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ORIGINAL ARTICLE

Neither gynecomastia nor galactorrhea is a common side effect of neuroleptics in male patients

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Abstract

OBJECTIVE: Gynecomastia is known to be a side effect of neuroleptics. The authors investigated the prevalence of gynecomastia and galactorrhea in a group of regularly neuroleptic-treated male patients.

METHODS: Gynecomastia was defined as a palpable, discrete button of firm subareolar tissue measuring at least 2 cm in diameter. The subjects were 100 male patients who were taking neuroleptic treatment regularly. Each patient gave informed consent for the research involved in this study.

RESULTS: (1) Palpable gynecomastia was present in 2% of the patient group, but not at all in the normal group. (2) Galactorrhea was not present in either patient or normal group. (3) The mean level of the serum prolactin in the group of patients without gynecomastia (n = 53) was significantly higher than that in the normal group (n = 35), but there was no significant difference in blood luteinizing hormone, follicle-stimulating hormone, testosterone (T), estradiol (E_2) or T/E_2 ratio between the groups. (4) The mean level of the T/E_2 ratio in the patients with gynecomastia tended to be higher than that in the group of patients without gynecomastia.

CONCLUSIONS: Overall, these results seem to indicate that (i) gynecomastia is not common in the Japanese population, and (ii) in male patients neither palpable gynecomastia nor galactorrhea is a common side effect of neuroleptics. To clarify the relation between gynecomastia and neuroleptic treatment, large prospective studies are required.

Abbreviations:

DA	dopamine
E_2	estradiol
E	estrogen
FSH	follicle-stimulating hormone
LH	luteinizing hormone
PRL	prolactin

Introduction

Gynecomastia is a discrete, palpable subareolar plate of tissue in the male breast [1]. Gynecomastia has been reported to be common in normal adult men [2]. Meanwhile, neuroleptic agents have been indicated to play a role in the cause of gynecomastia [1]. Considering these reports, we can easily hypothesize that gynecomastia is quite common in a sample with neuroleptic treatment. The present study was conducted to test this hypothesis.

In addition to the central focus of our study, we also investigated the prevalence of galactorrhea, since neuroleptics have been found to block the dopamine (DA) receptors and increase prolactin (PRL) levels [3, 4].

Methods

The study was carried out at the Department of Neuropsychiatry, Fujii Hospital. The inclusion criteria were male sex and taking neuroleptics regularly. The exclusion criteria were hepatic, renal or thyroid dysfunction. The patients who were taking drugs known to induce gynecomastia [1] were carefully excluded from the subjects. On the basis of these criteria, 100 patients (84 schizophrenics, 8 patients with anxiety disorders, and 8 patients with mood disorders) that met the DSM (Diagnostic and Statistical Manual of Mental Disorders)-IV [5] diagnostic criteria were obtained successively for the study. Fifty normal males were obtained as a control sample. The study was approved by the relevant ethics committees and was performed in accordance with the Declaration of Helsinki II. Informed consent was obtained from all subjects for the research in this study. The normal subjects and patients had respective ages of 51.5 years (SD = 15.3, range 21–85) and 48.8 years (SD = 11.8, range 21–75) (Table 1). The patients had been regularly treated for periods of 19.5 years (SD = 9.5, range 1–40).

Gynecomastia was defined as a palpable, discrete button of firm subareolar tissue measuring at least 2 cm in diameter [2].

Since the patients had been prescribed neuroleptics with various chemical structures, each neuroleptic was converted to its haloperidol equivalent using the dosage comparability table [6]; for depo neuroleptics, the procedure adopted was based on the equivalence table for long-term therapy [7]. The converted dosage of the patients was .27 mg/day/kg (SD = .32, range .00–2.35) (Table 1).

Blood samples for hormone estimation were drawn once from 55 patients and 35 normal subjects between 0600 and 0700 h. The sera were prepared and stored at –20 centigrade until the time of analysis. PRL, luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone (T) and estradiol (E_2) were assayed by a radioimmunoassay.

Statistical analyses were carried out using parametric tests (e.g. student t-test, Scheffe's test), if the data were normally distributed. Otherwise, the nonparametric tests (e.g. Mann Whitney's U-test, Kruskal-Wallis' test) were used.

Table 1. Demographic characteristics of subjects

	Normals	Patients			
		Total	Gyn. (-)	Gyn. (+)	
				Case 1.	Case 2.
	Mean (SD)	Mean (SD)	Mean (SD)		
N	50 (35¶)	100 (55¶)	98 (53¶)	1	1
Age (yrs)	51.5 (15.3)	48.8 (11.8)	48.5 (10.7)	48	38
Adm. periods (yrs)	-	19.5 (9.5)	21.8 (9.9)	22	1
Doses (mg/day/kg)†	-	0.27 (0.32)	0.26 (0.32)	1.04	0.01

Administration (Adm.); Gynecomastia (Gyn.).
† haloperidol-equivalents.
¶ the number of subjects from whom blood samples were drawn.

Results

1. Prevalence of gynecomastia and galactorrhea

While palpable gynecomastia was present in 2% of the patient group and was unilateral in both subjects, it was not present in the normal group.

Galactorrhea was not present in either patient or normal group.

2. Concentrations of each hormone

The serum PRL concentrations for the normal group and group of patients without gynecomastia were 6.34 ng/ml (SD = 3.65, range 1.7–17.3) and 18.49 ng/ml (SD = 14.71, range 3.2–75.9), respectively. Scheffe's test showed that the mean level of serum PRL in the patient group was significantly higher than that in the normal group ($p < .001$) (Fig. 1).

In the normal group and group of patients without gynecomastia, the blood LH concentrations were 7.88 mIU/ml (SD = 6.36, range 2.0–27.8) and 5.72 mIU/ml (SD = 3.80, range 1.3–20.7), respectively. There was no significant difference in the mean levels of the blood LH between the groups by Scheffe's test (Fig. 1).

In the normal group and group of patients without gynecomastia, the blood FSH concentrations were 13.30 mIU/ml (SD = 17.90, range 2.4–90.0) and 8.93 mIU/ml (SD = 7.85, range 1.8–46.3), respectively. There was no significant difference in the mean levels of the blood FSH between the groups by Scheffe's test (Fig. 1).

In the normal group and group of patients without gynecomastia, the blood T concentrations were 590.6 ng/dl (SD = 191.2, range 224–1107), and 561.5 ng/dl (SD = 148.6, range 234–847), respectively. There was no significant difference in the mean

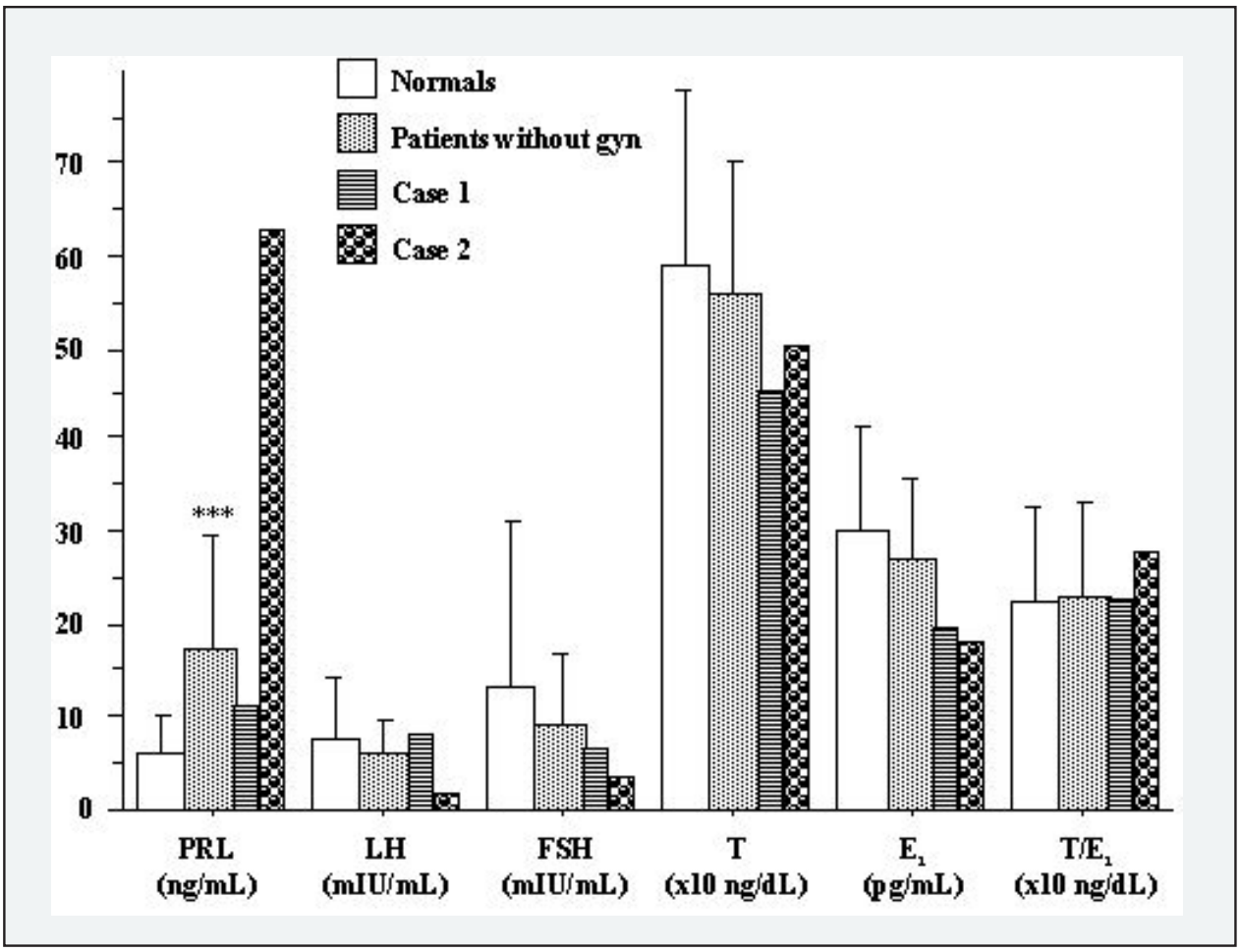

Fig. 1. Concentrations of each hormone.
Results are means with S.D. Units have been shown in parentheses below the names of each hormone. Only the mean level of the serum prolactin (PRL) was significantly different between the group of normals and patients without gynecomastia (gyn). Cases 1 and 2 show the data of each patient with gyn. Estradiol = E_2; FSH = follicle-stimulating hormone; LH = luteinizing hormone; T = testosterone. ***$p < .001$ versus normals by the t-test.

levels of the blood T between the groups by Scheffe's test (Fig. 1).

In the normal group and group of patients without gynecomastia, the blood E_2 concentrations were 30.0 pg/ml (SD = 11.3, range 10–54), and 27.0 pg/ml (SD = 8.9, range 10–51), respectively. There was no significant difference in the mean levels of the blood E_2 between the groups by Scheffe's test (Fig. 1).

Also, in the normal group and group of patients without gynecomastia, the blood T/E_2 concentrations were 22.3 x 10 (SD = 10.6, range 7.9–58.8), and 23.1 x 10 (SD = 10.1, range 7–56), respectively. There was no significant difference in the mean levels of the blood T/E_2 between the groups by Scheffe's test (Fig. 1).

The concentrations of PRL, LH, FSH, T, E_2 and T/ E_2 ratio in two patients with gynecomastia were shown in Fig. 1. Their T/E_2 ratio was not decreased, though PRL of one case increased markedly.

Discussion

Our results seem to indicate that (i) gynecomastia is not common in the Japanese population, and (ii) in male patients neither palpable gynecomastia nor galactorrhea is a common side effect of neuroleptics.

Firstly, the result obtained in our investigation of gynecomastia in normal men does not agree with older reports [1, 2]. Nuttall [2] and Carlson [1] detected gynecomastia in 36% and 32%, respectively, but we detected none. We cannot explain the difference, since they did not show any neuroendocrine data. Gynecomastia is thought to be caused mainly by enhanced estrogen (E) action and/or inhibited T action [1], since Es are known to have a stimulatory effect on mammary tissues [8]. Therefore, the difference in the prevalence of gynecomastia between the studies could be accounted for by the difference between the Japanese and American population in the rate at which the T/Es ratio attains a level sufficient to induce gynecomastia. To clarify the difference, we need further cross-racial studies.

Secondly, although, in males, gynecomastia and galactorrhea secondary to neuroleptics have been reported [9, 10], the frequency of them is unclear. In the present study, only two out of 100 male patients showed unilateral gynecomastia, and none of the male patients showed galactorrhea. Drug-induced gynecomastia is thought to be caused mainly by enhanced E action and/or inhibited T action [1]. Still, however, mechanisms of some drugs' action are unknown [11]. Although neuroleptics have been suggested to induce gynecomastia [10], evidence is insufficient. Neuroleptics have been found to block the DA receptors and increase PRL levels [3, 4, 12], but data for relationships between PRL and gynecomastia are contradictory [13]. Moreover, effects of PRL on gonadal function are inconsistent [14, 15]. Meanwhile, effects of neuroleptics on gonadal function are contradictory [15–20]. Unfortunately, we could not fully study the mechanism of drug-induced gynecomastia, because of the small sample and the small number of patients with gynecomastia. To clarify the relation between gynecomastia and neuroleptic administration, large prospective studies are required.

Lastly, Windgassen et al. [21] investigated the frequency of galactorrhea and reported that the prevalence rate was 19% in schizophrenic female patients on neuroleptics. In contrast to female patients, our results indicate that, in male patients, galactorrhea is rather a rare side effect of neuroleptics in clinical practice, though type of neuroleptics [17], dosage [22] and/or dosage duration [17, 23] must be taken into consideration.

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