Cognitive function is not impaired in people with a long history of migraine: a blinded study

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Cephalalgia


Little is known about the long-term consequences of migraine for cognitive functioning. This study compared older migraine patients with matched controls on four measures of cognitive ability, in a blinded design. Migraine patients and case-matched controls were recruited from the database records of a pre-existing study of ageing. Data were available from four tests of cognitive ability: verbal/arithmetical problem solving, spatial problem solving, processing speed, and vocabulary. There were no significant differences between the mean scores of migraine and control groups on any of the four cognitive tests. In addition, there were no significant differences between migraine and control groups in the effect of age on any of the four tests. A long history of migraine does not compromise scores on the four cognitive tests used in this study. These tests are predictive of memory and executive functioning in cognitive ageing, but it remains possible that lower-level cognitive processes, particularly as assessed by visual tasks, may be vulnerable to migraine.

Introduction

Migraine is characterized by episodic acute and severe disruptions of the brain parenchyma, which frequently result in severe to extremely severe head pain. This pain may be localized to one side of the head and be accompanied by sensitivity to light and/or sound and gastrointestinal disturbance. Approximately 25% of patients report migraine aura symptoms in advance of the head pain (1), which classically manifest themselves as spreading scintillations and transient blind spots in the left or right visual field. The acute attack is also associated with alterations in cognitive function, as demonstrated by two recent studies. Farmer et al. (2) reported reductions in working memory, reaction times, concentration and visual spatial processing in 28 migraineurs, studied ictally. Similarly, Sgaramella et al. (3) showed that migraineurs performed more poorly compared with non-migraineurs on prospective memory tasks.

In addition to the acute symptoms, migraineurs often experience a postdrome, which typically manifests with disorientation, clumsiness, mental and physical tiredness and impaired concentration (4). Significant and sometimes frequent disruptions of the physiology and cognitive functions of the brain, over several decades of life, raise the question of whether structural and functional deficits are observable in migraineurs with a long history of the disorder. Patients themselves are anxious about future attacks and may be concerned about their cumulative effect (5). Evidence of frank cerebral abnormalities in migraine sufferers identified by magnetic resonance imaging (MRI) scans has been equivocal, however. For example, Price et al. (6) studied 3647 patients aged ≥65 years, none of whom had a history of stroke. MRI scans showed that 31% of these had suffered silent infarcts of ≥3 mm in size, with the incidence of the silent infarcts being higher in the older patients and those with a history of...
migraine. Conversely, Wang et al. (7) retrospectively looked at the MRI scans of 402 patients with chronic headache and found that only 0.6% of migraine sufferers exhibited any major cerebral abnormality on MRI scan. Neither study controlled effectively for the confounding effects of age in their samples. A number of other studies with similarly mixed results are available in the literature (8, 9). Very recently, however, a large and well-designed study has demonstrated a significantly higher risk of subclinical infarcts in the cerebellar region; furthermore, risk was found to increase with increasing migraine frequency (10).

Relatively little attention has been paid to the question of long-term cognitive decline in migraineurs. Amongst the few available studies, findings are again equivocal. For example, neuropsychological impairment in migraine has been found to be significant (11), non-significant (12), and only significant for migraine with aura (13). The value of some studies is lessened by low subject numbers (14), and in others, the low mean age of the participants makes it unlikely that cognitive change could be ascribable to the cumulative effects of migraine (15). One recent study, using reasonable numbers and otherwise satisfactory methods, did not appear to use International Headache Society (IHS) criteria for migraine diagnosis (16). Most importantly, no study, as far as we are aware, has blinded participants to the purpose of cognitive testing. This raises the distinct risk of contamination of cognitive test results by what has been termed the ‘Rodney Dangerfield’ effect (17): patients may, consciously or unconsciously, reduce their performance on cognitive and neuropsychological tests in order to gain respect from their doctors for the seriousness of their condition.

The principal aim of the present study, therefore, was to examine aspects of cognitive function in migraine patients with a long history of the disorder, diagnosed according to IHS criteria, in a design that permitted blinding of the patients as to the purpose of the tests.

Method

Patients

Data from 74 migraineurs and 74 non-migraine controls, matched to the migraineurs for age and sex, were included in the study. The mean age of patients was 64.4 years (range 51–84 years; SD 7.2 years). Fifty-five (74%) were female, 19 (26%) male. Forty-five (61%) had migraine with aura, and 29 (39%) migraine without aura. Ethical approval of the study was granted by the Research Ethics Committee of the Department of Psychology, Warwick University, UK.

Design

The study was a single-blind, retrospective analysis of cognitive function data comparing case-matched groups of migraineurs and non-migraineurs. Inclusion criteria were: IHS migraine with or without aura (migraine groups only); complete database record (all groups). Exclusion criteria for all groups were: any major open or closed head injury, any history of stroke, or any history of epilepsy, on a self-report basis. It was not feasible to confirm negative histories with neuroimaging or electrophysiological tests. The exclusion criteria applied at the time of cognitive testing.

Cognitive tests

The cognitive function tests used were the AH4 test, the Mill Hill Vocabulary test and the Digit Symbol Substitution test. Each test is designed to examine a different aspect of cognitive function. The AH4 is a timed problem-solving test of fluid intelligence used for samples of average ability (18). It is a pen and paper test divided into two 10-min sections, with 65 verbal and arithmetic problems (e.g. seed is to plant as egg is to: 1 tree, 2 bird, 3 pollen, 4 oats, 5 potato) and 65 spatial problems. Crystallized intelligence was assessed by using the first part of the Mill Hill Vocabulary test (19), in which participants are required to select the best synonym for 33 target words from sets of six alternatives (e.g. ‘verify’ means: 1 dedicate, 2 confirm, 3 chastise, 4 change, 5 correct, 6 purify). The Digit Symbol Substitution test for processing speed is part of the Wechsler Adult Intelligence Scale–Revised (20). Participants are given a code in which each of the digits 1–9 is associated with a different symbol. Rows of randomly ordered digits are presented below the code and the task is to write down the correct symbols below as many digits as possible in 90 s.

 Procedure

All patients and controls were recruited from an existing database of 595 older volunteers over the age of 50 (62% women, 38% men), managed by the third author at the University of Warwick for the purpose of research into normal ageing. Recruitment of volunteers for the database was by
advertisement to the local general population. The database contained demographic details, a brief medical history, and the results of several cognitive tests that had been administered during the previous 5-year period. All the volunteers within the database had already undergone cognitive function testing prior to the commencement of this study; hence both patients and controls were blind to the migraine–control comparison at the time of testing.

All 595 volunteers were initially contacted by letter. Those with a self-reported history of migraine, and willing to participate, completed and returned an informed consent form and a brief medical questionnaire. On receipt of this form each patient was contacted by telephone to obtain detailed information regarding their migraine history. A standard telephone script based on the IHS criteria for migraine (21) was used for each interview. Once the telephone interview had taken place to confirm the migraine diagnosis, the cognitive function data for each volunteer were extracted from the database. Each migraine volunteer was then matched for age and gender with a control subject from the database according to the following criteria: (i) the self-reported medical history of the control could not contain any mention of migraine or severe headache, and (ii) people excluded from the patient group for any reason could not serve as controls. The cognitive function data from the resultant patient and control groups were compared statistically using standard parametric techniques within SPSS (SPSS Inc., Chicago, IL, USA).

Migraine demographics

The database held details for 595 elderly volunteers. Ninety-five identified themselves as migraine sufferers (16.0% of the database). The telephone interview confirmed migraine diagnoses in 82. Of the 13 excluded, seven were diagnosed as suffering from non-migrainous headache, four were not contactable and two no longer wished to be interviewed when contacted. The incidence of migraine within the database population was thus 13.9%. Of the 82 patients, 74 had full database records and were included in the study. There were 55 females and 19 males. Forty-five of the 74 patients had migraine with aura; 29 had migraine without aura. Patients had had migraine for an average of 35.4 years (SD 15.5 years); the average frequency of attacks is unknown.

Matching

Because of the matching procedure adopted, the ratio of males to females in patient and control groups was identical, and the mean age did not differ significantly (migraine 64.4 years; control 64.5 years; \(t(146) = 0.03; P = 0.97\)). Furthermore, groups did not differ significantly on self-report measures (as rated on 5-point scales: 1 = very poor, 2 = poor, 3 = fair, 4 = good, 5 = very good) of general health (migraine 4.00; control 4.00; \(t(146) = 0.00; P = 1.00)\), eyesight (migraine 4.01; control 4.09; \(t(146) = 0.80; P = 0.42\)), or hearing (migraine 4.00; control 4.14; \(t(143) = 1.23; P = 0.22\)).

Results

Cognitive tests

Mean scores on the cognitive test measures for patients with and without aura and their respective control groups are shown in Fig. 1. Scores for the cognitive function tests are based on raw scores and have not been adjusted for age or educational ability. For each cognitive function test, raw scores were submitted to a 2 × 2 univariate analysis of variance (ANOVA), with diagnosis (migraine vs. control) and aura (with aura vs. without aura) as between-subject factors. There were no significant main effects and no significant interaction in the AH41 data \(F[1,144] = 2.115, P = 0.15\) for diagnosis; \(F[1,144] = 0.085, P = 0.77\) for aura; \(F[1,144] = 0.223, P = 0.64\) for diagnosis \(\times\) aura). There were no significant main effects and no significant interaction in the AH42 data \(F[1,144] = 0.810, P = 0.37\) for diagnosis; \(F[1,144] = 0.264, P = 0.61\) for aura; \(F[1,144] = 0.020, P = 0.89\) for diagnosis \(\times\) aura). There were no significant main effects and no significant interaction in the Digit Symbol Substitution Task data \(F[1,143] = 0.777, P = 0.38\) for diagnosis; \(F[1,143] = 0.310, P = 0.58\) for aura; \(F[1,143] = 0.031, P = 0.86\) for diagnosis \(\times\) aura). Finally, there were no significant main effects and no significant interaction in the Mill Hill Vocabulary A data \(F[1,144] = 2.358, P = 0.13\) for diagnosis; \(F[1,144] = 0.867, P = 0.35\) for aura; \(F[1,144] = 0.263, P = 0.61\) for diagnosis \(\times\) aura). Across all four cognitive tests, therefore, there was no significant difference in scores between migraine patients and controls, either pooled or considered separately according to the presence or absence of aura.

The relationship of cognitive test measures with age was next examined for migraine and control groups. Plots and regression lines are shown in Fig. 2. As expected (22, 23), scores for fluid ability (AH41 and AH42) and processing speed [digit symbol substitution test (DSST)] declined with increasing age, whereas the crystallized ability score (MHA)
was stable across age. More importantly, the difference in slope of the regression lines between migraine and control groups, for each cognitive test separately, was examined using multiple linear regression with dummy-coded variables. There was no significant difference in slope between migraine and control groups for any of the four tests (for AH41: \( t = 0.88, P = 0.38 \); for AH42: \( t = 0.95, P = 0.35 \); for DSST: \( t = 0.06, P = 0.95 \); for MHA: \( t = 1.26, P = 0.21 \)).

**Discussion**

In this study, migraine patients both with and without aura did not differ significantly from age- and sex-matched controls on four cognitive test measures. The effect of age on cognitive test measures also did not differ across migraine and control groups. The groups were well matched for self-reported health and sensory measures, and the presence of neurological and other disorders with the potential to influence cognitive measures was ruled out by the exclusion criteria.

The design of this study confers a number of advantages. First, the blinding of patients and controls to the eventual use of their data in migraine research removes the possibility of exaggerated responding on the part of the patient. Second, at the time of administration of the cognitive tests, the experimenter was blind as to diagnosis, thus removing the possibility of any expectancy effects. Third, the use of a population-based sample may help to reduce the clinical representativeness problem often inherent in research with patients attending specialist centres (24).

The percentage of database respondents reporting a history of migraine was 13.9%, which is lower than epidemiological estimates of lifetime prevalence.
It is likely that this difference reflects either memory and/or reporting biases. The unusually high percentage of migraine with aura patients in the studied group (61% with aura, 39% without) is probably reflective of similar biases. In addition, several spontaneous comments during telephone interviews suggested that older UK patients fitting the diagnostic criteria for migraine without aura tended to avoid the word ‘migraine’ as a label, preferring terms such as ‘sick headache’ or ‘bilious attack’. This may also have contributed to the somewhat low incidence we observed. It should also be noted, however, that a bias to under-report or mislabel migraine might result in the inadvertent inclusion of ‘true’ migraine patients in the control group. This constitutes a limitation of the study’s telephone interview procedure. A further limitation is that it is very difficult to obtain a reliable retrospective estimate of either average migraine frequency or the type and effectiveness of migraine treatment over a lifespan. For this reason, frequency and treatment data were not sought in the telephone interview, and it remains an empirical question as to whether there may be differences in cognitive function according to frequency of migraine or the type of treatment.

The four cognitive tests explored in this study were not specifically chosen with an investigation of migraine in mind. However, it is important to note that both fluid ability (26) and processing speed (27), in particular, have been shown to be highly predictive of both memory and executive functioning in old age. For example, the DSST accounts for most of the age-related variance in memory performance (28). Furthermore, Park and colleagues (29) have shown that deterioration in processing speed rather than working memory is more influential in age-related variations in cognition. In addition to accounting for age-related decline in memory.
functioning, fluid intelligence measures have been directly associated with frontal lobe functioning (30). Crystallized intelligence was of interest, as it is generally regarded as being resistant to neurological insult; however, it is possible that neurodegenerative processes may affect this measure in older adults (31). Crystallized intelligence is thus potentially relevant to the general question of the cumulative effects of migraine.

Cognitive function in migraine, as assessed by these four tests, appears to remain intact even after a long history of the disorder. Although the tests do not permit strong inferences about the functional status of specific brain areas, the results of this study are consistent with the lack of any neuroimaging findings to date that identify subclinical infarcts or other deterioration of frontal areas in migraine patients. In contrast to frontal areas, Chronicle and Mulleners (32) argue that posterior brain areas, particularly the primary visual cortex, might be at risk of cumulative subclinical damage after a lifetime of migraine. It is evident from a wide variety of neurophysiological research (33–35) that the primary visual cortex is functionally altered in migraine, between attacks. All such research, however, has been cross-sectional in nature, and no available evidence directly addresses the question of whether the functions of posterior brain areas, including the visual cortex, deteriorate over repeated migraine attacks. The recent finding that the likelihood of subclinical posterior infarct increases with attack frequency (10) makes it an important goal to examine visual and cerebellar function in older migraine patients, using appropriate methods and research designs.

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