Unfavorable effects of hyperprolactinemia in autoimmune endocrine disorders

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Abstract
Prolactin is a hormone with a multidirectional proinflammatory action. It has an anti-apoptotic effect, enhances proliferative response to antigens and mitogens, as well as enhances the production of immunoglobulins and autoantibodies. Increased prolactin levels are commonly observed in various organ and multi-organ specific autoimmune diseases. In our article, we report a case of a woman who developed progression of autoimmune thyroid disorder and developed insufficiency of the zona glomerulosa when her prolactin levels were increased. A normalization of plasma prolactin levels by quinagolide and replacement of risperidone with aripiprazole improved her clinical condition. Our study suggests that, in some patients, hyperprolactinemia may predispose to the development and progression of autoimmune disorders of endocrine glands.

INTRODUCTION
Prolactin has been found to produce a multidirectional proinflammatory action. Besides lactotroph cells of the anterior lobe of the pituitary gland, the hormone is also secreted by many extrapituitary organs, including lymphocytes and other immune cells (Orbach & Shoenfeld 2007; De Bellis et al. 2005; Vera-Lastra et al. 2002; Neidhart 1998). By binding to its receptors, prolactin is able to activate the immune cells (Orbach & Shoenfeld 2007). Prolactin stimulates the maturation of T cells and impairs the negative selection of autoreactive B lymphocytes during B cell maturation (De Bellis et al. 2005). It has an anti-apoptotic effect and enhances proliferative response to antigens and mitogens (De Bellis et al. 2005). As a result, prolactin up-regulates Th1 cytokines, as well as enhances the production of immunoglobulins and autoantibodies and activates Th2 lymphocytes (Orbach & Shoenfeld 2007; Vera-Lastra et al. 2002). Increased prolactin levels are commonly observed in various organ and multi-organ specific autoimmune diseases, including systemic lupus erythematosus, rheumatoid arthritis, Sjogren's syndrome, systemic sclerosis, Addison's disease, type 1 diabetes mellitus and autoimmune thyroid disorders (Orbach & Shoenfeld 2007; De Bellis et al. 2005; Vera-Lastra...
et al. 2002; Neidhart 1998). However, the question whether plasma prolactin levels correlate with disease activity provided contrasting results (De Bellis et al. 2005). In our clinic, we observed that high prolactin levels exacerbated the course of autoimmune disorders in a young female.

At the age of 22, the index woman started to experience weight gain, constipation, fatigue, cold intolerance, muscle hypotonia and cramps, joint pains, coarse hair and brittle nails. Laboratory findings showed features of hypothyroidism (TSH – 23.2 mU/L, reference range: 0.4–4.5; free thyroxine: 8.7 pmol/L, reference range: 12.0–22.0; free triiodothyronine – 2.6 pmol/L, reference range: 2.6–6.0) and autoimmune thyroid disease (thyroid peroxidase antibody titer – 1560 U/mL, reference range to 100). The patient started treatment with L-thyroxine at the daily dose of 50 μg, which was gradually increased to 125 μg. The last dose of L-thyroxine provided an effective control of her thyroid function. Four years later, the patient developed amenorrhea and galactorrhea, which were accompanied by plasma prolactin levels of 185 μg/L (reference range: 5.0–25.0). A pituitary magnetic resonance imaging (MRI) scan confirmed the presence of a pituitary microadenoma, measuring 5 mm at maximum diameter. Because of a concomitant increase in plasma TSH (10.3 mU/L) and thyroid peroxidase antibody titer (to 2 560 U/mL), the daily dose of L-thyroxine was increased to 175 μg. The patient also received bromocriptine treatment, but, because of its poor tolerance, bromocriptine was replaced with quinagolide administered at the daily dose of 150 μg.

As a result of treatment, menses became regular, while galactorrhea resolved. Moreover, quinagolide treatment resulted in a normalization of plasma prolactin levels and led to a disappearance of the pituitary tumor. It also caused a decrease in TSH and thyroid peroxidase antibodies and therefore enabled to reduce the daily dose of L-thyroxine to 125 μg. Dopamine agonist treatment was continued for the following 2 years and terminated. At the age of 30, our patient was diagnosed with schizophrenia and was prescribed with risperidone (6 mg daily). Unfortunately, shortly afterwards amenorrhea and galactorrhea reappeared, which was paralleled by an increase in plasma prolactin levels (to 75 μg/L).

Because risperidone treatment improved schizophrenia symptoms in the index patient, a consultant psychiatrist decided to continue the treatment with this agent. However, after two months of risperidone treatment thyroid antibodies started to increase. During the period of two following years of treatment, the titer of thyroid peroxidase antibodies gradually increased, reaching the value of 3 200 U/mL, which was accompanied by an increase in the requirements for exogenous L-thyroxine (up to 200 μg daily). At the same time circulating prolactin levels remained elevated but stable. Because of weight loss and orthostatic hypotonia, we decided to determine adrenal cortex function. Despite normal levels of plasma morning cortisol (9.2 μg/dL, reference values: 5–20 μg/dL), ACTH (53 pg/mL, reference values: 20.0–60.0 pg/mL) and DHEA-S – 235.1 μg/dL, reference values: 80–450 μg/dL), the patient was seropositive for 21-hydroxylase antibodies and had increased supine plasma renin activity (10.3 ng/mL/hr; reference values: 0.3–2.8 ng/mL/hr) and reduced supine plasma aldosterone (22.1 pg/mL, reference values: 30–150 pg/mL). This picture suggested the initial period of autoimmune adrenal cortex destruction, because insufficiency of the zona glomerulosa often occurs earlier than insufficiency of the zona fasciculation, which is protected by locally secreted glucocorticoids (Betterle & Morlin 2011). The patient was prescribed with fludrocortisone (0.1 mg daily). Because the patient's clinical picture suggested that she may develop autoimmune polyglandular syndrome type 2, and knowing the relationship between hyperprolactinemia and autoimmune disorders, we decided to replace risperidone with aripiprazole (30 mg daily), which is a drug with a negligible effect on plasma prolactin (Brue et al. 2007). According to the prediction, the change of the drug resulted in a spontaneous reduction in plasma prolactin. But, what is even more important, this was accompanied by a reduction in thyroid peroxidase antibody titer and a decrease in the demands for L-thyroxine (from 200 μg to 150 μg daily). Moreover, 21-hydroxylase antibodies disappeared while plasma renin activity and plasma aldosterone normalized (2.2 ng/mL/hr and 62 pg/mL, respectively). Because hypotonia resolved, fludrocortisone treatment was terminated 8 months after the cessation of risperidone use.

Our report shows that clinical conditions associated with high prolactin levels may enhance thyroid and adrenal autoimmunities. In the index patient, this relationship was very clear and did not seem to be accidental. Increased plasma prolactin levels independently of their background (pituitary microadenoma and neuroleptic treatment) resulted in a worsening of thyroid function and an increase in thyroid and adrenal cortex antibodies. In turn, a normalization of plasma prolactin levels each time led to an improvement in the results of endocrine tests. Taking into account that autoimmune disorders, particularly those of the thyroid gland, as well as hyperprolactinemia are endocrine problems relatively frequently observed in the general population, the fact that our study is the first to show the association between them indicates that unfavorable effects of prolactin excess is observed probably only in predisposed patients. Taking into account that prolactin levels were higher when the patient had prolactinoma than during risperidone treatment and that they remained at the similar levels during the whole period of risperidone administration, it seems that there may exist some threshold prolactin levels, above which patients are more prone to the development of autoimmune disorders. Previous studies mainly emphasized that increased prolactin levels may reflect autoimmune process and contribute to their worse course. Our report indicates...
that in some patients hyperprolactinemia may be one of the causative factors. Because quinagolide treatment reversed hyperprolactinemia-induced changes in thyroid and adrenal cortex function, this drug and probably also other dopamine receptor agonists may bring some benefits to patients with autoimmune disorders, at least to those of them with elevated prolactin levels.

Conflict of interest statement
The authors declare that there is no conflict of interest.

REFERENCES