Etiology of Hodgkin lymphoma (C81) in Central and South America

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The etiology of Hodgkin lymphoma is complex and poorly understood, although comparisons of its age-specific incidence rates, specific incidence patterns by sex, and specific subtypes by socioeconomic status have provided critical clues. This section focuses on infection-related factors, sex, socioeconomic status, and tobacco smoking in relation to the Central and South American region.

Epstein-Barr virus

Epstein-Barr virus (EBV) is a herpes virus that is highly prevalent worldwide and the age at primary infection varies considerably. Exposure to EBV is related to indicators of low socioeconomic status (i.e., overcrowded living conditions and poor sanitation) [1]. In its evaluation of biological agents as human carcinogens, the International Agency for Research on Cancer concluded that there was sufficient evidence that EBV is a definite human carcinogen [1]. Strong mechanistic data support the oncogenic role of EBV in Hodgkin lymphoma and the mechanisms involved in the process include cell proliferation, inhibition of apoptosis, genomic instability, and cell migration [1]. EBV-associated malignancies may result from viral reactivation due to interactions with other co-factors [1]. Patients with Hodgkin lymphoma have been shown to have high levels of antibodies against EBV several years before its development [2], and predictors of strong associations between the pathogen and the disease are: young age (< 15 years) or older age (> 45 years), residence in a developing country, sex (male), nodular sclerosis, and mixed cellular histology [3].

Primary infections with EBV during childhood are usually subclinical but those that occur at later ages (adolescence or early adulthood) can result in infectious mononucleosis (an acute form of primary infection) which occurs in 25–75% of EBV-positive subjects [1]. In developing countries, 80% of children are infected with EBV by the age of 3 years, whereas primary infections in developed countries often occur during adolescence or young adulthood [3].

In a recent meta-analysis of 119 studies conducted worldwide (including 16 studies from Argentina, Brazil, Colombia, Costa Rica, Honduras, Mexico, and Peru), Lee et al. [4] found that the prevalence of EBV in patients with classic Hodgkin lymphoma varied by geographical region, age, sex, and histological subtype. In Central and South America, the prevalence of EBV positivity in classic Hodgkin lymphoma patients was 60.5% (95% confidence interval [CI], 53.8–66.9%) which was much higher than that in North America (31.8%; 95% CI, 25.3–39.1%), Europe (35.5%; 95% CI, 31.8–39.4%), and Asia (55.5%; 95% CI, 51.5–59.5%) but was lower than

that observed in Africa (74.2%; 95% CI, 65.1–81.6%). They also showed that the prevalence of EBV in classical Hodgkin lymphoma was higher in children than in adults (69.7% vs 41.1%, respectively), and was higher in males than in females (summary odds ratio [OR], 1.754; 95% CI, 1.510–2.038 in 50 studies).

In a stratified analysis, Lee et al. [4] reported a striking variation in the prevalence of EBV in classic Hodgkin lymphoma by subtype: 66% in mixed cellularity, 52% in lymphocyte-depleted, 47% in lymphocyte-rich, and 29% in nodular sclerosis cases. They also reported a strong positive association between EBV and mixed cellularity (OR, 3.799) and an inverse association between EBV and nodular sclerosis (OR, 0.313), but null associations between EBV and lymphocyte-depleted and lymphocyte-rich subtypes. The prevalence of EBV was higher in patients with advanced clinical stages of classic Hodgkin lymphoma (OR, 1.212; 95% CI, 1.073–1.369 vs early stage) but was not associated with patient survival. In the studies conducted in Central and South America, EBV was only associated with an increased risk of the mixed cellularity subtype (OR, 4.658; 95% CI, 2.917–7.44 in 15 studies, with evidence of heterogeneity).

In a retrospective analysis, Kanakry et al. [5] showed that pretreatment plasma EBV positivity (measured by quantitative polymerase chain reaction) was an independent predictor for the failure of treatment among patients with classical Hodgkin lymphoma. Plasma EBV-DNA positivity at 6 months was associated with poor outcomes compared with plasma EBV-negative patients. This finding interestingly suggests that EBV could not only be involved in the pathogenesis of HL but could also play a role in the clinical outcome of the disease. EBV-DNA could be considered as a prognostic biomarker if these results were validated in a prospective setting.

Immunosuppression

HIV-1 is a human carcinogen that causes Hodgkin lymphoma via immunosuppression (indirect action) [1]. A meta-analysis of 11 cohort studies conducted in Australia, Europe, and North America showed that the incidence of Hodgkin lymphoma was 11 times higher among those with HIV/AIDS than in HIV-negative individuals (standardized incidence ratio, 11.03; 95% CI, 8.43–14·4 in 7 studies) [6]. Mixed cellularity and lymphocyte-depleted subtypes are prevalent in patients with HIV infection and in developing countries in general [7]. A study in the USA showed that the risk of Hodgkin lymphoma is 7.6-fold (95% CI, 4.1–13.1-fold) greater after the onset of AIDS than before. Indeed, a linear increase in the risk was observed from early pre-AIDS to post-AIDS (P for trend < 0.0001) and 85% of the Hodgkin lymphoma tissue samples (n = 15) were also positive for EBV [8]. However, HIV-related Hodgkin lymphoma represented only a small proportion of the total disease burden [8].

Post-transplantation lymphoproliferative disorders (PTLD) are a group of conditions related to profound immunosuppression following solid organ or haematopoietic transplantation [9, 10]. In a meta-analysis of four cohort studies, solid transplant recipients had nearly 4 times the risk of Hodgkin lymphoma than the general population (standardized incidence ratio, 3.89; 95% CI, 2.42–6.26) [6]. Hodgkin lymphoma is very rare (< 5%) in patients with PTLD but is always related to an EBV infection [9, 10] and is mainly of the mixed cellularity subtype [10]. Patients with mild

autoimmune diseases treated with methotrexate have also been shown occasionally to develop an EBV-positive Hodgkin lymphoma-like lesion [11].

In children with congenital and acquired immunodeficiency, the incidence of Hodgkin lymphoma is high and a population-based study in children (aged < 14 years) with AIDS in the USA revealed that the incidence was 18 per 100 000 (rate ratio [RR], 62; 95% CI, 2–342) 2 years after the diagnosis of AIDS [12]. In a matched case–control study among children aged 0–14 years, the Children´s Oncology Group indicated that cases of Hodgkin lymphoma were 1.7 (95% CI, 0.98–2.91) times more likely to report having an EBV infection less than 1 year before diagnosis than controls; case siblings reported having a prior infection more frequently than controls (OR, 2.04; 95% CI, 1.01–4.14) [13].

Tobacco smoking

The possible association between tobacco smoking and the risk of Hodgkin lymphoma remains controversial [14]. In a pooled analysis of 12 case–control studies, the International Lymphoma Epidemiology Consortium found that ever-smokers had a 10% (95% CI, 1–21%) higher risk of Hodgkin lymphoma than never-smokers; the risk of current smokers was higher for mixed cellularity (OR, 1.60; 95% CI, 1.29–1.99) and EBV-positive classic Hodgkin lymphoma (OR, 1.81; 95% CI, 1.27–2.56) than that of never-smokers while smoking was not associated with the risk of nodular sclerosis or EVB-negative Hodgkin lymphoma. The International Consortium concluded that, even if smoking was not associated with all subtypes, cigarette smoking should be categorized as a modifiable risk factor for Hodgkin lymphoma [15]. Sergentanis et al. [16] made similar observations regarding smoking and the risk of Hodgkin lymphoma in a meta-analysis of 21 studies; ever-smokers and current smokers had higher risks than never-smokers (RR, 1.15; 955 CI, 1.02–1.30 for ever-smokers; RR, 1.33; 95% CI, 1.12–1.57 for current smokers) and such associations were stronger in men (RR, 1.38 for current smokers; RR, 1.66 for ever-smokers). Associations between smoking and Hodgkin lymphoma were stronger with an increased duration of smoking (per 10 years), number of cigarettes per day (per 10 cigarettes), and number of pack–years of smoking (per 10 pack–years), although no associations were found for former smokers or the number of years since quitting smoking (increments per 10 years).

Other factors

Ethnic differences in rates of Hodgkin lymphoma have been reported in the USA [17]. Evens et al. [18] showed that the incidence of Hodgkin lymphoma during 1992–2007 among whites and Asian/Pacific islanders followed a bimodal age distribution but blacks had a less clear bimodal pattern. In Hispanics, the incidence reached a peak at the age of 20–29 years, after which the rates increased exponentially until reaching the highest level at the age of 70–79 years and were higher among Hispanics (7.0 per 100 000) than in whites (4.5 per 100 000) at an age of more than 65 years. US-born Hispanics and Asian/Pacific islanders had a significantly higher incidence of Hodgkin lymphoma in the subgroup aged 20–39 years than their foreign-born counterparts, but the rates became similar after the age of 40 years. Survival rates also varied by ethnicity; blacks and Hispanics had lower survival rates than whites and Asian/Pacific islanders after adjusting for socioeconomic factors.

These results suggest that a combination of genetic, lifestyle, and environmental factors may explain the variation in Hodgkin lymphoma observed across the world. A growing body of evidence from case–control, twin and familial aggregation, and population-based registry studies suggests that a family history of Hodgkin lymphoma may play a role in the development of this disease; however, whether or how extrinsic risk factors interact with genetic susceptibility remains unknown [19–23].

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