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Original scientific paper

Diagnostic Value of Thyrotropin Releasing Hormone Test in 129 Patients with Suspected Tumoral Hyperprolactinemia

L. Smirčić-Duvnjak[1], B. Vizner[2], M. Koršić[3], M. Sekso[2] and M. Berković[2]

[1] University Hospital for Diabetes, Endocrinology, and Metabolic Diseases »Vuk Vrhovac«, Zagreb, Croatia

[2] Center for Neuroendocrinology and Pituitary Diseases, Department of Endocrinology, Diabetes and Metabolic Diseases, University Hospital »Sestre milosrdnice«, Zagreb, Croatia

[3] Department of Endocrinology, Diabetes and Metabolic Diseases, University Hospital Center »Zagreb«, Zagreb, Croatia

A B S T R A C T

In 129 hyperprolactinemic (PRL ≥100ng/mL) and 100 normoprolactinemic patients (PRL 0–25 ng/mL), max. PRL (the difference between maximal prolactin (PRL) after thyrotropin releasing hormone (TRH) injection and basal value) was compared with basal PRL and computed tomography (CT) of the sellar region. In 122 hyperprolactinemic patients max. PRL was <100%, while tumor was found in 106 of them. In the remainder seven hyperprolactinemic patients max. PRL was ≥100% and CT showed no tumor. A significant difference in max. PRL between hyperprolactinemic patients without and those with verified adenoma was found and showed a significant negative correlation with basal PRL. Between 122 hyperprolactinemic patients with max. PRL <100%, mean basal PRL and duration of clinical symptoms were significantly lower in 16 patients with normal CT compared to 106 patients with tumor. All normoprolactinemic patients showed max. PRL ≥100% and no tumor on CT. PRL stimulation disturbance precedes tumor visualization and represents a decisive diagnostic parameter in hyperprolactinemic patients with no tumor signs.

Introduction

Hyperprolactinemia represents the most common disorder of the hypothalamus and pituitary gland in humans. It may be caused by different mechanisms including autonomous prolactin secretion by a pituitary adenoma, reduced or miss-

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ing dopamine effect on the lactotrophs, and stimulation of the lactotroph cells overriding physiological inhibition[1]. While a lack of dopaminergic inhibition or enhanced stimulation can be easily excluded by clinical investigation and evaluation of the patients history, the diagnosis of prolactinoma can be difficult.

Numerous efforts have been made to identify an efficacious functional test for distinguishing tumoral hyperprolactinemia from a nonneoplastic condition[2–4].

Although a blunted prolactin response to thyrotropin releasing hormone test (TRH) stimulation defined as less than a doubling of the basal level was considered to be a decisive factor, evidence of some prolactinoma patients showing normal prolactin response has diminished its diagnostic value[4–7].

The introduction of computed tomography (CT) has markedly improved the diagnosis of microprolactinomas but not all can be detected with this technique[8,9].

The present study was undertaken in an attempt to identify the real diagnostic role of the TRH test, which could possibly eliminate a need for performing CT scan of the pituitary and to establish a rational diagnostic procedure in patients with hyperprolactinemia.

Patients and Methods

A group of 129 patients (105 women and 24 men, mean age 42±9 years) with hyperprolactinemia 100 ng/mL, detected during evaluation of galactorrhea, amenorrhea and sexual disturbances, were included in the study. All had normal thyroid function, no signs of acromegaly and Cushing's disease, and were taking no medications known to elevate serum prolactin level. One hundred control subjects (89 women and 11 men) were drawn from a group of normoprolactinemic patients referred to our institution for the evaluation of nonfunctional adenoma and presenting with symptoms of headache and visual disturbances.

All 100 control subjects underwent basal hormone serum measurements, TRH test and CT. All patients gave their informed consent to participate in the study

Basal prolactin value was determined at rest, after an overnight fast and expressed as a mean value of three measurements on different days. It was measured by the radioimmunoassay method (RIA) of double antibodies, using the reagents provided by Biodate. The sensitivity of the assay was 1.5–2 ng/mL, intra -assay coefficient of variation 3.6%, inter -assay coefficient of variation was 5.8%. Normal ranges of PRL in our laboratory are 0–15 ng/mL for men and 0–25 ng/mL for women.

Thyrothropin releasing hormone (TRH -Roche) was administered as an intravenous bolus in a dose of 200 g. Blood was drawn for prolactin measurement from an indwelling catheter before the injection and at 20 min. intervals ending 120 minutes after the injection. A normal prolactin response was defined as at least a doubling of the basal value and expressed as delta maximum (max.), i.e., the difference between the maximal prolactin level after the injection and the basal value.

Anterior pituitary function was assessed by measurement of serum thyroxin, estradiol, cortisol, progesterone, growth hormone (GH), thyroid stimulating hormone (TSH), corticotropin (ACTH), luteinizing hormone (LH), follicle stimulating hormone (FSH).

All hormones were determined by RIA.

All patients underwent computed tomography of the pituitary (Siemens Somatom) with 2 mm cuts of the sella.

In both groups max. was compared with basal prolactin value and CT scan.

Statistical analysis was performed by ^{2} test, Mann Whitney and Kruskal Wallis test for unpaired data.

Results

Prolactin basal value in the study group ranged from 100 to 9324 ng/ml (mean value 396.26± 912.14). In 122 patients max. PRL was lower than 100% and CT scan detected tumor in 106 patients: microprolactinoma in 46 and macroprolactinoma in 60 of them (Table 1).

max., ranging from –70% to 150%, showed a significantly negative correlation with basal prolactin level (^{2}=24.05 p<0.001 Kruskal-Wallis) (Figure 1).

The difference in max between patients with normal CT and verified adenoma was statistically significant (^{2}=9.8 p<0.01 Kruskal-Wallis) (Figure 2).

In the control group basal prolactin level ranged from 1.5 to 25 ng/ml (mean value = 10.17 ±6.58). All subjects showed at least double increase in basal prolactin level after the TRH injection, ranging from 150 to 500%, while on CT scan there were no signs of tumor.

In the study group, the prolactin response expressed in terms of % from

TABLE 1
LABORATORY DATA AND CT APPEARANCE IN 129 HYPERPROLACTINEMIC PATIENTS

Basal PRL (ng/mL)	N	Δ max. PRL		CT appearance		
		100%	< 100%	Normal	Micro-adenoma	Macro-adenoma
100–101	18	3	15	7	6	5
102–105	8	1	7	4	3	1
106–110	5		5	1	2	2
111–120	8	3	5	5	3	
121–130	15		15	5	7	3
131–140	12		12	1	6	5
141–150	2		2			2
151–160	5		5		1	4
161–170	5		5		2	3
171–180	4		4		3	1
181–190	3		3		2	1
191–200	3		3		2	1
201–210	2		2		1	1
211–230	4		4		2	2
231–240	5		5		2	3
241–300	3		3		2	1
301–500	4		4		1	3
501–700	7		7		1	6
701–1000	6		6			6
1001–2000	7		7			7
2001–2500	2		2			2
9324	1		1			1
Total	129	7	122	23	46	60

* max. PRL = the difference between maximal PRL after TRH injection and basal value

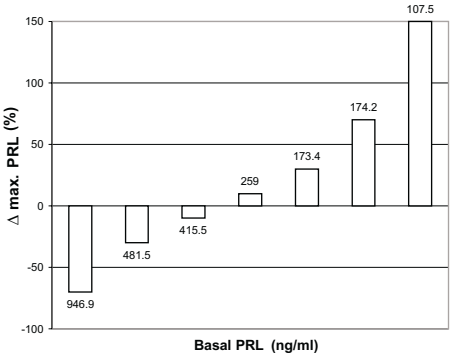

Fig. 1. Relationship between max. PRL and basal PRL in patients with hyperprolactinemia.

max. PRL = difference between maximal PRL after TRH injection and basal value

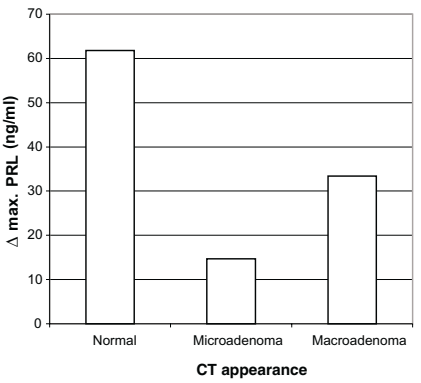

Fig. 2. Relationship between max. PRL and CT appearance of the sellar region in patients with hyperprolactinemia.

max. PRL = difference between maximal PRL after TRH injection and basal value

TABLE 2
CLINICAL AND LABORATORY DATA IN 23 HYPERPROLACTINEMIC PATIENTS WITH NORMAL CT APPEARANCE OF THE SELLAR REGION

Patients (N=23)	Normal response to TRH test (N=7)			Blunted response to TRH test (N=16)			p
	X	SD	Median	X	SD	Median	
Age (years)	37.7 ±	13.4	44.0	38.4 ±	9.1	38.0	>0.05
Basal PRL (ng/mL)	107.5 ±	8.9	104.5	112.0 ±	11.9	109.0	>0.05
max. PRL* (ng/mL)	128.3 ±	17.5	131.5	33.3 ±	38.2	35.6	<0.005

max. PRL = difference between maximal PRL after TRH injection and basal value

baseline with 95% confidence limits ranged from 11 to 104% in patients with normal CT appearance, 2 to 18% in patients with verified microadenoma and 3 to 24% in those with verified macroadenoma. In the control group prolactin response expressed in terms of a % from baseline ranged from 351 to 497%.

Among 23 patients of the study group with normal CT appearance, statistically significant difference was found in Δ max. PRL (Table 2).

Among 122 patients with blunted prolactin response to TRH, mean basal prolactin level and duration of clinical symptoms were significantly lower in patients with normal CT scan (Table 3).

Discussion

Our results clearly indicate that dynamic testing provides more precious diagnostic information than basal prolactin value, proposed by some authors as the most valuable diagnostic parameter of tumoral hyperprolactinaemia[10,11]. We have documented a statistically significant negative correlation between the PRL response to TRH and its basal value.

This finding is in contrast with data published by Ghigo which failed to demonstrate a correlation between basal value and PRL response to TRH in 72 hyperprolactinemic patients and those by Assies which have documented the corre-

TABLE 3
CLINICAL, LABORATORY DATA AND CT APPEARANCE IN HYPERPROLACTINEMIC PATIENTS WITH Δ MAX. PRL < 100%

CT appearance	Normal (N=16)			Adenoma (N=106)			U	p
	X	SD	Median	X	SD	Median		
Age (years)	38.4 ±	9.1	38.0	43.5 ±	12.0	44.0	606	> 0,05
Basal PRL (ng/ml)	112.0 ±	11.9	109.0	455.1 ±	992.0	167.0	243	< 0,001
Δ max. PRL (ng/ml)	33.3 ±	38.2	35.6	25.4 ±	122.5	23.7	732	> 0,05
Duration of clinical symptoms (months)	18.2 ±	6.0	18.0	78.1 ±	38.8	76.4		< 0,05

lation only in normoprolactinemic patients[6,12].

We further tried to establish whether in patients with blunted prolactin response tumor visualization on CT scan could be expected. A significant difference in prolactin response to TRH between patients with normal CT appearance and verified adenoma was documented. However, many authors have reported that tumoral hyperprolactinemia cannot be determined by TRH stimulation[13–15]. We believe that controversies over the role of TRH test are enhanced by the disparity in the definitions of normal and abnormal prolactin responses[6,15,16]. It is obvious that with a less stringent definition of normality some patients with adenoma might have a response considered to be normal. The dose of TRH used by the various authors also differs, which makes the result incomparable[6]. The number of previously reported hyperprolactinemic patients was small and their basal prolactin level was less than 100 ng/mL[13, 14,16].

In the present study the prolactin response was blunted in 122 of 129 patients while tumor was visualized in 106 of them. Tumor was not present in seven patients with normal response to TRH. It has to be emphasized that statistically significant difference among 23 patients with normal CT appearance was observed only in max. On the other side, max. in patients with blunted response and normal CT or visualized tumor was not significantly different.

The similarity of prolactin dynamics among these patients indicates an existence of a tumor which is not radiologically detectable. Furthermore, it was previously documented that prolactin stimulation disturbance can precede radiological visualization by one to three years[17].

The probability of tumor existence increases with higher basal prolactin level and longer duration of clinical symptoms[17]. In fact, in patients with blunted prolactin response but normal CT finding, mean prolactin value was significantly lower compared to patients with blunted response but documented tumor by CT. The duration of clinical signs and symptoms were significantly longer in patients with visualized tumor compared to those with no tumor signs.

We conclude that TRH test should be performed before CT scan in all hyperprolactinemic patients. As PRL stimulation disturbance can precede radiological tumor visualization, blunted PRL response to TRH in patients with no tumor signs suggests a presence of a radiologically undetectable adenoma. In patients with PRL increase > 100%, the persistence of a normal PRL response to TRH can be used as a periodic marker for the absence of an adenoma, whereas the loss of this response would indicate the need for performing CT scan.

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L. Smirčić-Duvnjak

University Hospital for Diabetes, Endocrinology, and Metabolic Diseases »Vuk Vrhovac«, Dugi dol 4a, 10000 Zagreb, Croatia

DIJAGNOSTIČKA VRIJEDNOST THYROTROPIN RELEASING HORMON (TRH) TESTA U 129 BOLESNIKA SA SUSPEKTNOM TUMORSKOM HIPERPROLAKTINEMIJOM

SAŽETAK

U 129 bolesnika s hiperprolaktinemijom (PRL 100 ng/mL) i 100 normoprolaktinemičnih ispitanika (PRL = 0–25 ng/mL), uspoređivan je max. PRL razlika između maksimalnog porasta prolaktina (PRL) nakon intravenske primjene thyrotropin releasing hormona (TRH) i bazalne vrijednosti) sa bazalnom razinom PRL i nalazom kompjutorizirane tomografije (CT) selarne regije. Vrijednost max. PRL <100% nađena je u 122 bolesnika s hiperprolaktinemijom, dok je tumor dokazan u njih 106. U preostalih sedam bolesnika s hiperprolaktinemijom max. PRL bio je 100%, a na nalazu CT-a nije nađeno znakova tumora. Nađena je statistički značajna razlika u max. PRL između bolesnika s hiperprolaktinemijom sa i bez dokazanog tumora na CT-u te značajna inverzna korelacija max. PRL s bazalnom razinom PRL. Između 122 bolesnika s hiperprolaktinemijom s max. PRL <100%, srednja vrijednost bazalne razine PRL i trajanje kliničkih simptoma bili su značajno niži u 16 bolesnika s urednim nalazom CT-a hipofize u usporedbi sa 106 bolesnika s dokazanim tumorom. U svih ispitanika s normoprolaktinemijom max. PRL bio je 100% a nalaz CT-a uredan. Poremećaj stimulacije prolaktina prethodi vizualizaciji tumora i u bolesnika s hiperprolaktinemijom a bez znakova tumora na nalazu CT-a predstavlja značajan dijagnostički parametar.