Long-term follow-up of women with amenorrhea-galactorrhea treated with bromocriptine

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Summary: The present study is aimed at investigating whether long-term use of bromocriptine on patients affected by amenorrhea and galactorrhea may improve the clinical picture after discontinuation of treatment. For this reason 26 patients with amenorrhea and galactorrhea have been studied. Sixteen had high PRL values and 10 were normoprolactinemic. The normoprolactinemic patients underwent a TRH test. All the patients underwent computed skull axial tomography (CT scan) and were treated with bromocriptine, at a daily dosage variable from 2.5 to 10 mg for an average period of 26 months.

After discontinuation of treatment, follow-up was carried-out for 20 months. Eighty-seven percent of the patients affected by amenorrhea, galactorrhea and hyperprolactinemia had regular menses, in 75 of the patients galactorrhea completely disappeared. Of the ten patients with normoprolactinemic amenorrhea and galactorrhea, only those who positively responded to the TRH test had regular menstruation and showed disappearance of galactorrhea. Upon discontinuation of treatment amenorrhea recurred in 68% of the cases whereas galactorrhea recurred in 80%. CT scans revealed disappearance of 3 microadenomas and reduction in size of the macroadenoma.

Long-term use of bromocriptine represents the first choice treatment for the syndrome of galactorrhea-amenorrhea. In case of relapse, treatment must be continued for an undefined period of time.

INTRODUCTION

A high PRL enhances hypogonadism which, in severe cases, may cause amenorrhea frequently associated with galactorrhea.

In recent years, various studies have proven the effectiveness of dopamine agonist drugs in treating hyperprolactinemia as they lower the PRL concentrations ([1, 10, 3, 15]).

The most studied and employed among these drugs appears to be bromocriptine (BRCR). It restores the ovulatory function in women affected by hyperprolactinemic amenorrhea and normoprolactinemic amenorrhea (in some selected cases) by either reducing or eliminating the secretion of milk, when present, from the breast. BRCR reduces the size of the prolactinomas, in some cases up to complete elimination ([12, 14, 16]). To establish whether long-term BRCR treatment results in a better clinical status, after di-

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Table 1. — *Epidemiologic features of patients with hyperprolactinemic amenorrhea-galactorrhea and hypofiseal adenomas.*

Age	Parity			Estro-Prog.	Psychotropic Drugs	Galactorrhea		Hypophiseal Adenoma PRL secreting	
	Multipara	Nullipara	Primipara			Bilateral	Monolateral	Micro	Macro
21		+					+		
22	+					+			
27	+					+		+	
34	+					+			
30	+			+	+		+		
20			+			+			
20	+					+			
25	+			+		+		+	
21				+			+		
28	+						+	+	
32	+			+		+			+
29		+			+	+		++	
36	+					+			
27		+		+		+		+	
24	+					+		+	
23	+					+		+	

scontinuation of therapy, we interrupted BRCR treatment in 26 women with amenorrhea and galactorrhea and had them undergo a long follow-up.

MATERIALS AND METHODS

In the past 8 years, 26 patients with amenorrhea and galactorrhea have been referred to our Unit. Sixteen of them had raised PRL levels, whereas just 10 were normoprolactinemic (Tables 2-3).

All of them had normal gonadotropin levels and had their menses after a 5-day oral administration of 20 mg medroxy progesterone-acetate (Positive Map Test).

Age ranged from 20 to 36 years with a mean age of 26 years. Sixteen were pluriparous, 2 were primiparous, 8 were nulliparous.

Eight patients had used estroprogesterones as contraceptives for a period of 5 years, whereas 4 regularly took psychotropic drugs.

None of patients complained of other concomitant endocrine diseases. Galactorrhea, present in all patients, appeared to be halfway between a translucid liquid similar to colostrum and milk itself. It was bilateral in 20 patients, spontaneous in 4, stimulated by the patient herself in 10 cases and evidenced during clinical examination in the remaining cases.

Secretion from the mammary gland was obtained by exerting pressure on the entire breast, starting from the bottom and pushing towards the nipple.

All patients underwent computerized skull tomography (CT scan) at the end of treatment which was repeated when pituitary adenomas were detected.

TRH tests (200 μg TRH IV) were performed on 10 patients with normoprolactinemic amenorrhea-galactorrhea. All patients were treated with a daily dosage of bromocriptine ranging from 2.5 mg to 10 mg for a period of 26 months.

Treatment began with small subdivided doses taken at meal-time and was gradually increased (not more than 2.5 mg a week) up to a useful dosage to maintain prolactin levels within normal ranges.

RESULTS

CT scans showed, in patients with amenorrhea, galactorrhea and hyperprolactinemia, the presence of 1 microadenoma in 6 patients, 2 microadenomas in 1 patient and 1 macroadenoma, about the size of

Table 2. — *Epidemiologic features of patients with normoprolactinemic amenorrhea-galactorrhea and hypofiseal adenomas.*

Age	Parity			Estro-Prog.	Psychotropic Drugs	Galactorrhea		Hypophiseal Adenoma PRL secreting	
	Multipara	Nullipara	Primipara			Bilateral	Monolateral	Micro	Macro
20			+			+			
22		+		+			+		
28	+			+		+			
24		+			+	+			
34	+			+		+			
26		+			+		+		
30	+					+			
25	+					+		+	
32	+					+			
30		+				+			

1.5 cm, in another patient; only one patient with normoprolactinemic amenorrhea and galactorrhea had a microadenoma (Tables 2-3). TRH tests resulted positive in 8 patients with a 3.5 increase of basal circulating PRL value after TRH administration.

Fourteen (87%) out of 16 patients with amenorrhea, galactorrhea and hyperprolactinemia had menstruation: 13 within the first 16 weeks of treatment, 1 patient at 20 weeks. Galactorrhea was completely depleted in 12 patients (75%) in an average period of 14 weeks, in another 4 patients there was an expressible reduction of secretion (Table 3).

Upon discontinuation of treatment, amenorrhea, on the whole, recurred in 11 patients (78%), in 9 patients within 6 weeks and in 2 within 24 weeks (Table 3).

Galactorrhea recurred in 11 patients (68.7%) within 8 weeks (Table 3). Out of 10 patients with normoprolactinemic amenorrhea-galactorrhea, only those who tested positive for TRH tests (8 patients) had menstruation; 5 after 8 weeks, 3 after 12 weeks with normalization of galactorrhea in a mean period of 12 weeks (Table 4).

After discontinuation of treatment, amenorrhea recurred in 4 patients (50%) within 12 weeks; galactorrhea recurred in 5 patients within 9 weeks (Table 4).

Two patients who did not respond to TRH tests failed to benefit from bromocriptine therapy. The situation remained as such during follow-up. Seven patients (31%) had regular menstruation for the entire follow-up period, whereas no secretion from the nipple was noticeable in 4 patients (15%). At the end of treatment, CT control scans did not detect 3 microadenomas and showed a reduction in size of the macroadenoma (1.5 cm versus 0.8 cm).

DISCUSSION

Elevated plasma (primary or secondary) prolactin levels are almost costantly associated with hypogonadism. It is not surprising if the correlations existing between prolactin secretion and gonadal function are kept well in mind. Elevated prolactin concentrations exert their hypogonodal action at various levels; at the hypotalamic level they reduce the pulsatile release of GnRH and inhibit secretion through a selective modulation on the levels and turnover of dopamine; at the hypofiseal

Table 3. — *Patients (16) with hyperprolactinemic amenorrhea-galactorrhea bromocriptine therapy response and recurrence of amenorrhea and galactorrhea after discontinuation of therapy.*

	Resolution				Recurrence		
	Amenorrhea		*Galactorrhea*		*Amenorrhea*		*Galactorrhea*
	~16 wks	~20 wks	~14 wks		~6 wks	~24 wks	~8 wks
Ps	13	1	12	Ps	9	2	11

Table 4. — *Patients (10) with normoprolactinemic amenorrhea-galactorrhea bromocriptine therapy response and recurrence of amenorrhea and galactorrhea after discontinuation of therapy.*

	Resolution				Recurrence	
	Amenorrhea		*Galactorrhea*		*Amenorrhea*	*Galactorrhea*
	~8 wks	~12 wks	~12 wks		~12 wks	~9 wks
Ps	5	3	8	Ps	4	5

level they cause the fall of GnRH receptors and an inhibitory effect on the release of LH from the anterior pituitary gland; at the ovarian level they interfere with ovarian estrogen release after FSH stimulation and inhibit GnRH receptors ([5, 7, 9, 8, 11]). These pathogentic mechanisms lead to abnormal ovarian functioning such as menstrual irregularities, short luteal phases, anovular menstruations and amenorrhea.

There is, however, little or unclear understanding of the pathophysiology concerning galactorrhea associated with amenorrhea without hyperprolactinemia.

There are cases of transient functional hyperprolactinemia where PRL levels are shown to have significant variances and an isolated PRL dosage may result in being within normal ranges.

These forms of hyperprolactinemia are detected through a dynamic evaluation of prolactin secretion after a TRH test.

Transient hyperprolactinemia can be diagnosed when, after TRH stimulation, the basal value of prolactin has increased more than 3.5.

It is consequently advisable to have patients with normoprolactinemic amenorrhea and/or galactorrhea monitored for PRL secretion in order to visualize an alternative pattern of secretion ([2, 4, 13]).

When galactorrhea and failed TRH test response are evident, the presence of abnormal PRL molecules, biologically active but radioimmunologically undetectable it would be hypothesized.

Furthermore, the two patients who negatively responded to the TRH did not benefit from BRCR treatment; this would suggest that abnormal PRL molecular secretion may be regulated by abnormal D2 dopaminergic receptors found in the anterior pituitary gland cells.

Excellent results have been obtained by BRCR therapy in all those cases where an expressible pathologic PRL secretion was evident.

Bromocriptine, indeed, reduces PRL levels both by increasing the tuberinfundibular dopaminergic tone and by directly acting upon the dopaminergic receptors of the anterior pituitary gland ([6]).

Anti-tumorous activity of bromocriptine has recently been documented and also confirmed in our present study by the depletion of the 3 microadenomas and the reduction of the macroadenoma ([12, 14]).

Normalization of PRL concentration induced by bromocriptine results in a normal gonadotropin secretion with enhancement of pulsatile LH release, and causes the return of regular, frequently ovulatory, menstrual cycles. However, we have observed, during 20 months of follow-up, that 68% of the patients who had participated in this study complained of recurring amenorrhea and 80% of the patients of recurring galactorrhea. It could be suggested that part of this effect may be due to a re-enhancement of pathologic PRL secretion. It is interesting to observe how galactorrhea decreases faster than amenorrhea (9 weeks versus 24 weeks).

Thirty-one percent of the patients had normal menstrual cycles during the entire follow-up, resulting in biologically persevering with a normal secretory pattern. It must be pointed out that 4 (50%) out of 8 patients who positively responded to the TRH test had regular menstruation during the entire 20 month follow-up; it could be postulated that the mechanisms regulating prolactin secretion in these patients were less involved in the phenomenon.

In conclusion, treatment for amenorrhea-galactorrhea may be carried-out by the use of dopamine agonists and in particular by the use of bromocriptine as primary drug therapies in all those cases with raised prolactin secretion or in normoprolactinemic cases with positive TRH test responses.

Since the rate of recurrence of these symptoms after discontinuation of therapy is high, treatment must be protracted for a long period of time (2-3 years) before interruption and, in case of relapse, treatment must be continued for an unspecified period of time.

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