and the same two patients were positive for 17α-OH and/or P450scc Abs. One StCA-negative patient was positive for 17α-OH Abs. ACA and 21-OH Abs were detected in two of 26 patients (8%). In addition, one patient was positive for 21-OH Abs alone. The patients that were StCA and/or 17α-OH Abs and P450scc Abs positive were also positive for ACA and/or 21-OH Abs (Table 2).

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**Table 2** Abs in sera from 57 patients with POF without AD.
was found in all these patients.

Out of six patients with POF without AD (two from group 2 and four from group 3) who were ACA and 21-OH Abs positive (Table 2), two patients developed clinical AD 3 and 5 years after the onset of POF respectively.

The cytogenetic analysis was carried out in six patients (three from group 2 and three from group 3) who were negative for StCA, ACA, 17α-OH Abs, P450scc Abs and 21-OH Abs. A normal karyotype was found in all these patients.

Abs in control groups

The prevalence of StCA, ACA and Abs to steroidogenic enzymes in control groups (assessed using the same assay systems as described in the Materials and methods) have been reported previously. In particular, StCA were found in none of 338 healthy individuals and in seven of 8755 (0.08%) patients with various autoimmune diseases (16). 17α-OH Abs by IFA were not detected in any of 28 healthy blood donors or 37 patients with non-adrenal autoimmune diseases (8). P450scc Abs were undetectable by IFA in 20 healthy blood donors and 30 patients with non-adrenal autoimmune diseases (8). ACA were found in one of 338 (0.3%) of sera from healthy subjects and in 62/8755 (0.7%) of sera from patients with non-adrenal autoimmune diseases (16). Six of 243 (2.5%) of sera samples from healthy blood donors had low levels of 21-OH Abs by IFA and six of 323 (1.8%) of non-adrenal autoimmune patients were positive for 21-OH Abs (15).

Discussion

In this study, we assessed the evidence of the autoimmune involvement in patients with POF associated or not associated with autoimmune diseases using specific and sensitive Abs tests.

There was no difference in the age at onset of POF in patients with or without autoimmune AD, but in those with APS type 1 the disease tends to appear at a younger age compared with other groups. This could be due to a genetic predisposition of patients with APS type 1 to develop autoimmune disorders at a younger age. This predisposition may be related to the mutations of the AIRE gene that is involved in regulating immune tolerance (9, 20).

In all patients with POF and autoimmune AD the serological markers of clinical AD, i.e. ACA and/or 21-OH Abs, were found. Furthermore, 14/15 (93%) of these patients were positive for at least one other Abs to steroidogenic enzymes (17α-OH Abs and P450scc Abs) or StCA. The levels of these Abs were comparable with those observed in patients with various forms of APS or isolated AD (4, 8, 9, 15, 21). This is in agreement with the previous reports on the prevalence of Abs in patients with adrenal autoimmunity and POF (4, 8, 9, 15, 21). In the StCA- and/or 17α-OH- and/or P450scc Abs-positive patients, the ovarian failure may be related to the presence of lymphocytic oophoritis. In a different study, a typical pattern of lymphocytic oophoritis was shown in all patients with POF positivity for StCA in whom an ovarian biopsy was performed (6). However, some patients with autoimmune adrenal disease are positive for StCA (20% of patients) and 17α-OH and/or P450scc Abs (30% of patients) in the absence of gonadal failure (4, 8, 21). StCA have been shown to be good markers of potential autoimmune POF in these patients (9, 21) and are closely related to 17α-OH and P450scc Abs (4, 8, 21). However, the value of 17α-OH and P450scc Abs alone for the prediction of POF has not yet been demonstrated.

Patients with POF and AD who are negative for StCA and 17α-OH and/or P450scc Abs would benefit from further investigation in order to detect possible non-autoimmune causes of POF. For example, in our study the only AD patient with POF who was StCA, 17α-OH and P450scc Ab negative was diagnosed with Turner’s syndrome following karyotyping.

In our study, ACA, StCA and Abs to 21-OH, 17α-OH and/or P450scc were found in 8–12% of patients with POF associated with autoimmune disease other than AD (Table 2). In the third group of patients (isolated POF), ACA, StCA and Abs to 21-OH, 17α-OH and/or P450scc were detected in 10–13% of patients (Table 2). This suggests that some patients classed as isolated POF may show markers of adrenal and gonadal autoimmunity. However, the group we have studied cannot be considered representative of isolated POF in general, as these patients had been ‘selected’ for Ab testing by their doctors.

The prevalence of ACA, StCA and Abs to 21-OH, 17α-OH and/or P450scc in groups 2 and 3 was lower than in patients with POF and AD (Table 1) or in patients with autoimmune adrenal disease without POF (see above). In contrast, it was higher than in patients with non-adrenal autoimmune diseases without POF (0.7–1.8%) or healthy blood donors (0.3–2.5%) (15, 16, 22). The observation of a relatively high prevalence of adrenal and gonadal Abs in patients with POF without autoimmune adrenal disease should be confirmed in studies on larger and unselected groups of patients. In particular, the same criteria to classify patients as isolated POF should be used.

ACA and 21-OH Abs in patients without AD are recognized markers of a risk of developing adrenal failure, particularly in children (16, 23). Two of our patients with isolated POF who had detectable ACA and 21-OH Abs have indeed progressed to adrenal insufficiency 3 and 5 years after the onset of POF, respectively. These two patients were also positive for
StCA and for P450scc Abs and they may not be true representatives of isolated POF. POF in these patients may be an early manifestation of underlying autoimmune adrenal disease (potential or subclinical). ACA/21-OH Abs measurements in these patients may be helpful in order to monitor the adrenal function. Although it is not possible to prevent development of autoimmune adrenal failure at present, an early diagnosis should be helpful in taking measures to prevent an adrenal crisis.

We were unable to study the relationship between StCA, 17α-OH and/or P450scc Abs positivity and lymphocytic infiltration of the ovary in the patients. However, previous studies have indicated that these antibodies may be important markers of lymphocytic oophoritis (6).

In the case of patients with POF who are negative for all the Ab markers of lymphocytic oophoritis, studies of the genetic pattern, imaging of the ovary and an ovarian biopsy may well be appropriate in order to assess the cause of ovarian failure. An ovarian biopsy should help to identify the patients with lymphocytic infiltration characteristic of oophoritis even though Abs to steroidogenic enzymes are not detectable (6). In a small proportion of patients with autoimmune diseases, the Abs may not be present in serum at the time of diagnosis (24). In addition, an ovarian biopsy may reveal the absence of ovarian follicles or fibrotic ovaries with a few or numerous follicles, the latter being characteristic of the ovary resistant syndrome (Savage’s syndrome) (6). The gonadotropin receptor blocking Abs have been reported to be involved in the ovary resistant syndrome (25); however, the presence of these has not yet been confirmed (26). Furthermore, in Ab-negative patients with POF an ovarian biopsy may be helpful in the diagnosis of rare cases of POF caused by granulomatous or infiltrative diseases (1).

To date, attempts to identify specific ovarian autoantigens involved in the autoimmune response in POF have been unsuccessful (27–32). Abs to the (as yet unidentified) 51 kDa antigen present in granulosa cells and in placenta have been described in a few patients with POF associated with APS type 1 and isolated AD (33) but their significance is not clear at present. The Abs to 3β-hydroxysteroid dehydrogenase in patients with POF have been reported (34); however, they are rare in POF patients (32) and in those with APS type 1 (35).

Our study confirms a recent observation (32) that, when POF is associated with AD, StCA, 17α-OH and/or P450scc Abs are present in the majority of patients and are likely to be associated with autoimmune oophoritis. StCA, 17α-OH and/or P450scc Abs are detected in a much lower proportion of patients with POF associated with non-adenral autoimmune diseases or isolated POF. Measurement of ACA/21-OH Abs in some patients with POF may be important in identifying patients at risk of developing overt AD.

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