Effect of long-term cabergoline therapy on the immunological pattern and pituitary function of patients with idiopathic hyperprolactinaemia positive for antipituitary antibodies

A. De Bellis*, A. Colao**, A. Savoia, C. Coronella, G. Tirelli, M. Conte, R. Pivonello*, A. Bellastella, A.A. Sinisi, A. Bizzarro¹, G. Lombardi², G. Bellastella

Chair of Endocrinology, ¹Chair of Immunology, Department of Clinical and Experimental Medicine and Surgery “F. Magrassi, A. Lanzara”, Second University of Naples, Italy, ²Department of Molecular and Clinical Endocrinology and Oncology, Federico II University of Naples, Italy

Short title: Prolactin, cabergoline and pituitary autoimmunity.

Key words: antipituitary antibodies, idiopathic hyperprolactinemia, lymphocytic hypophysitis, cabergoline

* Annamaria De Bellis and Annamaria Colao have contributed equally to the manuscript.

Correspondence:
Annamaria De Bellis MD
Chair of Endocrinology
Department of Clinical and Experimental Medicine and Surgery
“F. Magrassi, A. Lanzara”,
Second University of Naples
Via Pansini N. 5, 80131 Napoli – Italy
Telephone number: 39-81 5666634
Fax number: 39-81 5666628
E-mail annamaria.debellis@unina2.it
Summary

Objective  The occurrence of antipituitary antibodies (APA) in patients with idiopathic hyperprolactinemia (IH) and the effects of dopamine agonists on these antibodies and long-term pituitary function outcome have been so far not evaluated. This longitudinal study was aimed at investigating, in patients with IH the occurrence of APA and the effect of cabergoline on the pituitary function and behaviour of APA.

Design  Sixty six patients with IH were studied. APA (by indirect immunofluorescence) and pituitary function were investigated every year for 3 years.

Results: Seventeen patients resulted APA positive (Group 1) and 49 APA negative (Group 2). Eight patients of Group 1 (Group 1a) and 24 of Group 2 (Group 2a) were asymptomatic and then not treated; instead, 9 patients in Group 1 (Group 1b) and 25 in Group 2 (Group 2b), showing symptoms of hyperprolactinemia, were treated with cabergoline for 2 years.

Among the untreated patients, during the follow-up, those APA positive (Group 1a) showed an increase of APA titers and PRL levels with partial pituitary impairment in some of them; instead those APA negative (Group 2a) persisted negative with normal pituitary function despite persistent hyperprolactinemia. Among the treated patients, those APA positive (Group 1b) showed normalization of PRL levels, APA disappearance and recovery of pituitary function (when initially impaired) during cabergoline treatment, persisting also at last observation (off-therapy). Instead all patients of Group 2b persisted APA negative during the follow-up with normalization of PRL levels and stable normal pituitary function during cabergoline therapy but showing a further increase of PRL at the last observation.

Conclusions: The presence of APA in some patients with idiopathic hyperprolactinemia suggests a possible occurrence of autoimmune hypophysitis at potential/subclinical stage; an early and prolonged cabergoline therapy could interrupt the progression to an overt clinical stage of the disease. However, the small amount of patients investigated suggests caution against generalization
of our assumption and prompts to further controlled studies on a more numerous population to verify these conclusions.
Introduction

Many studies support a modulatory role of prolactin (PRL) on the immune system (1,2). Its action begins through the binding to a specific membrane receptor on the immune cells triggering a cascade of events leading to many immune effects (3-6). Hyperprolactinemia has been often described in active phase of non organ-specific autoimmune diseases but also of some organ-specific autoimmune diseases as Addison’s disease, type 1 diabetes mellitus, Graves’ disease, Hashimoto’s thyroiditis, and celiac disease (7-14); moreover, an increased prevalence of several antibodies in subclinical stage of autoimmune diseases has been described in patients with hyperprolactinemia (10). The increased serum PRL levels in autoimmune diseases could reflect on the one hand an increase of pituitary secretion and on the other hand a direct production by lymphocytes infiltrating the aggressed organs (2). Hyperprolactinemia has been frequently observed in patients with lymphocytic hypophysitis (LYH); moreover, antipituitary antibodies (APA) have been detected in some patients with this disease but their pathogenetic role is still discussed (12,15-18). However, the detection of APA has been at least considered good marker of possible pituitary autoimmune involvement (17-20), especially in patients with other autoimmune diseases (21); thus, the evaluation of these antibodies in patients with idiopathic hyperprolactinemia (IH) could be useful to disclose cases of autoimmune pituitary disease with pituitary function still normal or mildly impaired.

Dopamine agonists, usually employed as antiprolactinemic drugs have been shown to induce remission of some active autoimmune diseases in hyperprolactinemic treated patients suggesting a possible role in improving both hyperprolactinemia and autoimmunity (22-23) but its beneficial effect on the course of LYH is still discussed (15). The aim of this 3 year longitudinal study was two fold: first, to search for APA in a cohort of patients with IH; second, to investigate the effect of long-term therapy with a dopamine agonist (cabergoline) on the over-time behaviour of APA and pituitary function in patients with symptomatic hyperprolactinemia with respect to that of a control
Materials and methods

Patients
During an organ-specific autoantibody screening performed from 1996 to 2001 in a large cohort of patients with hyperprolactinemia, 71 patients with idiopathic hyperprolactinemia (age range 28–40 years; 57F, 14M), newly diagnosed at the Endocrine Units of Federico II and Second University of Naples, were recruited for this study. The diagnosis of idiopathic hyperprolactinemia was established on the basis of the following criteria: evidence of a normal pituitary-hypothalamic region on magnetic resonance imaging (MRI) and absence of other causes of increased prolactin levels (such as drug-induced hyperprolactinemia, primary hypothyroidism, chronic renal or hepatic failure,) (24).

Transversal Study:
In all patients, anti-pituitary antibodies, other organ-specific antibodies and anterior pituitary function were evaluated.

Longitudinal Study:
According to the guidelines of the Pituitary Society, on the basis of the presence/absence of symptoms of hyperprolactinemia (25), 37 patients (age range 28–40 years, 31F/6M) without symptoms of hyperprolactinemia did not receive any treatment, while 34 patients (age range 30–39 years, 24F/10M) with clinical features of hyperprolactinemia (oligo-amenorrhoea, galactorrhea, anovulatory infertility in women; impotence, decreased libido and infertility in men) underwent cabergoline therapy for 2 years. Cabergoline was administered orally at a single starting dose of 0.5 mg in the first week and then at a dose of 0.5 mg twice weekly. After 4 months of treatment, the dose of cabergoline was again reduced to a single dose of 0.25 mg twice weekly, because in all
patients the PRL values decreased to < 5 μg/L. In all asymptomatic and symptomatic patients, APA and anterior pituitary function were evaluated every year for 3 years after the first observation; the last observation in treated patients was performed one year after cabergoline withdrawal. Moreover, treated patients underwent a complete echocardiographic study at start and at the end of the follow-up to verify a possible valvular heart alteration caused by long-term cabergoline treatment (26-29). Finally, MRI of hypothalamic-pituitary region was repeated in APA positive patients at the end of the follow-up. All patients gave written informed consent to the study which was approved by the local institutional review boards (review boards of Department of Molecular and Clinical Endocrinology and Oncology, Federico II University of Naples and of Department of Clinical and Experimental Medicine and Surgery “F. Magrassi, A. Lanzara”, Second University of Naples).

**APA evaluation**

APA were investigated by an indirect immunofluorescence method on cryostat sections of young baboon pituitary gland (supplied by BioSystem Italia s.r.l), as previously described (30). In particular, fluorescein isothiocyanate (FITC) conjugated goat anti human total Ig sera were used to detect the presence of APA. Then, positive serum samples were tested with fluorescein isothiocyanate (FITC) conjugated goat anti human total IgG, IGM and IGA sera separately. Taking into account our previous experience, we used an arbitrary cut-off of 1:8 considered able to discriminate the positive samples (31). Fifty sera of healthy adults (35F; 15M) were used as controls for APA evaluation.

**Anterior pituitary function**

Hormonal pituitary function was appropriately investigated in all patients. In particular, basal anterior pituitary hormones were evaluated in duplicate: corticotropin (ACTH), growth hormone (GH), thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), luteinizing hormone (LH) and PRL were determined by IRMA, using commercial kits. Specimens were
obtained by inserting a needle catheter in recumbent patients after nocturnal rest. Samples for PRL were pretreated with polyethylene glycol (PEG) in order to exclude the occurrence of macroprolactinemia (32). Only patients whose PRL levels still exceeded the normal range of values (4-19 μg/L for females and 4-16 μg/L for males) were enrolled into the study. The dynamic behaviour of some of these hormones was also studied by testing their response to appropriate stimuli. In particular, GH and cortisol secretions were also investigated by testing their response to GHRH-arginine test (33) and to standard ACTH stimuli (34), respectively, considering as normal a GH response > 16.5 μg/L and a cortisol response > 550 nmol/L, following the cut-off referred to non overweight normal adults. Moreover, target organ hormones (free T4, free T3, testosterone, estradiol, progesterone and cortisol, by RIA) and insulin-like growth factor 1 (IGF1) by IRMA, were also evaluated using commercial kits. Taking into account the negative influence of hyperprolactinemia on the pituitary-gonadal function, the data regarding the longitudinal variations of gonadotropins and gonadal hormones have not been considered in the present study due to the difficulty of explaining whether possible changes of these hormones could be attributed to variations of prolactin levels "per se" or to variations of pituitary autoimmunity.

Statistical analysis

Data are expressed as mean ± SD, unless otherwise specified. Nonparametric test were used because of the non-Gaussian distribution of the data. Comparison within each subgroup were evaluated using Wilcoxon test. Differences between the frequencies were evaluated by a Fischer’s exact test. Spearman's rank-correlation analysis was used to calculate the association between APA titres and PRL levels. A value of $P$ less than 0.05 was considered statistically significant.

Results

Five female of 37 asymptomatic hyperprolactinemic patients were excluded from the study because their PRL levels resulted increased due to interference of macroprolactinemia and then 32
asymptomatic (28F;4M), and 34 symptomatic (24F;10M) patients were finally enrolled into the study.

The presence of APA (all of IgG sub-class), with titres ranging from 1:16 to 1:128, was evidenced in 17 out of 66 patients (25.7%) (Group 1) while the remaining patients resulted negative for APA (Group 2) (Fig.1). None of the 50 healthy control sera resulted positive for APA. The characteristics of Group 1 and Group 2 are summarized in Table 1.

All patients of both groups showed normal TSH and free thyroid hormone levels; moreover PRL levels were not significantly different between the two groups. With regard to the secretion of other hormones, no hormonal alterations were evidenced in patients of Group 2. Basal and cortisol response to ACTH and GH response to GHRH+ arginine were significantly lower in Group 1 with respect to values evidenced in Group 2.

In particular, 6 out of 17 (35%) patients of group 1 showed partial pituitary impairment, characterized by subclinical ACTH deficiency (normal basal cortisol and ACTH values but cortisol response to ACTH ranging from 400 to 475 nmol/L) and/or mild GH deficiency (GH response to GHRH+ arginine < 16.5 μg/L but > 9 μg/L). These patients did not receive replacement therapy.

At last, the prevalence of other organ specific antibodies were significantly higher (p<0.01) in group 1 with respect to group 2. In particular 13 out of 17 patients positive for APA showed presence of anti thyroperoxidase and/or thyroglobulin antibodies; some patients showed also presence of islet cell antibodies and parietal cell antibodies even if without overt clinical diseases, while none of them showed presence of non organ specific antibodies. As regard the longitudinal study performed in the two groups of patients, 8 patients of Group 1 were untreated because asymptomatic (Group 1a) and 9 treated because symptomatic (Group 1b). Moreover, 24 asymptomatic patients of Group 2 were untreated (Group 2a) while 25 symptomatic patients were treated (Group 2b).

The longitudinal behaviour of APA during all the follow-up period in all patients is depicted in Fig.2. All patients of Group 1a showed the presence of APA during all the follow-up with a
significant increase of their titres at the second year (titres ranging from 1/32 to 1/128, $p=0.003$ with respect to the starting values) and at third year (titres ranging from 1/64 to 1/256, $p=0.001$ with respect to the starting values). All patients of Group 1b showed during the follow-up the disappearance of APA since the first year of cabergoline therapy until the last observation one year after the stopping of therapy. All untreated and treated patients of Group 2 persisted negative for APA during all the follow-up.

The behaviour of pituitary function in untreated and treated patients of both groups during the follow-up is depicted in Fig.3. All patients in Group 1a showed a progressive increase of PRL levels with respect to the starting values. Moreover, in these patients a significant progressive decrease of ACTH and GH levels was observed until the end of the study. In particular, all of them showed, at the end of the study, GH response to GHRH + arginine $< 9 \mu g/L$, accompanied in 7 patients by a significant decrease of cortisol response to ACTH and decrease of ACTH levels occurring already at the second year in 2 patients (who were thus excluded from the study to undergo an appropriate replacement therapy) and at the third year in the other 6 patients. Instead, all patients of Group 1b showed during cabergoline therapy PRL levels $< 5 \mu g/L$ with an increase of values off therapy, but still persisting in the normal range. Moreover, these patients showed normal pituitary function at the first and the second year of cabergoline therapy persisting also at the last observation off therapy. In particular, 5 out 9 patients who had initially normal pituitary function, persisted stable during all the follow up, while the 4 with partial pituitary impairment at the start of the study showed a recovery of anterior pituitary function during the follow-up. Among the patients in Group 2, all those untreated (Group 2a) showed at the 2nd and the 3rd year of the follow-up PRL values significantly lower with respect to values evidenced in untreated patients positive for APA (Group 1a). Instead, all patients of Group 2b showed PRL levels $< 5 \mu g/L$ during cabergoline therapy but a significant increase of values 1 year after cabegoline withdrawal exceeding the normal range and significantly higher with respect to values evidenced in treated patients of Group 1b. The levels of other pituitary hormones were normal in all patients of Group 2 during all the study span.
In particular, GH response to GHRH + arginine was significantly higher in untreated and treated patients of Group 2 with respect to those of untreated and treated patients of Group 1, whereas cortisol response to ACTH was significantly higher only in untreated patients of Group 2 (Group 2a) at the second and the third year observation with respect to that of untreated patients of Group 1 (Group 1a) at the same times. In patients of Group 1 (Group 1a and 1b, respectively), APA titres were significantly correlated to the PRL levels during the longitudinal study \((r=0.793; p= 0.019\) and \(r= 0.878; p= 0.004; r= 0.700; p= 0.036; r= 0.809; p= 0.008\) at the start of the study and at the second year in Group 1a and in Group 1b respectively; \(r= 0.827; p=0.029\) at the third year in Group 1a. In particular, in Group 1a high titres of APA were correlated with high levels of PRL during all the follow-up; instead in Group 1b high titres of APA were correlated with high levels of PRL at the start of the study; the absence of APA was correlated with low levels of PRL levels 2 years after cabergoline therapy; this correlation disappeared after 3 years of the follow-up when APA were negative but PRL levels were in the normal range. All patients of Group 1 showed normal characteristics of pituitary region on MRI at the end of the study. The thyroid function was persistently normal in untreated and treated patients of both Group 1 and 2. Finally none of treated patients of Group 1b and 2b showed echocardiographic alterations at the start and at the end of the study.

**Discussion**

This study demonstrates that patients with idiopathic hyperprolactinemia, positive for APA, could belong to a potential/subclinical stage of autoimmune hypophysitis which can progress to clinically overt phase of the disease and that a long-term cabergoline therapy seems to be able to interrupt this progression.

Idiopathic hyperprolactinemia is a benign very frequent condition even if some studies suggested an high prevalence of many antibodies as anti DNA, anticardiolipin anti nuclear and anti thyroid antibodies without clinical evidence of autoimmune diseases (10). Kramer et al. (35) showed in
untreated IH patients a percentage of TgAb and TPOAb significantly higher than that observed in treated IH patients and in controls, thus suggesting a significant greater occurrence of subclinical autoimmune thyroiditis in untreated than in treated IH patients. Recent studies performed on the prevalence of LYH in patients with other autoimmune diseases demonstrated that APA are present in 24% of patients with clinical autoimmune thyroid diseases and that the majority of them show mild/subclinical GH deficiency suggesting that APA may be considered good markers of a possible autoimmune pituitary involvement (21).

In this connection the present study showed that 25% of our patients with IH resulted APA positive and 35% of them showed a subclinical pituitary impairment. Another important result of this study was that 75% of APA positive patients showed also presence of thyroid antibodies without clinical autoimmune thyroiditis. This result suggests that our patients with apparently IH positive for APA could belong to a potential/subclinical stage of LYH and they may be included in the majority of cases in autoimmune polyendocrine syndrome type 3.

High PRL levels have been frequently observed in patients with LYH accompanied by enlargement of pituitary gland on MRI. Hyperprolactinemia in some of such cases, could be caused by a decrease in the dopamine delivery to the anterior pituitary due to stalk compression by pituitary suprasellar inflammatory mass (18). Instead, other mechanisms have been suggested when the autoimmune process is confined at the sellar region (10,17,18), as occurring in our APA positive patients with IH and normal pituitary function or partial pituitary impairment but without pituitary enlargement on MRI. In particular, a bi-directional communication between the immune system and PRL could have determined an increase of PRL release by both lactotrophs and directly by the immune cells infiltrating the pituitary (2,5,10). In fact, the absence of findings on MRI does not exclude the occurrence of autoimmune pituitary process in our APA positive patients because some cases of biopsy proven lymphocytic hypophysitis with slight pituitary lymphocytic infiltration, do not show significant findings on MRI (36).
The results of our longitudinal study first demonstrate that all untreated hyperprolactinemic patients positive for APA at the start of the study show persistently high PRL levels during all the follow-up span with progressive increase of APA titres over-time accompanied by worsening of anterior pituitary function. In previous studies we demonstrated that some organ-specific autoantibodies, when persisting over-time at high levels (titre > 1:8) in untreated patients with subclinical autoimmune diseases, can be associated with progressive worsening of the respective glandular function until a clinically overt stage of the autoimmune diseases (37-39). Moreover, in a recent longitudinal study we demonstrated in children with idiopathic short stature positive for APA, but with normal GH response to the stimuli, that the persistence of APA for two years was accompanied by impairment of this response suggesting that APA, when present at high titres, could be good predictive marker of autoimmune GH deficiency (40). With this in mind we suggest that a longitudinal follow-up of APA may be useful in hyperprolactinemic patients positive for these antibodies in order to predict those of them prone to progress from a potential/subclinical to an overt phase of autoimmune pituitary disease, possibly allowing to interrupt this progression with an appropriate early therapy.

In this connection, the other crucial result of this longitudinal study regards the effects of long-term cabergoline therapy in patients with idiopathic hyperprolactinemia positive for APA. In particular, a 2 year cabergoline therapy in our APA positive patients was able to induce decrease of PRL levels, disappearance of APA and recovery of pituitary function, when impaired at the start of the study. These therapeutic benefits persisted also one year after the stopping of treatment. Some authors evidenced remission of active systemic lupus erithemathosus and active rheumatoid arthritis in hyperprolactinemic patients treated with bromocriptine, suggesting a causal relationship between hyperprolactinemia and autoimmune diseases and a possible immunosuppressive, other than antiprolactinemic effect of dopamine agonists (22,23). In patients with LYH, dopamine agonists seem to be able in lowering the hyperprolactinemia and improving visual field alterations but the beneficial impact of these agents on the course of the disease is still unproven (15,17)
because longitudinal studies on the long-term effects of these drugs are lacking in the literature. Moreover, with regard to the cabergoline, a drug with high affinity for the dopamine receptor D2, recent reports suggest that it plays an inhibiting role on several proinflammatory cytokines (41) and antagonizes the effects of VEGF exerted at tissue level through the binding of this factor to its receptor VEGF-R. The VEGF-VEGFR unit increases angiogenesis and vascular permeability, both known to favour the expansion of the inflammatory and autoimmune processes (42-43). Cabergoline, preventing these actions, could contribute to interrupt the autoimmune inflammatory cascade. This is particularly important for processes involving pituitary gland because VEGF is expressed at pituitary level (44,45) and its expression is under dopaminergic inhibiting control: in fact, the treatment with D2 receptor antagonist, haloperidol, induced in mice increase of both VEGF expression and PRL release (44). Thus, conversely, the dopamine agonist cabergoline could improve pituitary autoimmune inflammation both reducing PRL production and inhibiting VEGF expression.

In conclusion, the results of our longitudinal study confirm the relationship between hyperprolactinemia and autoimmunity, suggesting that, even if idiopathic hyperprolactinemia is usually a benign condition, the presence of APA in about 25% of cases could identify a particular subgroup of patients with potential/subclinical autoimmune hypophysitis. Thus, the monitoring of APA in such patients seems to be useful to predict a progression towards an overt phase of this disease. Our results also strongly suggest a possible immuno-inhibitory effect of cabergoline during a long-term therapy in such patients. Thus, an early and prolonged cabergoline therapy is advisable in those positive for APA because it seems able to induce progressive disappearance of these antibodies with recovery of a normal anterior pituitary function when previously impaired. This is probably due to the capability of cabergoline to interrupt the pituitary cell damage through normalization of PRL levels and inhibition of cytokines, vascular hyperpermeability and angiogenesis, all factors responsible for triggering and perpetuating the autoimmune inflammatory pituitary process with consequent possible remission. However, the small amount of patients
investigated suggests caution against generalization of our assumption and prompts to further controlled studies on a more numerous population to validate these conclusions.

References


Legend to figures:

Figure 1. Antipituitary antibodies detected by immunofluorescence method:
A: positive serum sample showing intracytoplasmatic immunofluorescence of pituitary cells.
B: negative control serum.

Figure 2. Longitudinal behaviour of antipituitary antibodies (APA) in patients with idiopathic hyperprolactinemia.

○: Asymptomatic untreated initially APA positive patients (Group 1a)
●: Symptomatic initially APA positive patients treated with cabergoline for 2 years (Group 1b)
□: Asymptomatic untreated initially APA negative patients (Group 2a)
■: Symptomatic initially APA negative patients treated with cabergoline for 2 years (Group 2b)

Figure 3: Behaviour of anterior pituitary function at start of the study and during a 3 year follow-up in APA positive (group 1) and APA negative (group 2) patients.

Group 1a and 2a, untreated patients;
Group 1b and 2b, patients treated with cabergoline for two years after the first observation (year 1 and 2) and after one year from cabergoline withdrawal (year 3)

Data are expressed as mean ± SD

* p< 0.02 vs the basal values of the same group

p< 0.01 comparing the values of Group 1b vs those of Group 1a at the same time of observation

p< 0.02 comparing the values of Group 2b vs those of Group 2a at the same time of observation

◇ p< 0.02 comparing the values of Group 2a and 2b vs those of Group 1a and 1b respectively at the same time of observation
**Table 1.** Basal characteristics of patients with idiopathic hyperprolactinemia positive (group1) and negative (group 2) for antipituitary antibodies

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (No=17)</th>
<th>Group 2 (No=49)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>3/14</td>
<td>13/36</td>
<td>NS</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>31.0 ± 4.4</td>
<td>33.5 ± 3.9</td>
<td>NS</td>
</tr>
<tr>
<td>fT3 (pg/mL)</td>
<td>3.9 ± 0.6</td>
<td>4.0 ± 0.6</td>
<td>NS</td>
</tr>
<tr>
<td>fT4 (pg/mL)</td>
<td>11.3 ± 1.8</td>
<td>11.7 ± 1.8</td>
<td>NS</td>
</tr>
<tr>
<td>TSH (mU/mL)</td>
<td>1.6 ± 0.3</td>
<td>1.5 ± 0.4</td>
<td>NS</td>
</tr>
<tr>
<td>Prolactin (μg/L)</td>
<td>45.2 ± 11.1</td>
<td>46.0 ± 11.6</td>
<td>NS</td>
</tr>
<tr>
<td>ACTH (pmol/L)</td>
<td>4.6 ± 2</td>
<td>5.0 ± 0.8</td>
<td>NS</td>
</tr>
<tr>
<td>Basal Cortisol (nmol/L)</td>
<td>308.2 ± 56.2</td>
<td>370.0 ± 40.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cortisol response to ACTH (nmol/L)</td>
<td>556.6 ± 98.6</td>
<td>654.5 ± 22.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>GH response to GHRH+arginine (μg/L)</td>
<td>16.2 ± 4.5</td>
<td>26.8 ± 3.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Presence of other organ-specific antibodies (%)</td>
<td>13 (76%)</td>
<td>4 (8 %)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD; NS: Not significant
Figure 1
Figure 2
Figure 3