Which test for multiple sclerosis?

MULTIPLE sclerosis (MS), a chronic neurologic disease affecting at least 250,000 people in the United States, can be difficult to diagnose. Scheinberg et al[1] found that the average length of time from symptom onset to diagnosis was 43 months. A determination may be even more difficult in the presence of atypical clinical features. Approximately 10% of patients who carry a diagnosis of MS have demonstrable alternative diagnoses.[2,3] Such difficulties result from the lack of a sensitive and highly specific test. We rely on clinical criteria supplemented by radiographic, electrical, and chemical laboratory evaluations.

■ *See Goren et al (pp 433–438)*

In this issue of the *Cleveland Clinic Journal of Medicine*, Goren et al[4] focus attention on some of the chemical tests. They present a careful comparison of four formulas commonly used to measure cerebrospinal fluid (CSF) serum immunoglobulin (Ig) G abnormalities (Tourtellotte's formula, Schuller's formula, IgG index, and IgG/albumin ratio). Each quantifies the exaggerated intrathecal humoral immune response that characterizes MS. All of the formulas incorporate the CSF concentrations of IgG and albumin, whereas three of the four also incorporate serum concentrations. They all attempt to demonstrate that the concentration of CSF IgG is selectively increased relative to the reference protein, albumin. Goren's discussion is important because the optimal laboratory method for detecting CSF IgG abnormalities has not been defined. Consequently, CSF IgG testing has not been standardized, even though newer diagnostic criteria incorporate CSF IgG abnormalities as laboratory support of the diagnosis.[5]

Goren reports that: 1. All four formulas distinguished subjects with clinically definite MS from subjects with low back pain but no evident neurologic disease. 2. Tourtellotte's formula was more sensitive than the other three in detecting MS (i.e., a greater proportion of MS patients had abnormal values when Tourtellotte's formula was used). Tourtellotte's formula also gave an abnormal result more frequently in control patients. This test was thus less specific for MS. 3. The authors used receiver operating characteristic curves to compare the four measures and found that Tourtellotte's formula and the IgG index were roughly equivalent and "better" than the other two formulas for distinguishing MS patients from a group consisting of both normals and patients with other neurologic diseases.

What do their results mean? Do the results suggest one of these formulas is "better" than the others? Goren and colleagues are appropriately cautious in their interpretations. Numerous prior investigators have shown that many different CSF IgG parameters distinguish patients with MS from normal subjects. Such a comparison may be useful in the earliest stages of analyzing a particular diagnostic parameter, but is not helpful in determining the value of a given test in clinical practice. A putative diagnostic test analyzed in this manner will appear to be more sensitive and specific than will be the case in the clinical setting, where a sick patient with a particular disease must be distinguished from a similarly sick patient who has a different disease. Thus, more relevant comparisons—as have been made here—are needed to determine the real performance of a test in clinical practice.

It is no surprise that the most sensitive test, Tourtellotte's formula, was the least specific. As the sensitivity of a diagnostic method increases, the specificity usually decreases. This inverse relationship seems to be a property of diagnostic methods. An easily grasped example of this aspect of diagnosis is serologic testing for systemic lupus erythematosus (SLE). Antinuclear antibodies (ANA) are found in a high proportion of SLE patients, but the finding is nonspecific in that a significant proportion of patients with other conditions have detectable antinuclear antibodies. Antibodies to double-stranded DNA, on the other hand, are relatively restricted to SLE patients, but are seen less frequently. In

clinical practice, a highly sensitive test such as the ANA is often used for clinical screening, while the diagnosis is then frequently confirmed with a more specific test.

The "best" CSF test probably depends on the purpose of the test, an issue not considered in Goren et al.[4] For example, a clinician may want evidence for the presence of organic disease in a patient with symptoms but no signs. Consequently, the most sensitive test (in this case, Tourtellotte's formula) is most likely to yield significant diagnostic information. A positive test predicts the presence of organic disease, but the results are not specific for MS. The clinician should be aware that a negative result using a highly sensitive test significantly decreases the probability of the disease in question. In different circumstances, the neurologist may wonder whether a patient has MS when the presence of neurologic disease is clear but other diagnoses such as cerebrovascular disease are possible. In that situation, the more specific test (in this case, Schuller's formula) is more likely to provide the most useful information, since a positive result will increase the clinician's confidence in the diagnosis. Thus, the "best" test depends not only on performance characteristics of the test, but on clinical circumstances. Since all four formulas reported by Goren are calculated using the same four parameters, perhaps they should all be calculated for review by the clinician.

The issue of the "best" CSF test is even less clear and more complicated. Many methods to demonstrate CSF "oligoclonal bands"—electrophoretically restricted cathodal IgG—have been described,[6] but their relative diagnostic value is unclear compared with the quantitative measures considered here. Furthermore, high CSF concentrations of free kappa light chains have been reported in MS patients, and this finding may be much more specific for MS than any of the IgG tests already mentioned.[7]

What is the role of CSF testing in the process of diagnosing MS? Lumbar puncture can be used as an adjunct to the clinical examination, and the finding of CSF IgG abnormalities can be used to support the diagnosis. But does this mean that every patient who may have MS also needs CSF testing? In my opinion, the answer is no. In the absence of a perfect diagnostic marker, testing is useful when there is both a reasonable possibility that the disease is present and also some doubt whether the disease is present.[8] If the disease is in its early stages or is benign, the doubt is likely to derive from a paucity of clinical evidence. In more advanced cases, the doubt is likely to derive from the possibility of an alternative diagnosis.[3] In either case, CSF testing combined with brain imaging and electrodiagnostic studies may provide useful information. When there is little doubt about the diagnosis after careful clinical evaluation, however, little benefit would be derived from continued laboratory testing.

Although Goren does not clearly say which of the four formulas studied was the best, the point is re-emphasized that there is no specific laboratory test for MS—not CSF IgG testing, not magnetic resonance imaging, not evoked potential testing. Each of these evaluations may be useful, but only in the context of a careful neurologic history, record review, and physical examination by a neurologist skilled in the diagnosis of MS.

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