Chapter 7

Cognitive Declines During Migraine and Cluster Headaches Are Caused by Cerebral 5HT Neurotransmitter Dysfunction

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Introduction and Neurological Mechanisms of Headaches

During the 1990s, 26 million US citizens (majority women) suffered recurrent migraine headaches [1]. Migraine is debilitating and incapacitating, resulting in poor performance at workplace or in school [2, 3].

If cluster headaches (CHs) and chronic daily headaches (CDHs) are included among the types of vascular headaches classified by the International Headache Society (IHS) [4], numbers of US headache sufferers will increase further. By definition, migraine headaches that increase in frequency to more than 15 per month become transformed into CDH.

Recurrent CHs are rarer but in some ways similar to migraine. Men are affected more than women, and cephalalgia is often said to be more severe [5, 6]. CHs are more strictly unilateral than in migraine and are pathognomonically associated with tearing, pupillary changes, and conjunctival injection with redness of ipsilateral eye. Since lacrimation drains into ipsilateral nostril, unilateral nasal dripping results. Like recurrent migraine, CHs are intermittent but may increase in frequency until 15 days of headache per month are exceeded and then by definition are transformed into chronic CH.

Migraine, with and without aura, with other variants of vascular headache which include CH and CDH, appears to be initiated by neuronal discharges releasing neurotransmitters from the upper brain stem – trigeminal system, resulting in unilateral cerebral vasoconstriction, causing auras, followed by vasodilatation of intracranial and extracranial blood vessels, causing the ipsilateral headaches and has provoked cortical spreading depression [7, 9] and changes in posterior cerebral cortical excitability predisposing to photopsias [10]. Other symptoms accompanying migraine headache include nausea, vomiting, visual auras followed by cephalalgia due to cerebral hyperemia which are promptly terminated by sumatriptan administration (or other similar triptans) administered by injection, inhalation, mucus membrane absorption under the tongue, or ingestion.

Cerebral blood flow and metabolism are both reduced during auras of migraine [11] followed by increased cerebral perfusion during headache, which are promptly relieved by sumatriptan injection. It is generally considered that during the aura phase of migraine, cerebral metabolism and perfusion are reduced, to be followed later by cerebral hyperemia in the headache phase. Both are caused by release of neurotransmitters initiated by discharges arising from the upper brain stem and trigeminal system. The headache phase is accompanied by painful cerebral vasodilatation. The aura phase and later headache *with mental confusion and difficulty thinking* are due to temporary imbalance of cerebral neurotransmitter and serotoninergic systems. With injection or oral administration of sumatriptan, 5HT (serotonin) receptors of both neurons and blood vessels are stimulated: promptly correcting the neuronal and cerebro-vascular transmitter disorders, with restoration of neuronal 5HT function to normal.

Headache-related transient cognitive impairments last for about an hour, making it difficult for students to

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complete homework resulting in declines in academic performance. Similar headache-related problems occur among adults resulting in poor work performance or housewives who report difficulty completing their household chores.

Vascular headaches affect all ages, usually beginning around age 5, deteriorating family and interpersonal relationships. Headache-related cognitive impairments persist until headaches subside, following natural or drug-induced sleep or following administration of serotoninergic receptor agonists including sumatriptan and other triptans.

Possible influences of vascular headaches on psychometric test scores – mini-mental status examinations (MMSE), cognitive capacity status examinations (CCSE), and Hamilton Depression Rating Scales (HDRS) scores – across time were evaluated among 182 vascular headache subjects. When headache-free subjects established stability of the "mini" test battery. Confounding effects of depression were not found to influence cognitive test scores when subjects were headache free.

The vascular headaches, when "headache present," induced cognitive declines which were analyzed. Stability of CCSE, MMSE, and HDRS scores across time was evaluated among 182 subjects who made at least two clinic visits labeled "headache-present" or "headache-absent." There were no significant changes in MMSE, CCSE, and HDRS test scores at different time intervals measured across many different clinic visits labeled "headache-absent" which confirmed stability of "mini" test battery scoring.

History

Early investigations concerning cognitive declines during migraine attacks are as follows:

The first study to utilize standardized, documented measures for testing cognitive performance among sufferers from migraine during headache intervals and later when headache free was reported by Black et al. in 1997 [12]. These authors tested 30 migraineurs utilizing standard, structured interviews of their own design. Subjects were tested when headache free, and the same tests were repeated during confirmed migraine headache intervals. Impairments of immediate attention, sustained attention, and recall of test materials were evaluated by comparing serial testing of each subjects' responses to verbal conversation scoring recent and remote recall of events.

In 1999, Mulder et al. [13] reported comparable results utilizing self-administered mechanical evaluation systems with timed responses obtained by standardized questions. Responses were graded for accuracy including neurobehavioral assessments which were tested among the migraineurs, with and without aura. These standard tests were administered during headache intervals and repeated 30 h later when headache free after completion of a good night's sleep. Migraineurs with aura showed residual slowing of response times when headache free but all subjects recovered completely or improved to near-normal status when tested 30 h later, when severe headaches had subsided.

Experimental Studies of Treatments

Review of earlier studies including descriptions of new insights and causal interpretations:

The present report summarizes and expands earlier investigations by the author, when he was working with different co-workers before his retirement and closing his Cerebrovascular Research and Headache Clinic. In his clinical investigations his standard "mini" neuropsychometric test batteries were serially administered. These studies included large series of prospective, clinical trials among the author's practice with patients suffering from different types of headaches. Results were compared with a selected group of normal volunteers who were also being treated for different degrees of organic cognitive impairments varying from mild cognitive impairment to dementia. All long-term studies included serial neurological and physical examinations combined with the serial "mini" neuropsychometric test batteries as described. Results were correlated at intervals, among all subjects but particularly among vascular headache patients when they reported headaches to be present or absent. Headache sufferers were of four different types: (1) migraine with aura, (2) migraine without aura, (3) migraine converted to chronic daily headaches (CDHs) and cluster headaches (CHs). Tension-type headaches were excluded.

Earlier publications validated the "mini" test battery according to reliability, stability, and specificity for each of three test instruments utilized [14–18], among headache sufferers. Test instruments used proved to be highly reproducible [14–16] as the "mini" test battery was used among the headache sufferers when headaches were present or absent. One article on methods identified and described domains of cognitive impairments found to be present during vascular headaches [15]. Domains most affected included "deficits in attention," "digit span," "learning new words," "immediate recall," "calculation," "abstraction," and "overall cognitive functioning."

Mini-mental state examination (MMSE) [19, 20] and cognitive capacity screening examination (CCSE) [21–23] were combined when utilized for testing cognition. The two tests take 20–30 min or less to administer. Both quantify general cognitive test performance and identify different cognitive domains that may be affected [20–26]. The Hamilton Depression Rating Scale (HDRS) was included which quantitates changes pertaining to mood and affect. HDRS is sensitive for detecting episodes of depression which sometimes accompany vascular headaches. The HDRS scale was scored, at each visit, to exclude confounding depression, since severe depression may decrease cognitive test performance.

Experimental designs were longitudinal over 15 years. Subjects returned every 3–12 months to clinic so that mood and cognition were tested at each visit. Whenever possible, test performances were compared during different intervals, labeled "headache-absent" and "headache-present."

All subjects tested were neurologically and psychometrically normal when headache-absent. Volunteers with history of severe head injury or psychiatric disorders, drug, alcohol, or substance abuse were excluded.

"Mini-cognitive test battery" was administered during structured neurobehavioral interviews at each clinic visit. During headache-present intervals, volunteers were administered oral sumatriptan (Imitrex), 100 mg, or other "tailored" triptans including zolmitriptan, 5 mg, or as orally disintegrating tablets of Maxalt MLT, 10 mg, by sublingual administration. Subjects could thus be re-tested shortly after triptan-induced headache-free intervals. By these means cognitive testing was repeated during intervals with headache present, or headache free, after headaches subsided, either spontaneously or by pharmacologically induced triptan administration.

Presence or absence of vascular headaches was noted during interviews that were made to correlate clinical observations with changes in the "mini" cognitive test battery. When headache absent, all participants had normal neurological examinations, normal CT and MRI brain scans.

Participants

Patients with headaches were classified according to IHS into four types [4] displayed in Table 7.1.

In the first IHS headache classification, chronic daily headaches (CDHs) and transformed migraines were omitted but later, CDHs were still shown to have headache intervals similar to migraine and thus met IHS criteria, although migraine headaches had become many times more frequent, exceeding 15 or more headache days each month [7, 8]. Table 7.1 lists participants classified into four headache types, according to IHS criteria [4] modified to include subjects with CDH, as follows: (1) migraine with aura; (2) migraine without aura; (3) periodic cluster headaches; and (4) migraine transformed to CDH. Subjects with tension-type headaches were excluded, since they did not exhibit cognitive impairments when headaches present. Furthermore, tension-type headaches are clinically milder, diffuse, bilateral, and with "constricting" or "band-like" features. Subjects with chronic cluster were excluded because they were seldom headache free.

After signing informed consent, 196 subjects were admitted to a prospective trial. Total cohort of vascular headaches consisted of 136 women and 63 men. Mean age was 46 ± 2 years. One hundred thirty-three suffered from migraine without aura; 39 suffered from migraine with aura, 11 had periodic CH, and 13 had CDH. Subjects spoke fluent

Table 7.1 Different types of vascular headaches classified according to IHS criteria

	Numbers of subjects ratios (women:men)	Age, years (mean ± SD)
Migraine with aura	39 (32:7)	47 ± 13
Migraine without aura	133 (95:38)	45 ± 11
Cluster headaches	11 (2:9)	51 ± 10
Chronic daily headaches	13 (4:9)	50 ± 17
Total	196 (133:63)	46 ± 2

Modified from Meyer et al. [14].

English and had completed high school and the majority received higher education by attending colleges, universities, or advanced technical or administrative training programs.

At clinic visits, medical and neurological examinations, MMSE combined with CCSE and HDRS were completed. Normative CCSE and MMSE values among these highly educated subjects fell between 27 and 30. Interrater reproducibility was excellent, with high specificity and sensitivity of cognitive testing. CCSE has less ceiling effects than MMSE, with retesting reliability of ±2.

Hypotheses to Be Tested

Trials were designed to measure cognitive declines liable to occur among a large group of volunteers with different types of vascular headaches, with headaches present, during clinic visits. Additional hypotheses analyzed were whether or not cognitive declines during headache-present intervals were influenced by subjects' age, gender, or type of headache.

Ethical Treatment

Prophylactic therapy was continued as prescribed for prevention of vascular headaches during the trial. These included calcium channel blockers (principally verapamil), beta blockers (principally propranalol), and anti-depressant and anxiolytic agents (principally amitriptyline). Abortive therapy initiated at headache onset included serotonin (5HT) receptor agonists such as sumatriptan (Imitrex) and similar "tailored" serotonin receptor agonists, i.e., zomig and maxalt.

Results

Accumulated data were analyzed from all clinic visits among 77 eligible subjects who had, at least, one clinic visit with headache present and one visit with headache absent. These 77 subjects had a total of 436 visits, 112 with headache present and 324 visits with headache absent (Table 7.2). As shown in Table 7.2, there were significant declines in CCSE and MMSE test scores during intervals with "headache present" when compared with intervals with "headache absent."

There were no significant changes in MMSE, CCSE, and HDRS test scores at different time intervals measured across different clinic visits labeled "headache-absent," confirming stability of test battery. There were no significant changes measured by the same or two different raters, among headache-free subjects. There were also no discernible age-related declines between ages 45 and 51 years for cognitive test scores, among subjects labeled "headache-absent." Confirming that, in this study, age alone did not influence "mini" cognitive battery test scores when headache free. No confounding effects of depression, measured by HDRS test scores, influenced cognitive test scores when headache free. As shown in Table 7.2, there were significant declines in CCSE and MMSE test scores when "headache-present" intervals were compared with "headache-absent" intervals.

Table 7.2 Mean CCSE, MMSE, and HDRS test score changes during visits with headache absent or headache present according to headache types

Headache type	Patients	Headache status at clinic visit	CCSE*	MMSE**	HDRS
Chronic daily headache (CDH)	5	Absent headache	28.9 ± 1.3	29.2 ± 0.8	1.5 ± 3.2
		Present headache	24.2 ± 2.2	27.8 ± 2.8	4.5 ± 5.7
Cluster headache (CH)	7	Absent headache	27.7 ± 4.1	28.4 ± 1.5	5.1 ± 4.7
		Present headache	25.3 ± 3.1	26.5 ± 0.18	3.7 ± 3.7
Migraine with aura (MA)	17	Absent headache	29.5 ± 2.0	28.6 ± 2.0	5.9 ± 4.5
		Present headache	24.8 ± 3.6	26.4 ± 2.2	5.3 ± 5.2
Migraine without aura (MO)	48	Absent headache	29.5 ± 1.1	29.0 ± 1.5	6.8 ± 5.6
		Present headache	25.0 ± 1.7	26.7 ± 1.5	7.1 ± 6.8

Both CCSE and MMSE values declined significantly when pooled vascular headaches present were compared to headache absent. HDRS scores did not change significantly.
*$p < 0.0001$; **$p < 0.001$.

HDRS showed no significant changes at intervals with headaches absent or headaches present so that depression was not a confound. Both CCSE and MMSE declined significantly during headache-present intervals; CCSE declined to a greater, more significant degree than MMSE measured during same headache-present intervals.

Possible influences of headache type, according to IHS classification into types 1, 2, 3, and 4, or any possible effects of gender or advancing age, on headache-present-induced cognitive declines were analyzed next.

Gender, and advancing age of subjects tested, exerted significantly different effects on severity of cognitive declines during headaches. Among women, mean CCSE scores decreased more during headache-present intervals ($p < 0.02$) showing mean declines of –4.8 points. Among men, mean CCSE scores declined less than women, during headache-present intervals showing a mean decline of –3.6 points. Likewise, among younger subjects CCSE scores declined more during headache-present intervals, than among the older subjects ($p < 0.2$). In younger subjects during headache-present intervals, mean scores declined greatly by –4.8 points, compared to –3.7 among older subjects. No significant differences of CCSE declines during headache-present intervals were noted among the four different headache types according to IHS classifications.

McNemar analysis revealed no significant differences in specificity between overall MMSE and cognitive capacity screening examination (CCSE) testing. During headache intervals, however, 85.7% of subjects registered below normal scores, but CCSE declines during the same headache intervals; only 49.4% subjects registered MMSE scores below normal. During the same headache-present intervals CCSE scores showed greater sensitivity ($p < 0.0001$) in recording the declines compared to concurrent MMSE scores. CCSE scoring is more reliable and more sensitive than MMSE scoring for registering cognitive declines among a highly educated cohort of volunteers.

During headache intervals among all four types of vascular headaches migraine with aura, migraine without aura, CDH, and CH, all showed significant declines occurred in cognitive test performance ($p > 0.0005$) consonant with their subjective complaints. These cognitive declines were best measured by CCSE compared with MMSE. During headache intervals women showed greater cognitive declines than men. Likewise, during headaches younger subjects showed greater cognitive declines than older. Headache-related cognitive declines involved attention, but also all other cognitive domains tested: including immediate recall, digit retention, arithmetic, calculation, acquisition of new words, and abstract thinking.

Among these highly educated volunteers, CCSE proved more sensitive than MMSE for detecting cognitive declines, among all types of vascular headaches. Results provide pharmacological and physiological evidence that vascular headache sufferers have justifiable reason to be unable to function normally in workplace, home, school, university, or college and may be responsible for marital discord, impaired social functioning, and neurobehavioral problems.

Results indicate that pharmacologic stimulation of serotoninergic (5HT) receptors of brain and cerebral blood vessels plays key parts in terminating vascular headaches and restoring cognitive performance. Recent PET studies of cerebral serotonin synthesis confirm widespread increases in brain serotonin (5HT) synthesis at the onset of each migraine attack. Sumatriptan administration promptly restores cerebral 5HT metabolism to normal. Regional cerebral blood flow measures by PET confirm that upper brain stem neurones, including trigeminal nuclei, become activated and initiate migraine attacks. Results described show 5HT cerebral receptors are better developed among women with vascular headaches than among men, although both genders show cerebral 5HT receptor declines during advancing age. Such observations support clinical experience that migraine headaches decline in frequency and severity during aging, particularly among women. This clarifies why migraine headaches decrease during aging, and after age 70, with few exceptions, often cease.

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