J Headache Pain (2004) 5:S85–S87
DOI 10.1007/s10194-004-0116-3

Marcello Fanciullacci
Massimo Alessandri
Francesco De Cesaris
Umberto Pietrini

Arterial hypertension and migraine: comorbidity or something else?

M. Fanciullacci (✉) • F. De Cesaris
U. Pietrini
Centro Cefalee,
Department of Internal Medicine,
University of Florence, Villa Monna Tessa,
Viale Pieraccini 18, I-50127 Florence, Italy
e-mail: fanciullac.marcello@tiscalinet.it
Tel.: +39-55-4296516
Fax: +39-55-4223549

M. Alessandri
Centro Cefalee,
Division of Internal Medicine,
Ospedale Misericordia, ASL 9, Grosseto, Italy

Abstract Several studies on patients observed in headache centers show an association between headache, including migraine, and arterial hypertension. As both these pathologies have an elevated prevalence in the general population, their association in the same patient could be casual and does not indicate a real comorbidity. Recent studies undertaken on the general population show results that seem to exclude a comorbidity between the two pathologies. Basal elevated diastolic and systolic pressures are not associated to the emergence of a migraine, whereas for subjects with systolic pressure over 150 mmHg, the risk of developing a nonmigrainous headache is less than 30% compared with normotensive subjects. However, other recent studies suggest that the association between arterial hypertension and migraine consists in the sharing of genetic abnormalities involving the angiotensin-converting enzyme (ACE): a greater availability of angiotensin II, due to a higher activity of ACE, seems to be a pathogenetic mechanism common to arterial hypertension and migraine. The possible pathogenetic role of ACE in migraine and in other headaches seems to be confirmed by several clinical studies that show the efficacy of drugs that inhibit ACE or block angiotensin II receptor. Recent prospective studies have evaluated risk factors for the chronicity of episodic migraine and have shown that arterial hypertension appears to play an important role because a higher incidence of this disease has been observed in patients with episodic migraine transformed into chronic type.

Key words Arterial hypertension • Migraine • Comorbidity • ACE

Introduction

The association between arterial hypertension and migraine has been discussed for several years. However, numerous studies that have examined the relationship between these two pathologies have not explained the meaning of their concomitant presence in the same patient.

Casual association between arterial hypertension and migraine

Numerous studies on patients observed in headache centers show an association between headache (including migraine) and arterial hypertension [1, 2]. As both these pathologies have an elevated prevalence in the general

population, their association in the same patient could be casual and should not indicate a real comorbidity, a term used to indicate the noncasual concomitant presence of two pathologies.

Two recent studies undertaken on the general population show results that seem to exclude a comorbidity between the two pathologies. In one prospective study with a follow-up of 11 years, there was no association between basal elevated diastolic and systolic pressures and the emergence of migraine, whereas subjects with systolic pressure over 150 mmHg showed a risk of developing a nonmigrainous headache of less than 30% compared with normotensive subjects.

This result complies with the possibility that hypertension could cause hypoalgesia [3]. The second study suggests that migraine is really more frequent in normotensive patients [4].

Noncasual association (comorbidity) between arterial hypertension and migraine: possible role of ACE

Recent studies suggest that the association between arterial hypertension and migraine consists in the sharing of genetic abnormalities involving the angiotensin-converting enzyme (ACE) that could cause a background for the development of both pathologies. A greater availability of angiotensin II, due to a higher activity of ACE, could in fact be a pathogenetic mechanism common for arterial hypertension and migraine. Yet in 1988 it was demonstrated that in migrainous subjects the plasma concentration of ACE did not show the circadian variations observed in healthy subjects; in migraineurs, this nonperiodicity could be an inappropriate degradation of ACE-dependent substrates [5].

In the beginning of the 1990s, Rigat et al. [6] published a study that is considered a milestone in the research on the ACE gene. These authors found a genetic polymorphism characterized by the binomial insertion/deletion of a DNA fragment of 250 bp. The allele with the fragment was called I, the one without the fragment was called D. This polymorphism is transmitted by a mendelian mechanism. The distribution of the three genotypes is 18% for type II, 46% for type ID, and 6% for type DD. This work also demonstrated that the subjects with DD genotype showed the most elevated plasma concentration of ACE. Starting from these data, Paterna and colleagues observed that migraineurs without aura have a higher incidence of the DD genotype than control subjects, with a greater plasma activity of ACE. They also found the frequency of attacks was more elevated in migrainous patients with DD genotype than in migrainous patients with the other genotypes (II and ID) [7].

The possible pathogenetic role of ACE in migraine and in other headaches seems to be confirmed by several clinical studies showing the efficacy of drugs that inhibit ACE or block angiotensin II receptor. Captopril, the first ACE inhibitor, was initially used by Sicuteri in an open study of patients affected by migraine or other primary headaches. This author, a pioneer in headache research, found a clear decrease in the number of painful crises [8]. This efficacy was confirmed in a placebo-controlled clinical study [9]. The prophylactic activity of captopril was attributed to its capacity to inhibit the degradation of endogen opioids, whose scarcity was considered, at that time, to be the starting point of the migraine crises. The observation that ACE inhibitors operate also in the central nervous system has implied that their prophylactic activity may depend on these central effects [10, 11]. Recently, a placebo-controlled clinical study, conducted according to the guidelines of the International Headache Society, has demonstrated the efficacy of lisinopril in prophylactic therapy of migraine [12]. The therapeutic mechanism of this drug has been related to its capacity to reduce the enzymatic activity of ACE, which is abnormally elevated in the migraineurs with DD genotype. More recent studies on antagonists of angiotensin II receptors seem to confirm the hypothesis that an increased availability of angiotensin II, due to an increased activity of ACE, could play a pathogenetic role in migraine. A meta-analysis of 12,110 patients treated with antagonists of angiotensin II receptors for arterial hypertension shows that these drugs reduce the risk of headache by more than one-third [13]. In a recent placebo-controlled clinical study, candesartan reduced the number of days with headache in migraineurs [14].

Although the mechanism by which ACE inhibitors and angiotensin II antagonists play a prophylactic role in migraine is not completely clear and this therapeutic action has yet to be confirmed in larger studies, these drugs could represent a new pharmacological class with a low index of side effects in the prophylaxis of migraine, especially in the presence of arterial hypertension.

Hypertension as a possible cause of the chronicity of migraine

It is well known that the presence of arterial hypertension in a patient affected by migraine is associated to an increased number of painful crises with major intensity [15] and to the transformation of an episodic headache into chronic daily headache [16, 17].

Recent prospective studies have evaluated risk factors for the chronicity of episodic migraine without aura in patients visiting headache centers. An increased incidence

of arterial hypertension was observed in patients with episodic migraine that develops into a chronic pattern [18].

Recently, a significant association with arterial hypertension was observed in subjects affected by transformed migraine who overuse nonsteroidal anti-inflammatory drugs (NSAIDs) [19]. These observations suggest that arterial hypertension can obstruct the natural improvement of migraine with age, favoring its chronicity.

References

1. Cirillo M, Stellato D, Lombardi C, De Santo NG, Covelli V (1999) Headache and cardiovascular risk factors: positive association with hypertension. Headache 39:409–416
2. Cooper WD, Glover J, Hormbrey JM, Kimber GR (1989) Headache and blood pressure: evidence of a close relationship. J Hum Hypertens 3:41–44
3. Hagen K, Stovner LJ, Vatten L, Holmen J, Zwart JA, Bovim G (2002) Blood pressure and risk of headache: prospective study of 22685 adults in Norway. J Neurol Neurosurg Psychiatry 72:463–466
4. Wieche M, Costa Fuchs S, Moreira LB, Stoll Moraes R, Fuchs FD (2002) Migraine is more frequent in individuals with optimal and normal blood pressure: population-based study. J Hypertens 20:1303–1306
5. Martelletti P, Cugini P, Letizia C, Di Palma L, Battisti P, Granata M, Scavo D, Goacovazzo M (1988) Altered circadian rhythmicity for angiotensin-converting enzyme activity in migraine. Clin J Pain 4:151–156
6. Rigat B, Hubert C, Alhenc-Gelas F, Combien F, Corvol P, Soubrier F (1990) An insertion-deletion polymorphism in the angiotensin I-converting enzyme gene accounting for half the variance of serum enzyme levels. J Clin Invest 86:1343–1346
7. Paterna S, Di Pasquale P, Martino S, Arrostuto A, Cascio Ingurgio N, Parrinello G, Gullotti D, Licata G (1992) Captopril versus placebo nella profilassi dell'emicrania senz'aura. Clin Ter 141:475–481
8. Sicuteri F (1981) Enkephalinase inhibition relieves pain syndromes of central dysnociception (migraine and related headaches). Cephalalgia 1:229–232
9. Paterna S, Di Pasquale P, D'Angelo A, Seidita G, Tuttolomondo A, Cardinale A, Miniscalchi T, Follone G, Giubilato A, Tarantello M, Licata G (2000) Angiotensin-converting enzyme gene deletion: polymorphism determines an increase in frequency of migraine attacks in patients suffering for migraine without aura. Eur Neurol 43:133–136
10. Geppetti P, Spillantini MG, Frilli S, Pietrini U, Fanciullacci M, Sicuteri F (1987) Acute oral captopril inhibits angiotensin converting enzyme activity in human cerebrospinal fluid. J Hypertens 5:151–154
11. Fanciullacci M, Alessandri M, Nicolodi M, Michelacci S, Sicuteri F (1993) Possible long-lasting inhibition of angiotensin converting enzyme by enalapril in human cerebrospinal fluid. Clin Sci 84:313–317
12. Schrader H, Stovner LJ, Helde G, Sand T, Bovim G (2001) Prophylactic treatment of migraine with angiotensin converting enzyme inhibitor (lisinopril): randomised, placebo controlled, crossover study. BMJ 322:1–5
13. Etminam M, Levine MAH, Tomlison G, Rochon PA (2002) Efficacy of angiotensin II receptor antagonists in preventing headache: a systematic overview and meta-analysis. Am J Med 112:642–646
14. Trovnik E, Stovner LJ, Helde G, Sand T, Bovim G. Prophylactic treatment of migraine with an angiotensin II receptor blocker; a randomized controlled trial. JAMA 289:65–69
15. Mathew NT (1999) Migraine and hypertension. Cephalalgia 19[Suppl 25]:17–19
16. Mathew NT, Stubits E, Nigam MP (1982) Transformation of episodic migraine into chronic daily headache. Headache 22:66–68
17. Grebe HP, Numes Da Silva MJ, Diogo-Sousa L (2001) Role of hypertension in comorbidity of chronic headaches. Rev Neurol 33:119–122
18. Manzoni GC, Torelli P (2003) Possible predictive factors for the chronic evolution of migraine without aura: a longitudinal clinical population-based study. Cephalalgia 23:641
19. Bigal ME, Sheftell FD, Rapoport AM, Tepper SJ, Lipton RB (2002) Chronic daily headache: identification of factors associated with induction and transformation. Headache 42:575–581