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Attributing a causal role to migraine “triggers”: is greater caution needed?

Smart phones and electronic diaries increase our ability to track behavioral and environmental factors temporally associated with migraine. But observational data do not establish causation.\(^1\,^2\) In assessing the true role of commonly perceived trigger factors, challenge studies are the gold standard.\(^1\) But little such research has been conducted, and results are unconvincing.\(^1\,^3\)

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In a recent study, more than three hundred people used a smartphone app daily to track prospectively both potential migraine triggers and actual migraine symptoms. On average, each participant recorded a total of 28 “triggers” over a ninety day period. But, of these 28 “triggers”, a mean of only two per person were significantly associated with increased risk of migraine in a specific individual.

Even with commonly-cited triggers such as sleep disruption, dehydration, stress and missed meals, fewer than a third of people who endorsed them found that these factors actually preceded a migraine episode. Individuals believe that their migraines are precipitated by a large number of widely heterogeneous factors, but few of these associations hold true on careful observational analysis. And here we are still discussing only association, not causation.

A paradox: triggers can be protective
A further complication is that factors associated with increased migraine risk in certain people seem to be protective in others. In a longitudinal study similar to that described above, of more than a thousand people with migraine who kept an electronic diary, 24 of 47 potential triggers were associated more closely with decreased risk of an episode than with increased risk. Among them were such commonly acknowledged triggers as caffeine, alcohol and chocolate.

A focus on triggers may lead to a sense of control, but also self-blame
Belief in trigger factors, and attempts to avoid them, are common. On the positive side, such efforts can give people with migraine a sense of empowerment. And, if the triggers are genuine, risk of migraine episodes will be reduced.

However, if triggers are not all that they seem to be, many people may unnecessarily be avoiding pleasurable experiences and activity, with reduced quality of life as a consequence. There is also a risk that failure to avoid perceived triggers will result in self-blame. And, if triggers are not truly causal, are we being distracted from the factors that are really responsible?

Alcohol and chocolate
In a web-based study of more than two thousand participants in the Leiden University migraine project, wine (especially red) was cited as a common trigger by almost 78% of participants, but drinking wine consistently led to an attack in only 8.8%.

No double-blind study showed a significant effect of chocolate ingestion on migraine risk
Along with wine, chocolate is widely believed to precipitate migraine. However – and here we do have data from gold-standard challenge studies – the evidence for this belief is weak. Researchers recently reviewed the three studies which had tried to provoke an attack by having a person eat either chocolate or an indistinguishable non-chocolate control such as carob.

In one study, there was a clear trend towards a greater frequency of headache following chocolate exposure. But no study showed a statistically significantly greater frequency of headache following chocolate ingestion than following ingestion of the control substance.

“Triggers” as prodrome not cause
Because they precede a migraine episode, factors such as food cravings and disturbed eating patterns have been considered possible triggers. But recent evidence from functional imaging suggests they may in fact be symptoms of a brain dysfunction that is already evolving – which would account for their temporal association with migraine without there being a causal role. 

An alternative explanation for the co-occurrence of certain behaviors and migraine episodes – along with an appreciation of the inconsistent evidence found both by careful observation and in experimental studies – are contributing to a reappraisal of the central role of traditional “triggers”.

However, it remains entirely possible that there are genuine triggers for migraine in certain individuals, that the threshold for a causal effect varies, or that triggering requires a combination of factors rather than any one operating in isolation. It should also be noted that the evidence for certain classes of trigger – notably hormonal fluctuations – is strong and consistent.
A broad range of areas within Alzheimer’s disease research were covered in the AAN Virtual 2022 poster session, ranging from vascular risk factors and biomarkers to quality of life and COVID-19 mental health impact.
Highlights in Alzheimer's disease research from AAN Virtual 2022
Age-related risk factors and updated prevalence estimates

Vascular risk factors for dementia vary with age suggesting the need for age-specific dementia risk scores. McGrath and colleagues1 studied which risk factors should be prioritised at particular ages using Framingham Heart Study data. At age 55 the most important factors were systolic blood pressure and diabetes mellitus (DM), at age 65 non-stroke cardiovascular disease, at ages 70 and 75 DM and stroke, and at age 80 DM, stroke and antihypertensive use (protective).

Need for age-specific dementia risk scores

Gillis et al.2 have updated United States (US) prevalence estimates for Alzheimer’s disease (AD) taking into account racial/ethnic diversity. They used data from a variety of sources including the Centers for Disease control and Prevention Wonder 2021 database. Updated estimates for mild cognitive impairment (MCI) due to AD (amyloid beta positive) were 6.9 million for ages ≥50 years (5.7%) and 5.7 million for ages ≥65 years (9.8%). For mild AD dementia the figures were 2.5 million for both ages ≥50 years (2.1%) and ≥65 years (4.2%). These estimates are higher than those derived using pre-2021 publications. The authors suggest this is due to previously under-represented populations and will be important to consider in future clinical trial design and recruitment.

Additive effect of aging and plasma biomarkers

Aging is the main risk factor for most neurodegenerative diseases. Cividini and colleagues3 used MRI imaging to look at changes in cortical thinning across the lifespan in healthy brains to help understand the additive effect that aging may have in these diseases. Decreased thickness was seen in 97% of cortical regions with advancing age, with highest cortical thinning in the temporal, frontal and parietal lobes and insular cortex, and least in the occipital lobe. They concluded that observing the trajectories of normal brain aging helps to identify those areas that might be more vulnerable to neurodegeneration.

Identify cortical areas more vulnerable to neurodegeneration

A combination of plasma neurodegenerative and inflammatory cytokine biomarkers to identify AD patients was the proposal from Chenna et al.,4 who compared a range of nervous system proteins in plasma from 72 AD patients (mild, moderate and severe) to 64 healthy controls. There were significant increases in median levels of NF-L, t-Tau, p-Tau181, IL-6, IL-10, and TNFα in the combined AD group relative to controls (p<0.0001).
CSF testing, quality of life and COVID-19-related mental health

Krivanek and Gale\textsuperscript{5} looked at clinical practice prior to published appropriate use criteria (AUC) for cerebrospinal fluid (CSF) biomarker testing in AD diagnosis. Clinical data was available for 105 patients in a tertiary care dementia clinic, who would all have met AUC, with the most common (53.3%) criteria ‘MCI or dementia with onset before age 65’. In 48.5% of cases the results of CSF testing led to a change in initial diagnosis. The least stable diagnoses were ‘dementia’, ‘neurodegenerative process’, and ‘cognitive impairment of unknown aetiology’, and the most stable was ‘AD’.

\textbf{In 48.5% of cases the results of CSF testing led to a change in initial diagnosis}

Villarejo-Galende and colleagues\textsuperscript{6} assessed patients’ experience of living with early AD using a range of patient-reported outcomes. Their study included 149 patients with mild or prodromal AD and mean disease duration 1.3±1.7 years. 22% of patients reported depressive symptoms and 94% mild-to-moderate hopelessness. The Quality of Life in AD Scale (QoL-AD) scores were positively correlated with GSES scores and negatively correlated with BDI-FS, SSCI-8, RADIX practical and emotional consequences, and BHS scores. Better understanding the patient’s perspective could facilitate implementing individualized supportive strategies to improve QoL.

\textbf{Understanding the patient’s perspective could facilitate} improving QoL

Finally, Kim et al.\textsuperscript{7} reported on the impact of the COVID-19 crisis on the mental health of dementia patients. In 2021 they conducted a telephone survey of 2080 patients registered as having dementia with a response from 1038 caregivers. The study asked which, if any, neuropsychiatric symptoms had been aggravated by the recent pandemic. At least one aggravating symptom was experienced by 26.4% of patients, predominantly depression/dysphoria (44.5%), sleep disturbance (9.5%) and delusions (9.1%). A more preemptive strategy to manage such symptoms would help both patients and caregivers.

**Making the diagnosis**

Significant overlap between the clinical features of Parkinson’s disease (PD), multiple system atrophy (MSA) and progressive supranuclear palsy (PSP) can make diagnosis a challenge. Olszewska and colleagues\(^1\) reported their novel Real-Time Quaking-induced Conversion (RT-QuIC) protocol that enables rapid detection of alpha-synuclein in cerebrospinal fluid using a minimally invasive cervical skin biopsy. Combining the results with serum neurofilament light chain measurement achieved 100% sensitivity/100% specificity in distinguishing MSA from PD and 100% sensitivity/93% specificity for MSA versus PD/PSP/healthy controls.

**Could smell therapy improve apathy?**

In Alzheimer’s disease and mild cognitive impairment there appears to be an association between olfactory dysfunction and apathy, which share anatomical pathways, suggesting smell therapy as a potential therapeutic approach for apathy. Nunez and colleagues\(^2\) were interested if there was a similar relationship in PD, using data from 486 patients with PD followed for 5 years in the Parkinson’s Progression Markers Initiative Study. They found no association between apathy and olfactory dysfunction, no difference in olfaction between patients with and without apathy, and no difference between patients with and without olfactory dysfunction in their time to develop apathy (all p>0.05). This highlights the clinical heterogeneity in neurodegenerative disorders.

**Training the mind and the gait**

Shaji and colleagues\(^3\) were interested in the use of mindfulness-based interventions (MBI) for newly diagnosed patients with PD. They enrolled 25 patients for an 8-week program, with assessment using a number of measurement

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**Combining the results achieved 100% sensitivity/100% specificity in distinguishing MSA from PD**

**They found no association between apathy and olfactory dysfunction**
instruments at baseline, 8 weeks and 3 months. There was significant improvement in both motor and neuropsychiatric deficits, with increased mindfulness and emotional wellbeing and reduced stress. These were seen immediately following the MBI and maintained at 3-month follow-up.

**Significant improvement in both motor and neuropsychiatric deficits**

Gait training is an important part of rehabilitation for patients with PD. Amin et al.4 studied factors influencing the response to a 10-week gait training program in 19 patients. Greater improvements in gait speed in unadjusted and age-adjusted models were independently associated with better baseline memory performance and lower MDS-UPDRS Part III scores, but not with baseline executive function. The authors suggested that memory may be more important than other cognitive domains in effective gait rehabilitation, and degree of motor involvement will also influence the response.

**It’s a team game**

Specialized physiotherapy (PT) reduces complications and healthcare costs for patients with PD. Talebi and colleagues5 looked at whether this was also true for specialized occupational therapy (OT) and speech and language therapy (SLT). Their retrospective observational study of 51,464 patients with PD used healthcare expenditure data from the Netherlands. The authors confirmed the inverse association between specialized PT and the incidence of complications and demonstrated this was also true for specialized OT. A similar trend for specialized SLT was not statistically significant.

**Memory may be more important than other cognitive domains in effective gait rehabilitation**

**Inverse association between specialized PT and OT and the incidence of complications**

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Global cognitive dysfunction can be present before, during and after an attack.
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Cognitive dysfunction associated with the prodromal and postdromal phases of migraine was emphasized by Nazia Karsan (Clinical Fellow, King’s College Hospital, London, UK) in her Migraine World Summit 2023 interview focused on non-pain aspects of the condition.³ For many patients, inability to concentrate and even difficulties in reading, writing and speaking – along with somnolence – add greatly to the migraine burden, especially when they interfere with study or work, Dr Karsan said. Such non-pain symptoms are present in both prodromal and recovery phases⁴ which, taken together, mean a migraine episode may last for up to four days. Disability outside the headache phase contributes greatly to morbidity. And these important elements of what is a heterogeneous disease can be difficult to communicate to friends, family and work colleagues, Dr Karsan commented.
In the pre-headache phase, the brain is already functioning abnormally.

Employers in particular may not regard migraine as a serious condition.
“Triggers” may reflect already evolving functional abnormalities

Migraine is a brain disorder, and the brain controls so much of the body that we should not be surprised that the range of associated symptoms reflects widespread dysfunction.

Other notable non-pain symptoms include irritability, mood swings, neck stiffness, sensory hypersensitivities such as photophobia, and abnormal eating behaviours like skipping meals and cravings for cheese or chocolate.

Phenomena like these have traditionally been considered as possible migraine triggers, but they may in fact be symptoms of a brain dysfunction that is already evolving. Dr Karsan suggested. If this is true, and such experiences actually reflect premonitory brain changes, avoidance of bright lights or certain foods, for example, may not help in preventing a full-blown migraine episode.

Brain scans validate patient experience

Imaging studies in people with spontaneous migraine attacks and in those triggered by nitroglycerin infusion show good correlations between areas of abnormal brain function and patients’ experiences during the premonitory phase.

The cingulate cortex, involved in mood and cognition, shows up on MRI imaging during the prodrome as well as the acute phase, with regions of the pons and medulla implicated in the pain.

Acute headache is the major symptom of migraine, but we also need research into non-pain aspects if we are more effectively to treat and abort an episode, Dr Karsan said. Clinical trials relating to CGRP inhibition have looked at effects on a range of disabling symptomatology and on return to functional ability, and have shown promising results.

We need to think about intervening before the process escalates to pain, and to recognize that patients are not necessarily “back to normal” once their headache has gone. This fact is massively under-recognized, Dr Karsan argued.

Stigma also contributes to burden

It is not just symptoms of migraine that impose burden. It is also stigma. The causes of migraine morbidity extend from the neurological to the sociological.

Partly because the symptoms of migraine cannot be seen, and there are no lab tests to define it, migraine is considered by some to be a condition that sufferers may exaggerate, possibly to obtain advantage, said Dr Robert Shapiro, of the University of Vermont College of Medicine, Burlington, USA.

The stigma associated with the disease may come from family and friends, work colleagues and employers, health professionals, and even patients themselves, Dr Shapiro commented during his Migraine World Summit interview. This unsupportive social environment can limit the ability of people with migraine to live full and productive lives.

Importantly, it may lead those with the condition to conceal symptoms and avoid seeking effective treatment. Hence stigma has a direct effect on the physical morbidity associated with migraine as well as imposing an unnecessary psychological burden.

More positively, Dr Shapiro is hopeful that in the next decade or so we will have biomarkers – perhaps including imaging of the kind described above – which can provide a definitive objective diagnosis of migraine. Meanwhile it is important to continue efforts to educate the health community and the wider public about the realities faced by those with the condition.

3. Transcript of interview of Nazia Karsan by Lisa Horwitz, Migraine World Summit 2023.
Evidence supporting the key role of neuroinflammation in Alzheimer’s disease was presented by Professor Charlotte Teunissen, Amsterdam, the Netherlands, at EAN 2022. She highlighted genome-wide association studies, a study demonstrating a role for both anti- and pro-inflammatory neuroinflammation, and a pathophysiological subtype linked to inflammatory proteins.
A key role for neuroinflammation

Neuroinflammation plays a key role in Alzheimer’s disease, said Professor Teunissen. Age, genes and other risk factors are linked to impairment of the blood–brain barrier (BBB) and oxidative stress, which activate microglia, leading to accumulation of amyloid and tau and neurodegeneration.1

Genome-wide association studies have demonstrated this key role, explained Professor Teunissen. Many AD risk genes, which are clustered into inflammatory response, lipid metabolism, and endocytosis groups, are involved in the immune response.2

In addition, many AD-associated genes are highly expressed in microglia, added Professor Teunissen. Heat maps depicting relative expression levels of GWAS-identified AD risk genes among central nervous system cell types show increased expression of proteins related to the genes in microglia.3

When does neuroinflammation start to play a role in the disease process?

Microglial activation appears to occur very early in the AD process, and increases with severity of AD,4 Professor Teunissen said. Early changes are also seen in familial AD with early abnormalities in cerebrospinal fluid pTau, amyloid-beta 42 (Aβ42)/Aβ40 and chitinase-3-like protein1 (YKL-40) suggesting that synaptic damage, neuronal injury and neuroinflammation begin soon after the initial brain amyloid accumulation.5

Evidence for a biphasic pattern of inflammation increases the complexity, added Professor Teunissen:

• The first peak is probably an early protective reaction with activation of a neuroprotective phenotype of microglia with the production of anti-inflammatory cytokines (interleukin (IL)-13 and IL-14)
• The second peak is characterized by activation of a proinflammatory phenotype of microglia with the production of pro-inflammatory cytokines (tumor necrosis factor-alpha, IL-1beta, and inducible nitric oxide synthase)6

Role of inflammatory biomarkers in early disease

Cerebrospinal fluid biomarkers can be used for early and differential diagnosis and for identifying patients for trials, said Professor Teunissen. Three pathophysiological subtypes of AD have been identified by proteomic analysis of CSF:7

• Subtype 1 patients have increased expression of plasticity-related processes
• Subtype 2 is linked to an elevation of inflammatory proteins
• Subtype 3 is associated with BBB dysfunction

Although the biomarkers are aspecific they can be used for stratification, for example patients with an inflammatory phenotype might benefit most from anti-inflammatory treatments, concluded Professor Teunissen. The next step is to validate the subtypes in trials.

This satellite symposium was supported by Novo Nordisk.
Hormonal events in women such as menarche, menstruation, pregnancy, and menopause as well as the use of OCs and HRT may be linked to the frequency and severity of migraine attacks — a fall in plasma estrogen levels can trigger attacks of migraine without aura, whereas higher estrogen levels seem to be protective.

Migraine is twice as common in women as in men (cumulative incidence 43% in women, 18% in men), and the 1-year prevalence of migraine is three times higher in women.

Estrogen and migraine pathophysiology
Menarche

Among 484 people with migraine there was a significant lifetime female preponderance for both MO and MA (male:female ratio 1:2.2 and 1:1.15, respectively), but the female preponderance for MO only becomes apparent after menarche5.

MA, migraine with aura; MO, migraine without aura

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All three ER subtypes — ERα, ERβ and GPER — are extensively expressed throughout migraine-related regions, in particular the hypothalamus (a putative migraine initiator) and the trigeminal ganglia and spinal trigeminal complex (involved in nociception)4.

The actions mediated by ERα, ERβ and GPER are not clear, but these receptors are frequently colocalized with CGRP and CGRP receptors, and oxytocin and oxytocin receptors, suggesting the likely involvement of CGRP and oxytocin4.

CGRP, calcitonin gene-related peptide; ER, estrogen receptor; GPER, G protein–coupled estrogen receptor; HRT, hormone replacement treatment; MO, migraine without aura; OCs, oral contraceptives; OXT, oxytocin.
Pregnancy

Most women with migraine, especially those with menstrual migraine, experience less severe migraine as they progress during pregnancy—among 47 pregnant women, MO improved during the first, second, and third trimesters in 47%, 83%, and 87%, and completely remitted in 11%, 53%, and 79% of the women, respectively.

Menstruation

Among 5725 women with migraine, menstruation was the most common migraine trigger factor and was reported by 78%.

Among 607 menstruating women with migraine >18 years of age, use of a prospective headache e-diary revealed that two-thirds of the women had menstrual migraine but pure menstrual migraine was rare (<1%).
Perimenstrual migraines are longer duration and associated with higher triptan intake than migraines in women without menstrual migraine; women with menstrual migraine may therefore be at increased risk for medication overuse headache and conversion to chronic migraine.

Among 47 pregnant women with MO, migraine recurred during the first week after childbirth in 34% and during the first month in 55%; breastfeeding seemed to protect from migraine recurrence postpartum.

MO, migraine without aura

Menopause

During perimenopause the fluctuating circulating sex hormone levels are often associated with worsening or a change in migraine patterns.

Headache significantly decreases in the transition to and after menopause.

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