Inflaming the need for migraine biomarkers

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Biomarkers for neurologic disease take many forms (e.g., genetic, biochemical, structural, and functional) and have established and emerging applications in research and clinical practice.[1,2] Their potential roles include detecting preclinical disease, supporting earlier or more accurate diagnosis, defining biologically homogenous subgroups of patients, predicting treatment response, assessing prognosis, and measuring change in disease severity (table). In addition, biomarkers may offer insight into the mechanisms underlying the initiation, progression, maintenance, or remission of illness.[2]

The article by Dearborn et al.[3] in the current issue of *Neurology*® is an important step toward developing biomarkers for migraine. The authors assessed 2 candidate biomarkers, adiponectin and leptin, both adipocytokines, secreted primarily by fat cells. The hypothesis that adipocytokines may be migraine biomarkers emerges from epidemiologic studies, experimental models, and biological theory.[3,4] Epidemiologic studies show that obesity is a risk factor for migraine and that among persons with migraine, obesity is associated with higher baseline headache frequency and with the new onset of chronic migraine.[5,6] In animal models, proinflammatory mechanisms are pronociceptive; inflammatory mediators applied to the dura mater promote the development of central sensitization and allodynia.[7] Thus, inflammatory biomarkers made in adipocytes are plausibly linked to the onset, persistence, and progression of migraine.[7]

In this context, Dearborn et al.[3] conducted a prospective case-cohort study in the Atherosclerosis Risk in Communities Study (ARIC). Blood for biomarkers was drawn at baseline (1987–1989) and migraine status was determined about 6 years later (1993–1995). The study showed that adiponectin levels were associated with an increased risk of migraine in men (odds ratio [OR] per SD unit: 1.86; 95% confidence interval [CI] 1.15–3.01) but not in women (OR per SD unit: 1.05; 95% CI 0.80–1.37). Leptin was not associated with migraine status.

The association of adiponectin levels with migraine 6 years later is compatible with at least 2 processes, which could operate simultaneously. Perhaps higher adiponectin levels are associated with an increased risk of the new onset of migraine. Under this scenario, adiponectin could be considered a marker for preclinical migraine or a predictor of migraine onset (table). Alternatively, higher adiponectin levels may be associated with more persistent migraine in those with migraine at baseline. Under this second scenario, adiponectin could identify a persistent migraine subgroup, making it a prognostic marker (table). In ARIC, migraine status was not determined at baseline. Because migraine onset peaks in the early 20s, in this sample with a mean age of 53 at enrollment, most people with migraine at follow-up probably also had it at baseline.[8] Longitudinal studies in samples whose migraine status is known at baseline are required to assess the relative importance of adiponectin as a predictor of migraine onset and as a predictor of disease duration.

Like many seminal studies, the present report raises intriguing possibilities. Future studies should use adiponectin and other biomarkers to define homogenous subgroups of people with migraine (table). For example, men with migraine and high levels of adiponectin may have more frequent or severe headaches, higher rates of allodynia, more disability, and an increased risk of persistence or progressive disease. As natural subgroups are identified based on clinical features and biomarkers, next steps would include looking for corresponding genes and patterns of treatment response.[9,10]

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See page 2211

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Table Uses of and approaches to studying biomarkers in neurologic disease

Biomarker purpose	Usual approach	Analysis using the standard approach	Alternative approach	Comments on Dearborn et al.
Detecting preclinical disease or predicting disease onset	Cohort study of disease-free individuals; marker should predict disease onset over time	Time-to-event model over clinically relevant follow-up times using biomarker as predictors	Nested case-control study	Migraine status at baseline is unknown; time to migraine onset is unknown
Early or accurate diagnosis	Cross-sectional study of persons with and without (early) disease	Relative odds of disease given positive biomarker status	Sensitivity and specificity of the marker; results may vary with setting (clinical vs population-based) and cut scores	Assumes migraine status at year 6 reflects migraine status at baseline
Define biologically homogeneous groups	Identify and contrast biomarker positive and biomarker negative persons with disease	Standard parametric and nonparametric statistics	Latent class models including the biomarker to detect statistically defined groups	Not evaluated
Predict treatment response	Stratified analysis in observational study or randomized controlled trials contrasting biomarker-positive and -negative individuals	Stratified analysis by biomarker status or model with terms for biomarkers and interactions with treatment	Stratified randomization by biomarker status	Not evaluated
Assess prognosis	Follow individuals with and without the biomarker to assess outcomes	Measure of outcome could be headache days per month, disability, health-related quality of life, time to chronic migraine onset, time to remission	Simple cross-sectional study; manipulate the biomarker and assess change in prognosis	Not evaluated
Measure change in disease	Serial measures of the biomarker track with trajectory	Association of status and change in the biomarker with a clinical outcome measure	Model using lag variables and various progression measures	Not evaluated

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