

# Biomarkers in ALS

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As many of you know only too well, establishing a diagnosis of ALS is not always a rapid, straightforward, or error-free process. ALS may initially present with symptoms which are similar to those seen in many other more common conditions. For example, individuals presenting initially with slurred speech may be suspected of having a stroke or a brain tumor. In those presenting with limb weakness, the examining physician often suspects a nerve root impingement in the neck or back, or a peripheral nerve entrapment such as a carpal tunnel syndrome. Individuals with generalized weakness or diffuse fasciculations may be suspected of having a metabolic or autoimmune disorder for which a number of blood tests are drawn. And, of course, infectious processes or malignancies are a concern in those with muscle wasting and weight loss. The battery of tests performed usually is extensive, and typically includes many blood tests, imaging studies (generally MRI scans of the brain and spine), and one or more EMG/nerve conduction studies (electrical studies of nerve and muscle). Lumbar punctures (spinal taps) are often performed, and muscle or nerve biopsies may be done on occasion as well. Eventually, the diagnosis of ALS is made by the presence of certain clinical findings such as muscle weakness, atrophy and fasciculations, combined with EMG/nerve conduction studies that demonstrate specific features. All the other testing serves only to rule out other disorders, meaning that individuals with ALS characteristically have normal MRI scans, blood work, and cerebrospinal fluid (CSF). A concern that I often hear from patients who are presenting for a diagnosis is: "I know something is wrong, but all my tests are normal."

It has long been clear to those of us caring for individuals with ALS that it would be of great value to have at least one other diagnostic test which, if positive, would be indicative of ALS, just as a chest x-ray can demonstrate a pneumonia, or an MRI can permit a diagnosis of multiple sclerosis, or a lumbar puncture can confirm meningitis. Physicians and scientists call such positive test results "biomarkers," because they serve as biological markers for particular diseases. In patients with ALS, one logical place to search for biomarkers is the CSF, which contains proteins from affected neurons (nerve cells) and glia (supporting cells) of the brain and spinal cord. Presumably these should be different in individuals with ALS than in those without the disease, permitting such biomarkers to be used in the diagnosis of ALS. In addition, the identification of specific biomarkers should lead to insights into the underlying mechanisms of ALS. Finally, it is hoped that biomarkers will be a means to measure effects of treatments by acting as a means to measure disease progression.

A collaborative study involving the University of Pittsburgh and Massachusetts General Hospital was one of the first to identify such a panel of biomarkers in the CSF, and several groups since then have looked at a number of potential biomarkers. Our ALS research group, led by James Connor, PhD, and Ryan Mitchell, an MD/PhD student, has recently studied a panel of 33 proteins in the CSF of patients with ALS, and compared the concentrations of these proteins to those found in the CSF of individuals without ALS. We found that 14 were significantly different between the ALS and control groups, with 12 being higher in the ALS group and 2 being higher in the control group. Using the 5 proteins which demonstrated the largest differences between the ALS and control groups, we found that we could identify patients with ALS with 93.5% accuracy. Such findings hold great hope for better diagnosis. The 5 proteins which differed most between our ALS patients and controls also provided some insight into the underlying mechanisms of ALS, because of their effects on microglia, a non-nerve cell within the central nervous system, and on inflammation. Both microglial activation and inflammation are believed to play roles in ALS pathogenesis. We were fortunate to have the opportunity to present this information at the 18th International Symposium on ALS/MND in Toronto in this past December.

Although our biomarker panel was not able to show differences between those patients with limb vs bulbar (speech/swallowing) onset or to show a relationship between biomarkers and duration of disease prior to lumbar puncture, our study was a relatively small, preliminary one of 44 individuals with ALS and 33 individuals without ALS. We now hope to obtain CSF from a larger number of patients to confirm and expand our findings. Eventually, we hope to determine whether these biomarkers change in affected individuals over time. In this way, we hope that our studies of biomarkers, and those of others, will lead not only to an additional, useful tool for diagnosis, but also to better insight into disease mechanisms. Certainly a better understanding of the mechanisms underlying ALS is an important step toward the development of more effective treatments. And, ultimately, that is the goal sought by all physicians and scientists involved in this work.