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NOTE

An Acromegalic Patient with Pulsatile Secretion of Growth Hormone (GH) Coincident with the Slow-Wave Sleep

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Abstract. A 43-year-old woman was admitted to our hospital for further treatment of acromegaly with high plasma GH and IGF-I levels after transsphenoidal adenomectomy and subsequent treatment with bromocriptine. Physical examination and magnetic resonance imaging (MRI) showed an active acromegalic appearance with residual pituitary macroadenoma. Laboratory findings revealed an increase in basal levels of plasma GH (21.3 μg/L) and plasma IGF-I (470 ng/ml). Plasma GH levels were suppressed from 21.3 μg/L to 9.9 μg/L following oral administration of 75 glucose and did not respond to either TRH or LHRH injection. When plasma GH levels were measured after repeated blood sampling every 20 min for 24 h and sleep stages were analyzed, there were three GH peaks during the night which corresponded to the slow-wave sleep. Mean plasma GH levels which corresponded to the slow-wave sleep stages were much greater than those of other sleep stages during the night. After the patient was treated with intermittent sc injections of octreotide (40 μg/every 2 h, 480 μg/day) in combination with oral administration of bromocriptine (15 mg/day, t.i.d.), episodic GH release was somewhat suppressed but plasma GH levels were slightly increased, corresponding to the slow-wave sleep stage during the night. Mean plasma GH levels were much higher during the sleeping period than the waking period for 24 h before and after the treatment. These findings suggest that GH secretion is correlated to the slow-wave sleep in this particular patient with pituitary GH producing adenoma.

Key words: Acromegaly, GH, Pulsatile secretion, Slow-wave sleep, Octreotide

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ACROMEGALY is characterized by a typical clinical appearance associated with hypersecretion of GH for 24 h, abnormal responses of plasma GH including incomplete suppression by glucose administration or a paradoxical increase after TRH [1–3] and/or LHRH [4], hyperresponse to GHRH [5] and a decrease after dopaminergic stimulation [6]. In normal subjects, GH is secreted in a pulsatile manner under the hypothalamic regulation via GHRH and somatotropin release inhibiting factor (SRIF), with a close relationship to the slow-wave sleep during the night. The GH pulse is more frequent, and plasma GH levels at both the interpulse and the nadir were much higher in acromegalic patients than in normal subjects [7]. Furthermore, it has been reported that GH secretion during the night is not related to the slow-wave sleep in acromegaly [8, 9]. There has not been any report on the detection of pulsatile GH secretion associated with slow-wave sleep in acromegalic patients. When a GH secreting pituitary tumor was removed, plasma GH levels were improved but the pattern of secretion was not completely normalized [10]. Paradoxical GH responses to a number of GH stimuli were recognized in many patients with acromegaly. The relationship between the spontaneous pulsatile GH secretion and such paradoxical responses of GH has not been fully elucidated.

In the present case, we report an interesting rare

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case of acromegaly with a pulsatile GH secretion corresponding to the slow-wave sleep during the night.

Case Report

A 43-year-old woman was admitted to our hospital for further treatment of increased plasma GH and IGF-1 levels after transsphenoidal adenomectomy followed by bromocriptine treatment. She had a past history of duodenal ulcer at the age of 18 yr and adenomatous goiter at the age of 37 yr when she had undergone left hemithyroidectomy. Changes had been pointed out in her facial appearance since the age of 35 yr. Her feet and hands gradually became enlarged. At the age of 38 yr, she was diagnosed as having acromegaly when her basal plasma GH level was high (28 μg/L), and magnetic resonance imaging (MRI) revealed a pituitary macroadenoma with an extension to the internal carotid artery. She has never suffered from a headache, visual disturbance, amenorrhea or galactorrhea. The pituitary tumor was partially resected by transsphenoidal surgery and histologicaly it was a GH producing pituitary adenoma. Although she was treated with bromocriptine after the surgery, plasma GH levels were not sufficiently suppressed to 37 μg/L at a dose of 15 mg/day (t.i.d. po).

Physical examination revealed that she was 158.0 cm tall and weighed 62.0 kg. Blood pressure was 108/60 mmHg. Her skin was moist. Such acromegalic features as enlargement of the nose, hands, feet and soft tissues were remarkable. The palpebral conjunctiva was slightly anemic. There was an operation scar due to left hemithyroidectomy and the right lobe of a goiter was palpable (5.5 × 3.3 cm). No superficial lymph node was palpable. There was no abnormal finding in the chest or abdomen except hepatomegaly.

Clinical course

Endocrinological examination was performed after admission when all the previous treatment was interrupted. Basal plasma GH (21.3 μg/L), urinary GH (110.3 ng/day) and plasma IGF-I (470 μg/L) levels were consistently high. As shown in Table 1, plasma GH levels were not suppressed by oral administration of 75 g glucose. Neither TRH (500 μg, iv) nor LHRH (100 μg, iv) administration increased plasma GH. Plasma GH increased after GHRH (100 μg, iv) injection.

The patient was then treated with bromocriptine (15 mg/day, t.i.d., po) in combination with intermittent SC administration of octretide (40 μg/every 2 h, 480 μg/day) by means of a portable infusion pump (Nipro, SP3I) for 4 weeks. Plasma GH was considerably decreased and IGF-I lowered, but not normalized. Plasma GH did not respond to TRH or LHRH administration.

Blood samplings for 24 h

Blood sampling for 24 h in combination with

Table 1. Endocrinological loading tests in a patient with acromegaly before treatment with octreotide and bromocriptine

	Time (min)	0	30	60	90	120
Glucose (75 g, po)	Glucose (mg/dl)	103	137	144	129	73
	IRI (μU/ml)	6.9	50.7	57.4	106.7	41.3
	GH (μg/L)	21.3	17.0	15.7	11.6	9.9
TRH (500 μg, iv)	TSH (μU/ml)	1.49	15.67	12.38	8.38	6.08
	PRL (μg/L)	3.4	10.9	5.3	5.0	3.9
	GH (μg/L)	20.6	20.7	21.1	19.1	17.6
LHRH (100 μg, iv)	LH (mIU/ml)	2.4	13.9	12.0	12.1	14.1
	FSH (mIU/ml)	3.8	4.7	5.2	7.3	6.2
	GH (μg/L)	15.9	15.8	19.2	21.0	16.3
GHRH (100 μg, iv)	GH (μg/L)	14.6	18.6	18.0	24.2	22.4

sleep stage analysis during the night was performed before and 4 weeks after the start of the treatment. For blood sampling, a heparinized catheter (Kowarski-DAKMED), thromboresistant blood withdrawal needle and tubing set (DAKMED Inc., NY) were used for sampling from an antecubital vein 24 h before the experiment. Deambulation was free and meals were served at 0800 h, 1200 h and 1800 h. Blood samples were collected for 24 h with an ambulatory withdrawal pump (DL6-5L, CORMED Inc., NY) at a flow rate of 3.0 ml/h and fractionated every 20 min with a fraction collector (FRAC 200, Pharmacia AB, Sweden). Plasma samples were immediately centrifuged and stored at −20 °C until assayed.

Sleep analysis

The patient went to bed at 2130 h, when the light was turned off. EEG and sleep analysis was performed with an Oxford-Medilog ambulatory cassette recording system (Oxford-Medilog System, Abingdon, U K). The sleep stage was analyzed by means of an Oxford-Medilog 9200 automatic sleep scoring system and supervised by visual analysis [13]. The sleep stages were divided every min into five stages: 1, 2, 3, 4 and rapid eye movement (REM). Stage 3 and 4 were considered to be the slow-wave sleep.

Plasma GH assay and statistical analysis

Plasma GH levels were determined in duplicate by the highly sensitive enzyme immunoassay as previously reported [12]. The minimum detectable quantity of GH was 3 ng/L with a sample volume of 20 μl. GH profiles were analyzed by the Cluster methods [13]. A 2 × 2 test Cluster configuration was used with two data points for the test nadir and two points for the test pulses, respectively. The relationship between GH secretion and sleep stages was analyzed by plasma GH levels and corresponding sleep stages 10 min before and after each sampling time. Statistical evaluation was performed by ANOVA in combination with Welch's *t*-test. $P<0.05$ was considered significant.

GH secretion for 24 h and sleep stages

Profiles of plasma GH and sleep stages before and after the treatment are shown in Fig. 1. Five

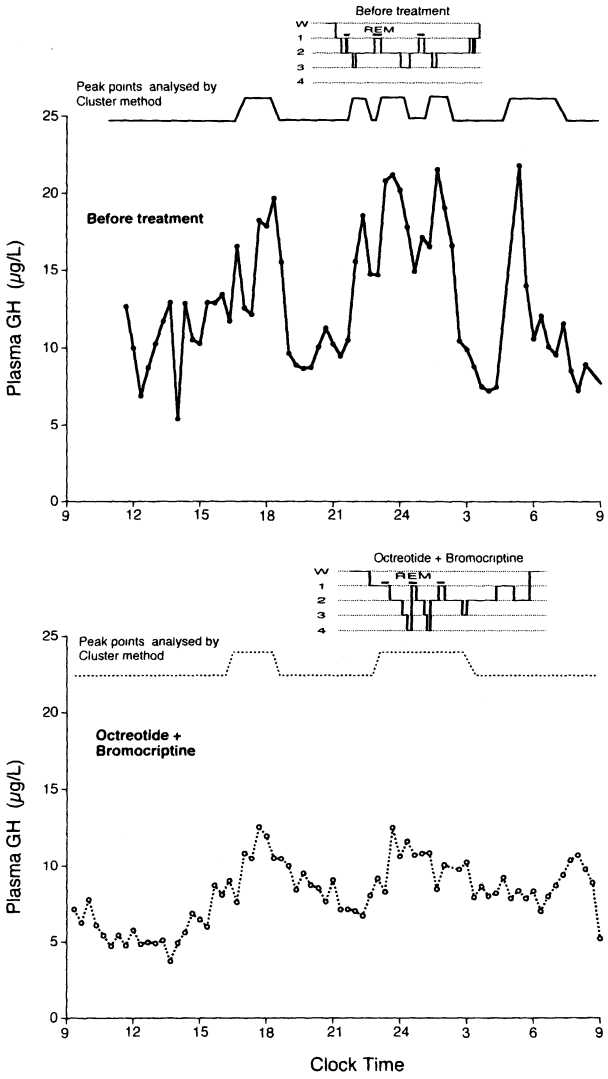

Fig. 1. Profiles of spontaneous GH secretion for 24-h in an acromegalic patient before and after treatment with octreotide and bromocriptine. Octreotide was intermittently injected sc (40 μg/every 2 h, 480 μg/day) and bromocriptine was given po (15 mg/day, t.i.d.). Solid and dashed lines show plasma GH levels before and after the treatment, respectively. W, 1, 2, 3, 4 and REM show wake, stage 1, 2, 3, 4 and rapid eye movement sleep, respectively. Peaks of GH secretion were analyzed by the Cluster method with a 2 × 2 test Cluster configuration.

peaks of GH secretion were detected by Cluster analysis before the treatment. Three of 5 peaks were detected during the night, and corresponded to the slow-wave sleep. On the other hand, two small peaks of GH secretion were detected when the patient was treated with bromocriptine and octreotide, an analog of SRIF. Both peaks

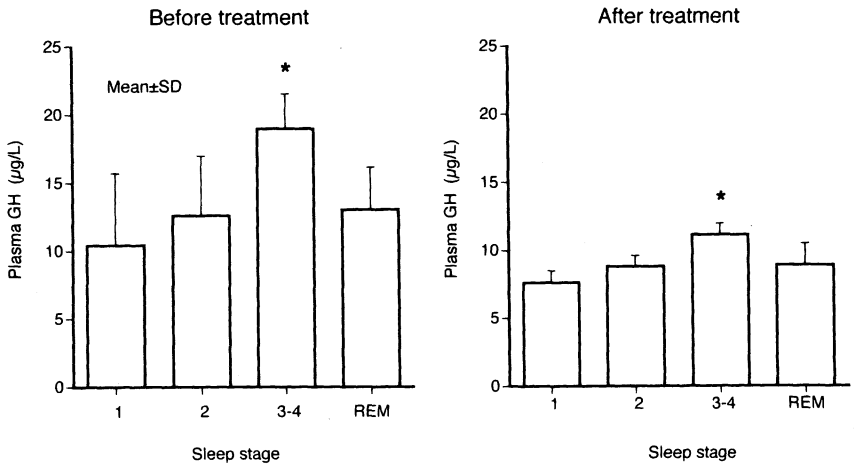

Fig. 2. Correlation between plasma GH levels and slow-wave sleep stages during the night in a patient with acromegaly before and after treatment with octreotide and bromocriptine. Plasma GH levels were analyzed by corresponding sleep stages extending 10 min before and after each sampling time. Mean (± SD) plasma GH levels were much higher in sleep stages 3–4 than in other sleep stages before and after the treatment. * indicates $P<0.05$ *vs.* other sleep stages.

corresponded to the slow-wave sleep.

As shown in Fig. 2, when the relationship between plasma GH levels and sleep stages was further analyzed, the mean (± SD) plasma GH levels which corresponded to the sleep stage extending 10 min before and after the sampling time were much greater than those which corresponded to other sleep stages before the treatment (stages 3–4, 19.0 ± 2.6 μg/L *vs.* stage 1, 10.2 ± 5.3 μg/L, stage 2, 12.6 ± 4.4 μg/L and REM, 13.0 ± 3.1 μg/L, $P<0.05$, respectively). After the treatment, the mean (± SD) plasma GH concentrations corresponding to sleep stages 3–4 were also slightly but significantly greater than those of other sleep stages (stages 3–4, 11.1 ± 0.8 μg/L *vs.* stage 1, 7.6 ± 0.9 μg/L, stage 2, 8.8 ± 0.8 μg/L and REM, 8.9 ± 1.6 μg/L, $P<0.05$, respectively).

The mean plasma GH levels for 24 h during the treatment with octreotide and bromocriptine were considerably lower than those before the treatment (8.3 ± 2.1 μg/L *vs.* 12.5 ± 4.4 μg/L, $P<0.0001$). The mean plasma GH levels were higher during the sleeping period (n=21) than in the waking time (n=41) before the treatment (14.9 ± 4.8 μg/L *vs.* 11.1 ± 3.3 μg/L, $P<0.005$), whereas the mean plasma GH levels were still higher during the sleeping period (n=21) than in the waking time (n=49) after the treatment in the night than the day time before treatment (9.1 ± 1.5 μg/L *vs.* 7.7 ± 2.2 μg/L, $P<0.005$). Mean plasma GH levels of the peak fraction and the nadir fractions considerably decreased after the treatment with octreotide and bromocriptine (peak GH, 16.6 ± 4.0 μg/L *vs.* 10.4 ± 1.3 μg/L, $P<0.0001$ and nadir GH, 10.4 ± 1.3 μg/L *vs.* 7.3 ± 1.7 μg/L, $P<0.0001$, respectively).

Discussion

In a patient with acromegaly, we demonstrated that plasma GH was spontaneously changed in a close correlation with the slow-wave sleep stage during the night after incomplete transsphenoidal surgery, although we did not have a chance to evaluate plasma GH levels for 24 h before surgery.

In normal subjects, GH is known to be secreted in a pulsatile manner with a peak value every 2 to 3 h [14, 15]. The sleep-dependent rhythm is characterized by a large burst appearing early in the course of slow-wave sleep [14, 15, 18]. GH secretion is also regulated by a sleep-independent and ultradian rhythm, which is influenced by age, sex, stress, nutrition and other factors [16, 17]. The ultradian rhythm of GH secretion is regulated by the complex interaction of at least two hypothalamic hypophysiotrophic factors, GHRH and SRIF

secretion [19], which are counterregulatory factors for GH release. GHRH and SRIF are secreted tonically from the hypothalamus into the hypophyseal portal blood and the GH secretion is superimposed upon this steady state release, which forms an additional rhythmic surge of each peptide [19]. GHRH is considered to be instrumental in the maintenance of pulsatile GH secretion. Furthermore, the pulsatile secretion of GH seems to be regulated by GHRH because anti-SRIF antiserum was unable to block episodic GH surges in the rat [20]. On the other hand, basal secretion of GH is dependent on SRIF release [21].

The patient with acromegaly was reported to have an abnormally rapid GH pulse frequency characterized by high interpulse and nadir GH levels [7]. Nocturnal GH secretion was not generally recognized, and even if excessive GH secretion were observed during the night, there is no obvious relationship between nocturnal GH secretion and slow-wave sleep in acromegaly [9]. Furthermore the abnormal GH secretion is not completely normalized in surgically cured acromegalic patients [10].

Completely cured acromegaly could be considered to be indicated by normal basal GH secretion without any paradoxical response to TRH and/or LHRH in combination with sufficient suppression of GH due to oral glucose administration. The persistence of a paradoxical GH response indicates the possible presence of GH producing tumor tissue [1, 2] although some investigators indicated that paradoxical GH response may be expressed only when hypothalamus-pituitary interactions are intact [3].

The pathophysiological causes of acromegaly are not fully clarified. There have been two hypothetical theories: of hypothalamic and pituitary origin. The hypothalamic theory explains that increased tonus of hypothalamic GHRH results in hyperstimulation of pituitary GH secretion, followed by producing a pituitary tumor [7]. But it has not been demonstrated that GHRH secretion into the pituitary portal blood increases in acromegaly. Recently a point mutation of Gs protein subunit was detected in about 40% of the pituitary tumor in acromegalic patients, suggesting that a trigger of the onset of acromegaly might be, at least partly, the pituitary gland [22].

It is difficult to distinguish two causes in individual acromegalic case. Plasma GH responses to the stimulation tests could not differentiate by themselves the origin of the hypothalamus and the pituitary in acromegaly. On the other hand, a 24-h spontaneous GH profile could indicate whether pituitary GH secretion is regulated by hypothalamic secretion of GHRH and SRIF, when spontaneous GH secretion is assessed with the sleep-related cycle. In the present case, spontaneous GH secretion was well correlated with the slow-wave sleep stage during the early period of sleep, and no paradoxical responses of plasma GH to TRH or LHRH administration was recognized. These findings suggest that the hypothalamic regulation of spontaneous GH secretion might be preserved in the present rare case.

It was previously reported that GH secretion during the night was hardly suppressed by bromocriptine in acromegaly [9]. In the present case, concomitant administration of octreotide and bromocriptine considerably but insufficiently suppressed GH release during the night. Such patients with acromegaly could be effectively treated with an anti-serotoninergic agent which could inhibit hypothalamic GHRH involved in the hypersecretion of GH [23, 24].

In conclusion, we report a unique case of acromegaly with pulsatile secretion of GH corresponding to the slow-wave sleep during the night.

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References

1. Faglia G, Paracchi A, Ferrari C, Beck-Peccoz P (1978) Evaluation of the results of trans-sphenoidal surgery

in acromegaly by assessment of the growth hormone response to thyrotropin-releasing hormone. *Clin Endocrinol (Oxf)* 8: 373–380.
2. Arosio M, Giovannelli MA, Riva E, Nava C, Ambrosi B, Faglia G (1983) Clinical use of pre- and postsurgical evaluation of abnormal GH responses in acromegaly. *J Neurosurg* 59: 402–408.
3. Marinis LD, Mancini A, Zuppi P , Anile C, Maira G (1990) Paradoxical growth hormone response to thyrotropin-releasing hormone in acromegaly. Clinical correlation and prognostic value. *Acta Endocrinol (Copenh)* 122: 433–449.
4. Giustina G, Reschini E, Paracchi M, Cantalamessa L, Cavagnini F, Pinto M, Bulgheroni P (1974) Failure of somatostatin to suppress thyrotropin-releasing factor and lutenizing hormone releasing factor-induced growth hormone release in acromegaly. *J Clin Endocrinol Metab* 38: 906–909.
5. Wood SM, Ch'ng JLC, Adams EF, Webster JD, Joplin GR, Mashitu K, Bloom SR (1983) Abnormalities of growth hormone release in response to human pancreatic growth hormone-releasing factor (GRF 1–44) in acromegaly and hypopituitarism. *Br Med J* 286: 1686–1691.
6. Chiodini PG, Liuzzi A, Botalla L, Cremascoli G, Silvestrini F (1974) Inhibitory effects of dopaminergic stimulation on GH release in acromegaly. *J Clin Endocrinol Metab* 36: 1259–1262.
7. Barkan AL, Stred SE, Reno K, Markovs M, Hopwood NJ, Kelch RP, Beitins IZ (1989) Increased growth hormone pulse frequency in acromegaly. *J Clin Endocrinol Metab* 64: 1225–1233.
8. Carlson HE, Gillin JC, Gorden P, Snyder F (1972) Absence of sleep-related growth hormone peaks in aged normal subjects and in acromegaly. *J Clin Endocrinol Metab* 34: 1102–1105.
9. Chihara K, Kato Y, Abe H, Furumoto M, Maeda K, Imura H (1977) Sleep-related growth hormone release following 2-brom-a-ergocriptine treatment in acromegalic patients. *J Clin Endocrinol Metab* 44: 78–84.
10. Semer M, Faria ACS, Nery M, Salgado LR, Knoepfelmacher M, Wajchenberg BL, Liberman B (1995) Growth hormone pulsatility in active and cured acromegalic subjects. *J Clin Endocrinol Metab* 80: 3767–3770.
11. Sforza E, Vandi S (1996) Automatic Oxford-Mediog 9200 sleep staging scoring: Comparison with visual analysis. *J Clin Neurophysiol* 13: 227–233.
12. Sohmiya M, Kato Y (1992) Renal clearance, metabolic clearance rate, and half-life of human growth hormone in young and aged subjects. *J Clin Endocrinol Metab* 75: 1487–1490.
13. Veldhuis JD, Johnson ML (1986) Cluster analysis: A simple, versatile, and robust algorithm for endocrine pulse detection. *Am J Physiol* E486–E493.
14. Evans S, Faria ACS, Christiansen E, Ho KY, Weiss J, Rogol AD, Johnson ML, Blizzard RM, Veldhuis JD, Thomer MO (1987) Impact of intensive venous sampling on characterization of pulsatile GH release. *Am J Physiol* 252: E549–E556.
15. Albertsson-Wikland K, Rosberg S (1988) Analyses of 24-hour growth hormone profiles in children: Relation to growth. *J Clin Endocrinol Metab* 67: 493–500.
16. Zadik Z, Chalew SA, McCarter RJ Jr, Meistas M, Kowarski AA (1985) The influence of age on 24-hour integrated concentration of growth hormone in normal individuals. *J Clin Endocrinol Metab* 60: 513–516.
17. Ho KY, Evans WS, Blizzard RM, Veldnuis JD, Merriam GR, Samojlik E, Furlanetto R, Rogol AD, Kaiser DL, Thorner MO (1987) Effects of sex and age on the 24-hour profile of growth hormone secretion in man: Importance of endogenous estradiol concentrations. *J Clin Endocrinol Metab* 64: 51–58.
18. Sadamatsu M, Kato N , Iida H , Takahashi S , Sakaue K, Takahashi K, Hashida S, Ishikawa E (1995) The 24-hour rhythms in plasma growth hormone, prolactin and thyroid stimulating hormone: Effect of sleep deprivation. *J Neuroendocrinol* 7: 597–606.
19. Tannenbaum GS, Ling N (1984) The interrelationship of growth hormone (GH)-releasing factor and somatostatin in generation of the ultradian rhythm of GH secretion. *Endocrinology* 115: 1952–1957.
20. Tannenbaum GS (1988) Somatostatin as a physiological regulator of pulsatile growth hormone secretion. *Horm Res* 29: 70–74.
21. Tannenbaum GS (1991) Neuroendocrine control of growth hormone secretion. *Acta Paediatr Scand* 372 (suppl): 5–18.
22. Landis CA, Harsch G, Lyons J, Davis RL, McCormick F, Bourne HR (1990) Clinical characteristics of acromegaly patients whose pituitary tumors contains mutant Gs protein. *J Clin Endocrinol Metab* 71: 1415–1420.
23. Murakami Y, Kato Y, Kabayama Y, Tojo K, Inoue T, Imura H (1986) Involvement of growth hormone (GH)-releasing factor in GH secretion induced by serotoninergic mechanisms in conscious rats. *Endocrinology* 119: 1089–1092.
24. Chihara K, Kato Y, Maeda K, Matsukura S, Imura H (1976) Suppression by cyproheptadine of human growth hormone and cortisol secretion during sleep. *J Clin Invest* 57: 1393–1402.