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High prolactin levels as a worsening factor for migraine

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Abstract Many factors should be considered when an episodic migraine worsens and becomes chronic. Prolactin (PRL) was linked to the origin of pain in patients with microprolactinomas who developed different types of headaches. Our team carried out studies on 27 patients with a background of episodic headaches that became chronic. The patients were evaluated by means of a general examination, a neurological examination and a hormonal profile. Of the 27 patients, 7 of them had an increased level of prolactinaemia. All the patients were women, ranging from 17 to 57 years of age. Four of them had a pure form of migraine without aura, whereas 3 patients had both migraines without aura and tension-type headaches. They suffered from headache for a period ranging from 3 to 32 years and their headache became chronic 4–12 months prior to the visit. Their headache did not change in type, but only in severity and frequency. Two patients had no symptoms referable to high PRL levels; 4 patients had irregular menses or amenorrhoea. One of these patients also suffered galactorrhoea and two of these patients had a microprolactinoma at MRI; one patient was using estro-progestinic drugs, so her menstrual alteration could not be considered. The patients were followed-up for a period of 6–16 months. Six patients responded favourably after being treated with cabergoline, although some had already tried other drugs, which, however, had no effect on their headache. One patient improved after ceasing to take estro-progestinic, in spite of increased levels of PRL. Therefore, on this basis, PRL levels should always be considered when headache worsens. It is an adjunctive worsening factor, which can be easily eliminated.

Keywords Hyperprolactinaemia · Chronic headache · Chronic migraine · Prolactin

Introduction

Migraine is a very complex condition; in fact its physiopathology is not completely clear [1]. It is believed that many neurotransmitters are implicated in this process [2], and hormones have been shown to play a major role in women [3]. Among the neuroendocrinological alterations, disorders of the hypothalamic-hypophysial axis are believed to be implicated in the pathogenesis of primary

headache syndromes. Premonitory symptoms in migraine suggest a transient hypothalamic dysfunction, such as polyuria, polydipsia, food craving and mood disturbances [4, 5]. Some authors suggest a hypersensitivity of dopamine receptors based on the observation that migraineurs showed higher PRL after taking dopaminergic agents [6–9]. Reduced responsiveness of pituitary lactotroph cells to the action of dopaminergic agents has also been postulated [10]. In 1989, Awaki et al. [11] actually suggested a serotoninergic hyperfunction rather than a dopaminergic dysfunction. Until a few years ago, headache related to pituitary tumours was thought to be due to the mass effect of the tumour itself and to dural stretch [12, 13]. Levy et al. [14] reported how patients with microadenomas may suffer from severe disabling headache whilst patients with large macroadenomas may not have headache at all. This evidence shows that a tumour mass is not correlated to the presence or intensity of the headache, thus, the cause of the headache lies in something other than the volume of the tumour. The same concept was also considered by other authors who described the presence of headache in patients with microprolactinoma [15, 16]. Referring to the type of headaches related to prolactinomas, the articles published up to now have cited cases of trigeminal autonomic cephalalgias (TACs) [15], short lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) [16, 17] and migraine in only one case [17]. In reference to this single case of migraine, the patient, a 40-year-old woman, had a previous history of migraine many years before, until the age of 20. When she was in her 40s, migraines appeared once again, followed by amenorrhoea two months later, together with an increased headache frequency, reaching up to two attacks per week. She had high prolactin (PRL) levels due to a microprolactinoma. When treated, firstly with bromocriptine and later with cabergoline, she had a worsening of headache, thus, both therapies were interrupted, and migraine transformed into hemicrania continua [18]. Using only indomethacin solved the case. Moreover, both cases suggest that PRL could have a direct role in initiating or worsening headache itself, considering that headache and amenorrhoea were coincident [17].

Correlation between increased nocturnal levels of PRL and cluster headache with nocturnal recrudescence has been reported [19]. The study showed an altered regulation of PRL secretion, both during active cluster periods as well as during symptom-free intervals, rather than a synchronising event between PRL secretion and pain, as suggested by Polleri et al. [20].

There are only two articles containing data which seemingly link migraine to hyperprolactinaemia, however, the authors did not consider them related. According to the study regarding geomagnetic earth activity, carried out by Stoupel [21], an increase in magnetic activity corresponds to an increase in PRL levels and a worsening of migraine. The study carried out by Russian authors, dealing with the application of phototherapy in children suffering from headache [22], showed there was an increase in PRL levels and a better mood, but no migraine variation. Many articles report normal PRL values in migraineurs [8, 11]. However, chronic migraines remain the main problem to deal with. Determining what factors make migraines become chronic is certainly not a simple task, nevertheless, in view of all the above-mentioned elements, we can consider the possibility that PRL could, to some extent, be responsible.

Patients and methods

Our team carried out a prospective observational open study in order to evaluate whether PRL levels could be related to the worsening of an episodic migraine. Our headache centre is a second-level centre with neurologists expert in headache disorders; patients reach the centre after undergoing a first-level check-up carried out by neurologists. We recruited following unselected patients who arrived for the first time to the headache centre, suffering from chronic headache; their headaches had to have a frequency of at least 15 days per month and had to have been chronic for at least three months prior to the visit. They had to have a background of episodic migraine without aura in line with the current ICHD-II criteria [23]. The recruitment lasted one year. The patients were then followed-up in the second-level service of our hospital for headache disorders. Patients gave informed consent for research. A neurologist of the headache centre, a specialist in internal medicine and a specialist in endocrinology visited all of the patients. All the patients underwent the following tests: magnetic resonance imaging (MRI) of the brain, electroencephalography (EEG), X-ray scan of the neck, odontological evaluation, general blood test, hormonal screening and PRL profile. Other examinations were prescribed only in certain cases when necessary. Serum PRL was tested with immunofluorometric assay (TOSOH Bioscience, Japan). PRL levels were measured twice in a day during the same morning; we considered higher than normal values in both samples as being pathological. A blood test was repeated within 3 months. Values over 800 μIU/l for women and over 400 μIU/l for men [24] can be referred to as being abnormal. The blood samples were all taken in the same laboratory. Each patient was followed-up for at least 6 months. Therapy, consisting of 0.5 mg of cabergoline twice a week, was suggested when a microadenoma or high serum PRL levels were found. Cabergoline was considered effective in cases where patients referred a minor number of days of headache per month.

Ethical approval

All necessary Ethics Committee approvals were assured for the reported study.

Results

During a period of one year, we recruited 27 patients suffering of chronic migraine: 1 man and 26 women, with ages ranging from 17 to 71, and a mean age of 42; 17 of them had a pure form of migraine, whereas 10 had both migraine and tension-type headache. Headache characteristics were similar throughout the whole group and in the subgroup of patients with high PRL levels. They had headaches for a period lasting from 3 to 50 years, with a mean duration of 22 years. Their headaches became chronic during the mean 1.3-year period before their first visit (range, 3 months–10 years). All of the patients were diagnosed as having chronic migraine, in line with the current classification [23].

Each patient had at least one associated disease; 10 patients showed only 1 identified associated pathology, whereas 17 patients showed more than one associated disease that may have been the cause of the worsening (refer to data on the above-mentioned pathologies in Table 1). Five patients abused analgesics, one of whom was in the high PRL subgroup; we did not classify their headache as overuse headache because they improved by simply correcting their co-morbidity.

No major alterations in the blood tests were recorded, except for PRL. FH and LSH were also measured, and were within normal range. The value was higher only in postmenopausal women, proportionally to their age; other women of the same age had a normal PRL. Of the 27 patients, 7 had hyperprolactinaemia. The mean PRL serum level was 597 (range 31–3300) for all the patients, and 2174 (range 1176–3300) in the seven patients with pathological PRL values. After treatment, the PRL mean value in the treated patients was 482 (range 10–1808). All of them were women, their ages ranging from 17 to 57. Four patients had a pure form of migraine without aura, whereas 3 patients suffered from both migraine without aura and tension-type headache. Their menses were regular prior to headache worsening. As well as headache worsening, 2 patients had irregular menses, two had amenorrhoea and one of these

Table 1 Characteristics of the patients recruited

	General sample	Sample with high PRL levels	
		Baseline	After therapy (6–12 months)
Number of patients	27	7	
Women	26	7	
Men	1	–	
Headache type			
Migraine	17	4	
Tension-type	–	–	
Both	10	3	
Mean age, years (range)	42 (17–71)	27 (12–57)	
Mean headache duration, years (range)	22 (3–50)	13 (2–10)	
Mean duration of chronic headache, months (range)	15 (3–120)	9 (4–32)	
Mean headache frequency, days per month (range)	23 (15–30)	20 (15–30)	2 (1–6)
Mean PRL levels (range)	597 (31–3300)	2174 (1176–3300)	482 (10–1808)
Presence of other associated diseases[a]			
Only one	10	–	
More than one	27	–	
No. patients with chronic use of drugs at entry	21	2 (oxcarbazepine; insulin for diabetes)	
Therapy	Main correcting co-morbidity[b] 1 patient stopped taking estroprog.	6 patients cabergoline 0.5 mg twice/week	
Abnormal pituitary MRI	–	Microadenoma (2 patients)	

[a]The principal, associated diseases were: allergy; psychiatric diseases; sleep disorders; muscle contractures of the face, head, cervical and spine; autoimmune diseases; thyroid dysfunctions

[b]3 patients with tricyclic antidepressant, 2 patients, beta-blockers, 6 patients SSRI (of these 1 patient also beta-blockers), 4 patients benzodiazepine. Of the whole group, 13 patients were also using drugs for other diseases they suffered from (sartane, ACE inhibitors, acetylsalicylic acid, antihistaminergic, beta-stimulators, alphalytics, steroids, atypical antipsychotics, drugs for thyroid dysfunctions)

patients also had galactorrhoea. During headache worsening, only one patient was taking estroprogestinic drugs. This patient showed menstrual irregularity after interrupting her hormonal therapy. The patients' headache history lasted from 3 to 32 years and their headaches became chronic during the 4–12 months prior to the visit. They were followed-up for a period ranging from 6 to 16 months.

Six patients with high PRL serum levels, suffering from headache, were treated with 0.5 mg of cabergoline twice a week, even if some had no other symptoms of hyperprolactinaemia (amenorrhoea, galactorrhoea, etc). Their headache improved within a few months and, once again, became episodic. In only two cases (patients 5 and 6) headache changed characteristics and became a tension-type headache; these two patients had a microprolactinoma at MRI. Their headache, a typical migraine without aura, developed together with menarche, although symptoms of hyperprolactinaemia developed only after a number of years. The seventh patient simply stopped taking estroprogestinic; her headache improved despite her PRL increasing to 1808; after ceasing to take estroprogestinic, her menses became irregular.

Table 2 Characteristics of the patients with high PRL serum levels

	Pt 1	Pt 2	Pt 3	Pt 4	Pt 5	Pt 6	Pt 7
Previous headache type	MWA[a]	MWA	MWA	MWA	MWA	MWA	MWA
Headache type at entry	MWA	MWA	MWA	MWA+T	MWA+T	MWA+T	MWA
Headache type after therapy	MWA	MWA	MWA	MWA	T+MWA	T	MWA
Age, years	44	57	38	41	17	22	22
Age of headache onset, years	14	25	18	21	14	12	12
Duration of chronic headache, months	4	6	6	12	6	12	4
Mean headache frequency at entry, days per month	30	15	15	30	30	>15	15
Mean headache frequency[b] after therapy, days per month	1	6	<1	3[c]	1	<1	2
Mean PRL levels at entry	>3000	1176	2914	2964	1200	2400	1266
Mean PRL levels after therapy, time in months after commencing therapy	434 (3 mts)	300 (3 mts)	474 (5 mts)	270 (3 mts)	<10 (12 mts)	78 (12 mts)	1808 (12 mts)
Patients with chronic use of drugs, entry	OXC	–	–	Insulin	–	–	Estroprogest
Other diseases	–	(1)	(2)	(3)	–	(4)	(5)
Microadenoma at MRI	–	–	–	–	3 mm	4 mm	–
Symptoms of high PRL (other than headache)	Irregular menses	–	–	Irregular menses	Amenorrhoea	Amenorrhoea, galactorrhoea	Irregular menses[e]
Therapy	CBG	CBG	CBG	CBG	CBG, relaxation	CBG	Estroprogest dismission
Duration of follow-up (months)	6	8	6	13	12	12+12	12[d]

All patients were women. *MWA*, migraine without aura; *T*, tension-type headache

[a]Menses related

[b]Frequency at time of PRL measuring control

[c]After 13 months headache frequency was one day per month

[d]Headache worsened and galactorrhoea occurred four months after ceasing to take cabergoline, but the basal level of PRL was within normal levels. Again, after treatment with cabergoline both symptoms remitted. Tension-type headache with an important depressive syndrome appeared, and the patient did not show up for the follow-up after four months

OXC, oxcarbazepine; *CBG*, cabergoline; *Relax*, relaxation therapy

Other diseases: (1) at 29 years old hysterectomy for uterine myoma; (2) arterial hypertension normalised by therapy; (3) diabetes mellitus, treated with insulin for many years and cystinuria; monolateral nephrectomy for giant kidney stone; history of irregular menses was attributed to important systemic dysfunction due to severe diabetes and cystinuria; (4) important depressive syndrome; (5) coagulant S protein deficiency

The general characteristics of the patients studied are described in Table 1. In Table 2 the characteristics of the seven patients with high PRL serum levels are shown.

Discussion

PRL was first measured in patients already suffering from chronic headaches. We believe that a patient's improvement can be correlated to a decrease in PRL levels in regards to the modification and time relation between PRL serum level normalisation and headache severity improvement during follow-up. Except for patient 7, the only treatment given was 0.5 mg of cabergoline, twice a week. Cabergoline was later used to experiment on three other patients suffering from chronic migraine and psychiatric comorbidity and who, because of their psychiatric pathology, had no pain relief after trying all the conventional treatments. They showed no improvement, but further studies need to be done. Referring to patient 7, we interpreted her improvement as being the result of her no longer taking estroprogestinic drugs. We cannot explain why the patient, who experienced an increase in PRL, did not worsen.

Two main central systems are believed to play an important role in migraine pathogenesis. Some authors have suggested hypersensitivity of dopamine receptors based on the observation that migraineurs showed higher PRL after taking dopaminergic agents [6–9]. Reduced responsiveness of pituitary lactotroph cells to the effect of dopaminergic agents has also been postulated on the basis of a less marked inhibition of PRL secretion to L-dopa in migraine [10]. It is difficult to explain our result, or similar ones reported in the literature, by using this hypothesis. In fact, we would expect patients treated with cabergoline to worsen. We should also expect headache worsening after PRL reduction. Awaki et al. [11] tested pituitary function by means of a Triple Test (TRH, LH-RH, insulin) in women suffering from migraine and a group of controls consisting of healthy women, in order to study simultaneously adeno-pituitary function. This test produced an increase of PRL both in migraine and controls, but the increase was significantly higher in migraineurs. TSH also increased in both groups, but this rise was less evident in patients (although not significantly). These authors suggested a serotoninergic hyperfunction rather than a dopaminergic dysfunction, in fact dopaminergic hypofunction can cause PRL hyperresponse, but it should also cause increased TSH secretion, because dopamine inhibits TSH secretion. The authors' results cannot be explained by dopaminergic hypofunction alone. Serotonin is known to increase PRL secretion and decrease TSH secretion, therefore serotoninergic hyperfunction could explain the previous data. Dopaminergic hypofunction could be the consequence of serotoninergic hyperfunction, because of the inhibitory effect of serotonin on dopamine neurons. In relation to Awaki et al.'s results, we could justify our results. In fact, in this case, both cabergoline treatment and lower PRL can explain migraine improvement.

Different headache types may be triggered by prolactinomas, but in cases of microprolactinomas, tumour size and dural stretch are unlikely to cause headache [17]. Treatment with dopamine agonist can determine various responses [25]. Dopamine antagonists have been used successfully in acute migraine treatment [26], and there is evidence that alterations in dopamine may occur during migraine attacks [27]. Alteration of headache phenotypes after administration of dopamine agonists suggests that headache syndromes associated with prolactinomas may be the result of alterations in the dopamine-prolactin axis rather than simply caused by the mass effects of the tumour, also because the headache begins months before hormonal symptoms for pituitary disorders appear [17, 25]. The theory, stating that neuroendocrine mechanisms can be an important factor in triggering and aborting headache, is supported by the result of studies regarding the analgesic effect of somatostatin analogues [28–31]. Our seven cases seem to support the theory that high PRL levels alone are implicated in making the headache chronic. The headache type, in fact, did not change in the patients that we studied, it just worsened, but subsequently improved after taking cabergoline for a few months. The seventh patient is the only exception. Her headache improved in spite of PRL growth. In this patient the factor that could have caused her headache to worsen was probably estroprogestinics; this therapy also stimulates PRL secretion [32]. In this case we cannot really suspect pituitary dysfunction, but only pituitary stimulation due to an estrogenic influence. Another hypothesis that can be mentioned is to consider headache in these patients as a possible secondary headache due to hyperprolactinaemia in predisposed subjects, such as migraineurs. What seems strange is that headache maintains the typical characteristics of migraine, and in patients 5 and 6, after improving, it no longer seems to be migraine, but instead tension-type headache. We can propose that what is already suggested for other types of headache by other authors can also be applicable to migraineurs, and that serotoninergic dopaminergic systems, and perhaps other hypothalamic hypophysial mechanisms, are important in determining migraine expression. It is difficult to understand the whole system completely because of the wide presence and interaction between all of the transmitters and hor-

mones. Furthermore, it is probably incorrect to state that one rather than another of these systems is or is not implicated in migraine physiopathology.

When dealing with a patient and when considering the worsening of a primary headache, it is important to evaluate different co-factors even if headache maintains the same characteristics. Considering previous reported cases as well as ours, PRL levels should always be considered as a cause of worsening, even if menstrual alteration or galactorrhoea are not present and MRI is normal. In fact, if confirmed, it is a possible adjunctive worsening factor, which can be easily eliminated.

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