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Detection of a Silent Pituitary Somatotroph Adenoma in a Patient with Amenorrhea and/or Galactorrhea: Paradoxical Response of GH in TRH or GnRH Provocation Test

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SYMPTOM of amenorrhea and/or galactorrhea is commonly observed in the patients reported with a silent somatotroph adenoma [1–7]. How to identify a patient with a silent somatotroph adenoma among female patients with a history of amenorrhea and/or galactorrhea has implications of clinical importance. In order to obtain a solution to this problem, we measured the serum GH and PRL values repeatedly and studied GH dynamics after TRH or GnRH stimulation in 6 female patients with a history of amenorrhea and/or galactorrhea, half of them being confirmed endocrinologically to have a silent somatotroph adenoma. In addition, the tumors were investigated by immunohistochemistry including a catalyzed signal amplification (CSA) system, non-radioisotopic in situ hybridization (ISH) and confocal laser scanning microscopy (CLSM).

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Case Materials

The endocrinological and histopathological findings of 6 female patients with a history of amenorrhea and/or galactorrhea are summarized in Table 1. The endocrinological and histopathological features of patient 1 were described in our previous report [8].

Six female patients with a history of amenorrhea and/or galactorrhea had a pituitary microadenoma (Hardy's grade1) or an adenoma with slight suprasellar extension (Hardy's grade2A), revealed by magnetic resonance imaging (MRI). Their serum GH and PRL values were measured repeatedly and GH dynamics after TRH or GnRH stimulation were studied. Paradoxical responses of GH were observed in 3 patients (patient 1-3) (Fig. 1), who were hospitalized for further endocrinological examination. Their pituitary tumors were removed by transsphenoidal surgery and examined histopathologically. All these three patients had no residual tumor revealed by postoperative MRI.

Histopathological examination (patient 1-3): histopathological examination confirmed GH-immuno-

Table 1. Summary of endocrinological studies in 6 female patients, presenting amenorrhea and/or galactorrhea

	Age	Amenorrhea	Galactorrhea	PRL (ng/ml)	GH (ng/ml)	IGF-1 (ng/ml)	Paradoxical response of GH in TRH loading test	in GnRH loading test	Suppression of GH in OGTT
1–3: patients with a silent somatotroph adenoma									
1	25y.o.	+	+	17–24	2.1–15.1	180–220	+	+	+
2	20y.o.	+	−	4.8–26.0	0.54–30.9	220	+	±	+
3	25y.o.	+	−	4.9–8.8	1.1–5.98	180–210	+	+	−

	Age	Duration of symptoms	Irregular response of GH in bromocriptine loading test	Postoperative GH (ng/ml)	Paradoxical response of GH in postoperative TRH loading test	in postoperative GnRH loading test	Postoperative clinical symptoms
1	25y.o.	1 year	+	0.83–2.62	+	−	regular menstruation no galactorrhea
2	20y.o.	7 months	+	1.47–4.13	+	−	regular menstruation
3	25y.o.	1.5 years	+	0.94–5.39	−	−	regular menstruation biphasic basal body temperature

	Age	Amenorrhea Duration of symptoms	Galactorrhea	PRL (ng/ml)	GH (ng/ml)	IGF-1 (ng/ml)	Paradoxical response of GH in TRH loading test	in GnRH loading test
4–6: patients without paradoxical responses of GH in TRH or GnRH provocation test								
4	28y.o.	+ 5 year	−	4.9–26.3	0.2–0.45	190	−	−
5	35y.o.	+ 2 year	−	37.3–98	2.94–26.1	200	−	−
6	32y.o.	+ 2 year	−	61.3–92	0.17–0.92	180	−	−

PRL: normal range for woman: 1.4–14.6 ng/ml
GH: normal range for woman: 0.66–3.68 ng/ml
IGF-1: normal range: 100–315 ng/ml

Summary of histopathological studies in 3 female patients with silent somatotroph adenomas, presenting amenorrhea and/or galactorrhea

	Hematoxylin-eosin staining	IHC (indirect method) GH	PRL	CLSM GH positive SG	*In situ* hybridization GH mRNA	PRL mRNA	Pit-1 mRNA
1	chromophobe	+(CSA)	+	+	+	+	+
2	acidophilic-chromophobe	+	+	++	+	+	+
3	acidophilic-chromophobe	+	+	++	+	+	+

IHC: immunohistochemistry
CSA: catalyzed signal amplification
CLSM: confocal laser scanning microscopy
SG: secretory granule

positivity in all the three pituitary adenomas; in one of them a highly sensitive immunohistochemistry, CSA system, was utilized. GH mRNA expression was also revealed and GH-immunopositive secretory granules were noted in all the three pituitary adenomas under CLSM.

These endocrinological and histopathological findings confirmed the adenoma as a silent somatotroph

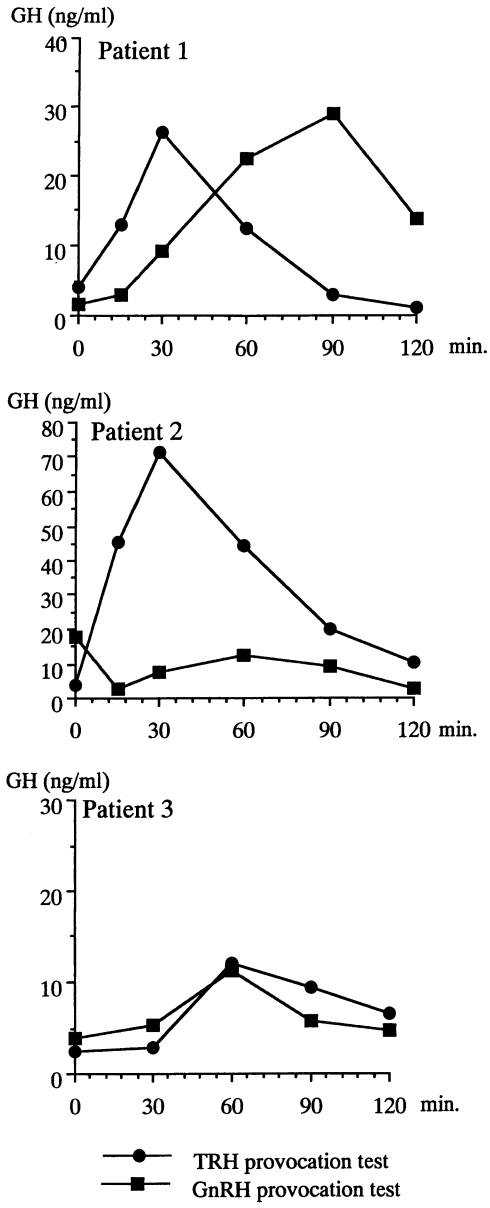

Fig. 1. Both TRH and GnRH provocation tests showed paradoxical rises of serum GH in patients 1 and 3. TRH provocation test showed a paradoxical response of GH, and GnRH provocation test showed an irregular secretion of GH in patient 2.

adenoma, presenting no clinical features of acromegaly.

Comparison of serum GH and PRL values between 3 patients with a silent somatotroph adenoma (patient 1-3) and 3 patients having a microadenoma without paradoxical responses of GH in TRH or GnRH provocation tests (patient 4-6): mean serum GH value of the 3 patients with a silent somatotroph adenoma was 7.44 ng/ml (SD: 8.81), ranging from 0.54 to 30.9 ng/ml, whereas that of the 3 patients without paradoxical responses of GH in TRH or GnRH provocation tests was 2.72 ng/ml (SD: 6.66), ranging from 0.15 to 26.1 ng/ml. There is a statistically significant difference between the mean serum GH values of the two groups (Student's t-test, $p<0.05$) (Fig. 2). Mean serum PRL value of the 3 patients with a silent somatotroph adenoma was 15.84 ng/ml (SD: 13.60), ranging from 4 to 59 ng/ml, whereas that of the 3 patients without paradoxical responses of GH in TRH or GnRH provocation tests was 58.93 ng/ml (SD: 34.59), ranging from 4.6 to 92 ng/ml. There is a statistically significant difference between the mean serum PRL values of the two groups (Student's t-test, $p<0.001$) (Fig. 2).

Discussion

The aim of this study is the preoperative endocrinological identification of a patient with a silent somatotroph adenoma among female patients with a history of amenorrhea and/or galactorrhea. The strategy for the endocrinological identification of a silent somatotroph adenoma was proposed, based on the endocrinological and histopathological findings of 3 patients with a silent somatotroph adenoma.

The first step for the detection of a silent somatotroph adenoma is the meticulous study of GH dynamics, together with repeated measurement of basal levels of GH and PRL. Paradoxical rises, including an irregular secretion, of serum GH in either TRH or GnRH provocation tests were observed in all three patients with silent somatotroph adenomas, and this can be interpreted as an important clue for the identification of a silent somatotroph adenoma. Repeated measurement of serum GH and PRL levels showed that serum GH level is higher and serum PRL level is lower in patients with a silent somatotroph adenoma than in those patients without paradoxical responses of GH in TRH or GnRH provocation tests.

The second step for the precise diagnosis of a silent somatotroph adenoma is the histopathological demonstration of GH production in the adenoma cells, using immunohistochemistry including CSA system, ISH studies and CLSM.

In all three patients with silent somatotroph ade-

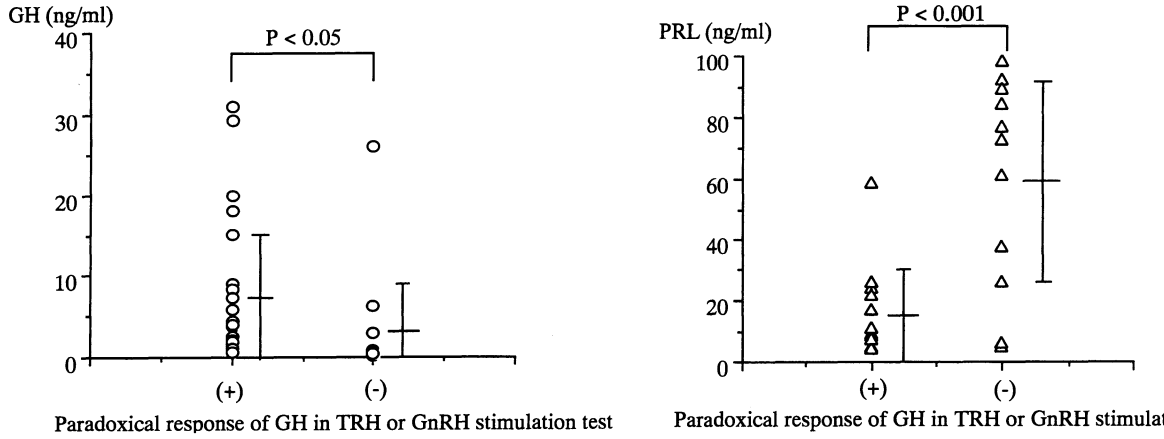

Fig. 2. Comparison of serum GH and PRL values between 3 patients with a silent somatotroph adenoma and 3 patients having a microadenoma without paradoxical responses of GH in TRH or GnRH provocation test. Mean serum GH value of 3 patients with a silent somatotroph adenoma was higher than that of 3 patients without paradoxical responses of GH in TRH or GnRH provocation tests. Mean serum PRL value of 3 patients with a silent somatotroph adenoma was lower than that of 3 patients without paradoxical responses of GH in TRH or GnRH provocation tests.

nomas regular menstruation was restored after successful surgical removal of the adenoma. Moreover, in one patient biphasic basal body temperature was restored, which suggested the regularly maintained ovulation. As shown in this patient, the postoperative disappearance of paradoxical responses of GH in both TRH and GnRH provocation tests is a hallmark of the endocrinological cure, i.e., regular menstruation and regularly maintained ovulation. Surgical removal of a silent somatotroph adenoma in a patient with amenorrhea and/or galactorrhea can be beneficial for the restoration of menstruation and ovulation, therefore, the preoperative endocrinological identification of a patient with a silent somatotroph adenoma among female patients with a history of amenorrhea and/or galactorrhea is interpreted as having clinical importance.

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