

Diagnosing CFIDS: An Immunologist's Perspective

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Our group in Miami has been actively working to better understand CFIDS since 1985. This work has focused on the immunologic abnormalities seen in the majority of patients, both in a descriptive (How often? How severe? How specific or diffuse in the CFIDS population?) and mechanistic fashion (What causes this problem? Which cytokines help to make the problem persist? What drives the high level of cell activation? How do the various cells interact? What role does re-activation virus play in the vicious cycle?). Some of this work has helped to develop a sense of diagnostic certainty in the evaluation of CFIDS patients, as well as to identify subgroups that are immunologically different from the majority of CFIDS patients evaluated.

The Clinical Diagnosis

First, of course, we attempt a clinical diagnosis, using the CDC criteria to help to eliminate other illnesses that also present with fatigue. The CDC criteria are particularly useful to investigators to define study populations in a uniform way and reduce the risk of comparing "apples to oranges" in the final analysis. For individual patients, the CDC criteria are less useful, as they rigidly eliminate people with any other preexisting health problems. A strict application of the CDC criteria is appropriate for a scientist worrying about purity of data sets, but it is frustrating indeed for CFIDS patients with preexisting and stable illnesses who are being denied disability status based on the CDC criteria. Whether a patient meets the CDC criteria can be established by gathering history and through physical examination. The time spent obtaining a careful history of present illness cannot be overrated and often exceeds the classic one-hour appointment.

Having established a clinical diagnosis based on the CDC criteria (or based on the criteria with the exception of a preexisting stable medical illness), we would go on to a laboratory workup. Part one of that evaluation would be designed to eliminate other possible illnesses. This is done in a cost-effective fashion with a CBC with differential and platelet count, Chem 23, thyroid function screen, ANA and rheumatoid factor, and a sedimentation rate (ESR).

Evaluation of the Immune System

We have found the immune evaluation to be quite important, as it not only helps classify the patient, but often helps to direct the care of the patient. At minimum, such an evaluation must touch on three points:

1: Level of T Cell Activation

While there are many markers of T cell activation, including soluble markers (B2 microglobulin, soluble CD8 receptor, soluble IL2 receptor), the most sensitive in CFIDS is CD3+CD26+ phenotype by flow cytometry, the T cell expressing transferrin receptor.

In "normals," about 18 percent of circulating T cells express this activation marker, while CFIDS patients show double to triple these levels of activation. Other phenotypic markers help to fill out the picture. CD8+DR, or activated cytotoxic T cells, are elevated in the majority of patients with recent exacerbations, but seem to normalize during healthier times. Other phenotype subsets tell the clinician whether there are adequate numbers of certain cell types, or disproportionate numbers of functional subsets.

2: Diminished Cell Function

CFIDS patients have diminished T and B cell function in response to cell activators (mitogens) in culture. The most sensitive is diminished response to Poke-weed mitogen (PWM), which reflects poor T and B cell interaction. Even more remarkable is the very poor ability of NK cells to kill virally infected target cells in culture, a test which is most accurately reported as percent cytotoxicity and is calculated on a "per effector cell" basis. This means the test should tell you the number of killed target cells in a given period of time for every natural killer cell in the assay. People with CFIDS often have very diminished NK cell function, and this function seems to improve during relatively "good" times, and worsen during relatively "bad" times. While we routinely look at both mitogen response and NK cytotoxicity, I believe assessing NK cytotoxicity is more important. We also routinely assess B cell function by looking at immunoglobulin production. Basically, this is accomplished by looking at total immunoglobulins (IgG, IgA, IgM), at IgG Subclasses (IgG, IgG2, IgG3, IgG4) and, if these suggest an immunoglobulin production defect, response to vaccine challenge (with killed, never live vaccines). A clinical history heavy on recurrent bacterial infections of a serious nature more strongly suggests a B cell defect of immunoglobulin production.

3: Evidence of Viral Reactivation

Serology for common reactivation viruses such as EBV, CMV, and HHV-6 adds further evidence that the immune dysfunction now quantified is of a serious enough nature to cause secondary viral reactivation. Serology is difficult to interpret, however, and is confounded by the presence of polyclonal T and B cell activation, which causes "false positive" low-titer positive serology for autoantibodies, VDRLs, etc. When a system is polyclonally activated, it can also falsely "bump" the baseline titers of protective antibodies to old viral infections, and not necessarily reflect actual chronic viremia. The buzz words "viral load" would be ideally suited to CFIDS, as what would be most useful would be accurate knowledge of the amount of active virus infection at any given time -- a focus of the research effort by Dr. Jones' group in Denver and others. While the research goes on, the best information we have is that provided by viral serology testing - - EBV, CMV, and HHV-6 titers, one or more of which show a classic "reactivation" pattern in CFIDS patients.

While the clinical history tends to drive the workup in a particular direction, this "immune approach" reflects the thinking of the Miami group. Some individuals end up with other evaluations, occasionally autoimmune in focus; more frequently, fairly

standard allergy evaluations are ordered. Neurology and cognitive assessments are routine as well.

Assessing cytokine production and levels will begin to play a role as cytokine-specific therapeutic interventions are developed for the treatment of CFIDS.

Gaining A Better Understanding

The Miami group's enthusiasm and excitement are based on the sense that our understanding of the underlying immune defects are finally sharply focused. This clear understanding of the immune disorder is driving new therapeutic approaches. The group is feverishly working to develop protocols specifically designed to reduce T cell activation without harming cell function. Combination approaches to "calm" the system while enhancing cell function will follow.