Family Studies in Hodgkin’s Disease

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Summary

Surveys of Hodgkin’s disease have indicated an approximately threefold excess risk in first-degree relatives. It is suggested that the familial susceptibility results from a combination of genetic and environmental influences. The experimental identification of causal factors (e.g., oncogenic viruses, immune defects, and genetic markers) may be aided by the investigation of multiple-case families.

In etiological studies of patients with Hodgkin’s disease, the investigation of family members should help to clarify the role of genetic markers, such as HL-A antigens (5), and candidate environmental agents such as the Epstein-Barr virus. Whenever possible, this approach should be applied to the unusually susceptible individuals belonging to families with multiple cases of Hodgkin’s disease.

In a survey of Hodgkin’s disease at Memorial Hospital in New York, Raziz et al. (15) showed that the risk to close relatives was almost 3 times that of the general population. Despite the imprecise methodology of that study, a familial risk of approximately 3-fold is generally accepted for this disease (4, 10). This figure equals the magnitude of familial risk reported for a variety of other cancers (9). In all, about 100 multiple-case families with Hodgkin’s disease have been recorded in the literature; however, the number of well-documented and pathologically verified cases in each family has not exceeded three. Furthermore, the familial cases have not displayed any distinctive clinical or pathological features, although the age distribution has tended to be younger than usual.

It is not yet clear whether the tendency to familial concentration in Hodgkin’s disease is due to environment, heredity, or both. Reviews of familial Hodgkin’s disease have noted a peculiarity that suggests the influence of environment; the times of clinical onset for cases in a family have resembled one another more closely than have the ages at onset (4, 9, 10).

Environmental factors have been implicated also by the development of Hodgkin’s disease in husband and wife, but the 5 instances of concomitant disease reported to date probably do not exceed expectation (1). Indeed, the recent hypothesis that Hodgkin’s disease results from person-to-person transmission of an infectious agent (16, 17) does not seem entirely consistent with the relatively low level of familial aggregation seen in Hodgkin’s disease.

On the other hand, some instances of familial Hodgkin’s disease have suggested the role of genetic factors. We recently reported a familial aggregation of Hodgkin’s disease associated with idiopathic thrombocytopenic purpura and other disorders suggesting immune dysfunction (3). The array suggests a genetically determined disorder of immunological response with various manifestations. Order and Hellman (13) have presented evidence that Hodgkin’s disease results from viral transformation of T-cells (thymus-derived lymphocytes) leading to cell-mediated autoimmunity, T-cell depletion, and neoplasia. With this hypothesis in mind, the constellation of disorders in this family might be attributed to a genetic defect of T-cells. The notion that immune-response genes underlie familial susceptibility is consistent with the increased risk of Hodgkin’s disease in persons with inherited immune deficiency syndromes, particularly ataxia-telangiectasia (6). Subclinical immune deficiency has been reported in apparently normal members of multiple-case families with lymphoproliferative neoplasms other than Hodgkin’s disease (7, 14), so that family aggregates of Hodgkin’s disease should provide an excellent opportunity to study susceptibility mechanisms. A case of childhood Hodgkin’s disease has been reported previously in familial aggregation with subclinical immune defects (12).

In certain families, the tendency to lymphoma may not be limited to a specific cell type. For example, a patient was admitted recently to the NIH for treatment of Waldenstrom’s macroglobulinemia, with a monoclonal spike of IgM in the serum. Lymphosarcoma affected 4 siblings, 1 of whom had a child with Hodgkin’s disease (J. F. Fraumeni, Jr., and W. Wertelecki, unpublished data). Other family members had polyclonal elevations of IgM in the serum, and impaired cell-mediated immunity. Thus, this family seems to have a genetic defect of immunity expressed as various lymphoproliferative disorders, including a subclinical polyclonal gammopathy.

Further evidence of genetic mechanisms is suggested by 2 recent reports of familial Hodgkin’s disease in an inbred population, the Amish. In one family, Hodgkin’s disease developed during childhood in 3 cousins (8). In the other, the disease occurred in 2 brothers in their 20’s; each had HL-A types previously linked with Hodgkin’s disease (11).

If a relationship is demonstrated between familial cases of Hodgkin’s disease and specific HL-A antigens, the genetic basis for familial disease would be supported. Twin studies may be helpful in distinguishing genetic from environmental determinants in cancer, but the observations made so far on Hodgkin’s disease in twins have been too limited (2).

In conclusion, there is some tendency for Hodgkin’s disease to cluster in families, but it has been difficult to
determine whether genetic or environmental factors are primarily responsible. It seems likely that each factor is critically important, and may be delineated by laboratory studies of high-risk families.

References

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*Cancer Res* 1974;34:1164-1165.

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