Stress and migraine

Something expected, something unexpected

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Stress seems inescapable, or is that just my perception? This could be a statement about clinical practice, particularly completion of documentation; politics; modern life; or here, the pathophysiology of migraine. Only last year, *Neurology*® published a very challenging study demonstrating that alleged migraine triggers—flickering lights and strenuous exercise—were only about 10% likely to precipitate migraine in apparently susceptible individuals.[1] This contrasts with nitroglycerin for which 75% of migraineurs are triggered.[2] What of stress: surely, it is a trigger?

In this issue of *Neurology*, Lipton et al.[3] enrolled 22 patients in a 3-month electronic diary study and 17 completed the task of at least 30 days of diary entry, contributing 110 attacks and 2,011 diary entries. Stress was assessed with the Perceived Stress Scale and the Self-Reported Stress Scale, and the odds ratio for migraine occurrence was computed as a function of stress across time. The first finding was that the level of stress generally was not associated with migraine occurrence. The main positive finding was that a reduction in stress from one evening diary to the next by the Perceived Stress Scale was associated with increased migraine occurrence for up to 18 hours. This effect was still present when controlling for level of stress at all time points, and the Self-Reported Stress Scale gave the same broad results.

Is this just an artifact of the study size or of the more relaxed environs of New York City? Both seem unlikely. Many patients do report stress reduction as a trigger to their attacks—e.g., weekend headache in noncaffeine consumers—so the stress-reduction hypothesis has face validity. Moreover, a positive study in a small group is more likely to be important than a small result in a large group. Certainly, if there are enough data to see the reduction in attacks, then there should be enough to see the opposite. What is perhaps more interesting is that stress levels themselves did not track as a migraine trigger. Stress, at least the level rather than the change, can join flickering lights, strenuous exercise,[1] and chocolate[4] as celebrated failures when tested. There are parallels: daily hassles in pediatric migraineurs do not predict headache occurrence on that day or the next day, although more hassles occurred on the headache day.[5]

What could be the pathophysiologic mechanisms at play? The authors offer some possibilities. The "unmeasured mediator": prior stress causes missed meals or disturbed sleep, which are the antecedents to the attack; or are both just part of the premonitory phenomenology?[6] The "reversed cause and effect": there is increased vulnerability to stress in the premonitory phase and a normalization with the attack, and thus reduced perception of stress. The biological cause: a change in hypothalamic-pituitary axis–driven glucocorticoid activity, more so during stress and less afterward, with migraine triggered by the reduction in steroid level. All are testable hypotheses. If the last was true, one might hope for better than placebo outcomes in corticosteroid use in medication withdrawal settings.[7]

Into this mix, one could add "nothing" as the mechanism, by which I mean a variation on the brain normalization hypothesis. What if, for some patients, nothing changes but their perception of events? We know that migraine electrophysiology normalizes as the attack is about to begin[8] and we can demonstrate activations in the migraine premonitory phase in brainstem and cortical regions using functional imaging, which could easily account for sensory and other perception changes.[9] It is possible that there is no link to stress levels overall, perhaps because as the patient's brain function alters, the ability to cope with exogenous inputs varies. We accept this to be true for light and sound, and in an attack, call it photophobia and phonophobia without for a minute trying to measure light and sound itself. If, during the premonitory phase, the brain normalizes some functions as the attack commences, might that not be perceived as less stress, even if exogenous factors were unchanged?

Moreover, these concepts do not need to be all or nothing: it is entirely possible that both change and an exaggerated perception conspire to trigger or promote the ensuing attack. Migraine is a complex brain disorder and explanations may require turning over many pieces of the puzzle.[10]

What do we tell our patients and what can we do in practice? I have said for many years to patients: be boring—a little grief regularly and no excesses. It is silly

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advice since it would make life less interesting, although it is in keeping with the study findings. I think we can say to patients there is an emerging consensus that the migraine brain is vulnerable to change, such as sleep and stress, and therefore best kept stable. We can say there is good clinical evidence—the new study—and both electrophysiologic[11] and imaging evidence[12] to seek advice, when required, to learn to cope with stress. Now this may be because it makes life more tolerable rather than alters migraine expectancy, but since migraine is the single biggest source of neurologic disability in the world,[13] improving function is quintessentially good neurologic practice.

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