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REVIEW ARTICLE

Neuropsychological assessment in migraine patients: a descriptive review on cognitive implications

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Abstract Migraine is considered a disabling disorder with highly prevalence in population. Recent studies report that migraine patients have a cognitive decline associated to structural brain alterations. We search on PubMed and Web of Science databases and screening references of included studies and review articles for additional citations. From 519 studies identified, only 16 met the inclusion criteria. All studies were conducted on 1479 migraineurs (190 non-migraine headache and 11,978 controls subject) and examined the association between migraine and cognitive impairment. The results are discordant. Indeed, while cognitive deficits during the attack of migraine are now recognized, only few studies confirmed the presence of cognitive impairment in migraine patients. Given the prevalence of migraine in the population (especially among women), and the early age of the population, an association between migraine and cognitive impairment could have substantial public health implications. Future studies should determine if specific migraine characteristics, for example, attack frequency, may impact the association between migraine and cognitive decline.

Keywords Cognitive impairment · Migraine · Neuropsychological evaluations

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Introduction

Migraine is considered a disabling disorder with a highly prevalence in population [1–3]. It is estimated that 11% (303 million) of the global population, suffers from this disorders [4]. The International Classification of Headache Disorders (ICHD) includes among the primary headache: (a) the tension-type headache; (b) migraine with aura; (c) migraine without aura [5]. The tension-type headache causes a slow oppressive pain that can be episodic or chronic. Migraine, instead, is a chronic disease with episodic manifestations that can increase in frequency over the years [6].

Particularly, migraine is characterized by attacks that last from 5 to 20 min (however, less than 60 min) and consists in recurrent reversible focal neurological symptoms. Migraine without aura manifests by recurrent headache lasting 4–72 h. It is characterized by unilateral location, with moderate or severe intensity, associated with nausea, vomiting and heightened sensitivity to stimuli, such as light (photophobia), sound (phonophobia) and movement [7]. Migraine worsens daily living activities, precludes the possibility of leisure and a normal social life, compromises the psychological well-being. Migraine patients are more subjected to anxiety and depressive syndrome [8].

Recent studies report that migraineurs have a cognitive decline [9]. It is known that structural brain lesions are associated with an increased risk of cognitive decline, it has been hypothesized that migraine may be a progressive brain disorder associated with an increased risk of cognitive impairment. Indeed, magnetic resonance imaging (RMI) studies showed that migraine is associated to the hyperintensities of white and gray matter [10–12]. Moreover, headache patients show a decrease volume of gray

matter, in the parietal and frontal lobe [13]. Some authors [14] found that four cognitive domains being undermined in migraineurs: cognitive efficiently, memory, learning and psychomotor speed.

In particular, during migraine attacks patients reported feeling of distraction, difficulty to concentrate at their usual speed, and they have difficulty in performing mental tasks and retrieving names. Furthermore, the migraineurs show a decrease of processing information speed, sustained concentration, working memory, visual-spatial processing, alertness/fatigue, [15, 16] immediate and sustained attention and verbal learning [17].

This descriptive review focused on studies that investigated the association between migraine and cognitive function.

Methods

Search strategy

This review was conducted on the effect of migraine in cognitive function.

Studies were identified by searching on PubMed (1969 (the first related published article)–January 2016) and Web of Science database (1995–January 2016).

The search combined the following terms: ("migraine disorders"[MeSH Terms] OR ("migraine" [All Fields] AND "disorders" [All Fields]) OR "migraine disorders" [All Fields] OR "migraine" [All Fields]) AND ("cognition disorders" [MeSH Terms] OR ("cognition" [All Fields] AND "disorders" [All Fields]) OR "cognition disorders" [All Fields] OR ("cognitive" [All Fields] AND "impairment" [All Fields]) OR "cognitive impairment" [All Fields]).

The search terms were identified into title and abstract. We selected only English texts.

After duplicates had been removed, all articles were evaluated based on title, abstract and text.

Studies that examined the relationship between migraine and cognitive function were included, after they fulfilled the following criteria:

(a) The sample population included migraine patients.
(b) Studies specifically assessed the relationship between migraine and cognitive function.
(c) The longitudinal studies to assess the effect of migraine in cognitive function.
(d) We excluded case studies and migraine associated to other organic diseases.

Results

Of 519 studies identified, only 16 met the inclusion criteria (Fig. 1). All studies were conducted on 1479 migraineurs, 190 non-migraine headache and 11,978 control subjects. In these studies, the authors examined the association between migraine and cognitive impairment (Table 1). Three studies tested a sample of women; three studies included migraine patients and their familiars.

Influence of migraine in cognitive functions

Le Pira et al. [18] assessed cognitive function in thirty migraineurs: (a) 14 with aura; (b) 16 without aura; (c) 14 healthy subjects. All subjects were submitted to neuropsychological evaluation with Boston Scanning Test [19], Raven's Progressive Matrices 47 [20], FAS [21], Rey Complex Figure [22], Digit Span [23], Corsi Block-Tapping Test [24], California Verbal Learning Test (CVLT) [25], and Hamilton Depression Rating Scale [26]. Groups differences were found in short and long term recall of Rey Complex Figure, in Boston Scanning Test and in some subtest of CVLT (short-term memory, number of clusters at the second repetition and at long term recall). Subjects with and without aura were affected on visuospatial memory tasks but only migraineurs without aura showed deficit in verbal performances and attention.

Migraine patients (in particular migraine without aura) showed a cognitive impairment in complex evaluating tests and in executive functions. Camarda et al. [27] tested 45 patients without aura and 90 controls with a cognitive battery: Mini Mental State Examination (MMSE) [28], Token Test [29], the Intelligence Brief (TIB) [30], Italian Version of National Adult Reading Test (NART) [31], Trail Making Test Part A (TATa) and B (TATb) [32], Phonemic Fluency (PF) [33], Wisconsin Card Sorting Test (WCST) [34], HDRS and Hamilton Anxiety Rating Scale (HARS) [35]. Age at onset of migraine, length of migraine history, and duration and intensity of migraine attacks were associated with alteration in attentional performances and in executive functions.

A more recent study by Zhang [36] assessed the time perception in twenty-seven migraineurs and twenty-seven healthy controls. All subjects were evaluated with neuropsychological tests, including MMSE, Verbal Fluency Task (VFT) [37], Digit Span Forward and Backward, The State-Trait Anxiety Inventory (STAI) [38] and the Beck Depression Inventory (BDI) [39]. The authors used a temporal reproduction task to assess the estimation of duration of visual stimulus. The study showed impairments in cognitive function, particularly in time perception.

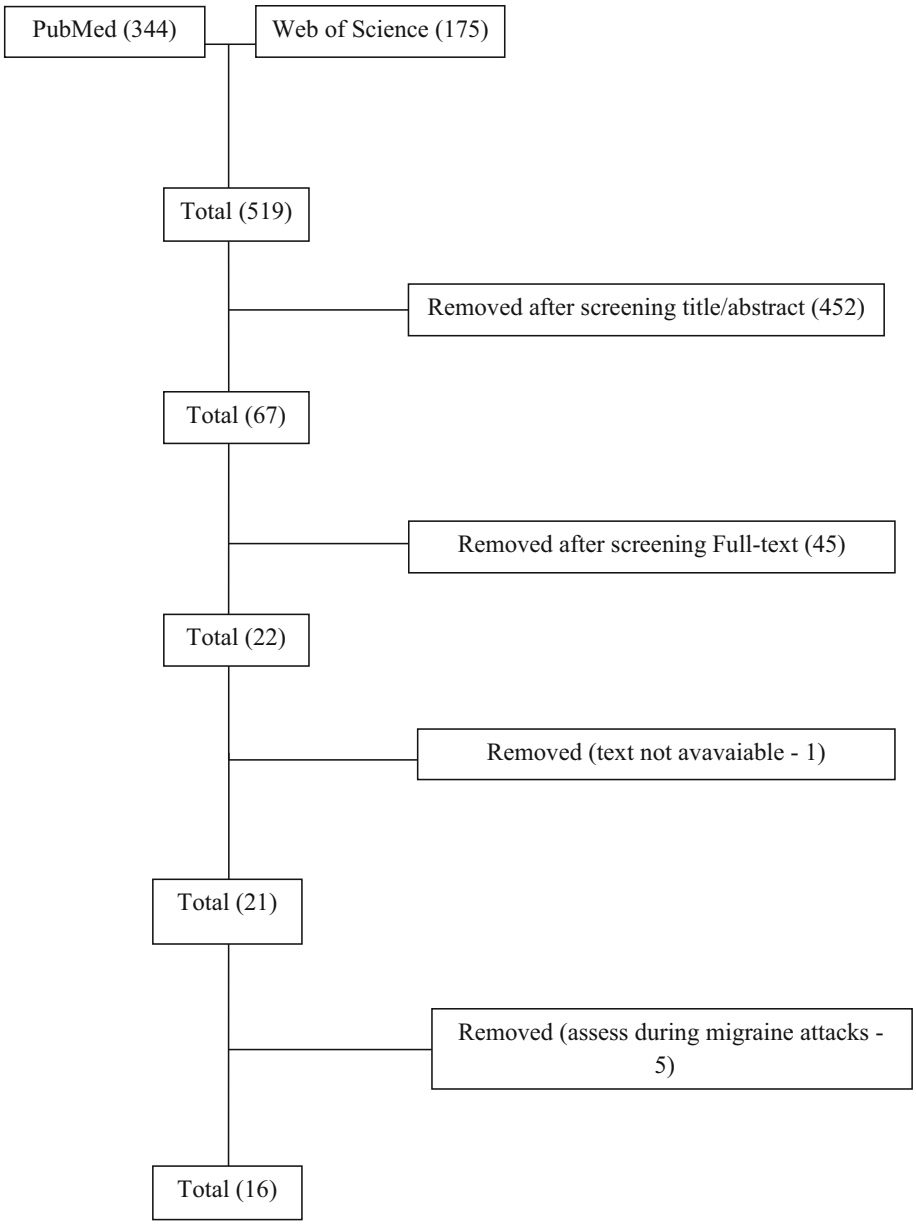

Fig. 1 Search and selection of eligible articles

Martins et al. [40] recruited 367 controls and 111 patients: 61 migraine headache and 50 non migraine headache. For a neuropsychological evaluation the authors used tests that investigated executive functions: MMSE, CVLT, Wechsler Memory Scale (WMS III) [41] TATa and TATb, Semantic and Phonemic Verbal Fluency, Stroop Color Word Task [42], Digit Span, Symbol Digit, Wechsler Abbreviated Scale of Intelligence (WAIS) [43] Vocabulary And Matrix Reasoning Subtest Information, Famous Faces Test [44], Battery Scale Depression (geriatric depression scale GDS) [45], Memory Complaints (SMQ) [46]. The comparison with the control groups showed a decrease in response time, attention and processing speed in migraineurs headaches, while non-migraine headaches presented the worst performance in memory tests, with a tendency to confabulations.

The study conducted by Kalaydjian [47] evaluated the association between migraine history, memory and cognitive function in a population of middle-aged subjects. The sample includes 204 migraineurs, 95 with aura and 109 without aura, and 1244 control subjects. All subjects underwent to MMSE and memory tests with immediate and delayed recalls. The results showed that migraineurs (especially those with aura) had a lower ranking in the immediate and delayed memory test.

Zeitlin and Oddy [48] enrolled 99 subjects suffered from severe migraine for 10 years or more and their spouses. All

Table 1 Studies assessing cognitive abilities in migraine patients

References	Aim of study	Socio-demographic characteristics	Neuropsychological evaluation	Outcomes
Zeitlin et al. [50]	To assess whether there was a cortical disturbance and cognitive impairment in patients with severe migraine	99 Subjects with migraine (age 36.3). The spouses of migraine subjects were used as controls (age 35.3)	The Stroop Color/Word Test TATa TATb Leeds Psychomotor Tester PASAT The National Hospital Forced Choice Recognition Test For Words And Faces The Mill Hill Vocabulary Scale. The Middlesex Hospital Questionnaire	Migraineurs showed alteration in motor speed and decision making ability Personality trait influenced ability to performance on cognitive test
Leijdekker et al. [73]	The aim was the assessment of relationship between migraine and cognitive impairment in patients with a long history of migraine	37 Female migraineurs (age 38.4), 26 without and 11 with aura, and 34 females non-migraineurs (age 39.1)	Two subtests of the WAIS NES The self-report Measures	There were not differences between the two female groups
Mulder et al. [72]	To assess differences between migraine attack and the other remain cognitive deficits	30 Subjects with migraine: 20 without aura (18 women and two men, mean age 24.9), ten with aura (eight women and two men, mean age 24.3), and 30 controls	NES2 VAS	This study did not support the idea that a migraine attack induces neuronal alterations that affects cognitive functions during the post-ictal period, but only a slowdown in the first 48 h after the attack
Le Pira et al. [20]	To evaluate cognitive alterations in migraine patients	30 Migraineurs: 14 whit aura (11 women and three men, age 32.21), 16 without aura (15 women and one man, mean age 34.12), and 14 control subjects (12 women and two men, mean age 33.86)	Boston Scanning Test Raven's Progressive Matrices 47 FAS Rey Complex Figure Digit Span Corsi Block-Tapping Test CVLT Hamilton Depression Scale	Migraine patients showed impairment in visual-spatial ability and memory. Migraineurs without aura showed impaired in verbal performances and attention
Jelicic et al. [56]	The aim of this study was to evaluate the domain of memory and process speed in young and middle-aged patients. Observational longitudinal study	1869 Patients, 99 whit migraine(65 women and 35 men, mean age 52) and 1768 headache-free (mean age 52)	LDST VLT	There were no differences between the two groups
Pearson et al. [59]	To assess the aspect of cognitive function in patients with a long migraine history	74 Migraineurs (55 women and 19 men, mean age 64.4) 45 with and 29 without aura, 74 non migraine	AH4 Test Mill Hill Vocabulary Test Digit Symbol Substitution Test Part of the WAIS-Revised	Authors not found differences

Table 1 continued

References	Aim of study	Socio-demographic characteristics	Neuropsychological evaluation	Outcomes
Kalaydjan et al. [48]	To assess the association of a lifetime history of migraine between migraine headaches and cognitive functions	1244 Subjects non migraine (mean age 52.7) and 204 migraine (174 women and 30 men, mean age 47.5): 95 with and 109 without aura	Immediate And Delayed Recall (Rey) MMSE	In this study authors found the difference between migraine and controls (specially migraine with aura)
Camarda et al. [29]	To evaluate if migraine without aura was associated with impairment in executive functioning	45 Subjects with migraine without aura (31 women and 14 men, mean age 33,6) and 90 controls (52 women and 38 men, mean age 31.2)	MMSE Token Test TIB TMTa TMTb PF WCST HDRS HARS	The authors found differences between migraineurs with aura, and non-migraineurs control
Schmitz et al. [16]	To investigate simultaneously cortex structure and executive functions in both of groups	24 Adult female migraineurs, eight whit aura and 16 without aura (mean age 45.5) and 24 female control subjects (mean age 41.50)	MARS battery GO/NO GO The Motor Stroop The Visual-Spatial Switch Task	In this study the authors didn't found significantly differences between migraineurs and non-migraineurs controls
Baars et al. [64]	To evaluate the long-term effects on migraine patients and pharmacotherapy	1823 Subjects. 99 were migraineurs (63 women and 36 men, mean age 47.1) and 1724 were subjects of control (847 women and 877 men, mean age 51.8)	MMSE VLT Stroop Color Word Test Letter Digit Substitution Test	In this study the authors did not found differences between migraineurs and non-migraineurs controls
Rist et al. [65]	To assess consequences of migraine on cognitive function during up to 5 years of follow-up	1188 Subjects have been recruited of which 938 had no several headaches (mean age 68.9), 65 were non-migraine headache(mean age 69.3), 143 had migraine without aura and 24 migraineurs with aura (mean age 69.0)	MMSE Digit Symbol Substitution Test from the Wechsler TATa TATb The Rey 15-Word Memory Test Raven's Progressive Matrices Benton Visual And Facial Recognition Tests Finger Tapping Test Word Fluency	The authors did not found significant differences between migraineurs and controls
Koppen et al. [71]	To assess cognitive performance in perceptual, attentional or memory during the first 48 h after migraine attack	16 Migraine patients: 13 migraine without aura and three migraine with aura (15 women and one man, mean age 58) and 18 controls(15 women and three men, mean age 59)	E-prime software: Perceptual Organization (global -local) ANT N-back	The authors did not found differences

Table 1 continued

References	Aim of study	Socio-demographic characteristics	Neuropsychological evaluation	Outcomes
Dresler et al. [75]	To determine whether there are specific differences between clinically important subgroups of cluster headache	97 Headache patients were included, 27 with chronic cluster headache 26 with episodic cluster headache in the active period, 22 with episodic cluster headache outside the active period, 24 patients with migraine and 31 controls	TATa TATb Go/Nogo Task Stroop Color Word Task	The authors did not found differences between migraineurs and subjects control
Zhang et al. [38]	To explore the impairment of time perception with a specific task	27 Migraine patients (20 women and seven men, mean age 33.60) and 27 healthy controls (21 women and six men, mean age 31.96)	MMSE VFT Digit Span (forward and backward) STAI BDI	The study showed impairment in time perception
Rist et al. [69]	To assess the association between migraine and cognitive decline among woman	6349 Subjects, 853 reported migraine history; of these 195 migraineurs whit, 248 migraineurs without aura and 410 women whit a past history of migraine (mean age 65 or older)	MMSE Boston Memory Test Category Fluency Test	The authors did not show correlation between migraine and cognitive deficits
Martins et al. [42]	To detect the long-term impact of migraine and other headaches on cognitive function specially executive function	367 Individual did not complain of headaches (213 women and 154 men, mean age 66.8). 61 subjects had a diagnosis of migraine (56 women and five men, mean age 61.9), and 50 were classified as having not migraine headache (37 women and 13 men, mean age 69.3)	MMSE CVLT WMS III TMTa TMTb Semantic and Phonemic Verbal Fluency Stroop Test Digit Span Symbol Digit WAIS Vocabulary And Matrix Reasoning Subtest Information Famous Faces Test GDS SMQ	The authors suggest that cognitive impact is not specific to migraine but might be associated to headache

subjects were evaluated with the Stroop Color/Word Test, the TATa TATb, the Paced Auditory Serial Addition Test (PASAT) [49], the National Hospital Forced Choice Recognition Test for Words and Faces [50], the Mill Hill Vocabulary Scale [51], and the Middlesex Hospital Questionnaire [52]. Migraine patients presented anxiety, obsessive trait and somatic complaints. The personality trait influenced the ability cognitive to performances. Another factor that worsen the cognitive performance was the use of some drugs, in particular ergotamine.

Studies without a correlation between migraine and cognitive deficits.

Jelicic et al. [53] conducted a longitudinal study to assess two aspects of cognitive functions: (a) memory and (b) information processing speed in patients with and without migraine. For this study, 1869 subjects aged between 25 and 80 years were recruited. The neuropsychological evaluation was composed by letter digit substitution test, symbol digit modalities test (LDST) [54] and verbal learning test (VLT) [55]. This study did not show differences between migraineurs and control subjects in cognitive performances.

A similar study was conducted by Peterson et al. [56]. The authors investigated cognitive functions in 74 migraine

patients with a long clinical history and 74 control subjects. The tests used were Alice Heim Group Ability Test (AH4) [57], Mill Hill Vocabulary Test, Digit Symbol Substitution Test, part of the WSSI-Revised, which evaluated essentially four cognitive domains: verbal/arithmetic problem solving, spatial problem solving, processing speed, and vocabulary. There were no differences between migraineurs with and without aura if compared with control subjects. A long history of migraine seems to influence cognitive functions.

Schmitz n. et al. [13] investigated the cortical structure and executive function in 24 migraine patients (eight with and 16 without aura) and 24 control subjects. Maudsley Attention and Response Suppression battery (MARS) [58, 59], in particular, go/not go task [60], the motor-Stroop task, and the SWITCH visual-spatial task were used for neuropsychological evaluation. Neuroimaging data showed a decreased gray matter volume in frontal and parietal lobe. In addition, the patients were slower during set-shifting task execution. They suggested that this delayed response time correlated with the reduced gray matter volume.

A longitudinal study was conducted by Barrars [61] on 1823 participants, where only 99 were migraine and the other were controls. The study investigated the effects of migraine diagnosis on cognitive performance and on performance over time. MMSE, VLT, the Stroop Color Word Test, Letter Digit Substitution Test were administered for memory, processing speed and executive functions. Participants were tested at baseline and after 3 and 6 years. This study did not show that migraine had effect on cognitive performance over time.

A similar longitudinal study was conducted by Rist et al. [62] on 1170 subjects: 938 headaches, 65 non-migraine headache, 167 migraineurs (24 with aura). They were carried out five follow-up sessions, but only three evaluated the cognitive functions. The neuropsychological battery was composed by MMSE, Digit Symbol Substitution Test from the Wechsler, TATa TATb, the Rey 15 Word Memory Test [63], Raven Progressive Matrices, Benton Visual and Facial Recognition Tests [64], Finger tapping Test [65], and Word Fluency. During these various evaluations, the scores in cognitive tests decreased, except MMSE and verbal fluency test, even if it was not a significant statistical difference. In fact, according to this study, there was no significant correlation between migraine and cognitive impairment.

Another longitudinal study was conducted by the same research group [66]. The sample consisted of a total of 6349 women of which 853 migraine:195 with aura, 248 without aura, and 410 with a history of migraine. The tests used for the evaluation of cognitive functions were: MMSE, Boston Memory Test [67], and Category Fluency Test. No correlation between migraine and cognitive deficits was found. In verbal fluency tests, however, migraine with aura had a lower score than the other groups.

Koppen et al. [68] investigated the influence of migraine in cognitive functions at different levels of processing, in particular, attention, working memory and perceptual organization. The tests were made up of tasks constructed whit E-prime software; in particular, perceptual organization, attention and working memory task [68]. The sample was composed by 13 migraines without aura, three migraine with aura and 18 control subjects. Subjects were evaluated with cognitive task at three time points: (a) at first day without the migraine, (b) after 24 h after migraine attacks, and (c) after 12 days without headache. The authors did not found evidence for changes in cognitive performance on the post-attack phase, as indicated by the absence of any interaction between session, group, and cognitive measures. However, differences were observed between migraine patients and controls respect to the organization of local and global visual stimuli.

A similar study in plus session was conducted by Mulder et al. [69]. The sample size was composed by 30 migraine patients, 20 without and ten with aura, and 30 controls. The neuropsychological evaluation was composed by Neurobehavioral Evaluation System (NES2) [70]. All subjects completing a Visual Analog Scale (VAS) [71] to determine the headache severity of the preceding migraine attack. During the baseline session, migraine patients showed equal cognitive accuracy as controls within all domains of cognitive functions. However, they were slower if compared to controls during the memory tasks. In addition, only migraine patients with aura were significantly slower in attention domains.

Dresler et al. [72] investigated correlations between specific subgroups of cluster headache in neuropsychological tests to evaluate monitoring, response inhibition, cognitive control, and executive functions. The successful performance in these tests requires the integrity of neural networks associated to prefrontal cortical areas. The study included 95 headache patients, 27 with chronic cluster headache, 26 with episodic cluster headache in the active period, 22 with episodic cluster headache outside the active period, 24 patients with migraine and 31 controls. The tests used were TATa, TATb Go/Nogo Task, and Stroop Color Word Task. Not significant differences between migraine and control group were found, even if a worse performance in Stroop interference emerged in migraine.

Leijdekkers et al. [73] studied the relationship between headache and cognitive impairment in migraine with aura. The neuropsychological tests were Groninger Intelligence Test, two subtests of WAIS (the block design test and the symbol digit substitution task), the Neurobehavioral Evaluation System (NES) [74] and a questionnaire to

investigate the frequency, duration and intensity of the attacks. No differences were observed between migraine patients and control subjects in cognitive performance. However, migraine showed higher anxiety levels and depressive symptoms than control subjects.

Discussion

Migraine is a very common and debilitating disease that causes significant limitations in daily life with effects on emotional-behavioral and relational aspects. Specific causes that favor the onset of disease are not recognized. Recent MRI studies showed an association among history of severe headache, decreased cortical volume and number of white matter hyperintensities [10]. The brain stem is also involved in migraine pathophysiology, and specific activation of the dorsal rostral pons and periaqueductal gray matter have been reported during migraine [75]. These cerebral alterations seem to be associated to decline in cognitive performance. Indeed, migraineurs showed a slowdown in the execution of neuropsychological tests [13, 40, 68, 69]. Furthermore, some authors found a worsening in some test scores, such as attention and executive functions [40, 62, 66, 68]. However, the results of the studies that have investigated cognitive impairment in migraine are discordant. Indeed, while cognitive deficits during the attack of migraine are now recognized [69], only few studies confirmed the presence of cognitive impairment in migraine. The factors that could contribute to these inconsistent results are probably due to methodological aspects or related to problems concerning the diagnosis [27], patient selection biases, different neuropsychological assessment [61], a lack of distinction between migraines patients with and without aura, the absence of matched control group and the sample size. Furthermore, especially in longitudinal studies, another factor that could alter the results may be the dropout of patients [53, 56, 61].

Conclusions

A migraine condition may involve the onset of a severe disability that affects the quality of life. Given the prevalence of migraine in the young population (especially among women), an association between migraine and cognitive impairment could have substantial public health implications. Although some authors reported a cognitive impairment in patients with migraine, others seem to not confirm these results. Future studies should determine if specific migraine characteristics, for example, attack frequency, may impact the association between migraine and cognitive decline.

Compliance with ethical standards

Conflict interest The authors report no conflicts of interest.

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