Autoimmune Polyglandular Syndrome Type II: Epidemiological, Clinical and Immunological Data

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Abstract

Background: Autoimmune polyglandular syndrome (APS) is characterized by the coexistence of several autoimmune diseases, affecting predominantly the endocrine glands. APS type I is distinguished from type II in which autoimmune thyroiditis, Addison’s disease and diabetes type 1 predominate. This article summarizes extensive epidemiological, clinical, and immunological data of a large population of Tunisian patients with APS II.

Methods: In a retrospective case finding study, we collected data from patients with APS type II who had been treated in our endocrine outpatient clinic between 1980 and 2007. One hundred and six patients fulfilled the criteria of APS II.

Results: Among these patients, 73 were female and 33 were male (mean age 36 and 42 years, respectively; P = 0.04). The mean age at the onset was 38 ± 14.9 years. Of the 106 patients, 76 had hypothyroidism due to autoimmune thyroiditis while 23 had hyperthyroidism (Grave’s disease). Sixty-six patients had type I diabetes mellitus (60.6% females and 39.5% males; P = 0.01). Addison’s disease was diagnosed in 39 patients, primary hypogonadism in 12 cases (11 females and one male), and neuro-hypophysitis was less frequently noted (n = 6). The most frequent coexistence of APS component diseases was between type I diabetes and thyroid disease (56.2%). The time interval between the advent of the first and the second autoimmune endocrinopathies varied considerably with longest time intervals between diabetes type I and thyroid disease and shortest time intervals between Addison’s disease and thyroid disease. Regarding autoantibodies in patients with APS II, anti-thyroid peroxidase antibodies were detected in 67.6%, thyroid stimulating hormone-receptor antibodies in 58%, and anti-thyroglobulin were less frequently positive (43.3%). Type I diabetes-associated antibodies against islet cell (islet cell autoantibodies) and glutamic acid decarboxylase were found in 23.6% and 51.8%, respectively. Antibodies to adrenal cortex were observed in 9.7% and ovarian antibodies in 8.8%.

Conclusion: The present study indicates that most patients with autoimmune thyroid disease will not develop additional endocrine disease. If they do, when a thyroid disease was as a first component disease, the time interval until the onset of a further autoimmune disease was relatively short and when thyroid disease was a second component disease a longer period of time elapsed.

Keywords: Autoimmune polyglandular syndrome; Autoimmunity; Antibody

Introduction

Autoimmune polyglandular syndrome (APS) or autoimmune polyendocrine syndrome are rare immune endocrinopathies characterized by the coexistence of at least two endocrine gland diseases that are based on autoimmune mechanisms. Neufeld and Blizzard suggested a classification of APS based on clinical criteria only [1, 2].

APS I, also known as an autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy, is a rare disease affecting young subjects [3, 4]. The highest prevalence has been found in Iranian Jews and Finns [3, 5, 6]. The clinical diagnosis of APS I is made in patients who present with two of the following three cardinal symptoms: chronic candidiasis, acquired hypoparathyroidism, and Addison’s disease [1-3].

Patients develop autoantibodies that correlate with affected tissues and show immune-mediated destruction of endocrine organs. APS is inherited in an autosomal recessive pattern and is now known to be caused by mutations in the autoimmune regulator gene [5-7].

APS II is characterized by Addison’s disease associated
with autoimmune thyroid diseases (ATDs) (Schmidt’s syndrome) and/or type I diabetes mellitus (DM) [1, 2]. Compared to type I and II, APS type III does not involve the adrenal cortex [8]. Apart from the absence of adrenal failure, APS type II and III represent a series of genetically influenced diseases that frequently coexist because they share susceptibility genes [9].

APS II is much more common than APS I and occurs in adulthood, mainly in the third or fourth decade, having an estimate prevalence of 1.4 - 2/100,000 in the general population and a higher incidence among females [10].

APS II is commonly associated with additional autoimmune diseases, such as celiac disease, pernicious anemia, chronic hepatitis, hypergonadotropic hypogonadism and vitiligo [10].

APS II is a heterogeneous group of diseases with modes of inheritance that are complex and ill defined. Approximately, half of the patients with APS II have relatives with autoimmune disorders; the most known genetic determinant of susceptibility to APS II represents the human leucocyte antigens (HLAs) region [9-11].

It is highly likely that there is a complex interaction between non-HLA loci and environmental factors [10].

In certain families, individuals from several generations may be affected and the disease transmission is consistent with a dominant mode of inheritance involving one or, at most, a few major genes [9].

The aim of this study is to investigate epidemiological, clinical and immunological data from a large group of patients with APS II.

**Materials and Methods**

In a retrospective case finding study, we collected data from patients with APS type II who had been treated in our endocrine outpatient clinic between 1980 and 2007. One hundred and six Tunisian patients fulfilled the criteria of APS II.

Adrenal insufficiency was confirmed by a low serum cortisol sample drawn between 6:00 and 8:00 am or an unstimulated serum cortisol after cosyntropin test (serum cortisol level less than 200 ng/mL after 30 and/or 60 min) with an increase in serum ACTH levels.

The thyroid abnormalities and DM are diagnosed in the conventional manner: thyrotropin secreting hormone (TSH) and serum-free thyroxin are used to diagnose thyroid disease, and the recommended diagnostic criteria for DM are based on a fasting blood glucose level.

Hypergonadotropic hypogonadism was diagnosed by enhanced follicle stimulating hormone and low testosterone levels.
in men and low estradiol levels in women.

The diagnosis of autoimmune hypophysitis was made after carefully exhaustive analyses of other causes of pituitary gland damage.

All hormone levels were measured with radioimmunoassay or immune-radiometric assay. The loading tests of the pituitary hormones to the respective hypothalamic stimulating hormones were performed when necessary.

ELISA was applied for autoantibodies against thyroid peroxidase (TPO; positive > 100 UI/mL), thyroglobulin (Tg; positive > 70 UI/mL), TSH receptor (positive > 2 UI/mL) and glutamic acid decarboxylase (GAD; positive > 10 UI/mL). Indirect immunofluorescence was used for adrenal cortex, ovarian, islet cell autoantibodies (ICAs), and antinuclear (AAN).

**Statistical analysis**

Group comparisons were performed by the use of Chi-deux-test for qualitative variables and Student’s t-test for quantita-
tive variables. ANOVA test compared several variables. Statis-
tic software was used: SPSS (version 13), R 2.6.0 (free),
NTSYSpc 2.1, SPAD (version 4.5), and Matlab (version 7).
Statistical significance was set at P value less than 0.05.

Results

One hundred and six patients with APS II have been fol-
lowed regularly in our endocrine outpatient clinic since
1980. Seventy-three were females and 33 were males, which
corresponds to 2.21 female to male ratio. The mean age of
occurrence is 38 ± 14.9 years. The incidence of new cases
has one peak during 20 - 30 years and a larger peak in the
fourth and fifth decades. The age when our patients devel-
op APS II is earlier in females (mean age 36 years) than in
males (mean age 42 years) with P of 0.04. A family history
of autoimmune diseases was noted in 43.3%, with highest
frequency of ATDs of 31.1%.

The analysis of clinical data showed that ATD had the
highest prevalence (n = 99; 93.4%), with an unequal number
of Hashimoto thyroiditis (HT) (n = 76; 76.7%) and Grave’s
disease (n = 23; 23.2%).

Type I DM, in the second position, was observed in 66
patients. Addison’s disease was noted in 39 cases (36.8%),
whereas hypergonadotropic hypogonadism (n = 12; 11.3 %)
and neuro-hypophysis (n = 6; 5.6%) occurred less fre-
quently (Fig. 1A).

With regard to non-endocrine autoimmune component
diseases, vitiligo (n = 6; 5.6%) was most frequently ob-
erved, followed by alopecia areata (n = 4; 3.7%) and Sjo-
gren’s syndrome (n = 3; 2.8%). The other autoimmune dis-
ese occurred less frequently (Fig. 1B).

Type I DM was the first component disease of APS in
47.1% of cases, whereas thyroid disease was objected in
44% and Addison’s disease in 24.5% of cases. Concomitant
presentation occurred in 25 cases (26%), with most frequent
association between thyroid diseases and Addison’s disease
(52%).

The most frequent coexistence of APS component dis-
eases was between DT1 and ATD (56.2%). Less commonly,
coexistence occurred between thyroid and Addison’s disease
(26%); the other associations were less frequent (Fig. 2).

The time interval between the manifestation of the first
and second autoimmune endocrinopathies varied consid-
erably (Fig. 3), with the longest time interval between type I
diabetes and thyroid disease (127 months = 10.3 years), but a
shorter time interval between Addison’s disease and thyroid
disease (17.6 months = 1.4 years).

In general, when a thyroid disease was present as a first
component disease, the time interval until the onset of a fur-
ther endocrinopathy was relatively short (4.3 years between
thyroid/diabetes and 1.4 years between adrenal/diabetes with
non-significant differences between these time intervals). On
the other hand, when thyroid disease was the second com-
ponent disease, a longer period of time elapsed (10.3 years
between diabetes/thyroid and 5.3 years between adrenal/
thyroid with non-significant differences between these time
intervals). The difference between time intervals in thyroid/
other endocrinopathy (30 months = 2.5 years) and other en-
docrinopathy/thyroid (122 months = 10.1 years) is statisti-
cally significant (P = 0.00003).

Regarding autoantibodies in patients with APS II, an-
tibodies against TPO were the most frequent (67.6%), an-
tibodies against TSH-R (58%), antibodies against Tg were
less frequent (43.3%). Type I diabetes-associated antibodies
directed against GAD were found in 51.8 % and ICA in only
23.6%. Other autoantibodies were less frequent: anti-adrenal
cortex were positive in 9.7% and anti-ovarian in 8.8% of
cases.

ATDs in APS II

ATDs were present in 99 patients, the mean age of occur-
rence was 38 years and the trend of presentation is shown in Figure 4. HT had the highest prevalence (n = 45 with goiter and n = 31 without goiter) whereas Grave’s disease was noted in 23 cases.

Grave’s disease was manifested at an earlier age (mean age: 33 years), goitrous HT (mean age: 35 years) and atrophic HT later (mean age: 46 years); the difference between ages is statistically different.

The female/male ratio was 2.8. No significant male to female preponderances were noted for ATD and their different component.

Anti-TPO and/or anti-Tg antibodies were detected in 74.6% of patients with ATD with a higher level of antibodies in HT (mean level of anti-TPO: 1,700 UI/mL; anti-Tg: 1,600 UI/mL).

**Type I DM**

Among our patients with APS II, type I DM was present in 63% of cases. Type I DM was manifested earlier, and the mean age of presentation of DM was 31 years.

Significant female preponderances were noted for type I DM (P = 0.01). The female/male ratio was 1.53. Pancreatic-autoantibodies (ICA and/or anti-GAD) were positive in 55% of cases. Thirty-one percent of patients presented with a non-acute onset of diabetes and insulin therapy was instaurated after a mean duration of 4.7 years in these cases.

**Addison’s disease**

Among our 106 patients, 39 had Addison’s disease. The mean age at presentation was 39 years and the trend of presentation is reported in Figure 4.

Women are affected three times more often than men; the female/male ratio was 3.1. Adrenal crisis revealed the disease in 20.5% of cases. The antibodies of anti-adrenal cortex were positive only in 21.8% of cases because they were analyzed many years after the disease diagnosis.
Cluster analysis

Through the examination of various patient characteristics, clinical subgroups of patients with APS II have been identified. Using a number of cluster analysis approaches in the examination of patients, we were able to identify four groups or “classes” of patients (Fig. 5): 1) Class I: the component of this group was manifested at an early age (mean age: 28 years), and it corresponded to patients who had frequently type I DM associated with Addison’s disease. 2) Class II: corresponded to females, whose mean age at presentation was 29 years, and presented goitrous HT and POF. 3) Class III: corresponded to adults whose mean age at presentation was 43 years, who had atrophic HT and Addison’s disease. 4) Class IV: corresponded to adult females whose mean age at presentation was 38 years, with the frequent association of type I DM and HT.

We concluded that if a young patient developed an Addison’s disease, he would have type I DM associated, but if he was an adult he would develop atrophic HT associated with Addison’s disease.

If a young woman had a HT, she would develop a POF, but if she was adult she would develop a type I DM.

Discussion

APS has become an increasingly recognized clinical entity in endocrinology, joining a growing list of disorders likely to be mediated by autoimmune pathogenic mechanisms.

There is controversy over the syndrome classification. According to Neufeld [1, 2], APS II refers to Addison's disease and thyroid autoimmunity or type I DM; APS III refers to thyroid autoimmunity and another autoimmunity (but not Addison’s disease). Others authors, with whom we tend to agree, consider all the above combinations in APS II [9].

Muir [9], considering that a distinction between APS II and III is arbitrary, suggested that APS II and III represent a series of genetically influenced diseases that frequently co-exist because they share susceptibility genes.

This study reports epidemiological, clinical and serological data of 106 patients with APS II. APS II is rather rare with the incidence of 1.4 - 4.5 cases/100,000 inhabitants [10]. The disease affected mainly adult women; the mean age at presentation is 35 years [10, 12, 13]. The female/male ratio is 2.7 - 3.7 [10, 12, 13]. In our study the mean age at presentation was 38 years with female/male ratio 2.21. Significant male and female preponderances were noted for type I DM.

Table 1. Prevalence of Component Disease in APS II

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<tr>
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<tr>
<td>Thyroid (%)</td>
<td>93.4</td>
<td>65.5</td>
<td>97</td>
</tr>
<tr>
<td>Type I DM (%)</td>
<td>62.3</td>
<td>60.9</td>
<td>35</td>
</tr>
<tr>
<td>Addison (%)</td>
<td>36.8</td>
<td>18.5</td>
<td>23</td>
</tr>
<tr>
<td>Gonadal failure (%)</td>
<td>11.3</td>
<td>5.3</td>
<td>16.1</td>
</tr>
<tr>
<td>Hypophysitis (%)</td>
<td>5.6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vitiligo (%)</td>
<td>5.6</td>
<td>19.9</td>
<td>19.3</td>
</tr>
<tr>
<td>Alopecia (%)</td>
<td>2.8</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Sjogren’s syndrome (%)</td>
<td>2.8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pernicious anemia (%)</td>
<td>1.8</td>
<td>5.3</td>
<td>16.1</td>
</tr>
<tr>
<td>Celiac disease (%)</td>
<td>1.8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Autoimmune hepatitis (%)</td>
<td>0.9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Immune thrombocytopenia (%)</td>
<td>0.9</td>
<td>0</td>
<td>0</td>
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</tbody>
</table>
Dittmar and Kahaly [12] noted a significant difference between males and females in type I DM and thyroiditis but he did not find a difference for manifest Graves’s disease and Addison’s diseases.

Familial aggregation of APS II and III does not seem to be inherited as Mendelian traits [9, 10, 14, 15]. In certain families, individuals from several generations may be affected and the disease transmission is consistent with a dominant mode of inheritance. Therefore, APS II appears to follow an autosomal dominant mode of inheritance with variable penetrance [9, 14, 15]. In our study, a family history of autoimmune diseases was noted in 43.3%, with highest frequency of ATDs (31.1%). Because of a 50% transmission rate from affected mothers to daughters, the production of anti-Tg and anti-TPO antibodies is considered to be an autosomal dominant gene [9, 10].

The most prevalent endocrinologic abnormality is ATD, occurring from 65.5% to 97% of APS II, followed by type I DM, which are reported to develop in 35% to 70%, Addison’s, being less frequent, occurred in 18.5% to 23% [10, 11, 13]. Other minor autoimmune disorders including gonadal failure and hypophysitis pernicious anemia occurred with different rates (Table 1).

Compared with the studies in literature (Table 1), the present study about patients with APS II found similar prevalence of thyroid disease as in Wyermann’s study [13], and similar prevalence of type I DM as in Dittmar’s [12] but a higher prevalence of Addison’s disease, hypophysitis and celiac disease. A lower prevalence of vitiligo and pernicious anemia was also noted. The prevalence of gonadal failure and alopecia areata was variable in different series.

Epidemiological data showed varying time intervals between the manifestations of different component diseases of APS II, with longest time interval between type I DM and thyroid disease and shortest time between Addison’s and thyroid disease.

Dittmar and Kahaly [12] also noted in a study of 151 patients with APS II that the longest time intervals were between type I DM and thyroid disease (13.3 ± 11.8 years) and between vitiligo and thyroid disease (16.3 ± 13.3 years), and the shortest time interval was between Addison’s disease and thyroid disease. Thus, time intervals between first and second component disease manifestations were significantly different, where thyroid disease and vitiligo, respectively, were the first disease component.

In the APS II series of Neufeld et al [1, 2] and in patients with type I DM, thyroid disease was the autoimmune condition with a later age of onset. Thus, polyglandular involvement among the total population of patients with ATD is infrequent and when it does occur, the onset of other APS components has often preceded the diagnosis of thyroid disease.

Irvine [15] reported that 69% of patients with autoimmune adrenalitis have concomitant ATD, with Grave’s disease and primary atrophic hypothyroidism being more common than goitrous autoimmune thyroiditis.

In our studies, 48.7% of patients with Addison’s disease have concomitant autoimmune disease, with primary atrophic hypothyroidism in 55.5% and goitrous thyroiditis in 33.3%.

The results suggest that early screening of patients with autoimmune endocrine diseases enhances the possibility of identifying patients at risk for APS II [10, 15].

Discrepancies may occur between the clinical expression of APS and the presence or absence of positive results of organ-specific serologic testing. Thus, positive autoimmune serologic results may precede the onset of clinical disease [10].

Refined endocrine function tests can now be performed

### Table 2. Prevalence of Positive Autoantibodies in APS II

<table>
<thead>
<tr>
<th>Autoantibodies against</th>
<th>Present study (106 cases)</th>
<th>Dittmar and Kahaly [12] (151 cases)</th>
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</thead>
<tbody>
<tr>
<td>TPO (%)</td>
<td>67.6</td>
<td>78</td>
</tr>
<tr>
<td>TSH-R (%)</td>
<td>58</td>
<td>48</td>
</tr>
<tr>
<td>Tg (%)</td>
<td>43.3</td>
<td>50</td>
</tr>
<tr>
<td>Parietal gastric cell (%)</td>
<td>-</td>
<td>54</td>
</tr>
<tr>
<td>GAD (%)</td>
<td>51.8</td>
<td>51</td>
</tr>
<tr>
<td>ICA (%)</td>
<td>5.6</td>
<td>23</td>
</tr>
<tr>
<td>Insulin (%)</td>
<td>-</td>
<td>42</td>
</tr>
<tr>
<td>Adrenal cortex (%)</td>
<td>9.7</td>
<td>26</td>
</tr>
<tr>
<td>Ovarian (%)</td>
<td>8.8</td>
<td>-</td>
</tr>
</tbody>
</table>
in the follow-up of patients suspected to have APS, and first-degree relatives could be screened every few years with standard tests for glycemia and for early or partial deficiency, which may indicate future glandular failure [10, 14, 16].

The frequencies of the relevant autoantibodies detectable at the clinical onset of the diseases constituting APS II are summarized in Table 2. Autoantibodies against TPO and Tg are the more frequent positive in APS. This is a positive correlation with the frequency of ATD which represents the most component of APS II [10, 11, 13]. Weyermann et al [13] noted a high percentage (70%) of his patients had high titers of antiparietal cell antibodies (APC). The clinical importance of APC is demonstrated by the associations of autoimmune gastropathy such as pernicious anemia, gastritis, and iron deficiency anemia. Christophe et al [17] noted that type I DM has a high prevalence of PCA (20.9%), and that anti-TPO were more frequent in PCA-positive patients than in those without PCA suggesting an association between gastric and thyroid autoimmunity.

Patients with polyglandular autoimmunity also have been reported to have an increased incidence of circulating non-organ-specific autoantibodies, including autoantibodies against mitochondria, single-stranded deoxyribonucleic acid and double-stranded deoxyribonucleic acid and ribonucleic acid [18].

Circulating immune complexes have been documented in patients with HT, Grave’s disease and insulin-dependent DM [19, 20]. In our study, circulating immune complexes, cryoglobulinemia and AAN antibodies were found in 23.8%, 14.2% and 13.5% of cases respectively.

HLAs play a role in conditioning T lymphocyte response to antigens, and the association of different HLA alleles with many autoimmune disorders has been shown [9, 21]. HLA-D subgroup DR3 and HLA-B8 have been found to be associated with APS II [22].

A degree of genetic polymorphism in the expression of the HLA-DR antigen subgroup may also account for this variability among families in the expression of APS II [12, 23, 24].

The role of HLA in APS II and its component diseases has been extensively examined using case-control association studies. Susceptibility is usually associated with the DR3DQB1*0201 and DR4DQB1*0302 haplotypes, particularly heterozygotes for the two haplotypes [9, 24, 25].

CTLA4 on chromosome 2 is a candidate gene for autoimmune diseases because of its important role in the T cell proliferate response. This locus has been related to type I DM and ATD, Grave’s disease and HT [21, 26]. CTLA4 gene may be one of the susceptible genes that can influence the onset of APS II and its component diseases.

Conclusion

A continued suspicion of other glandular hypofunction should be maintained in following patients with any type of endocrine gland hypofunction, since the risk of multiple glandular involvements is significant.

Autoantibodies are useful markers for the prediction of the development of APS.

In view of the possible long time interval between manifestation of the first and further autoimmune endocrinopathies, regular and long-term examination of patients with endocrine autoimmune disorders seems necessary.

References


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