Eur Arch Psychiatry Clin Neurosci (2000) 250 : 6–10

ORIGINAL PAPER

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Prolactin-secreting pituitary adenoma in neuroleptic treated patients with psychotic disorder

Received: 17 March 1998 / Accepted: 20 October 1999

Abstract Three patients with psychoses and concomitant prolactin-secreting pituitary tumours are described. Patients A and B had bipolar and schizoaffective disorders, respectively. They had both been treated with neuroleptics for 20 years before the prolactinomas were revealed. Patient C developed a paranoid psychosis after two years of continuous bromocriptine treatment for a pituitary tumour. In patient A the prolactin level was successfully normalized and a good antipsychotic effect was maintained by combined therapy with haloperidol and quinagolide but not bromocriptine. In patient B the prolactinoma was removed by surgery, in view of the serious nature of the psychotic disorder, to avoid psychotic relapse by treatment with a dopamine agonist. In patient C a good result was obtained with the combination of clozapine and bromocriptine. These case reports support the view that neuroleptics being dopamine antagonists and dopamine agonistic agents which are the primary treatment of prolactinomas can cancel out each other's effects. The combination of clozapine and quinagolide is recommended as the treatment of choice for most patients.

Key words Dopamine agonists · Neuroleptics · Psychotic disorder · Prolactinoma

Introduction

Patients with psychotic disorders are generally receiving long-term therapy with neuroleptics for symptom control (for review see Meise and Fleischhacker 1996). A few of these patients may have a concomitant prolactin-secreting pituitary tumour which also has to be characterized and treated.

Prolactinomas cause hypogonadism in both men and women. Impaired memory, depression and headache can also occur. If the tumour comprises the optic nerve it may cause impaired vision and visual field defects (Molitch 1995; Werder 1996).

The primary treatment of prolactinomas is pharmacological, i.e. with a dopamine agonist which activates D_2 receptors on the lactotrophs, causing inhibition of prolactin secretion and reduction of tumour size. Surgery may be an alternative treatment, sometimes followed by radiation therapy (Flickinger and Rush 1996; Steven and Lamberts 1996; Reilly 1996).

Treatment of the psychosis includes various neuroleptics which block predominantly dopamine receptors of the D_2 class as well as other cell receptors to varying degrees (Leysen 1984; Schwartz et al.1992).

In patients with both psychosis and prolactinoma, choice of drug therapy is an important clinical problem. This can be ascribed to the fact that when dopamine antagonists and dopamine agonists are used together they tend to cancel out each other's effects. Thus, efforts to normalize the prolactin levels and reduce tumour size are often unsuccessful and even less success may be achieved in maintaining an appropriate mental status in the patient.

In the present communication we present three patients with psychosis and prolactinoma. We discuss the two diagnoses in combination and appropriate treatment modalities.

Patients and methods

Patients

The three patients gave informed consent to publish their case reports. They were all admitted for evaluation at the Department of Endocrinology and Diabetology at the Karolinska Hospital, Stockholm. The endocrinological evaluation included serum samples of prolactin (PRL), growth hormone (GH), insulin-like growth factor I (IGF-I), LH, FSH, estradiol, testosterone, cortisol and thyroid hormones (TSH, T_3, T_4). In addition, an ophthalmological exami-

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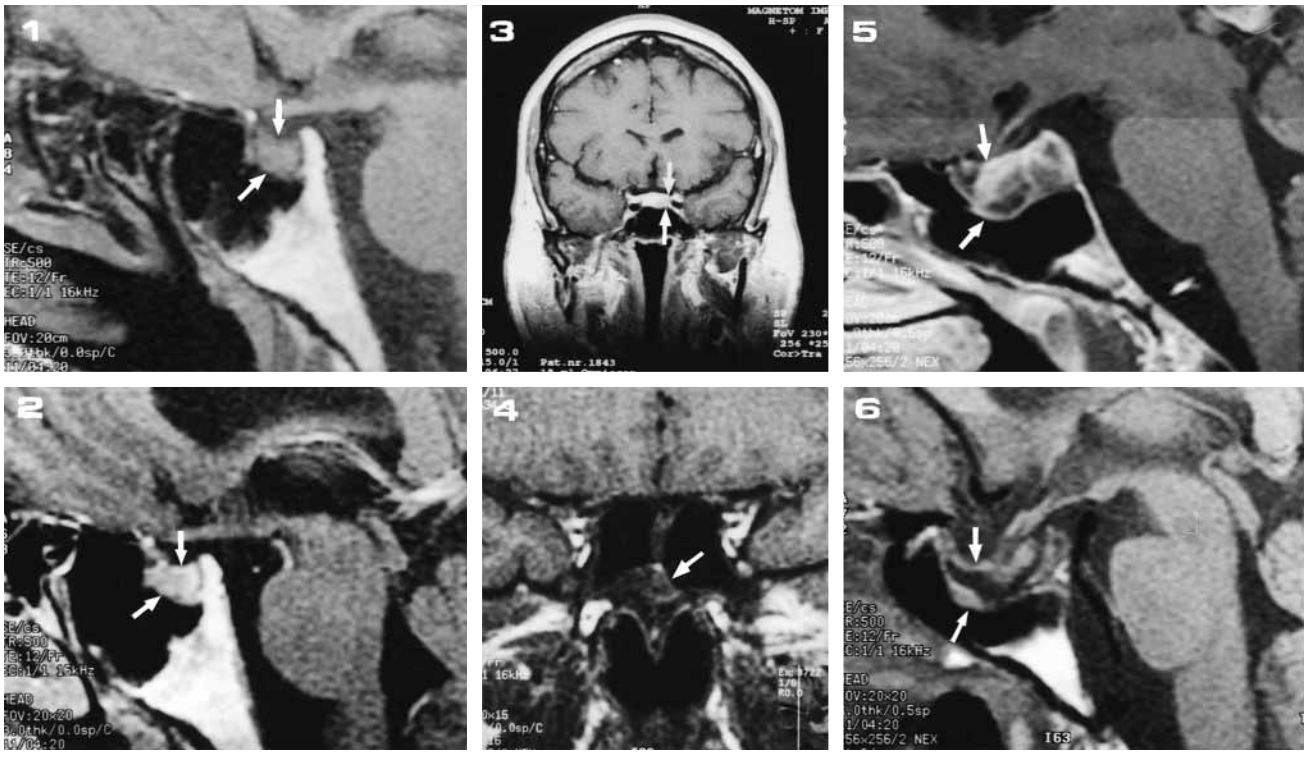


Figs. 1–6 Magnetic resonance images of the hypophyseal region

Fig. 1 Patient A. After 6 months of treatment with quinagolide the pituitary adenoma was still present

Fig. 2 Patient A. After a further 18 months of therapy with quinagolide a partial regression was noticed

Fig. 3 Patient B. At the time of diagnosis, the image showed a small intrasellar adenoma on the left-side of the pituitary

Fig. 4 Patient B. Postoperative MRI showed no signs of residual tumour tissue

Fig. 5 Patient C. The macroadenoma when imaged preoperatively in May 1993

Fig. 6 Patient C. In August 1995 the macroadenoma had decreased substantially

nation and magnetic resonance imaging (MRI) of the pituitary region were carried out. Evaluation of previous psychiatric journals was made retrospectively.

Methods

PRL, LH, FSH, estradiol, testosterone, cortisol and thyroid hormones were measured by commercial radioimmunoassay (RIA) kits (Wallac, Sweden and Diagnostic Products Cooperation, U.S.A.). GH was determined by an RIA according to Cerasi et al. (1966), modified by Luthman et al.(1990), and IGF-I was measured with an RIA method designed by Bang et al.(1991).

Magnetic resonance imaging (MRI) of the brain with T_1 and T_2 weighted images was performed using a 1.5 Tesla system (Sigma, GE medical systems).

Case reports

Patient A, a 48-year old man, was diagnosed with a bipolar disorder for the first time at age 29. He had been treated four times at a psychiatric clinic for mainly manic episodes in the beginning of the 1970s. Since 1972, he had been on continuous therapy with different neuroleptics, during periods in combination with lithium citrate.

In January 1991 he was admitted for endocrinological evaluation because of impotence, concentration difficulties and impaired memory during the previous five years as well as a recently discovered PRL value of 350 μg/l (ref for men < 15 μg/l). His medication at admission was haloperidol, 1 mg × 2.

The evaluation revealed PRL values between 256 and 333 μg/l and a testosterone level of 12 nmol/l (ref range 11–29 nmol/l). Ophthalmological examination was normal, whereas MRI showed an adenoma (diameter 1 cm) on the right side of the pituitary. Haloperidol treatment was withdrawn and bromocriptine, 1.25 mg × 1, was given. After one month the mental status of the patient started to deteriorate in a hypomanic direction. Bromocriptine was discontinued and haloperidol was reinstated which was followed by improvement of the mental status.

In view of the previous psychotic relapse when giving bromocriptine, the patient was referred for surgical treatment in September 1991. However, the surgeon was not successful in removing the adenoma. After the operation the patient's symptoms, i.e. the impotence, concentration difficulties and impaired memory, did not change and the PRL values remained elevated, 223–251 μg/l. A second attempt to give bromocriptine, 1.25 mg × 2, was made, this time during treatment with haloperidol, 1 mg × 2. However, the mental condition of the patient deteriorated once again six weeks later with hypomania. Then, bromocriptine was changed to the alternative dopamine agonist, quinagolide. Combination therapy with quinagolide (up to 0.375 mg/day) and haloperidol, 1 mg × 2, was successful with a maintained stable mental status. After one year of treatment, the PRL level was nearly normalized, 20 μg/l, and a partial tumour regression was confirmed by MRI (Figs. 1 and 2). Moreover, the patient regained his sexual potency despite unchanged testosterone level, 11 nmol/l.

Patient B was a 43-year old woman who had had recurrent psychoses since age 21 and had early on been diagnosed as a schizoaffective disorder. For 22 years she had received lithium citrate in combination with perphenazine with good antipsychotic effect. Current doses were lithium citrate 42 mg × 4 and perphenazine 16 mg × 2.

The patient had had amenorrhea since age 24 and over the last years she had also suffered from intermittent headaches and recurrent episodes of bilateral impaired vision. Upon evaluation in February 1994, an elevated PRL level, 210 μg/l (ref range for women 3–19 μg/l), was found.

MRI of the pituitary gland established the presence of an intrasellar, left-sided pituitary adenoma (diameter 1 cm) without visible suprasellar extension (Fig. 3). Ophthalmological examination revealed bitemporal quadrant hemianopsia indicating that the chiasma opticum was affected.

Neuroleptic treatment was considered necessary because of the serious nature of the patient's psychotic disorder. The combination with a dopamine agonist was considered hazardous in view of the risk of a psychotic relapse. Therefore, a transeptal-sphenoidal adenomectomy was carried out in November 1994, resulting in a radical macroscopic removal of the tumour. Postoperative MRI showed no signs of residual tumour tissue (Fig. 4).

The treatment with perphenazine and lithium was kept unchanged after surgery and the serum concentration of perphenazine was 3 nmol/l (ref range 2–3 nmol/l) and that of lithium 0.7 mmol/l (ref range 0.5–0.8 mmol/l). Postoperatively, there were no clinical signs of pituitary insufficiency. Moreover, PRL levels were lower, 80–100 μg/l. Levels of LH, FSH and estradiol were low as preoperatively, despite the less pronounced hyperprolactinemia. Cortisol, IGF-I and free T_4 levels were within normal ranges. Two years later, the PRL levels had further declined to about 70 μg/l, levels of LH, FSH, estradiol normalized and the patient's menstrual bleedings recurred.

Patient C was a man who had suffered from concussion at age 15 and had had subsequent intermittent headaches. In May 1989, when 23 years old, he was examined by an ophthalmologist because of vision impairment. The examination revealed bitemporal visual field defects and computed tomography (CT) established the presence of a pituitary macroadenoma that was 3 cm in diameter and penetrated into the left side of the sphenoidal sinus, probably growing into the left sinus cavernosus and with a suprasellar portion that was 1 × 1.5 cm in size. Endocrinological evaluation showed PRL levels between 2310 and 2630 μg/l, while testosterone (15 nmol/l) and the other hormones were normal.

Treatment with bromocriptine in increasing doses, up to 2.5 mg × 3, was started in July 1989. The patient's headaches disappeared and after 3–4 months the PRL level had declined to about 600 μg/l. The visual fields normalized and CT revealed a substantial reduction in tumour volume and complete disappearance of the suprasellar component.

To normalize the PRL level, the bromocriptine dose was increased, up to 15–22.5 mg/day. The therapy continued without side effects and the PRL level further decreased to approximately 130 μg/l. After ten months the patient developed an acute paranoid psychosis and was admitted to a psychiatric clinic. His symptoms included auditory hallucinations, paranoid delusions and thought disorders, and later on he fulfilled DSM-III-R criteria (American Psychiatric Association, 1987) for paranoid schizophrenia. The patient had no family history of psychiatric disorder.

At admission, the results of CT were similar to those obtained after the first period of bromocriptine therapy, i.e. an intrasellar, but not suprasellar, tumour was still present. Remoxipride, up to 300 mg/day, was introduced while the bromocriptine dose of 22.5 mg/day was maintained. This resulted in regression of the psychotic symptoms, whereas PRL increased notably, to 400 μg/l. Since the mental status remained stable, remoxipride was discontinued and bromocriptine was continued. PRL values returned to the level before remoxipride. However, two months later the patient again began having paranoid delusions.

Remoxipride, up to 300 mg/day, was, therefore, reinstated and in November 1993 an attempt to remove the tumour (Fig. 5) surgically was made. However, the operation could not be completed because the patient began to bleed profusely. Analysis indicated an acquired coagulation defect in thrombocyte function, possibly caused by bromocriptine. In 1994 the patient received external radiation of the tumour, with a total dose of 50 Gy. Thereafter, bromocriptine, 30 mg/day, and haloperidol, 2 mg/day, were administered and the PRL levels remained between 50 and 80 μg/l. Testosterone had decreased from 15 to 6 nmol/l (ref range 11–29 nmol/l), indicating a radiation-induced hypogonadism.

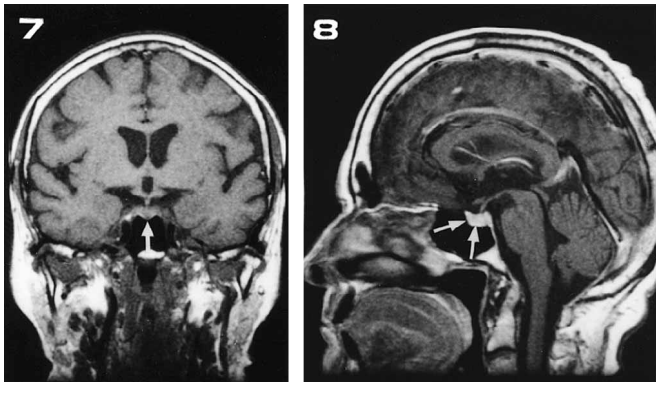
After another year the patient stopped taking haloperidol and a few months later he had a psychotic relapse. Zuclopenthixol, 4 mg/day, was initiated while maintaining the bromocriptine dose of 30 mg/day, whereafter his mental status stabilized. In August 1995, MRI showed a substantial decrement of the macroadenoma (Fig. 6). However, because of the still elevated PRL levels, 50–60 μg/l, zuclopenthixol was replaced by clozapine, 50 mg × 1, which resulted in a marked lowering of PRL values to 16–29 μg/l with maintained stable mental status. Thereafter, the patient continued taking clozapine, 50 mg × 1, in combination with bromocriptine, 30 mg/day, and after one year his mental status was still appropriate and the PRL levels remained below 30 μg/l.

Discussion

Even though conventional doses of classical neuroleptic drug increase serum PRL levels in patients with psychosis (Gruen et al.1978; Meltzer and Fang 1976; Meltzer et al.1975), PRL levels during chronic neuroleptic treatment are only slightly elevated or within the normal range in men, and in most women PRL levels seldom exceed 50 μg/l (De Rivera et al.1976; Melkersson et al. 1999). A prolactinoma should be suspected in women with PRL levels exceeding 100 μg/l and in men with levels above 50 μg/l according to Brismar et al. (1990). An earlier study in patients on long-term neuroleptic treatment showed no roentgenological signs of macroadenomas in 43 patients, based on skull x-ray analysis of the pituitary region. However, with skull x-ray it is hard to reveal a microadenoma (Lilford et al.1984).

In patients with psychotic disorder complaining of headaches and impaired vision, the possibility of a pituitary tumour should be considered. A prolactin-secreting pituitary adenoma should also be suspected in men with impotence and in fertile women with persistent amenorrhea.

Earlier, three neuroleptic treated patients with psychotic disorder and prolactinoma have been reported in the literature. Two patients had macroadenomas, detected after 10 and 15 years of neuroleptic therapy, respectively (Robbins



Figs. 7–8 Sella turcica and pituitary of normal size in frontal and sagittal projections

et al.1984; Weingarten and Thompson 1985). The third patient had a microadenoma, diagnosed after five years of antipsychotic medication (Daradkeh and Ajlouni 1988). Based only on these three cases and our two patients (A and B) it is not possible to conclude that the incidence of prolactinomas is increased among patients with psychosis on long-term neuroleptic treatment. In another study, 70 patients with schizophrenia and concomitant cerebral tumours and 6000 patients with cerebral tumours only were compared. A significant excess of hypophyseal adenomas, but not of other cerebral tumours, was found among the schizophrenic patients but, on the other hand, many of these schizophrenics were patients before neuroleptics had been introduced (Davison and Bagley 1969). Whether the incidence of prolactinomas is higher among schizophrenics due to long-term treatment with neuroleptics is hence not known for sure. Since neuroleptics have a D_2 dopamine receptor antagonistic effect, long-term therapy with such drugs will result in a continuous disinhibition of the lactotrophs. This in turn might lead to cell hyperplasia and, in the long run, to a pituitary adenoma. However, only one earlier radiological study has been carried out in which 10 patients with psychosis treated with neuroleptics for a long time showed sellar volumes within normal range, but in nine of the patients volumes were above the mean normal value (Asplund et al.1982).

In patients with psychotic disorder and concomitant prolactinoma individual therapeutic regimens should be considered. Based on the type and severity of the patient's psychotic disorder, one has to decide whether to treat the tumour pharmacologically or surgically. For patients with psychosis and prolactinoma good results can be obtained with pharmacological treatment (Gonzales and Michanie 1992). Surgery in turn should only be used if there is a good probability of removal of the entire tumour. In other words, the tumour should be intrasellar for the reason that in cases with supra-, para- or infrasellar extension the chance of radical surgery is small. Moreover, if a patient with an inoperable tumour does not respond to pharmacological treatment, radiation therapy should be considered.

In patient A the PRL level was successfully normalized and a good antipsychotic effect was maintained by dual therapy with haloperidol and quinagolide. However, the combination of haloperidol and bromocriptine resulted in a hypomanic relapse. An in vivo study has shown that quinagolide passes the blood brain barrier to a lesser degree than bromocriptine (Closse et al.1988) and could, therefore, be expected to exert a marked effect on the pituitary but less influence on the brain and the mental status. Quinagolide is also a relatively selective D_2 agonist (Charuchinda et al.1987; Closse et al.1985; Closse et al.1988) in contrast to bromocriptine that has a more unselective receptor profile (Beart et al.1986; Cash et al. 1987; McPherson and Beart 1983). Thus, it seems probable that quinagolide may be a more favourable dopamine agonist for patients with prolactinoma and psychotic disorder.

Gonzalez and Michanie (1992) reported a young female with a first-episode psychosis and a prolactinoma. This patient showed both tumour regression and improved mental status when the classical neuroleptics, i.e. haloperidol and thioridazine, were changed to the atypical neuroleptic clozapine in combination with bromocriptine.

In patient C bromocriptine was combined with different neuroleptics such as remoxipride, haloperidol, zuclopenthixol and clozapine in different phases. Optimal results were obtained with the combination of clozapine and bromocriptine, i.e. when the weak dopamine receptor antagonist was combined with the unselective agonist, bromocriptine (Andersen and Braestrup 1986; Beart et al.1986; Cash et al.1987; Leysen 1984; McPherson and Beart 1983).

The results of PET studies show that antipsychotic doses of clozapine give a lower D_2 occupancy than classical neuroleptics (Farde et al.1992; Nordström et al. 1995). This finding is consistent with the fact that clozapine also gives a less pronounced hyperprolactinemia (Meltzer et al. 1979; Kane et al .1981). Among the alternatives of neuroleptic drugs clozapine should accordingly be expected to have the lowest effect on growth of a PRL-producing tumour. Therefore, clozapine should be the preferable neuroleptic agent in treating such pituitary tumours in patients with psychotic disorder (Ovsiew, 1993).

In contrast, the three patients with psychotic disorder and prolactinoma described in the literature showed no satisfactory improvement in response to dual treatment with thioridazine and bromocriptine (Daradkeh and Ajlouni 1988; Robbins et al.1984; Weingarten and Thompson 1985). The failure concerning tumour treatment in these three cases might be attributed to the fact that the agonistic effect of bromocriptine on the D_2 receptors on the tumour cells was not strong enough to cancel out thioridazine's antagonistic action.

Case C demonstrates that treatment of a prolactinoma with bromocriptine can induce psychosis. This verifies previous reports (Boyd 1995; Turner et al.1984). Psychotic reactions to bromocriptine are also well known in the treatment of parkinsonism. However, in those patients, higher doses of bromocriptine, up to 150 mg/day, are used as well as several other substances with dopamine agonistic effect, often in combination therapy (Calne et al.1978; Serby et al.1978). Thus, one should be aware that patients with earlier episodes of psychosis or heredity of psychotic disorders may run a higher risk of developing a psychosis in response to bromocriptine. In these patients, quinagolide may be a better choice of dopamine agonist since it probably exerts less influence on mental status than bromocriptine (Closse et al.1988).

In summary, a prolactinoma should be suspected when patients with psychoses have amenorrhea, impotence, headaches or impaired vision together with a PRL level above 50 μg/l in men and 100 μg/l in women. If PRL is above these levels, the diagnostic work should be extended to include MRI and a broader hormonal survey. The combination of neuroleptics, that are strong dopamine antagonists, and dopamine agonistic agents may be problematic since such drugs may cancel out each other's effects. Quinagolide might be a favourable dopamine agonist, depending both on its lower passage via the blood

brain barrier and its relatively selective D_2 agonistic effect. Clozapine is the preferable dopamine antagonist since its effect on the lactotrophs in the pituitary is weak. Only if pharmacological treatment fails, should surgery and radiation therapy be considered.

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