Age-related Differences in the Trends of Fatal Hodgkin's Disease as a Consequence of Immune Experience

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SUMMARY

It has been proposed by MacMahon, on the basis of the variations among populations in the age distribution of fatal Hodgkin's disease, that there are two etiological factors, one important in young adults and the other important in middle-aged and elderly people. Correa has extended this by suggesting that those who died of the disease as young adults in developed countries would have succumbed to the disease as children under less favorable circumstances.

In England and Wales, the mortality rate from Hodgkin's disease doubled from 1911 to 1970. If there were two etiologies, it seems unlikely that they would remain in step with one another over such a long period, when it was clear that some factor of major etiological importance was changing. Examination of the trends with time of the age-specific rates confirmed the previously reported decline in children and rise in elderly people and revealed a rapid rise in the mortality of young adults of both sexes. These changes were not compatible with any reasonable variations in the diagnosis or classification of Hodgkin's disease.

Our data are compatible with the hypotheses that the etiology of the disease in young adults is different from that in elderly people and that the rise in the mortality of young adults is due to a transfer of deaths from the disease in childhood.

INTRODUCTION

After examination of the incidence and mortality statistics of the age distribution of Hodgkin's disease in different geographical areas, MacMahon and others proposed that there are at least 2 entities of independent etiology within the broad clinical and pathological definition of the disease (4, 17–19). They further proposed that, not only is the disease of multiple etiology, but that it includes infectious granulomatous and neoplastic components. Criticisms have been directed to the question of whether Hodgkin's disease is wholly neoplastic or partly granulomatous (23, 25) but not to the observation of geographical variations in the age distribution. Correa (5–6) and Correa and O'Connor (7) suggested, also largely from geographical data, that environmental circumstances altered the age distribution of the disease, improvement being associated with preven-

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a cohort is convenient for this purpose (15, 26). This statistic \( k_i \) for an age \( i \) between two 5-year age groups, \( i - 5 \) to \( i - 1 \) and \( i + 1 \) to \( i + 4 \), is defined thus:

\[
    k_i = \frac{\log y_i - \log y_{i-5}}{\log x_i - \log x_{i-5}}
\]

where \( y_i \) and \( y_{i-5} \) are the death rates for the 2 age groups, and \( x_i \) and \( x_{i-5} \) are the midpoints of the 2 age groups.

We were interested in the change with time of the age-specific rates and of the age-specific rates of change. To examine this, we fitted straight lines to the age-specific rates and rates of change, plotted against time. The slopes of these lines are plotted against age in the 2 charts.

**RESULTS**

The age-adjusted mortality rate from Hodgkin’s disease for all ages has risen at an average rate of 1.3% per year from 1911 to 1970 in both sexes. The rates and their changes with time are shown for broad age groups in Table 1, and the changes by 5-year age groups are shown in Chart 1. The rates have declined in children and increased in elderly people, as previously reported (17, 20). There is also a marked rising trend in young adults, with a maximum at ages 25 to 29 in females and at 30 to 34 in males.

To examine the effects of historical changes on particular age groups, we plotted the slopes of the lines fitted to the successive age-specific rates of change (Chart 2). The accentuation of the pattern found in Chart 1 indicates that the variations in the age-specific rates are not due to differences between cohorts but to age-specific effects of historical change on the behavior of the cohorts.

**DISCUSSION**

The data used were taken from a homogenous official tabulation (20). The coding system has not materially changed over the years (G. R. Petersen, unpublished Ph.D. thesis, University of Washington). Although they were able to go back only to the 1950’s, Hakama et al. (13) found a high degree of reliability in the diagnosis of Hodgkin’s disease, particularly in the fatal cases. There is no doubt that errors of diagnosis (both under- and over-reporting) occurred, particularly in the earlier periods. But there is no reason to suppose that such errors had the necessary age specificity to account for the observations. Further, the high death rates in children reported in Britain before 1940 appear to correspond with the high rates found today in children in such areas as Uganda (27) and various countries in South America (5).

MacMahon (17) postulated the existence of 3 distinct groups of cases: those in children, those in young adults, and those in older adults (age 50 and above). The difference in time trends reported here for children and young adults supports the distinction between these 2 groups. Further, the increase with time is more rapid beyond the age of 50 than it is between the ages of 35 and 49 (Chart 2). It would thus be possible, although uneconomical, to support from these data the existence of separate factors that changed in such a way as to cause a decline in the incidence of...
Hodgkin’s disease in children, a rapid rise in young adults, a slower rise in middle-aged people, and a rapid rise in elderly people. Examination of the data within cohorts (Chart 2) suggests that the negative rates of change in the 35- to 49-year age range are simply an expression of the return of the rates for the later cohorts to approximately the levels experienced by the earlier ones when they were middle-aged.

A number of investigators have found immunological abnormalities in patients with Hodgkin’s disease (1, 16); these have been found in patients at an early stage of their disease before treatment. As far as we are aware, there has not yet been a prospective demonstration of immunological abnormalities before the development of the disease, but this would be difficult because of the low incidence rate. Grufferman et al. (11) found that Hodgkin’s disease is more common in siblings than was expected, while adults who died of Hodgkin’s disease had a deficiency of childhood infections compared to their peers (21). Kaplan (14) commented that, “our observations suggested that the immunological abnormality might have a primary role in its pathogenesis.” Thus, there is much evidence in addition to that presented here supporting Correa’s hypothesis that children who would have developed the disease under the harsh conditions of the past (8, 24) are now able to persist in a healthy state until they develop it as young adults. This evidence, plus the recent failure to demonstrate contact between patients (22), suggests that epidemiological studies should be directed toward the long-term experience of adults who develop the disease.

Two further features of the data support the hypothesis of a transfer of deaths from childhood to adult life. In both sexes, the mean rate of increase of mortality for the whole age range of 0 to 35 is about 1% per year, similar to the rate of increase at 35 to 54 and 64+ years. Thus, the declining trend at ages 0 to 14 and the increased rise for ages 15 to 34 must be in approximate numerical balance. The declining trend in childhood in males was larger than it was in females (Chart 1), and the rising trend in middle age was also larger in males. This would be expected if proportionately more of the boys at risk were spared in childhood compared to girls and were thus available to develop the disease as adults.

In summary, a reasonable working model of the pathogenesis of Hodgkin’s disease is that a proportion of children (about 2 males to every female) are born with an immune defect. Such patients under preantibiotic conditions are likely to die of infections, and as these are controlled they can go on to develop Hodgkin’s disease, producing its rising rate. This liability to infections accounts for the high risk of tuberculosis in these patients and their high risk of having undergone tonsillectomy. Under poor conditions, children with the defect not only get infections but also develop Hodgkin’s disease; as conditions improve they are spared until the early years of adult life. The disease in elderly people may be associated with nonspecific factors and not with any long-term immune defect.

REFERENCES

Trends of Hodgkin's Disease

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