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ORIGINAL ARTICLE

Hormonal evaluation in schizophrenic patients treated with neuroleptics

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Abstract

The aim of this study was to hormonally evaluate schizophrenic patients on long-term treatment with neuroleptics. Twenty-eight patients (14 men and 14 women) on long-term therapy with different neuroleptics were investigated. Blood samples for prolactin (PRL), growth hormone (GH) and insulin-like growth factor I (IGF-I) were measured, as well as gonadotropins and testosterone in the males. In addition, clinical signs and symptoms of the neuroleptic side effects were evaluated. Seven out of 14 women had elevated PRL and five of the six fertile women in this group had menstrual disturbances. Twelve of the l4 men had normal PRL levels, whereas two had slightly elevated PRL without related symptoms. Four patients had low IGF-I levels, which in one case was combined with elevated PRL. We conclude that PRL levels in schizophrenic patients on long-term therapy with neuroleptics are elevated in about 50% of the women and in 10-20% of the men. Furthermore, irrespective of PRL levels or other hormonal disturbances, some patients on long-term neuroleptic therapy show low IGF-I levels, pointing at a possible interference with neuroleptics on the hypothalamic-pituitary regulation of GH-dependent IGF-I secretion.

Introduction

Treatment with dopamine antagonists like neuroleptics is known to cause hyperprolactinemia, since it causes deficiency of the prolactin inhibiting factor dopamine, by occupying the dopamine D_2-receptors on the lactotrophs in the pituitary (1,2,3). In addition, patients on short-term therapy with neuroleptics seem to get a higher increment in prolactin (PRL) levels, whereas in long-term dopamine antagonist treatment the hyperprolactinemia is less pronounced (4,5,6,7). However, some investigators disagree about the development of diminished PRL increments in patients on long-term medication with neuroleptics (2,3,8).

Dopamine antagonists are also expected to block hypothalamic postsynaptic dopamine receptors and therefore supposed to interact with the growth hormone (GH)-regulating systems in hypothalamus (9). As a consequence, the pituitary GH secretion may decrease, resulting in a reduced production in the liver of the GH-dependent growth factor, insulin-like growth factor I (IGF-I).

We have hormonally evaluated 28 patients (14 females and 14 males) on long-term therapy with neuroleptics due to schizophrenia in order to investigate whether hyperprolactinemia and its related symptoms occurs in different frequencies in women compared to men. We also studied the influence of neuroleptics on GH secretion by analyzing IGF-I and using it as a marker for suspect GH-deficiency.

Patients and methods

The study included 28 patients (14 men and 14 women) with the diagnosis schizophrenia according to DSM-III-R criteria (10). The patients had no substance-related disorder or physical illness which could influence the hormonal evaluation, with the exception of patient no. 26 (Table 1) in whom liver cirrhosis was found in autopsy. Twenty-seven patients were on treatment with classical neuroleptics and one patient was receiving the atypical neuroleptic clozapine (Table 1). All patients had been on medication with neuroleptics for at least six months. Blood samples for analysis were fasting morning samples and oral neuroleptic medical treatment was given one hour before blood withdrawal and neuroleptic injections one day before, respectively. Prolactin, LH, FSH and testosterone (total) were measured by commercial radioimmunoassay (RIA) kits, (Wallac, Sweden and Diagnostic Products Cooperation, U.S.A). To determine serum levels of GH, a commercial RIA kit, with detection limit 0.3 μg/l was used (hGH RIA 100, Pharmacia, Sweden). Insulin-like growth factor I was measured with an RIA method designed by Bang et al. (11) and expressed as age-correlated standard deviation scores, based on samples from normal men and women (12). The detection limit was 8 μg/l. Including the extraction step, the intra- and interassay coefficient of variation (CV) were 4% and 11%, respectively. The patients' daily neuroleptic doses were converted to and expressed as chlorpromazine (CPZ) equivalents (13). In addition, clinical signs and symptoms of neuroleptic side effects were evaluated. Statistical analyses were performed using Statistica® for Windows (Statsoft, Inc., Tulsa, Oklahoma, U.S.A.) The strength of the relationship between two parameters was calculated by the nonparametric measure of correlation called Spearman rank correlation coefficient.

Results

Data on the patients are given in Table 1. All but two of the 14 men, number 7 and 12, (Table 1) had normal PRL levels. In these two patients, a modest increment of PRL was noticed, 18 and 16 μg/l, respectively, reference value <15 μg/l. All men had normal LH and FSH with corresponding plasma testosterone within normal range. However, one man, number 8, had "elevated LH and FSH" together with high testosterone but in this patient a high level of sexual hormone binding globulin (SHBG) was also found.

Prolactin levels were elevated in seven of the 14 women, patient nos. 18, 19, 21, 22, 23, 24 and 26 (Table 1). The age of these women ranged between 29 and 40 years, except for one woman who was 55 years old. Five of these women had menstrual disturbances whereas one (patient no. 24) had regular bleedings and one (patient no. 26) was menopausal. One woman with hyperprolactinemia (patient no. 23) also had galactorrhea. Of the seven women with PRL within normal limits, two had menopausal amenorrhea and the other five had regular menstrual bleedings.

Four patients, one man (no. 14) and three women (nos. 26, 27 and 28), had decreased IGF-I levels $<$ -2 SD (Figure 1). Of these four patients only one woman (patient no. 26) had hyperprolactinemia. This woman also exhibited low LH and FSH despite menopausal age, 55 years, but she had no signs of ACTH and/or TSH insufficiency and she also showed high GH levels. In addition, this woman was obese and showed no signs of malnutrition. In autopsy, liver cirrhosis was found, which can explain both the patient's GH and IGF-I levels (14). The other three patients with low IGF-I levels all exhib-

Table 1. Fourteen men (pat. no 1-14) and 14 women (pat. no 15-28) on long-term treatment with neuroleptics due to schizophrenia. Fasting blood levels of prolactin (PRL), LH, FSH, testosterone, growth hormone (GH) and insulin-like growth factor-I (IGF-I) are given. The neuroleptic drugs and daily reference doses (expressed as chlorpromazine equivalents) are also described.

Patient-number	Age (years)	PRL (µg/l)	LH (U/l)	FSH (U/l)	Testosterone (nmol/l)	GH (µg/l)	IGF-I (µg/l)		Neuroleptic drugs (mg)
Men		ref.range 3-15	ref.range 2-10	ref.range 2-12	ref.range 11-29	ref.range <8		Age-correlated SD-score	
1	29				19	<0.3	204	-0.59	chlorpromazine (150)
2	31				29	<0.3	262	0.43	clozapine (—)
3	38				26	0.5	168	-0.77	zuclopenthixol (300)
4	40				12	<0.3	246	0.73	haloperidol (400)
5	40				14	<0.3	158	-0.88	haloperidol, thioridazine (1620)
6	41				19	<0.3	174	-0.47	zuclopenthixol (185)
7	41				17	1.0	176	-0.43	pimozide (525)
8	45				36	<0.3	280	1.48	levomepromazine, perphenazine (105)
9	48				12	<0.3	119	-1.44	haloperidol (150)
10	49				26	<0.3	108	-1.73	perphenazine, thioridazine (436)
11	51				21	4.4	143	-0.60	perphenazine (80)
12	56				14	<0.3	221	1.26	perphenazine (139)
13	58				17	0.3	234	1.58	levomepromazine, thioridazine (325)
14	59				20	<0.3	61	-3.22	haloperidol (170)
Women		ref.range 3–19	ref.range 1–72 menopause 15–64	ref.range 1–25 menopause 30–150					
15	23	11				<0.3	160	-1.81	haloperidol (255)
16	28	19				<0.3	248	0.06	perphenazine (100)
17	29					<0.3	332	1.18	zuclopenthixol (40)
18	29					<0.3	254	0.21	perphenazine, thioridazine (410)
19	33					<0.3	244	0.29	thioridazine, zuclopenthixol (374)
20	34					0.7	219	-0.04	remoxipride, thioridazine (310)
21	35					0.4	225	0.11	perphenazine, thioridazine (646)
22	35					0.6	221	0.05	haloperidol, thioridazine (255)
23	39					<0.3	275	1.07	thioridazine (275)
24	40					<0.3	247	0.74	zuclopenthixol (300)
25	47					0.4	139	-0.94	haloperidol (191)
26	55					11	25	-6.68	perphenazine (160)
27	65					0.3	63	-2.76	perphenazine (232)
28	76					1.4	50	-2.96	perphenazine (42)

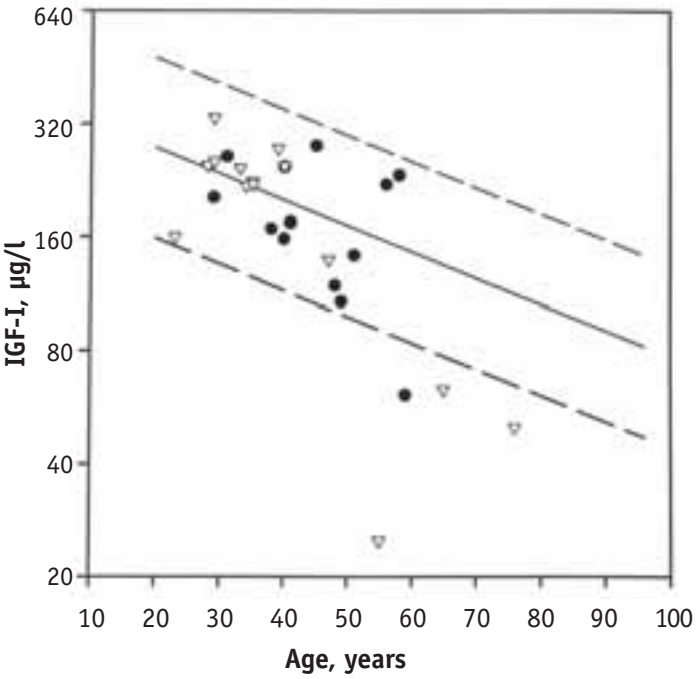

Figure 1. Insulin-like growth factor I (IGF-I) levels, expressed as age-correlated SD-scores related to age in 14 men (•) and 14 women (∇) on long-term therapy with neuroleptics due to schizophrenia.The normal range for age (mean ± 2 SD) is indicated.

ited normal levels of pituitary hormones together with normal PRL. They had no clinical symptoms of hypopituitarism, except the man with low IGF-I (patient no. 14), who complained of impotence despite normal testosterone. He was the only one of the 14 men who reported this symptom whereas the two men with slightly elevated PRL (nos. 7 and 12) did not complain of impotence.

The mean, median and range of the daily reference dose of neuroleptic drug, expressed as chlorpromazine (CPZ) equivalents are given in Table 2.

No correlations were found between the reference dose and PRL or IGF-I (expressed as age-correlated SD-scores), when the 27 patients receiving classical neuroleptics were investigated.

Discussion

In this study hyperprolactinemia was present in nine out of 28 patients (32%) on long-term treatment with neuroleptics due to schizophrenia. This is in consent with several other studies showing hyperprolactinemia in varying frequency in patients on therapy with neuroleptics (1,2,3). However, we found only a modest increment in PRL levels with the highest PRL noticed, 60 µg/l, in patient no. 26. This is in contrast to another report (15), where notably elevated PRL was found in several of the 43 patients studied. The patients were all on long-term therapy with phenothiazines and none of them showed any roentgenological signs of a pituitary tumour.

Hyperprolactinemia was a more common side effect in women on neuroleptics compared to men. Five out of six women with hyperprolactinemia and age below 40 years also exhibited menstrual abnormalities pointing at a disturbance in the secretion of gonadotropic hormones and sexual steroid hormones. To compare, the two men who had slightly elevated PRL had no effect on testosterone levels or clinical symptoms of sexual dysfunction. Another study (16) also showed a higher increment in PRL levels in women on neuroleptics compared to men, despite a lower dosage of neuroleptics in women. However the frequency of hyperprolactinemia was not described in that group of patients. Further-

Table 2. Mean, median and range of the daily dose of neuroleptic drug expressed as chlorpromazine equivalents in 27 patients on long-term treatment with classical neuroleptics. Figures also show the mean PRL levels in µg/l ± SD for all 27 patients, as well male as female patients, separately.

Group	n	Serum prolactin levels (µg/l)	Mean daily dose of neuroleptic drug (mg)*	Median daily dose of neuroleptic drug (mg)*	range (mg)*
Whole group	27**	15.6 ± 13.2	303	255	40–1620
Male	13	8.8 ± 4.9	353	185	80–1620
Female	14	21.9 ± 15.3	256	255	40–646

* dose expressed as chlorpromazine equivalents
** one male patient was treated with the atypical neuroleptic clozapine.

more, these patients were only evaluated 3 and 6 weeks after the onset of treatment (16).

The finding that some patients had low IGF-I levels with no signs of pituitary deficiencies at hormonal evaluation points at a possible effect of dopamine antagonists on the regulation of GH release and GH-dependent IGF-I production. The regulation of GH release is dependent on a complicated interaction between suprahypothalamic and hypothalamic neurotransmitters and neuropeptides. An influence of long-term dopamine antagonist therapy on GH secretion is plausible.

The dopamine antagonist may interfere with the release of GHRH and a stimulatory effect on somatostatin would be expected (17). In addition, three of the four patients with low IGF-I levels were the oldest patients in this material: 59, 65 and 76 years of age. Growth hormone secretion shows well-known age-related changes where GH response to GHRH is diminished with age and GH as well as IGF-I secretion is progressively down regulated (18). Our findings of decreased IGF-I levels in the oldest patients, despite correction of these values to age, may reflect a more vulnerable secretory system for GH release in elderly people resulting in an inhibitory action of long-term treatment with dopamine antagonists on GH secretion. However, a direct correlation between hyperprolactinemia and low IGF-I levels was not found in this material. To compare, excessive hyperprolactinemia is known to inhibit GH secretion (19) resulting in decreased secretion of the GH dependent IGF-I (20).

Hyperprolactinemia has also been shown to cause growth retardation in children with a spontaneous catch-up growth after treatment with dopamine agonists and normalization of PRL levels (21). The modest hyperprolactinemia in this patient material probably explains the lack of close correlation between hyperprolactinemia and low IGF-I levels.

In summary, we have found that hyperprolactinemia in patients on long-term therapy with neuroleptics is more common in women than in men. In addition, these women also had clinical symptoms like menstrual dysfunction related to their hyperprolactinemia. Furthermore, irrespective of PRL levels, two women and one man showed low IGF-I levels pointing at a possible interference with neuroleptics on the hypothalamic-pituitary regulation of GH dependent IGF-I secretion. Further studies are needed to confirm this effect of dopamine receptor antagonists on the GH-IGF-I axis.

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