

Anti-inflammatory effects of bromocriptine in a patient with autoimmune polyglandular syndrome type 2

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Abstract

Excessive prolactin release and/or receptor action may be implicated in the pathogenesis of many autoimmune disorders. We report here a case of a woman who developed Graves' disease and subclinical autoimmune adrenal failure, and was diagnosed as having autoimmune polyglandular syndrome type 2. Because of coexisting microprolactinoma she was treated with bromocriptine for 24 months. This treatment resulted in a normalization of thyroid and adrenal function tests (with the exception of 21-hydroxylase antibodies) and reduced monocyte cytokine release. Our study indicates that bromocriptine and probably also the remaining prolactin-lowering agents produce anti-inflammatory effects and may prevent or delay the progression of autoimmune disorders of endocrine glands.

INTRODUCTION

Prolactin, a hormone produced by anterior pituitary lactotrophs and various extrapituitary cells, has profound effects on proliferation and differentiation of a variety of cells in the immune system (De Bellis *et al.* 2005; Vera-Lastra *et al.* 2002; Neidhart 1998; Orbach & Schoenfeld 2007; Yu-Lee 2002). After binding to its specific receptor, which are distributed throughout the immune system (Vera-Lastra *et al.* 2002), prolactin stimulates the maturation of T lymphocytes, impairs the negative selection of autoreactive B lymphocytes during B cell maturation, inhibits apoptosis of lymphocytes, as well as enhances proliferative response

to mitogens and antigens (De Bellis *et al.* 2005). A number of studies have shown that excessive prolactin release and/or receptor action may be implicated in the pathogenesis of many autoimmune diseases, including systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome, Reiter's syndrome, psoriatic arthritis, systemic sclerosis, type 1 diabetes mellitus and autoimmune thyroid disorders (De Bellis *et al.* 2005; Vera-Lastra *et al.* 2002; Neidhart 1998; Orbach & Schoenfeld 2007; Yu-Lee 2002).

Recently, we have observed a woman who developed progression of Hashimoto's thyroiditis and insufficiency of the zona glomerulosa each time when her prolactin levels were increased (Krysiak

et al. submitted). In the present study, we report a case of another female in whom the clinical course of Graves' disease and subclinical adrenal insufficiency improved after long-term treatment with bromocriptine, and this clinical improvement was paralleled by a reduction in monocyte secretory function.

CASE PRESENTATION

A 31-year-old woman contacted our hospital because of asthenia, generalized weakness, palpitations, a 11-kg weight loss and nervousness. Physical examination revealed a smooth goiter with bruit, tremor and mild thyroid eye disease. Both lower limbs showed nonpitting edema and 'peau d'orange' appearance of the skin. Her TSH levels were suppressed (<0.005 mU/L, reference range: 0.4–4.3) while free thyroid hormone markedly elevated (free thyroxine: 35.1 pmol/L, reference range: 12.0–22.0; free triiodothyronine: 15.7 pmol/L, reference range: 2.8–6.0). The plasma titer of thyrotropin receptor antibodies was high (10.7 U/L, reference values <1.0), while thyroid peroxidase antibodies were only slightly elevated (64 U/mL, normal values <32). Based on the clinical and laboratory data, the patient was diagnosed as having developed Graves' disease, and therefore the treatment with methimazole (10 mg three times daily) and propranolol (40 mg three times daily) was commenced (the patient declined radioiodine therapy). Two months after the thyroid hormone levels had returned to the normal range, the patient discontinued her visits and terminated the treatment. Six months later, she contacted our department again because of weight loss (despite increased appetite, heat intolerance, irritability and tachycardia), suggesting the recurrence of hyperthyroidism, which was supported by the results of laboratory investigations (TSH <0.005 mU/L; free thyroxine: 31.8 pmol/L, free triiodothyronine: 19.2 pmol/L, thyrotropin receptor antibodies: 8.3 U/L). Standard treatment with methimazole at a daily dose of 45 mg was re-assumed, and six weeks later, the levels of TSH and free thyroid hormones normalized. We intended to continue methimazole treatment for the following 18 months. Because the patient's sister was diagnosed with autoimmune adrenal failure and excess of thyroid hormones is found to stimulate glucocorticoid metabolism (Lambert *et al.* 1998), after normalization of thyroid hormone function the patient was assessed for the presence of adrenal autoimmunity and dysfunction. Plasma renin activity assessed in the supine position was elevated (12.4 ng/mL/hr; reference values: 0.3–2.8), which was accompanied by slightly reduced plasma aldosterone levels (28 pg/mL; reference values: 30–150). The patient was found to be seropositive for 21-hydroxylase antibodies. Morning plasma ACTH (53 pg/mL) and cortisol (7.1 μ g/dL) levels were within normal limits (reference values: 5–20 μ g/dL and 10–80 pg/mL, respectively), while plasma dehydroepiandrosterone sulfate levels were at

the lower limits of normal (106 μ g/dL; reference values: 80–450). A 250 μ g ACTH stimulation test showed an inadequate serum cortisol response with a peak level of 12.9 μ g/dL (reference values >19.6). Because these results were consistent with the diagnosis of subclinical adrenal failure, the patient was classified as having autoimmune polyglandular syndrome type 2, and suggested to be regularly monitored. Although the patient continued methimazole treatment (10 mg daily), she visited our department again only after two years because of nipple discharge appearing in response to breast manipulation and oligomenorrhea. Based on high plasma prolactin levels (95 μ g/L; reference range: 5.0–25.0) and the presence of a microadenoma (6 mm at maximum diameter) found on a magnetic resonance imaging scan of the pituitary, prolactinoma was diagnosed. Although thyrotropin receptor antibody levels remained elevated (8.4 U/L), no abnormalities in the remaining thyroid function tests were found (TSH: 1.4 mU/L; free thyroxine: 16.7 pmol/L, free triiodothyronine: 4.82 pmol/L) and methimazole treatment after two years of administration was discontinued. Adrenal function tests gave similar results as before, with the exception of even lower peak cortisol levels in ACTH stimulation test (7.8 μ g/dL). Cultures of human peripheral blood monocytes, performed as described previously (Okopien *et al.* 2005a; Okopien *et al.* 2005b) (but for the first time in this patient), showed markedly increased monocyte release of TNF- α (3.2 ng/mL, reference range: 0.6–0.9), interleukin-1 β (235 pg/mL, reference range: 56–81), interleukin-6 (25.7 ng/mL, reference range: 4.1–8.4) and monocyte chemoattractant protein-1 (MCP-1) (35.5 ng/mL, reference range: 10.3–14.9).

Bromocriptine treatment (10 mg daily) resulted in a rapid disappearance of galactorrhea and restoration of menstrual cycles. Since the second month of bromocriptine treatment, plasma prolactin levels were within normal limits (8–17 μ g/L). A magnetic resonance imaging, performed 11 months later, showed no abnormalities in the pituitary gland. Clinical and imaging improvement was associated with a decrease in monocyte cytokine release (TNF- α : 2.0 ng/mL, interleukin-1 β : 183 pg/mL, interleukin-6: 16.8 ng/mL, MCP-1: 23.6 ng/mL) as compared with that from 12 months before. However, at this time, both thyroid and adrenal antibodies were still present. Also adrenal dysfunction persisted, although was less severe (plasma renin activity: 8.4 ng/mL/hr, peak cortisol level in ACTH stimulation test: 10.1 μ g/dL). The following 12 months of bromocriptine administration was required to demonstrate normal supine plasma activity (2.6 ng/mL/hr), normal peak cortisol response to 250 μ g cosyntropin (25.0 μ g/L) and normal plasma dehydroepiandrosterone sulfate levels (321 μ g/dL). Moreover, during the whole period of bromocriptine treatment, we observed normal TSH and free thyroid hormone levels, which were accompanied by a pro-

gressive reduction in thyrotropin receptor antibodies to the levels observed in the healthy population (0.8 U/L). However, throughout bromocriptine treatment, 21-hydroxylase antibodies did not disappear. Between month 12 and 24 of bromocriptine treatment we observed a further decrease in monocyte cytokine release. After 24 months of treatment, monocyte secretory function was only slightly enhanced (TNF- α : 1.0 ng/mL, interleukin-1 β : 114 pg/mL, interleukin-6: 10.6 ng/mL, MCP-1: 15.9 ng/mL) when compared with healthy people.

DISCUSSION

Our study is the first that has shown that bromocriptine treatment reversed the changes in thyroid and adrenal function induced by autoimmunity in a patient with autoimmune polyglandular syndrome. This may suggest that prolactin-lowering agents produce favorable effects in subjects suffering from autoimmune endocrine disorders.

Our patient was diagnosed as having autoimmune polyglandular syndrome type 2 because of the coexistence of Graves' disease and subclinical autoimmune adrenal failure. Interestingly, the patient's plasma renin activity and plasma aldosterone levels were abnormal, while disturbances of glucocorticoid function were observed only in a functional test. This observation, being in agreement with previous findings of other authors (Betterle & Morlin 2011), indicates that in the initial stage of autoimmune adrenal cortex destruction, failure of the zona glomerulosa usually precedes the development of insufficiency of the zona fasciculata. Probably the latter layer is protected from the destruction by locally secreted glucocorticoids (Betterle *et al.* 2002).

Both autoimmune disorders manifested earlier than prolactinoma. Certainly, we cannot exclude that a prolactin-secreting tumor preceded the development of Graves' disease and adrenal failure, but at the time of their initial manifestation remained undetected. Therefore, in the index patient excessive prolactin production may have either exacerbated or may even have contributed to the development of autoimmune polyglandular syndrome. Taking into account the high prevalence of prolactinoma (Kars *et al.* 2010) and endocrine autoimmune disorders (Betterle & Morlin 2011; Betterle *et al.* 2002; Tomer & Davies 1993), the fact that no previous study has reported a similar relationship between them suggests that unfavorable proinflammatory effects of excessive prolactin levels are clinically relevant only in susceptible patients. This may suggest that prolactin-lowering agents are effective in some patients with autoimmune disorders. In line with this hypothesis, we observed that bromocriptine effectively treated autoimmune thyroid disease and reversed autoimmune adrenocortical dysfunction. Interestingly, this effect was time-dependent, stronger

after 24 months than after 12 months of treatment. This contrasts with the fact that prolactin levels normalized only after several weeks of treatment. This may mean that bromocriptine produces its beneficial effect even in subjects with normal baseline prolactin levels.

At the time of the diagnosis of prolactinoma, monocytes of the patient activated with lipopolysaccharide released significantly increased amounts of TNF- α , interleukin-1 β , interleukin-6 and MCP-1 when compared with those of healthy subjects. Interestingly several cytokines including TNF- α and interleukin-1 β , which were determined in this patient, were reported to be involved in the activation of TSH receptor (Tomer & Davies 1993) and in adrenal destruction (Betterle & Morlin 2011; Betterle *et al.* 2002). Bromocriptine treatment reduced monocyte cytokine release and this effect increased with time. Our results show that bromocriptine may inhibit the cell-mediated immune response and that its beneficial effect observed in our patient is likely to be, at least partially, secondary to a reduction in proinflammatory cytokine release. Thus, the fact that after 24 months cytokine release in the index patient remained higher than observed in the healthy population may explain why 21-hydroxylase antibodies did not disappear.

To sum up, our study reported that bromocriptine administered because of coexisting prolactinoma normalized thyroid and adrenal function tests and reduced monocyte cytokine release in a patient with autoimmune polyglandular syndrome type 2. This suggests that bromocriptine and probably also the remaining prolactin-lowering agents produce anti-inflammatory effects in this clinical entity and may prevent or delay the progression of autoimmune disorders of endocrine glands.

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

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