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Relationship between high prolactine levels and migraine attacks in patients with microprolactinoma

D. Bosco · A. Belfiore · A. Fava · M. De Rose · M. Plastino · C. Ceccotti ·
P. Mungari · R. Iannacchero · A. Lavano

Abstract The pathophysiology of pituitary-associated headache is unknown, although structural and functional features of the tumour are proposed mechanisms. The objective of this study was to evaluate whether headache in a population with pituitary micro-adenomas was related to hyperprolactinemia. We recruited 29 patients with micro-prolactinoma and headache: 16 with migraine (group A) and 13 with tension-type-headache (group B). The pro-lactin (PRL) levels measured during attacks of headache were significantly higher in nine patients (56%) of group A and in one patient (8%) of group B. In four of the nine patients of group A, PRL increased after thyrotropin-releasing-hormone (TRH) test and induced severe attacks. After dopamine-agonist (DA) treatment, the headache improved in seven (44%) patients of the group A and in two (15%) patients of the group B. Three of the four patients in whom the TRH-test induced headache attacks, improved after DA treatment. We suggest that hyperprolactinemia may contribute to development of pain in migraine subgroups and further TRH-test could be used to predict which patients could benefit by DA therapy.

Keywords Hyperprolactinemia · Migraine ·
Headaches and neuroendocrine disorders ·
Tension-type headache

D. Bosco (✉) · M. Plastino
Operative Unit of Neurology, "S. Giovanni di Dio" Hospital,
Via Largo Bologna, 88900 Crotone, Italy
e-mail: nico_bosco@libero.it

A. Belfiore · A. Fava
Operative Unit of Endocrinology, University "Magna Graecia",
Catanzaro, Italy

M. De Rose · A. Lavano
Department of Neurosurgery, University "Magna Graecia",
Catanzaro, Italy

C. Ceccotti
Department of Neurosurgery, "Pugliese-Ciaccio" Hospital,
Catanzaro, Italy

P. Mungari
Department of Emergency Medicine, "S. Giovanni di Dio"
Hospital, Crotone, Italy

R. Iannacchero
Serv of Psychiatry Hospital, Lamezia Terme, Italy

Introduction

The clinical presentation of pituitary adenomas is dependent upon both structural and functional properties of the tumour [1]. It is unclear whether headache is a structural or a functional consequence of pituitary disease [2]. Nevertheless, even if a structural mode may be a plausible mechanism in cases of pituitary macro-adenomas and cavernous sinus invasion, it is not an acceptable explanation for micro-adenomas. Few studies reported that patients with micro-adenoma may suffer from severe headache, while patients with macro-adenoma may not have headache. This suggests that mass effect of the tumor is not always correlated to the presence or intensity of the headache [3] and that biochemical activity may be important in some forms of pituitary tumor-associated headache [4]. The hypothalamic–hypophysial axis dysfunction is believed to be implicated in the pathogenesis of primary headache syndromes [5]. A variety of headache phenotypes has been associated with pituitary tumors [6–9]. Some authors suggest a hypersensitivity of dopamine receptors, based on the observation that, some headaches showed higher prolactin (PRL) after taking dopaminergic agents [10]. Other authors suggested a

serotoninergic hyperfunction rather than dopaminergic dysfunction. Serotonin is known to increase PRL secretion and decrease thyrotropin (TSH) secretion [11]. Therefore, dopaminergic hypofunction could be the consequence of serotoninergic hyperfunction, because of the inhibitory effect of serotonin on dopamine neurons. In fact, in some patients with headache, the treatment with dopamine-agonists (DAs) can determine various responses, with worsening in some cases and improvement in others [12, 13]. The aim of this study was to evaluate whether high PRL levels may be correlated to some type of headaches in pituitary, tumor-associated.

Patients and methods

After complete description of the study, all patients gave their informed consent, in accordance with the official standards of the 1964 declaration of Helsinki, local laws and regulations, was approved by the Ethical Committee of "S. Giovanni di Dio" Hospital, Crotone, Italy. We recruited 29 (26 women and 3 men) unselected patients who arrived for the first time to the headache centre suffering from episodic migraine or episodic tension-type associated with microprolactinoma, in line with the current ICHD-II criteria [14], between February 2003 and May 2007. Patients with microprolactinoma and atypical migraine or other forms of headache were excluded from the study. Our headache centre is a second-level centre with neurologists, experts in headache disorders. Patients were recruited after a first-level check-up carried out by a neurologist, a neurosurger or an endocrinologist. The patients were successively divided in to two groups:

- *Group A* microprolactinoma and migraine (17 patients).
- *Group B* microprolactinoma and tension-type headache (12 patients).

At the beginning of the study, six patients had oligo-amenorrhoea (4 group A and 2 group B), two galactorrhea (1 group A and 1 group B) and 13 both galactorrhea and oligo-amenorrhoea (9 group A and 4 group B). Headache and amenorrhoea or galactorrhea were coincident in seven patients of the group A and one patient of the group B, while three patients of the group A and five of the group B were not coincident. Only in one patient of group A, we had no sure anamnestic data. Demographic and clinical characteristics of both groups are presented on Table 1.

All patients underwent the following tests: magnetic resonance imaging (MRI) with gadolinium of the brain, X-ray scan of the neck, odontological evaluation, general blood test, hormonal screening [luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, progesterone, T3, T4, thyrotropin (TSH), cortisol, ACTH, testosterone, growth

Table 1 Demographic and clinical features of 29 patients with headaches and microprolactinoma

	Group A	Group B
No. (%)	17 (59)	12 (41)
Age (years)		
Mean ± SD	34.6 ± 4.2	39.6 ± 4.3
Range	29–44	30–46
Sex (F/M)	15/1	11/2
Duration of disease		
Mean ± SD	7.8 ± 2.2	10.3 ± 2.8
Range	3–12	4.8–14
Attacks for month		
Mean ± SD	6.4 ± 1.8	9.1 ± 2.6
Range	3.3–9.4	3.8–12
Galactorrhea, No. (%)	1/17 (6)	1/12 (8)
Oligo-amenorrhoea, No. (%)	4/17 (23)	2/12 (17)
Galactorrhea and/or Oligo-amenorrhoea, No. (%)	9/17 (53)	4/12 (33)

Group A microprolactinoma and migraine, *group B* microprolactinoma and tension-type-headache

hormone (GH), insulin growth factor 1 (IGF1), somatostatine hormones (SH) and PRL profile]. PRL was evaluated by indwelling catheter inserted into an antecubital vein, at times 0–30 and 60 min. There was no significant difference between the three values, but we considered as "basal", the mean value of PRL at 60 min, at least in two consecutive attacks of headaches. Serum PRL was tested with immunofluorometric assay (TOSOH Bioscence, Japan). Values over 29.2 ng/mL for women and 17 ng/mL for men can be referred as being abnormal [15]. TSH and PRL were evaluated in basal condition and at least in two headache attacks. We considered as pathological when two consecutive results were higher than normal. The blood samples were all taken in the same laboratory. All MRI examinations included coronal and sagittal T1-weighted spin-echo sequences with a maximum slice thickness of 3 mm, before and after gadolinium-base contrast medium. The protocol excluded pituitary macroadenomas ($\emptyset \geq 10$ mm) with/or without cavernous sinus invasion.

The assessment of the tumor volume, was calculated using Cavalieri's principle and calculated after performing measurements of tumor diameter in three orthogonal planes, using the following equation [16]:

$$\text{Volume} = [4/3 \ \pi \ (a/_2 \cdot b/_2 \cdot c/_2)]$$

The presence and degree of cavernous sinus invasion were also documented on the basis of two different parameters [17]:

1. Encasement of the internal carotid artery.
2. Extension of the tumor into the compartment of the cavernous sinus.

Other criteria excluded patients receiving antiparkinsonian treatment or others drugs that could influence PRL levels.

The patients, successively, were evaluated with TSH and PRL-responses to thyrotropin-releasing-hormone (TRH) test. All patients were given cabergoline at a start dosage of 0.25 mg twice a week. Some patients required, successively, an increase to 0.5 mg twice a week.

Patients compiled a diary from 3 months before to 3 months after treatment with cabergoline, where they recorded the date, duration and intensity of each attack of headache.

Data were expressed as mean ± SD. The differences between two groups were compared using a non-parametric Wilcoxon rank sun test. Differences or changes were considered to be statistically significant if the P values were less than or equal to a level of 5%.

Results

During a period of 4 years, from 2003 to 2007, we recruited 29 patients (26 females and 3 males), affected from migraine (group A, 17 patients) or tension-type headache (group B, 12 patients) associated with microprolactinoma. The mean age was 34.6 ± 4.2 in the group A and 39.6 ± 4.3 in the group B. The mean duration of headaches was 7.8 ± 2.2 years in the group A and 10.3 ± 3.8 years in the group B, while attacks frequency/month was, respectively, 6.4 ± 1.8 in the group A and 9.1 ± 2.6 in the group B. Basal serum levels of LH, FSH, progesterone, estradiol, cortisol, ACTH, GH, T3, T4, TSH cortisol, ACTH, testosterone, SH, GH and IGF1 were normal in both groups. The mean "basal" level of serum PRL was moderately higher in the group A, although the difference between two groups was not statistically significant (group A vs group B: 118.6 ± 10.8 vs 106.9 ± 9.7; $p = 0.215$). During headache attacks, we registered a significant PRL increase from baseline, only in patients of the group A (attacks vs baseline: 150.6 ± 16.8 vs 118.6 ± 10.8 ng/mL; $p < 0.005$), while in the group B, no significant increase of PRL levels from baseline were registered in all patients (attacks vs baseline: 108.7 ± 8.7 vs 106.9 ± 9.7 ng/mL; $p = 2.5$). After TRH-test, PRL levels were significantly increased in patients of group A vs basal conditions (TRH-test vs baseline: 161.3 ± 27.4 vs 118.6 ± 10.8 ng/mL; $p < 0.001$), but not versus PRL levels during migraine (TRH-test vs attacks 161.3 ± 27.4 vs 150.6 ± 16.8 ng/mL; $p < 0.12$). Moreover, after TRH-test, no differences of PRL values were observed in patients of group B (TRH-test vs baseline: 107 ± 9.4 vs 106.9 ± 9.7 ng/mL; $p = 1.73$). No significant variations of TSH levels were documented in both groups in basal conditions, during migraine attacks or after TRH-test. In the group A, after cabergoline treatment, the PRL mean

was 74 ± 6.8 ng/mL and the migraine frequency attacks, evaluated by patients' diaries, improved in eight patients ($n = 8/17$, 47%), were unchanged in three ($n = 3/17$, 17.6%), worsened in two ($n = 2/17$, 11.7%) and in four ($n = 4/17$, 23.5%) cases migraines changed characteristics and became a tension-type headache. In the group B, after DAs treatment, the PRL mean was 68.2 ± 5.1 ng/mL; the headaches were unchanged in most cases ($n = 11/12$, 91.6%), only in one patient, we observed a moderate improvement (about 30% frequency/month attacks).

Moreover, after DAs treatment, we observed a significant improvement of galactorrhea in both groups of patients, while menstrual irregularity improved in 15 patients (group A: 11 and group B: 4) and was unchanged in the remaining patients.

Successively, we evaluated in each patient of both groups, the PRL-response during headache attacks. In seven patients (41%) of the group A, we registered a small and not significant PRL increase "no-responder" (baseline vs attacks: 127 ± 21.4 vs 136.8 ± 19.8 ng/mL; $p = 0.57$), while in the other ten patients (59%), was observed, a significant increase of PRL levels "responder" (baseline vs attacks: 101.5 ± 10.6 vs 205.6 ± 13.7 ng/mL; $p < 0.001$). In five of the ten "responder" patients, PRL levels increased after TRH-test and induced severe attacks. We observed no significant differences between PRL levels after TRH-test and during migraine attacks (attacks vs TRH-test: 205.6 ± 13.7 vs 198.4 ± 8.6 ng/mL; $p = 0.75$). Four of these patients ($n = 4/5$, 80%) improved after cabergoline treatment and one ($n = 1/5$, 20%) was unchanged. In the other patients of the Group A ($n = 13/17$, 76.4%), PRL increased after TRH test, but did not induce severe attacks. Finally in all patients of the group B, PRL scarcely increased after TRH-test and did not induce severe attacks. The results of both groups are presented on Tables 2 and 3.

Discussion

The presence of different types of headache in patients with microprolactinoma has been described in the literature; these included trigeminal autonomic cephalalgias (TACs) [6], short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) [7], trigeminal neuralgia [9] and also migraine in two cases [8, 18]. It has also been previously suggested that the dopamine–prolactin axis plays an important role in some primary headaches notably migraine [19, 20]. Our data confirm the hypothesis that most pituitary tumor-associated headaches have a neuroendocrine mechanism and suggest that the pathophysiology of pituitary-related tumor is more complex than it is considered. The fact that some cases of

Table 2 PRL and TSH values in basal conditions, during headache attacks, after TRH-test and after 3–6 months of cabergoline treatment in 17 patients with migraine (group A) and 12 patients with tension-type headache associated microprolactinoma (group B)

	Group A	Group B
PRL basal (ng/mL)	118.6 ± 10.8	106.9 ± 9.7
TSH basal (mUI/mL)	1.3 ± 0.5	1.4 ± 0.2
PRL during headaches[a] (ng/mL)	150.6 ± 16.8	108.7 ± 8.7
TSH during headaches (mUI/mL)	1.8 ± 0.2	1.6 ± 0.7
PRL after TRH-test (ng/mL)	161.3 ± 27.4	107 ± 9
TSH after TRH-test (mUI/mL)	7.1 ± 0.2	6.4 ± 0.8
PRL after cabergoline treatment (ng/mL)	74 ± 6.8	68.2 ± 5.1

All values are in mean ± SD

PRL prolactin, *group A* microprolactinoma and migraine, *group B* microprolactinoma and tension-type headache, *TSH* thyrotropin, *TRH* thyrotropin-releasing-hormone

[a] Mean level at least in two attacks of headaches

migraines can be dramatically improved or worsened by DAs treatment, in the absence of any measurable change in pituitary size, suggests that pituitary tumor-associated migraine may be a biochemical-neuroendocrine problem rather than a structural one. We observed that the mean values of PRL levels, evaluated during two consecutive attacks were higher in the majority of the patients with migraine and microprolactinoma (group A); in fact, in ten (59%) patients, the PRL levels were significantly higher from baseline and in five of these, the TRH-test induced an increase of PRL with severe migraine attacks (positive response to TRH-test). TSH also increased in both groups, but this rise is not significant. After treatment with cabergoline, we registered a reduction of PRL levels in all 29 patients and in eight patients of the group A, we also documented an improvement of migraine attacks. In four of

the eight patients, we observed a "positive response to TRH-test". We suppose, this state cannot be explained only by dopaminergic hypofunction, but also that prolactinomas presence has abnormal secretory behavior associated with lactotrope neoplastic alteration and/or separation of tumor cell mass from usual hypothalamic controls, with a consequent deregulation of PRL secretion [21]. Dopaminergic dysfunction could also be the consequence of a serotoninergic hyperfunction, because of the inhibitory effect of serotonin on dopamine neurons. This mechanism could also be the reason of increased TSH secretion. Besides, in four patients of the group A, cabergoline therapy induced a modification of headache pattern from migraine to tension-type headache; the same situation was described in two patients of a previous paper [8]. Our data suggest that tension-type headache does not seem to be influenced by hypothalamic–hypophysial axis dysfunction; in fact, in our patients with tension-type headache, PRL levels were unchanged both during headache attacks and after TRH-test. High levels of PRL could contribute to the development of certain pain disorders, possibly including neuro-modulation processing of sensory neurons in the trigeminal ganglia [22]. In our study, among the five migraine patients with "positive response" to TRH-test, four benefit from cabergoline treatment. Nevertheless, the small sample of patients does not allow to establish if TRH-test is really able to identify those cases in which dopaminergic system is directly involved in the pathogenesis of migraine, may be through an hypersensitivity of DA receptors mechanisms, as previously suggested by some authors [10]. Further studies, on a large sample of patients, are required to better investigate the neuroendocrine mechanisms associated with pituitary headache and if TRH-test could be used as screening test to predict which patients with hyperprolactinemia and migraine could benefit by DA therapy.

Table 3 PRL levels and clinical features of seven "no-responder" and ten "responder" patients of the group A

	Group A	
	No-responders	Responders
No. (%)	7 (41)	10 (59)
PRL basal (ng/mL)	127 ± 21.4	101.5 ± 10.6
PRL during headaches[a] (ng/mL)	136.8 ± 19.8	205.6 ± 13.7
No. of patients with "positive response" after TRH-test	0/10	5/10
PRL after TRH-test (ng/mL)	144.8 ± 10.6	198.4 ± 8.6
PRL after DA treatment (ng/mL)	82 ± 5.4	67.5 ± 9.2
Outcome of headache after DA therapy, No. (%)		
a (improvement)	3/7 (43)	5/10 (50)
b (worsening)	1/7 (14)	1/10 (10)
c (unchanged)	0/7 (0)	3/10 (30)
d (changed characteristics)	3/7 (43)	1/10 (10)

No responder patients with a no significant PRL increase during migraine attacks; *responder* patients with a significantl PRL increase, during migraine attacks; *positive response to TRH-test* patients with increase of PRL levels and migraine attacks; *PRL* prolactin; *TRH* thyrotropin-releasing-hormone; *DA* dopamine-agonist

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