Fibroblast growth factor 21, a biomarker for mitochondrial muscle disease

For many patients, a mitochondrial disease diagnosis is often difficult to establish with certainty, except in cases with a classical clinical presentation. Invasive and time-consuming methods, such as tissue biopsy and enzymatic studies, are frequently necessary before proceeding to molecular genetic analyses, because of the low specificity and sensitivity of existing less-invasive biomarkers, such as plasma or CSF lactate, pyruvic acid, or urinary organic acids. Moreover, histologic and biochemical investigation of muscle tissue is often nondiagnostic or may show secondary mitochondrial dysfunction due to aging or medication (e.g., HIV antiviral therapy), even in patients without mitochondrial disease. The introduction of next-generation DNA sequencing with the capability of rapid and simultaneous sequencing of mitochondrial and nuclear encoded genes further reiterates the necessity for a complementary assay with reasonable sensitivity and specificity in order to bypass current invasive testing, such as muscle biopsies.

A promising step in this direction was made by Tyynismaa et al., who discovered elevated levels of a metabolism-regulating protein, fibroblast growth factor 21 (FGF21), in response to respiratory chain deficiency in serum and muscle tissue from mice with mitochondrial myopathy due to C10orf2 (twinkle) mutations. Although the mechanism underlying augmented FGF21 levels in mice is unclear, this protein is intimately involved in energy metabolism regulation in several cell types, mainly in liver and muscle. During fasting it is upregulated in the liver and serves as a regulator of lipid oxidation and ketogenesis to provide energy for other tissues, while its metabolic role in muscle is unclear. A retrospective study showed the utility of FGF21 as a biomarker for human mitochondrial disorders, and showed that elevated serum FGF21 levels were associated with greater sensitivity in detecting respiratory chain disorders than other classical indicators, such as plasma lactate and pyruvate.

In this issue of Neurology®, Davis et al. present an exciting collection of additional evidence of the utility of FGF21 as a marker of mitochondrial respiratory chain disorders. In a prospective study, they measured FGF21 levels by an ELISA method in 54 Australian adults with a mitochondrial disorder and muscle involvement, which they compared against 66 control subjects and 20 patients with nonmitochondrial muscle disease. FGF21 outperformed other routinely used biomarkers for mitochondrial disease, with a sensitivity of 69% and a specificity of 95%, as compared to plasma levels of lactate (sensitivity 15%, specificity 98%), pyruvate (sensitivity 35%, specificity 83%), and lactate-to-pyruvate ratio (sensitivity 12%, specificity 98%). Although these findings suggest that plasma FGF21 concentrations may serve as a respectable screening method, their utility as a diagnostic marker of mitochondrial disorders is not as clear cut because they can be elevated in individuals without mitochondrial disease (such as in diabetes, obesity, nonalcoholic fatty liver, and others). Nevertheless, in the setting of high clinical suspicion of mitochondrial disease, an elevated serum level of FGF21 may suggest a change in current diagnostic algorithms. It provides further evidence of a mitochondrial disease and clinicians may consider proceeding to molecular analysis, thus bypassing classical invasive investigations such as muscle biopsy. However, if this approach does not provide a specific genetic etiology, histologic and biochemical assessment of affected tissues might still be necessary in order to finally establish a diagnosis.

The fact that serum FGF21 levels might be elevated in nonmitochondrial diseases emphasizes the importance of a careful history and physical examination and additional testing to exclude other disorders that alter FGF21 levels. Further studies are required to elucidate the exact underlying mechanism leading to elevated levels of FGF21 in mitochondrial and other conditions. It is unclear whether FGF21 might be elevated in respiratory chain disorders affecting systems other than muscle, such as liver or brain, that also express FGF21. Therefore, studies comparing FGF21 serum levels in patients with mitochondrial disease stratified according to phenotype and genotype vs a large control population, subcategorized according to nonmitochondrial muscle disorders, diabetes, and body

From the Departments of Medical Genetics and Neurology (R.G.), Mayo Clinic, Rochester, MN, and Newcastle University (R.H.), Newcastle upon Tyne, UK.

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mass index, are needed in order to define with further precision the sensitivity and specificity of FGF21 as a biomarker of respiratory chain diseases.

In this study, Davis et al. found a positive correlation between muscle weakness and serum FGF21 concentration. Previous animal studies correlated increased FGF21 expression with the number of COX-negative fibers, an indicator of disease severity. This important observation raises the exciting question of whether FGF21 might serve as a biomarker of the severity and progression of mitochondrial disease. FGF21 levels in blood were successfully used to follow up both efficacy and side effects of bezafibrate in a mouse model of mitochondrial myopathy. However, whether FGF21 can be used in future clinical trials as a biomarker of therapeutic response needs further confirmation.

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REFERENCES