Editorial

Common Variable Immunodeficiency Disorders (CVID) — Diagnoses of Exclusion, Especially Combined Immune Defects

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Diagnostic criteria for the various heterogeneous conditions that make up common variable immunodeficiency disorders (CVIDs) are important for individual patients' diagnosis, prognosis, and treatment, as well as for immunological research. Patients and their doctors need a precise diagnosis that relates to prognosis and therefore to appropriate treatment. Whereas patients with a combined immune deficiency (CID) might benefit from stem cell transplantation to correct both the T-cell defect and the B-cell deficiency, those with pure antibody failure do well with immunoglobulin replacement alone. Thus the definition of CVID has great clinical importance, although it remains a diagnosis of exclusion, and this has led to the term being used as a reason for replacement therapy rather than purely for diagnostic reasons in some countries.

Several attempts to refine the original 1999 European Society for Immunodeficiencies (ESID)-Pan-American Group for Immunodeficiency (PAGID) definition[1] have been made in the last 15 years, the most recent by the panel of the International Consensus document (ICON) on CVIDs.[2] This supports the previous suggestion, from the French group, to exclude those patients with low numbers of circulating T cells who have a type of CID, namely late onset combined immune deficiency (LOCID). In addition, the ICON recommends that flow cytometry to enumerate T, B, and NK cells is essential to identify those forms of CID that present as antibody failure but should no longer be considered within the CVID group.

The International Union of Immunological Societies (IUIS) Primary Immune Deficiencies (PID) committee emphasize the heterogeneous nature of CVID by ensuring that the newly described single gene defects in primary antibody failure syndromes be named after the gene in which the mutation is disease-causing (such as *ICOS* or *CD19*). They also define CVIDs as plural[3] and include LOCID as a distinct condition separate from CVID in the IUIS PID Classification.[4] This has encouraged the development of data for additional exclusion criteria for a diagnosis of CVID, as by Bertinchamp et al in this issue.[5]

The data in the article by Bertinchamp et al[5] come from the well-recognized and reliable DEFI database. DEFI is a French national study of adults with primary hypogammaglobulinemia. The objective was to compare 3 different CVID definitions (ESID/PAGID 1999, ESID 2014, DEFI 2015) using data from 521 patients with a diagnosis of primary hypogammaglobulinemia. Using the ESID/PAGID 1999 definition, 351 patients were classified as CVID. The 2014 ESID definition excluded 18% of patients, most of them with less severe disease, whereas 10% had a major T-cell defect. Given the French authors' previous publication relating to LOCID, Bertinchamp et al propose that opportunistic infections or very low naïve CD4+ T-cell counts should also exclude patients from a diagnosis of CVID. Using these criteria, 62 patients of the initial CVID population did not meet the new diagnostic criteria. It was notable that these patients accounted for 77% of the deaths within a 5-year period; these patients also represented the 12% with consanguinity. The authors conclude that opportunistic infections or very low naïve CD4 T cells define a separate group and that these patients warrant specific genetic studies in view of their poor prognosis, as well as needing more complex clinical care.

In regard to prognosis, it is now 8 years since the Northern European database showed that the clinical phenotypes of patients with CVID could be divided by disease-related complications and these phenotypes correlated with survival.[6] The divisions, into infection-free or particular disease-related clinical phenotypes, were confirmed with further data from France and the USA.[7] In contrast, attempts so far to define prognosis by B-cell immunophenotyping alone have been disappointing. Hence there is a need to find genetic and other markers, as well as T-cell numbers, that might indicate prognosis.

There have been many genetic studies in patients meeting the original criteria for CVID. However, identification of disease genes for monogenic forms explains only a very small percentage (2%-10%) of patients who turn out to have a disease-causing mutation in a single, nonredundant, gene. Such patients often have a family history and a T-cell defect, though the T-cell deficiency may not be apparent initially. Other findings in patients initially diagnosed as having CVID have included mutations in *TACI, CTLA-4, PIK3CD*, and many others,[8] but these have been reported in healthy individuals too, suggesting that these are susceptibility genes that contribute to but are not solely responsible for primary antibody failure, the common feature of all patients with CVID. Even genetic changes (mutations or variants) in *ARTEMIS*, a gene in which a defect was associated with a monogenic form of severe combined immune deficiency (SCID), have clinical phenotypes that range from SCID to antibody failure.[9]

Researchers need homogeneous groups of patients for laboratory, and especially, genetic studies. Ensuring that combined

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defects are clearly distinguished from primary antibody failures in which T cells are normal influences the choice of appropriate investigation between a candidate gene panel, exome, or even whole genome sequencing. Exome sequencing is profitable for defining those with a CID,[10] and whole genome sequencing has led to the identification of a number of immune pathways that may be defective in patients with sporadic CVID.[11] Other experimental strategies need to be considered for exploring the several pathways that contribute to sporadic CVIDs.

Evidence for polygenicity in sporadic, late onset CVIDs is accumulating. Late onset of disease, lack of a positive family history, phenotypic variation as well as the finding of genetic variants in healthy family members and in the general population add to the suggestion that several and/or many genetic variants will be involved in both the primary antibody failure component and the disease-related complications of CVID.[11] The evidence so far is laid out in 2 excellent reviews.[8,12] The role of susceptibility and modifier genes as well as environmental factors and somatic mutations,[13] in both CVIDs and other forms of immune deficiency syndromes, needs to be explored further in patients with well-defined clinical as well as immunological phenotypes.

The other important point by Bertinchamp et al is that of the remaining 244 patients who met the stricter criteria, only 18 (7%) patients were aged below 15 years at diagnosis. The importance of an appropriate diagnosis in those presenting in childhood cannot be overemphasized. In the study from Philadelphia, of the children diagnosed with CVID, approximately half had disease-related complications as well as lower T cells[14]; the authors commented that "the pediatric CVID population may warrant more aggressive intervention because of their potential for a longer disease duration and higher disease burden." A high proportion, if not most, of this group are likely to represent CIDs rather than sporadic, nonfamililal, antibody failure, known as CVID.

Basing a CVID diagnosis on measuring serum immunoglobulin levels, antibody responses, and flow cytometry is now relatively straightforward, and clinical factors contributing to the clinical phenotype, such as unusual infections or complications, must also be taken into consideration and documented carefully. Given differences in the criteria for diagnostic versus research and database purposes, the article by Bertinchamp et al is instructive. The authors point out the differences between patients with a family history of immune deficiency and sporadic cases, the importance of excluding those with even mild T-cell defects or unexplained opportunistic infections and probably those presenting in childhood.

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