**3¹P-MRS in Migraine: Fallen Through the Cracks**

Lakhan et al elegantly summarize a large body of neuroimaging data obtained from migraine patients in their paper “Structural and functional neuroimaging in migraine: Insights from 3 decades of research.” In doing so, they separated out aura, ictal, and interictal imaging data.¹ In the methods section, the authors state that from a literature search up to May 2012, “[A] review of all titles was conducted to include only pertinent publications.” While we appreciate a review of 3 decades of neuroimaging research inevitably leads to elimination of many papers, we think the entire body of phosphorus magnetic resonance spectroscopy (³¹P-MRS) studies in migraine should not have been left out.

A recent review article on MRS in migraine was based on 31 original articles, including 16 ³¹P-MRS and 15 proton (¹H-) MRS studies.² Lakhan et al have selected only 2 studies, both using the ¹H-MRS technique in migraine with aura, and summarize interictal MRS findings in migraine as “a decreased N-acetylaspartate signal and a slight increase in lactate peak” but there is no mentioning of ³¹P-MRS data at all. This came as a surprise as:

- the significance of the N-acetylaspartate (NAA) signal is unclear; NAA is considered a marker of neuronal (in particular axonal) integrity, is synthesized predominantly in neuronal mitochondria, and assumed to be involved in mitochondrial/cytosolic carbon transport.

³¹P-MRS provides information about metabolites that play key roles in tissue energy metabolism, including the high-energy phosphates adenosine triphosphate (ATP) – the principle donor of free energy in tissue – and phosphocreatine (PCr) – a reservoir for ATP generation through the creatine kinase reaction. Interictal phosphorous brain abnormalities were first reported in the late 1980s by Welch and colleagues. In the following decade, most ³¹P-MRS data were generated by the group from Bologna – including the late Dr. Montagna, who was an advocate of a mitochondrial component to migraine neurobiology – corroborating a decrease in PCr levels over and over again in different subtypes of migraine regardless of the brain region. In a recent ³¹P-MRS study at 3 Tesla using an absolute quantification technique, a significant decrease was observed in both high-energy phosphates, PCr and ATP, in the occipital lobe of migraine without aura patients compared with normal controls.³

The depletion of brain high-energy phosphates in steady state measurements reflects an imbalance between ATP production and ATP use in migraine patients, and suggests that the brain of migraine patients is compromised to deal with metabolic stress.

We do not know whether this imbalance is due to a primary mitochondrial dysfunction or secondary to alterations in brain excitability. The most reproducible interictal brain excitability alteration in neurophysiological studies in migraine is the lack of habituation in neuronal information processing, which may well be reflected in the absence

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of hemodynamic refractory effects observed in a recent interictal functional magnetic resonance imaging study in migraine without aura patients.\textsuperscript{6}

At present, there is no universally accepted model to explain migraine neurobiology, but there are at least 3 competing models (Figure), focusing on either a brainstem and/or diencephalic dysfunction,\textsuperscript{7} a human cortical spreading depression equivalent,\textsuperscript{8} or on the concept of a vulnerable cortex.\textsuperscript{9} In the conclusion of their review article, Lakhan et al refer to the former 2 models only, but fail to discuss the latter as it is partly based on \textsuperscript{31}P-MRS data.

![Figure](image.png)

Figure.—Diagram showing different migraine models. The activation of the trigeminovascular system (TVS) is either related to (A) a dysfunction of brainstem and/or diencephalic structures, (B) an increased metabolic strain due to a lack of habituation and/or a reduced mitochondrial energy reserve, or (C) a (silent) cortical spreading depression (CSD).

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REFERENCES
New Daily Persistent Headache: Disease or Syndrome?

We read with great interest the article “The Heterogeneity of New Daily Persistent Headache” by Robbins and Evans.1 We appreciate the authors’ contribution in expanding the understanding of new daily persistent headache (NDPH). In the current article, the authors try to distinguish NDPH from other primary and secondary types of headache disorders. We have a few concerns about this article. The authors discussed post-meningitis headache as an important cause or differential diagnosis of NDPH. The onset of post-meningitis headache may be like NDPH (continuous since onset). However, the clinical profiles or clinical setting of post-meningitis headache is entirely different from a typical NDPH, and it is less likely to be confused with NDPH.

The authors speculate that some patients classified as NDPH actually have viral meningitis that continues on to a chronic post-viral meningitis headache. The authors quoted the study of Almazov and Brand2 in support of their speculation. However, we think that patients in Almazov and Brand’s observations do not have chronic post-viral meningitis headache. Chronic postinfection (bacterial or non-bacterial) headache is a direct continuation of headache attributed to intracranial infection or meningitis. This part is lacking here. The study2 demonstrates “up to 80% patients with tension-type headache had a chronic or acute illness prior to the beginning of headaches, most commonly infectious diseases in the otolaryngologic regions.” The observation clearly indicates that the illness was prior to the beginning of the headache. There was nothing like “direct continuation of headache attributed to meningitis.” Moreover, infections of upper respiratory tract infection cannot be considered as intracranial infection (meningitis). To the best of our literature search, upper respiratory tract infection is not a common accompanying symptom of any type of meningitis. Therefore, these patients cannot be labeled as chronic post-viral meningitis headache.

Review of the literature suggests that upper respiratory tract infection or flu-like illness is the most common infection related to the onset of NDPH. The temporal relation of onset of the headache of NDPH to the infection has not been delineated in any study in the literature. In a retrospective study on patients with subacute daily headache (1-4 weeks durations), we observed that patients with a prior history of febrile illness are more likely to have neck pain and signs of meningismus (in addition to headache).4 Our observation,4 Almazov and Brand’s observation,2 and a few other observations5 suggest a possibility of postinfectious pathology (most likely immunological) in meninges in patients who have a prior history of infections before the onset of headache. We further suggest that the interrelation between meninges and infections may be like the interrelation of synovial membrane to various viral infections for the development of reactive arthritis, as synovial membranes and meninges are of same type of tissue (membranous connective tissue).5 We speculate a local immune reaction in the meninges in a subset of patients with NDPH who have a prior history of febrile illness. Moreover, as immune reaction may begin within 2 days after an antigenic challenge, postinfectious symptoms may start within febrile periods. As flu-like illness or other febrile illnesses are the risk factors for the development of NDPH, we hypothesize that a subset of patients in these groups may be because of postinfectious mechanisms in the meninges. Various recent observations suggest that meninges are rich in immune cells which are capable of releasing pro-inflammatory, neuroexcitatory mediators in response to inflammatory/imunological challenges.6 High cerebrospinal fluid pro-inflammatory cytokine (tumor necrosis factor-α), demonstrated in patients with NDPH, may be because of meningeal involvement secondary to immunological challenges.7

Therefore, NDPH with a history of febrile illness is more likely because of immunological (postinfectious) process rather than chronic postinfection (bacterial or nonbacterial) headache. There is a need to study the role of meninges in patients with NDPH (especially in patients with a history of febrile illness and with features of meningismus).

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