Reviewer's report

Title: Familial autoimmunity

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Reviewer: Noel Rose

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Autoimmune diseases have long been known to aggregate. A patient with one autoimmune disorder appears to have a greater risk of a second or even third autoimmune disease. In addition, in a family in which one case of autoimmune disease is diagnosed, a second or third genetically related member of the family is at somewhat greater risk of the same or even a different autoimmune disorder. The purpose of this review article is to “reintroduce” the term “familial autoimmunity” for this latter form of autoimmune disease aggregation. The article is dedicated mainly to reviewing the large body of published literature describing the co-occurrence of autoimmune diseases within the family. There is also an extensive discussion of “polyautoimmunity” defined as the expression of more than one disease in a single affected individual.

The topic of the article is of great importance in the understanding of autoimmune disease. On the practical side, information about co-occurrence of autoimmune diseases is of great value in determining the risk of additional autoimmune disorders with some specificity and precision in a patient. Similarly, such studies are of great potential value in quantitating the risk of an autoimmune disease in related family members. From an investigative point of view, the information from studies of co-occurrence of autoimmune diseases has already been shown to be of value in identifying genetic traits that are common to several autoimmune disorders, including those that have a relatively modest genetic effect.

Unfortunately, this review as presented does not well serve these purposes. The studies are listed with little or no evaluation. Most of them are too small to be of biologic or statistical significance and often lack controls. In addition, with respect to familial autoimmunity, no distinction is made between genetically based inheritance and common environmental exposures. No attention is given to degree of relatedness as an approximation of genetic concurrence. The data are useful only if related to the prevalence of each disease at a comparable age in the particular geographic area. Since most of the autoimmune diseases are relatively uncommon, large-scale studies in a particular population are necessary. The results are most useful if expressed quantitatively where the risk of a second or third disorder can be determined. With a few notable exceptions (eg., type 1 diabetes and autoimmune thyroid disease), the relative risk of co-morbidity is usually very low. The recent studies by Eaton, et al provide a model of how these investigations can be appropriately carried out.
The present review would be greatly strengthened if the authors go back to the original studies and determined whether they are large enough to draw statistically valid conclusions and whether appropriate control data on the epidemiology of each disease in the geographic area are provided. In assessing family histories, it is essential to consider confounding factors such as the likelihood that patients and families with multiple autoimmune disorders are more likely to receive medical attention and that family histories are likely to be biased if they are based on questioning only probands rather than normal controls.


Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.