Neurol Sci (2011) 32 (Suppl 1):S85–S88
DOI 10.1007/s10072-011-0545-0

MIGRAINE AND DEPRESSION

Migraine and depression: common pathogenetic and therapeutic ground?

F. Moschiano · D. D'Amico · I. Canavero · I. Pan · G. Micieli · G. Bussone

Abstract Migraine and depression are recognized as comorbid disorders on the basis of several epidemiological data and on the possibility of shared mechanisms. On the other hand, there is a lack of studies concerning therapeutic strategies in patients with this comorbidity. The aim of this paper is to briefly review the literature about the migraine and depression comorbidity and on the putative common neurobiological mechanisms, as well to discuss the possible therapeutic options in treating patients with both disorders.

Keywords Migraine · Depression · Comorbidity · Pathogenesis · Therapy

Introduction

A strong relationship between migraine and psychiatric disorders has been demonstrated [1–5], the most important comorbidities being mood, anxiety, and panic disorders [2, 4, 6]. The coexistence of psychiatric disorders may have relevant clinical implications influencing quality of life and disability levels as well as the course of migraine and its final prognosis [3, 6, 7].

Migraine and depression are comorbid: in population studies individuals with migraine are from 2.2 to 4.0 times more likely to have depression [4]. Understanding the inner nature of these relationships could have practical implications for diagnosis and specific treatments. Currently, the nature of the relationship is largely unclear, because most of the literature on the topic is of an epidemiologic nature [6], while pathogenetic mechanisms and therapeutic implications have been partially explored.

The aim of this work is to briefly review the literature about the comorbidity of depression and migraine, hypothesizing a common pathogenetic and therapeutic ground.

F. Moschiano (✉) · I. Canavero · I. Pan · G. Micieli
National Institute of Neurology, IRCCS C. Mondino Foundation, Via Mondino 2, 27100 Pavia, Italy
e-mail: franca.moschiano@mondino.it

D. D'Amico · G. Bussone
Headaches Unit, Neurological Institute "C. Besta" IRCCS Foundation, Milan, Italy

Comorbidity of depression and migraine

The association between migraine and depression has been previously evaluated in young adults by a number of population-based, cross-sectional studies.

In a population of patients aged over 65 years, Wang et al. [8] found that the risk of current depression was greater in elderly migraine patients than in non-migraine. Lipton [9] confirmed a higher risk of current depression among migraineurs, in a population-based case–control study conducted in a community setting.

Merikangas et al. [10] investigated 457 younger subjects and found a strong association between migraine and major depression (OR 2.22, 95% CI 1.1–4.8) in migraineurs compared to controls. In a population-based study, Breslau et al. [11] found that migraine was strongly associated with major depression (sex-adjusted OR 3.5, 95% CI 2.6–4.6).

In a prospective population-based study, Swartz et al. [12] confirmed a strong association between migraine and major depression (OR 3.1, 95% CI 2.0–4.8).

Prevalence of major depression in migraineurs accounts for about 28% of subjects [13, 14]. Increased rates of depression were found in migraine sufferers, with a higher

prevalence in those with migraine with aura than in those with migraine without aura; this difference being present also as far as suicide attempt rates [15–17].

Some longitudinal studies have shown that the relationship between migraine and depression is bidirectional: one disorder may increase the risk for the other and vice versa [5, 11, 18, 19]. In these studies, the risk of first-onset migraine in people with pre-existing depression ranged from 2.8 to 3.5 and, conversely, the risk of first-onset depression in people with preexisting migraine ranged from 2.4 to 5.8 [8].

Findings of a bidirectional relationship between migraine and depression suggest a common neurobiology.

Possible mechanisms underlying this relationship

Common pathogenetic mechanisms between migraine and depression have been hypothesized, including drug overuse, serotoninergic and dopaminergic dysfunction, ovarian hormone fluctuation and central sensitization [6, 20].

A serotoninergic dysfunction may be a possible common pathogenetic mechanism. Polymorphisms in the serotonin (5-HT) transporter have been associated with susceptibility to migraine [21–23] and frequency of attacks [24]. In migraineurs, increased concentrations of 5-HT during migraine attacks and decreased plasma levels of 5-HT between the attacks have been demonstrated [25]. A chronic low serotoninergic availability may predispose to cortical spreading depression and increases sensitivity of trigeminovascular pathways involved in migraine [25]. The 5-HTTLPR polymorphism in the promoter region of the 5-HTT gene is associated with depression and may influence sensitivity to stress and anxiety [26–30]. In addition, the efficacy of medications that increase central serotonin levels—such as selective serotonin agonists (triptans) or selective serotonin reuptake inhibitors (SSRI)—offers an indirect evidence for a shared serotoninergic dysfunction.

There is an evidence about the role of dopamine in migraine and in depression. An association between a particular dopamine D2 receptor genotype and comorbid migraine with aura, major depression and generalized anxiety disorders [31] has been reported. In addition, migraine prodromes are often characterized by dopaminergic symptoms and antidopaminergic compounds can often be helpful to treat them [32].

Migraine and depression are 2–3 times more common in women than in men [33, 34]. Ovarian hormones appear to play an important role in migraine as well as in depression through modulation of many neurotransmitters [35]. In fact, female migraineurs often experience migraine attacks associated with the fall of estrogen levels due to menses, and many women may suffer from mood disturbance during menses as well as during postpartum and perimenopausal period. In the late luteal phase of the menstrual cycle, women are at particular risk for migraine attacks and depression: during menses as the estrogen levels precipitously decline in association with an up-regulation of the sympathetic system and a down-regulation of the serotoninergic and GABAergic systems [36].

Both in migraine and depression, everyday experience indicates that the frequency of attacks can increase with time, and progress to chronic status, with poor recovery between episodes and development of drug resistance. This suggests that sensitization phenomena may underlie both disorders [37]. Some studies have hypothesized the implication of numerous sensory and emotional neural network [38–40].

There are many clinical evidences supporting the fact that depression plays a role in processing and perception of pain, and that depressed patients are more vulnerable to pain. Cutaneous allodynia is a clinical marker of central sensitization: it is common in both frequent and chronic migraine and in anxiety and depression [7, 41, 42].

Welch et al. [43] have shown the dysfunction of periaqueductal gray area in very frequent migraine; Videbech et al. [44] have reported evidence that repeated episodes of unipolar depression are able to reduce hippocampal volume.

The dysregulation of the hypothalamic-pituitary adrenal (HPA) axis seems to be involved in migraine and affective disorders [45, 46]. A proinflammatory mechanism has been hypothesized as a possible link between affective disorders, migraine and obesity [47], and the progression from episodic migraine to chronic migraine, with dysfunctions in tryptophan metabolism, serotoninergic transmission activation of HPA axis activation [47, 48].

Clinical and therapeutic implications

The first clinical implication of the previous considerations is that all patients presenting with frequent episodic or chronic migraine should be screened for psychiatric disorders and particularly for depression [49]. Secondly, the most appropriate treatment strategies for patients with comorbid migraine headaches and depression should be defined. It is known that psychiatric comorbidity contributes to poor prognosis and poor quality of life; on the other hand, there is a little evidence about treatment outcomes in patients with migraine and depression comorbidity. Heckman et al. prospectively examined the relationship between psychiatric disorders and treatment outcomes in a group of patients with primary headaches. Migraineurs with psychiatric comorbidity are certainly difficult patients, but

their expectations to improve are enhanced if psychiatric comorbidity is treated [50].

Literature data supporting a common pathogenetic ground for migraine and depression have not been adequately supported by scientific evidence on therapeutic efficacy of antidepressants. Although different antidepressants generally share a comparable efficacy in the treatment of depressive disorders, available data on their efficacy in headache prophylaxis are not definitive, and vary for the different classes/compounds. Specific therapeutic guidelines for the treatment of depression in migraineurs are lacking [6, 7]. Drugs which could negatively influence mood, such as flunarizine and beta-blockers, should be avoided [7]. Amitriptyline could be considered, but clinicians should know that the dose required for treating migraine may be insufficient to treat depression, and its adverse event profile should always be taken into account [51]. Nortriptyline, an active metabolite of amitriptyline commonly used for depression, has not been proven as a headache preventive agent [51]. Poor evidence supports the use of SSRI and serotonin norepinephrine reuptake inhibitors (SNRI) as migraine preventive agents, and their efficacy in treating both comorbid depression or anxiety and migraine symptoms has not been clearly demonstrated [7, 52, 53]. A number of studies reported an appreciable benefit in migraine prevention for sertraline, fluoxetine and venlafaxine [7, 53]. We note that only venlafaxine has been included among the compounds suggested for migraine prophylaxis by the recently published European Guidelines, the only other antidepressant being amitriptyline [54].

We note that future studies are needed to explore also possible surgical options. Chronic vagal nerve stimulation may be one of these, as it seems effective in depressive disorders [55], and preliminary data suggested its efficacy in patients with refractory chronic migraine and comorbid depression [56].

Conclusive remarks

The relationship between migraine and depression is still incompletely understood. Findings indicating a bidirectional influence between migraine and depression suggest common neurobiological mechanisms. There is a lack of studies concerning therapeutic strategies in patients with migraine and depression. Further studies are needed both to improve our understanding of this comorbidity and to address adequate treatment strategies in this clinically relevant subgroup of patients.

Conflict of interest The authors declare that there is no actual or potential conflict of interest in relation to this article.

References

1. Baskin SM, Lipchik GL, Smitherman TA (2006) Mood and anxiety disorders in chronic headache. Headache 46(Suppl 3):S76–S87
2. Radat F, Swendsen J (2004) Psychiatric comorbidity in migraine: a review. Cephalalgia 25:165–178
3. Lake AE, Rains JC, Penzien DB et al (2005) Headache and psychiatric comorbidity: historical context, clinical implications, and research relevance. Headache 45:493–506
4. Hamelsky SW, Lipton RB (2006) Psychiatric comorbidity of migraine. Headache 46:1327–1333
5. Breslau N (1998) Psychiatric comorbidity in migraine. Cephalagia 18(Suppl 22):56–61
6. Baskin SM, Smitherman TA (2009) Migraine and psychiatric disorders: comorbities, mechanisms, and clinical applications. Neurol Sci 30(Suppl 1):S61–S65
7. Finocchi C, Villani V, Casucci G (2010) Therapeutic strategies in migraine patients with mood and anxiety disorders: clinical evidence. Neurol Sci 31(Suppl 1):S95–S98
8. Wang SJ, Liu HC, Fuh JL et al (1999) Comorbidity of headaches and depression in the elderly. Pain 82(3):239–243
9. Lipton RB, Hamelsky SW, Kolodner KB et al (2000) Migraine, quality of life, and depression: a population-based case–control study. Neurology 55:629–635
10. Merikangas KR, Angst J, Isler H (1990) Migraine and psychopatology. Results of Zurich cohort study of young adults. Arch Gen Psychiatry 47:849–853
11. Breslau N, Schultz LR, Stewart WF et al (2000) Headache and major depression: is the association specific to migraine? Neurology 54:308–313
12. Swartz KL, Pratt LA, Armenian HK et al (2000) Mental disorders and the incidence of migraine headache in a community sample. Arch Gen Psychiatry 57:945–950
13. Patel NV, Bigal ME, Koloner KB et al (2004) Prevalence and impact of migraine and probable migraine in a health plan. Neurology 63:1432–1438
14. Mc Williams LA, Goodwin RD, Cox BJ (2004) Depression and anxiety associated with three pain conditions: results from a nationally representative sample. Pain 111:77–83
15. Fasmer OB, Oedegaard KJ (2001) Clinical characteristics of patients with major affective disorders and comorbid migraine. World J Biol Psychiatry 2:149–155
16. Oedegaard KJ, Angst J, Neckelmann D et al (2005) Migraine aura without headache compared to migraine with aura in patients with affective disorders. J Headache Pain 6:378–386
17. Oedegaard KJ, Neckelmann D, Mykletun A (2006) Migraine with and without aura: association with depression and anxiety disorder in a population-based study. The Hunt Study. Cephalalgia 26:1–6
18. Breslau N, Lipton RB, Stewart WF et al (2003) Comorbidity of migraine and depression. Neurology 60:1308–1312
19. Breslau N, Davis GC, Andreski P (1991) Migraine, psychiatric disorders, and suicide attempts: an epidemiologic study of young adults. Psychiatry Res 137:11–23
20. Antonaci F, Nappi G, Galli F et al (2011) Migraine and psychiatric comorbidity: a review of clinical findings. J Headache Pain [Epub ahead of print]
21. Juhasz G, Zsombok T, Laszik A et al (2003) Association analysis of 5-HTTLPR variants, 5-HT2a receptor gene 102T/C polymorphism and migraine. J Neurogenet 17:231–240
22. Todt U, Freudenberg J, Goebel I et al (2006) Variation of the serotonin receptor gene SLC6A4 in the susceptibility to migraine with aura. Neurology 67:1707–1709
23. Marziniak M, Mossner R, Schmitt A et al (2005) A functional serotonin transporter gene polymorphism is associated with migraine with aura. Neurology 64:157–159

24. Kotani K, Shimomura T, Shimomura F et al (2002) A polymorphism in the serotonin transporter gene regulatory region and frequency of migraine attacks. Headache 42:893–895
25. Hamel E (2007) Serotonin and migraine: biology and clinical implications. Cephalalgia 27:1295–1300
26. Rot M, Mathew SJ, Charney DS (2009) Neurobiological mechanisms in major depressive disorder. CMAJ 180:305–313
27. Lotrich FE, Pollock BG (2004) Meta-analysis of serotonin transporter polymorphisms and affective disorders. Psychiatr Gen 14:121–129
28. Caspi A, Sugden K, Moffit TE et al (2003) Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science 301:386–389
29. Lesch KP, Bengel D, Heils A et al (1996) Association of anxiety-related traits with polymorphisms in the serotonin transporter gene regulatory region. Science 274:1527–1531
30. Sen s, Burmeister M, Ghosh D (2004) Meta-analysis of the association between a serotonin transporter promoter polymorphism (5-HTTLPR) and anxiety-related personality traits. Am J Med Genet B Neuropsychiatr Genet 127:85–89
31. Perutka SJ, Price SC, Wilhoit TL et al (1998) Comorbid migraine wth aura, anxiety, and depression is associated with dopamine D2 receptor (DRD2) NNcoI alleles. Mol Med 4:14–21
32. Seligman MEP (1975) Helplessness: on depression development and death. WH Freeman and Company, San Francisco
33. Lipton RB, Stewart WF, Diamond S et al (2001) Prevalence and burden of migraine in the United States: data from the American Migraine Study II. Headache 41:646–657
34. Kessler RC, McGonagle KA, Zhao S (1994) Lifetime and 12-month prevalence of DSM-III R psychiatric disorder in the United States. Results from the National Comorbidity Survey. Arch Gen Psych 51:8–19
35. Peterlin BL, Katsnelson MJ, Calhoun AH (2009) The association between migraine, unipolar psychiatric comorbidities, and stress-related disorders and the role of estrogen. Curr Pain Headache Rep 13(5):404–412
36. Martin VT, Behbehani M (2006) Ovarian hormones and migraine headache: understanding mechanisms and pathogenesis—part I. Headache 46:3–23
37. Scher AI, Midgette LA, Lipton RRB (2008) Risk factors for headache chronification. Headache 48:16–25
38. Bigal ME, Lipton RB (2006) Modifiable risk factors for migraine progression. Headache 46:1334–1343
39. Smitherman TA, Penzien DB, Maizels M (2008) Anxiety disorders and migraine intractability and progression. Curr Pain Headache Rep 12:224–229
40. Monroe SM, Harkness KL (2005) Life stress, the "kindling" hypothesis, and recurrence of depression: consideration from a life stress perspective. Psychol Rev 112:417–445
41. Tietjen GE, Brandes JL, Peterlin BL et al (2009) Allodynia in migraine: association with comorbid pain conditions. Hedache 49:1333–1344
42. Lovati C, D'Amico D, Bertora P (2009) Allodynia in migraine: frequent random association or unavoidable consequence? Expert Rev Neurother 9(3):395–408
43. Welch KMA, Nagesh V, Aurora SK et al (2001) Periaquiductal gray matter dysfunction in migraine: cause or the burden of illness? Headache 41:629–637
44. Videbech P, Ravnkilde B (2004) Hippocampal volume and depression: a meta-analysis of MRI studies. Am J Psychiatry 161:1957–1966
45. Barden N (2004) Implication of the hypothalamic-pituitary-adrenal axis in the physiopathology of depression. J Psychiatry Neurosci 29:185–193
46. Peres MF, Sanchez DR, Seabra ML et al (2001) Hypotalamic involment in chronic migraine. J Neurol Neurosurg Psychiatry 71:747–751
47. Bigal ME, Lipton RB, Holland PR et al (2007) Obesity, migraine and chronic migraine: possible mechanisms of interaction. Neurology 68:1851–1861
48. Miura H, Ozaki N, Sawada M et al (2008) A link between stress and depression: shifts in the balance between the kynurenine and serotonin pathways of tryptophan metabolism and the etiology and pathophysiology of depression. Stress 11:198–209
49. Maizels M, Smitherman TA, Penzien DB (2006) A review of screening tools for psychiatric comorbidity in headache patients. Headache 46(suppl 3):S98–S109
50. Heckman BD, Holroyd KA, Himawan L et al (2009) Do psychiatric comorbidities influence headache treatment outcomes? Results of a naturalistic longitudinal treatment study. Pain 146:56–64
51. Smitherman TA, Walters AB, Maizels M et al (2010) The use of antidepressants for headache prophylaxis. CNS Neurosci Ther 1–8
52. Evers S (2008) Treatment of migraine with prophylactic drugs. Expert Opin Pharmacother 9(15):2565–2573
53. Colombo B, Annovazzi POL, Comi G (2004) Therapy of primary hedaches: the role of antidepressant. Neurol Sci 25:S171–S175
54. Evers S, Afra J, Frese A, Goadsby PJ, Linde M, May A, Sándor PS, European Federation of Neurological Societies (2009) EFNS guideline on the drug treatment of migraine—revised report of an EFNS task force. Eur J Neurol 16(9):968–981
55. Proietti Cecchin A, Mea E, Tullo V et al (2009) Vagus nerve stimulation in drug-resistant daily chronic migraine with depression: preliminary data. Neurol Sci 30(Suppl 1):S101–S104
56. Nahas Z, Marangell LB, Husain MM et al (2005) Two-year outcome of vagus nerve stimulation (VNS) for treatment of major depressive episodes. J Clin Psychiatry 66(9):1097–1104