Migraine and cognitive function

A life-course study

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Abstract—*Objective:* To investigate the association between migraine and cognitive ability among members of a longitudinal birth cohort study. *Methods:* Headache status was determined at age 26 (migraine, tension-type headache [TTH], headache-free control subjects) according to International Headache Society criteria, and data relating to cognitive and academic performance from ages 3 to 26 years were analyzed. *Results:* Study members diagnosed with migraine were subtly but significantly impaired, compared with those with TTH and headache-free control subjects, on tests of verbal ability (especially language reception) from ages 3 to 13, independent of headache history. Performance on other tasks, including reading, arithmetic, motor, and spatial ability, was normal. The association between migraine and verbal functioning also appeared to impact on later academic success. *Conclusion:* Findings suggest that the poorer verbal performance was unlikely to have resulted from cumulative attacks and may be due to developmental factors beginning in utero.

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Individuals who experience migraine appear to process auditory and visual information differently from those without migraine. Functional and electrophysiologic alterations in cortical functioning have been found during the migraine interval,[1-5] which may be associated with cognitive impairment as demonstrated on tests of perception,[6,7] psychomotor ability,[8] attention,[9-11] and verbal memory.[12,13] However, not all studies have found such cortical alterations[14] or cognitive performance decrements.[15,16] Thus, it remains unclear whether migraine is associated with cognitive efficiency and, if so, to what degree and specificity.

The inconsistency in the migraine literature might be a result of methodologic limitations. For example, studies have generally relied upon subjects who have been referred to neurologists or specialist headache clinics, resulting in a highly unrepresentative sample.[17] Moreover, few studies have used adequate comparison groups, and many are often constrained by the use of cross-sectional designs. It is generally preferable to employ longitudinal designs, where changes in the cognitive performance of migraineurs can be compared with corresponding changes in control subjects throughout development.

We investigated the association between migraine, tension-type headache (TTH) (diagnosed according to International Headache Society [IHS] criteria),[18] and cognitive performance among members of a representative cohort study over a period of 23 years. If the putative poorer cognitive performance of migraineurs is a consequence of the cumulative effects of headache attacks and thus a result of repeated vascular insult,[19,20] cognitive deficits should be first detectable later in life, and individuals with a childhood history of headache should perform more poorly than those with no history. Alternatively, if there were evidence of cognitive impairment that is specific to migraineurs from an early age, it would suggest that migraine is associated with atypical neurodevelopment in utero or infancy.

Methods. *Participants and general procedure.* The sample comprised members of the Dunedin Multidisciplinary Health and Development Study.[21] This is a longitudinal investigation of the health and behavior of a complete cohort of individuals born in Dunedin, New Zealand, between 1 April 1972 and 31 March 1973. Study members have been assessed individually on a wide variety of psychological and medical measures at ages 3, 5, 7, 9, 11, 13, 15, 18, 21, and most recently in 1998 and 1999 at age 26 (n = 980; 96.2% of the living cohort).

Primary headache diagnosis. As previously documented,[22,23] at the age 26 assessment, a registered nurse or medical practitioner asked 979 study members a series of questions concerning headache pain characteristics and symptoms in the last year (abstracted from the IHS classification). Almost 12% fulfilled IHS criteria for migraine (n = 114), and 11.1% were diagnosed with TTH (n = 109). Migraine was 3.5 times more frequent among women than men (95% CI 2.3 to 5.4), and TTH was 2.3 times more

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frequent among women (95% CI 1.5 to 3.4). Study members who reported headaches were excluded from analyses if they did not meet IHS criteria or if medical records indicated their headaches were likely due to head trauma.

Almost half (48%) of the migraineurs were taking at least one form of prescription medication during the last 12 months compared with 35% of control subjects and 55% of individuals with TTH. Only 3% of migraineurs were taking migraine medication.

To assess whether childhood headaches influenced cognitive performance, possibly owing to impaired concentration or school absence, study members were grouped according to whether headaches occurred during childhood (ages 7, 9, 11, or 13 years measured with the Rutter Child Scale A)[24] or later. There were no sex differences in those reporting childhood headache (54.1% boys).

Family socioeconomic status. Family socioeconomic status (SES) was measured on a 6-point scale[25] and analyzed as the average of the highest SES level of either parent at the study member's birth through to age 15. Study members were designated as growing up in families whose mean SES was low (Groups 6 and 5; e.g., oyster canner, car painter; n = 215, 21%), medium (Groups 4 and 3; e.g., butcher, secretary; n = 649, 63%), or high (Groups 2 and 1; e.g., architect, dentist; n = 167, 16%).

Maternal headache. At the age 26 assessment, study members' biologic mothers were asked if they had frequent headaches. Headache information was also available for mothers who accompanied their child to the age 5, 7, and 9 assessments and completed the Rutter Malaise Inventory B.[24] One hundred sixty-eight mothers (18.4%) were classified as having a history of headache based on a positive response during the age 26 assessment and at least one of the earlier assessments.

Cognitive and neuropsychological measures. The Peabody Picture Vocabulary Test (PPVT)[26] was administered at age 3 to assess receptive language ability and the Verbal Comprehension and Verbal Expression subscales of the Illinois Test of Psycholinguistic Ability (ITPA)[27] were administered at ages 7 and 9. The Wechsler Intelligence Scale for Children–Revised[28] was administered (omitting Comprehension and Picture Arrangement subtests) at ages 7, 9, 11, and 13. The Burt Word Reading Test (1974 revision)[29] was administered at ages 7, 9, 11, 13, 15, and 18. At age 11, a trained audiometrist tested pure tone thresholds; a speech-in-noise (SPIN) test that was developed by the audiometrist for use in New Zealand was administered at ages 11 and 13.

Hand preference[30] was determined at age 7, and information about the handedness of first-degree relatives was obtained from 563 study members at age 26 (58% of controls, 53% migraine, 62% TTH). Migraineurs were more likely to be mixed or left handed relative to control subjects (χ^2 = 3.2, p = 0.049) and to be slightly more likely than control subjects to have at least one left-handed relative (10% versus 7%).

School achievement and qualifications. Academic achievement was estimated from the total scores on New Zealand national exams and a standardized grading system during the final 2 years of high school (ages 15 to 17). Scores from the School Certificate Examinations ranged between 6 and 42 (mean = 22.0, SD = 7.4), and Sixth Form Certificate scores were based on sums of grades across up to six subjects (ranging between 6 and 54; mean = 26.0, SD = 10.1). At the age 26 assessment, information was obtained about postschool academic qualifications.

Data analysis. Repeated measures analyses of variance were performed on data obtained on more than one occasion. χ^2 and logistic regression analyses (odds ratios [OR] with 95% CI) were conducted for categorical measures. Sex, family SES, prescription drug use, and childhood history of headache were included as independent variables where sample size permitted. In preliminary analyses (data not shown), analyses of covariance were performed to ensure that effects reported below were not due to maternal history of headache, anxiety, or depressive disorder.

Results. The psychological and medical measures that were used in the following analyses are presented in the table. A repeated measures analysis of variance revealed that verbal IQ ($F[6,2145]$ = 0.74, p = 0.62) and performance IQ ($F[6,2142]$ = 1.2, p = 0.29) did not differ across

Table *Measures and age of assessment used in this study to determine medical, cognitive, and academic functioning of members of the Dunedin longitudinal cohort study*

Measures	Assessment age, y
Medical investigation	
Primary headache diagnosis (IHS)	26
Headache complaints (Rutter Child Scale A)	7, 9, 11, 13
Sensory functions	
Auditory reception and discrimination (SPIN)*	11, 13
Peripheral hearing (pure tone threshold)	11
Cognitive/neuropsychological measures	
Peabody Picture Vocabulary Test	3
Verbal IQ (WISC-R)	7, 9, 11, 13
Performance IQ (WISC-R)	7, 9, 11, 13
Burt Word Reading Test	7, 9, 11, 13, 15, 18
Verbal Comprehension (ITPA)	7, 9
Verbal Expression (ITPA)	7, 9
Hand Preference (HTLD/self-report)	7, 26
School achievement	
Certificate Examination (English/Math)	15–16
Sixth Form Certificate grades	16–17
Academic qualification	26
Family variables	
Family socioeconomic status	Birth, 3, 5, 7, 9, 11, 13, 15
Maternal history of headache	5, 7, 9, 26

Sample size fluctuates across various measures because of missing data.

* Study members were asked to repeat word lists (scored phonemically) that were presented orally at 60 dB sound pressure level above the child's pure tone threshold at 1 kHz in 1) two no-noise conditions, 2) two noise conditions with signal-to-noise ratios of 5 dB, and 3) two noise conditions with signal-to-noise ratios of 10 dB.

IHS = International Headache Society; SPIN = speech in noise; WISC-R = Wechsler Intelligence Scale for Children–Revised; ITPA = Illinois Test of Psycholinguistic Ability; HTLD = Harris Tests of Lateral Dominance.

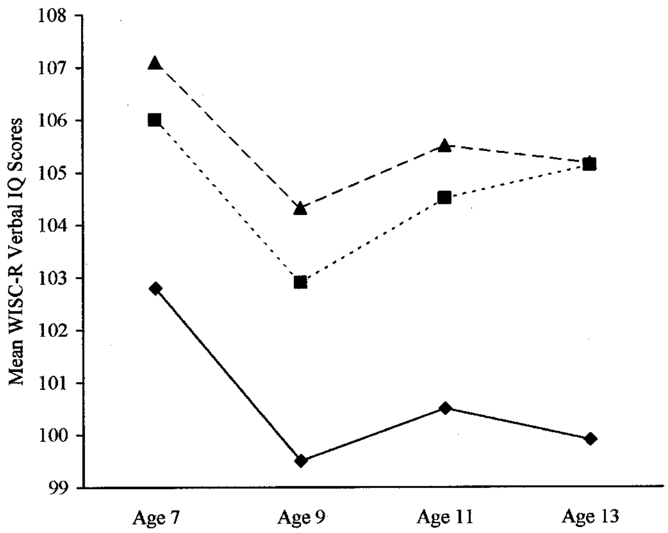

Figure 1. The mean verbal IQ scores at ages 7, 9, 11, and 13 of study members who were diagnosed at age 26 with migraine (n = 114) (◆), tension-type headache (TTH; n = 109) (■), or no headache (▲)(n = 739).

assessment age as a function of headache group (migraine, TTH, control subjects).

The main effect of group was significant only for verbal IQ, with migraineurs showing lower verbal IQ scores (mean = 100.6 ± 11.4) than both control subjects (mean = 105.7 ± 13.5; p = 0.019) and those with TTH (mean = 104.4 ± 13.8; p = 0.036). Figure 1 shows the mean verbal IQ scores for each headache group across the four assessment ages. Separate analyses revealed no sex differences in verbal IQ according to headache group; nor was there an effect of prescription drug use or a drug-use-by-group interaction (all $p > 0.50$).

To test the hypothesis that migraineurs with a history of childhood headache might be at increased risk for cognitive impairment due to missed educational opportunities, repeated measures analysis of variance was conducted on the verbal IQ scores. Mean scores at each assessment age for each headache group by childhood history and headache combination are presented in figure 2. The analysis showed a significant main effect of age (F[3,2106] = 11.3, $p < 0.001$), an age-by-headache-history interaction (F[3,2106] = 6.1, $p < 0.001$), and an age-by-headache-history-by-group interaction (F[6,2106] = 3.0, p = 0.006).

Analysis of simple effects by headache group at each assessment age (i.e., ages 7, 9, 11, and 13) revealed that those who had childhood headache scored consistently more poorly than those without a history on verbal IQ. However, this effect was restricted to those later diagnosed with TTH (all $p < 0.04$) and to those whose headaches did not persist (all $p < 0.03$). Among those with childhood headache, only 17% were later diagnosed with migraine and 9% with TTH. Importantly, migraineurs with childhood headache did not perform more poorly than control subjects at any assessment age.

A separate analysis with performance IQ (across the four assessment ages) did not reveal any main or interaction effects with childhood history of headache (history: 106.6 ± 12.6; no history: 110.5 ± 12.6).

With regard to family SES, study members with childhood headache (23.7%) were more likely to have come from low SES families than those without headache (17.9%) (χ^2 = 6.15, p = 0.046). In contrast, those who were diagnosed with migraine or TTH in adulthood did not differ from each other or from headache-free control subjects on family SES.

Timing of cognitive changes. Receptive language was measured at age 3 with the PPVT, which was strongly correlated with mean verbal IQ in this sample (r = 0.56, $p < 0.001$). Analysis of variance, with headache group and sex as independent measures, was used to test whether the poorer verbal performance in migraineurs occurred prior to the onset of headache symptoms. There was a significant main effect of group (F[2,902] = 3.4, p = 0.032), with those with migraine at age 26 (mean = 21.6 ± 9.2) performing more poorly than those with TTH (mean = 24.9 ± 8.9) and headache-free control subjects (mean = 23.8 ± 9.6). The main effects of sex and the group-by-sex interaction were not significant.

Global verbal deficit versus specific language difficulty. Considering that verbal IQ comprises different components of language functioning, we separately analyzed the Wechsler Intelligence Scale for Children–Revised subscales (i.e., information, similarities, arithmetic, vocabulary). Individual repeated measures analysis revealed that the headache groups differed at each testing age on the information (F[2,761] = 4.2, p = 0.015), similarities (F[2,701] = 6.1,

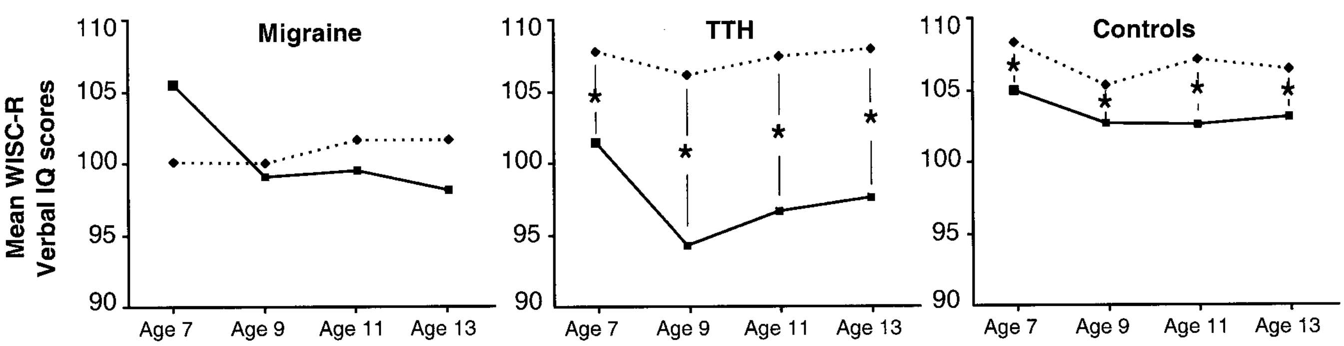

*Figure 2. The mean verbal IQ scores, across four childhood assessment ages, of study members diagnosed in adulthood with migraine (n = 114), tension-type headache (TTH; n = 109), or no headache (n = 739) as a function of childhood history of headache (solid line) or no history of headache (dotted line). Significant group differences are indicated (*p < 0.05). WISC-R = Wechsler Intelligence Scale for Children–Revised.*

$p = 0.002$), and vocabulary ($F[2,679] = 4.9$, $p = 0.007$) subscales but not the arithmetic subscale ($F[2,699] = 2.9$, $p = 0.067$). Post hoc Bonferroni tests showed that migraineurs performed significantly more poorly on each measure than control subjects. They also had lower scores on the information ($p = 0.09$) and vocabulary ($p = 0.056$) subscales than those with TTH, but only the similarities subscale was significantly lower.

Reading, verbal expression, and reception. Analysis of variance, with reading scores from the age 7, 9, 11, 13, 15, and 18 assessments as repeated measures, showed that reading performance did not change across time according to headache group ($F[10,3485] = 1.3$, $p = 0.20$). Interestingly, the reading ability of migraineurs was slightly better (mean = 72.6 ± 15.4) than that of control subjects (means = 70.9 ± 17.0) and those with TTH (mean = 70.6 ± 15.8), but the main effect of group was not significant. Similarly, verbal expression measured with the ITPA was not different between headache groups ($F[2,826] = 0.2$, $p = 0.85$).

In contrast, group differences on the measure of verbal comprehension at the same ages ($F[2,837] = 3.1$, $p = 0.049$) showed that those with migraine performed more poorly than control subjects ($p = 0.024$). Migraineurs also performed more poorly on the SPIN tests when the signal-to-noise ratio was at 10 dB ($F[1,473] = 3.9$, $p = 0.048$) but not at 5 dB signal-to-noise ratio or in the no-noise condition. There were no differences between groups on tests of pure tone audiometry thresholds (peripheral hearing).

Later academic performance. Study members with migraine (mean = 22.1 ± 7.2) scored more poorly than control subjects (mean = 23.8 ± 6.3; $p = 0.097$) and those with TTH (mean = 24.5 ± 6.9; $p = 0.068$) on their School Certificate exams and achieved significantly lower Sixth Form Certificate grades (mean = 22.8 ± 9.5) than control subjects (mean = 26.5 ± 9.8) and those with TTH (mean = 28.5 ± 10.7).

As expected, verbal IQ in childhood was a strong predictor of Sixth Form Certificate grades ($b = 0.539$, $t = 19.1$, $p < 0.001$), accounting for 40% of the variance in school performance. For every 4-point difference in verbal IQ, the model predicts a 2.16 difference in grades, indicating that the chance of school success was 9.5% less for students later diagnosed with migraine.

Those with TTH were slightly more likely than those with migraine to have achieved secondary school qualifications (84 versus 82%), but this difference was significant only for men (78 versus 63%; $p = 0.02$). A greater number of study members with TTH (26%) and control subjects (22%) had obtained a bachelor degree by age 26 compared with those with migraine (18%). Verbal comprehension during childhood was the strongest predictor of degree status in migraineurs, with the likelihood of receiving a bachelor degree increasing (OR 1.13; 95% CI 1.01 to 1.26) as comprehension scores on the ITPA increased.

Discussion. We tested the strength and direction of the association between migraine headache and cognitive function. Migraineurs had impaired verbal ability versus headache-free control subjects and individuals with TTH, particularly on measures of verbal comprehension. Migraineurs had normal reading, verbal expression, and mathematical skills.

The subtle verbal deficits exhibited by migraineurs may have impacted upon later achievement. Consistent with an earlier study,[31] high school grades and examination scores were significantly lower and fewer migraineurs achieved secondary school qualifications or degrees. Migraine sufferers also report significant social and work-related impairment and earn less than those without headache.[32]

If verbal impairment were a consequence of the cumulative effects of headache attacks, one would expect that individuals with a longer history of headache would perform more poorly than those with a shorter history. In our study, as in others, cognitive performance was unrelated to length of headache history,[10,12,33-34] medication use,[12] or severity and duration of migraine attack.[10,13] Moreover, because migraineurs performed significantly more poorly than those with TTH on verbal measures at ages 3, 7, 9, 11, and 13, the effect does not appear to be attributable to the negative influence of headache pain and discomfort in general or reduced educational opportunities. Taken together, the findings that verbal performance remained consistently lower than the other groups at each assessment age, was first identified at the age 3 assessment, and did not decline with age suggest that verbal performance was not significantly influenced by migraine attacks "per se."

The results make it more likely that migraine and verbal impairment are associated because of a shared risk factor, not because one causes the other. One proposed risk factor to explain the observed relation between migraine, left-handedness, and verbal deficit is related to delayed development of the left hemisphere in utero.[35,36] Anatomically anomalous patterns of cerebral asymmetry occur more often in left handers than right handers[37-39] and left and mixed handedness was more prevalent among migraineurs in the current study. This suggests that migraineurs may be at increased risk of anomalous cerebral dominance during neural development with concomitant problems in later receptive language acquisition.

Alternatively, subtle verbal dysfunction could relate to a generalized impairment in selective attention. Migraineurs have trouble adjusting attention and require more time for automatic processes as shown on tasks such as the "oddball" paradigm,[11] regardless of medication use and attack duration.[10] Other studies have found that migraine patients show both cortical hyperexcitability as well as a lack of habituation to repeated stimuli as measured by visual and auditory event-related potentials in the migraine interval.[2,6,11] In contrast, these anomalies are not observed during the migraine attack.[9]

Habituation to a stimulus is generally thought to be one of the most basic forms of learning and also thought to protect the brain from information overload.[11] As such, it has been suggested that the migraine attack is a protective vascular response to this potential information overload, particularly in the left hemisphere of the brain where verbal capacity may be limited.[40] Although our findings cannot at present confirm or refute either of these explanations, the findings do lend support to the idea that migraine headaches are of an early, constitutional origin.

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