Epidemiology of Childhood Hodgkin’s Disease: Is it Different in Developing Countries?

Veronique Dinand  
Laxman S. Arya

Childhood Hodgkin’s Disease (HD) is a lymphoma that displays characteristic epidemiological, clinical and pathological features according to various geographic areas, particularly according to the socio-economic level of a given country. India presents a similar sex, age and subtype distribution as other emerging countries: high male-to-female ratio, younger age at presentation, high proportion of advanced stages and presence of constitutional symptoms, predominance of mixed cellularity type of HD. The etiology of HD is still the subject of controversy and investigation, but it may occur as a sequel of a viral infection during early childhood, such as Epstein-Barr virus (EBV). Most cases of Indian childhood HD are associated to EBV, while genetic predisposition is seen in very rare cases.

Key words: Epidemiology, Epstein-Barr virus, Hodgkin’s disease,

Introduction

In 1990, countries with limited resources accounted for 86% of the world’s children (<15 years), a figure projected to increase to more than 90% by 2030(1). These countries bear most of the global burden of childhood cancer(2). First recognised by Thomas Hodgkin(3) in 1832, the etiology of HD is still subject to numerous speculations. Epidemiological findings suggest that it might have a different etiology in different age groups.

Definition

HD is a lymphoreticular malignancy characterised by a progressive painless enlargement of lymph nodes and defined by specific histopathological features. These include a partial or total replacement of nodal architecture by an inflammatory cellular background containing Reed-Sternberg (RS) cells or their variants. Characteristic RS cells are binucleate or multinucleate giant cells, with prominent nucleoli and abundant cytoplasm. The Rye morphologic classification has been modified with the addition of immunological markers in the World Health Organisation (WHO) classification(3).

Clinical presentation

Probably originating in a single lymph node, HD spreads by extension to contiguous nodes. The most common presentation of HD in children is a painless cervical lymphadenopathy, usually unilateral. Primary disease in a subdiaphragmatic site occurs in only about 3% of cases. Ann-Arbor staging classification(4) distinguishes four stages according to the extension of the disease at the moment of diagnosis. In western countries, 75% of newly diagnosed patients have early disease at presentation (stage I-II)(5-7). In less economically developed countries, however, more than half of the patients have advanced disease (stage III-IV)(8-11), perhaps because of delayed diagnosis and referral.
Constitutional “B” symptoms (unexplained fever, night sweats and weight loss) occur in 25-30% of cases reported in Western literature. Reports from developing countries show a greater incidence of B symptoms, in about 50% of cases.

**Incidence and age distribution**

With an annual incidence of about 0.5 cases per 100,000 children in the U.S. and in the European Union (EU)(12), HD accounts for 5 to 6% of childhood cancers and is the sixth most frequent childhood malignancy, after leukemias, brain tumors, neuroblastomas, nephroblastomas and rhabdomyosarcomas. Incidence of childhood HD is maximal in Latin-American countries, between 1 and 1.5 per 100,000 children(13). In developing countries, lymphomas are relatively common and HD is the fourth more common malignancy, after leukemias, brain tumors and non-Hodgkin’s lymphomas (NHL)(13). Age standardised incidence rate of HD in Indian children (both sexes) was reported 0.42 per 100,000 (Mumbai), equal to the incidence of NHL, HD being the fourth more common after acute lymphoblastic leukemia, brain cancer and retinoblastoma(14).

HD presents a bimodal distribution with regard to age, with a rise in incidence in young adults (20-34 years) and in the elderly (55-74 years)(15). In contrast, in developing countries the first peak occurs in children and teenagers; there is an inverse relationship between the incidence of the HD in children and young adults within countries according to their economic development(16). Such patterns of occurrence being similar to Epstein-Barr virus (EBV), tuberculosis and poliomyelitis infections, the role of an environmental exposure was suggested as a possible etiology of HD.

Reports from various countries with limited resources show that childhood HD occurs at a younger age than in western countries: as many as 20 to 30 % of childhood HD cases in developing countries occur before 5 years of age(10,17) against some 5% in industrialised countries (Table I).

**TABLE I—Sex, Age, Stage and Subtype Distribution of Childhood Hodgkin’s Disease in Various Countries.**

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>N</th>
<th>M:F</th>
<th>Mean age (Range)</th>
<th>&lt;5 yrs (%)</th>
<th>III-IV (%)</th>
<th>MC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hunger, et al.</td>
<td>USA (Stanford)</td>
<td>57</td>
<td>1.7:1</td>
<td>12 (4-17)</td>
<td>5</td>
<td>60</td>
<td>17</td>
</tr>
<tr>
<td>Shanker, et al.</td>
<td>UK</td>
<td>331</td>
<td>2.5:1</td>
<td>n.a.(2-15)</td>
<td>–</td>
<td>32.3</td>
<td>22</td>
</tr>
<tr>
<td>Schellong, et al.</td>
<td>Germany/ Austria</td>
<td>578</td>
<td>1.2:1</td>
<td>Median 13 (2.7-17.9)</td>
<td>5.5</td>
<td>31</td>
<td>24.2</td>
</tr>
<tr>
<td>Olweny, et al.</td>
<td>Uganda</td>
<td>48</td>
<td>2.4:1</td>
<td>–</td>
<td>–</td>
<td>77.1</td>
<td>41.7</td>
</tr>
<tr>
<td>Baez, et al.</td>
<td>Nicaragua</td>
<td>48</td>
<td>–</td>
<td>7.9 (3-15)</td>
<td>–</td>
<td>58.3</td>
<td>52.1</td>
</tr>
<tr>
<td>Kapoor G., et al.</td>
<td>India (Bombay)</td>
<td>147</td>
<td>6:1</td>
<td>–</td>
<td>–</td>
<td>37</td>
<td>65</td>
</tr>
<tr>
<td>Sackmann, et al.</td>
<td>Argentina</td>
<td>114</td>
<td>1.7:1</td>
<td>9 (2-17)</td>
<td>20.2</td>
<td>–</td>
<td>51.7</td>
</tr>
<tr>
<td>Çavdar, et al.</td>
<td>Turkey</td>
<td>175</td>
<td>3.1:1</td>
<td>7.8 (2.5-15)</td>
<td>29.7</td>
<td>65.3</td>
<td>60.6</td>
</tr>
<tr>
<td>Arya, et al.</td>
<td>India (Delhi)</td>
<td>218</td>
<td>9.6:1</td>
<td>Median 8 (2.7-14)</td>
<td>14.9</td>
<td>45.3</td>
<td>86.0</td>
</tr>
</tbody>
</table>

Abbreviations: N: number of cases. M:F male to female ratio. MC: mixed cellularity subtype.
Sex distribution

Pediatric HD presents a slight male predominance in Western countries (M:F ratio close to 1.5:1). However, there is a large male excess in less economically developed countries, with a M:F ratio between 2.5:1 and 5:1. These countries have a higher proportion of cases occurring under the age of 10 years, and male predominance is universally higher in that age group, with a M:F ratio of approximately 4:1.

India presents a significant male predominance in HD that much higher than in any other types of childhood cancers. For instance, a seven-year study of 617 cases of childhood cancers registered in Bangalore showed a M:F ratio of 1.8:1, whereas the 54 cases of childhood HD had a M:F ratio of 7.8:1(18). Likewise, the analysis of childhood cancers registered in All India Institute of Medical Sciences during a 5-year period showed a M:F ratio of 7.4:1 in HD, against M:F ratios in other cancers between 2:1 (neuroblastoma and retinoblastoma) and 4.0:1 (acute myeloid leukemia) (unpublished data). Similarly, childhood HD in Mumbai presents a M:F ratio of 6:1(19). The sex distribution discrepancy in HD between countries is not yet fully understood. It could be partly explained by the association existing between decreasing national economic status and increasing sex ratio in childhood cancers(20). In the case of India, it could also be due to poor health care access for females, reflecting the cultural disinterest in the female child. However, this hypothesis fails to explain why HD presents a much higher male predominance than any Indian childhood cancers.

Etiology of HD

Viral infection

In the west, features indicating high standard of living in early childhood are significant risk factors associated with the development of HD in young adulthood: single family housing, small family size and a high level of maternal education(21). HD in this age group might arise as a result of delayed exposure to a common infectious agent. Young adults (16-24 years) with a prior history of infectious mononucleosis have an increased risk of HD, whereas early exposure to chicken pox, measles, mumps, pertussis and rubella plays a protective role, possibly because it stimulates immunity(22). HD could be caused by a genetically determined abnormal immune response to a childhood infection. This hypothesis is supported by the increased incidence of HD among patients with immune deficiency states, such as ataxia-telangiectasia(23) or HIV infection(24). Host factors may also explain the male excess in childhood HD, via a different response to that infectious agent.

Attention was drawn on several lymphotropic viruses, particularly EBV, because of its clearly established association with malignant and non-malignant lymphoid proliferations. EBV’s association with HD was shown by various epidemiological(25), serological(26) and pathological studies(27, 28). In industrialised countries, EBV-associated HD represents 30 to 40% of all ages HD, while the proportion is significantly higher (70% to 100%) in patients with lower socio-economic status and in developing countries from Latin-America, Africa and Asia. China, Taiwan, Hong Kong and Japan have an intermediary association (60 to 65%). In India, EBV was found in 78% of all ages HD cases, and in 91 to 98% of children(29, 30). EBV-associated HD is more frequent in children below 10 years of age, in males, in less-developed regions and in mixed cellularity (MC) subtype(31). However, geographic variation of EBV-associated HD could be due to the higher proportion of
patients less than 10 years at diagnosis in series from developing countries (32).

Primary EBV infection occurs within a few months to years after birth in developing countries and only during the second and third decade of life in industrialised countries. Early exposure to EBV infection may play an etiological role in the pathogenesis of HD, especially in less economically developed countries where EBV seroconversion is almost universal by the age of 4 years. The detection of EBV genome in tumor tissues does not necessarily imply EBV’s direct involvement in the pathogenesis of HD, though the presence of EBV in a monoclonal episomal form (27) indicates that EBV infection precedes the expansion of the neoplastic clone, thus strengthening its causal role. However, the presence of EBV-negative HD cases suggests other possible pathogenic etiologies.

Armstrong et al have built a three-disease model for HD, on the basis of age at diagnosis and EBV status (33). The first entity is largely a disease of childhood, EBV-associated disease, with higher incidence in developing countries and usually of MC subtype. Development of HD is probably associated with early exposure to EBV infection, which occurs at a particularly young age in less economically developed countries. The second entity, predominantly affecting older adults, is also EBV associated, usually of MC subtype, and likely to be related to EBV reactivation events. The third entity predominantly affects young adults. It is more prevalent in developed countries, usually of nodular sclerosis (NS) subtype, and not EBV-associated. Since this age group has the maximum epidemiological evidence for an infectious etiology, it may be associated with the delayed exposure to another infectious agent.

Other lymphotropic herpesviruses have been studied, such as cytomegalovirus, human herpes virus 6 (HHV-6), HHV-7, HHV-8 (34-36). Molecular studies showed no evidence for their presence within H-RS cells. However, HHV-6 antibody titres are elevated in HD (37). TT virus has recently been found in more than 30% of nodular sclerosis HL tumor cells, often with co-infection with EBV (38).

Familial HD

Rare cases of familial HD have been reported. Most cases concern adults, and less than 7% of familial cases are seen in children (39). Familial HD might be caused by environmental factors, but EBV serological and in situ hybridisation studies suggest that EBV does not play an important role in familial HD (40). However, some cases may be due to a genetic predisposition to HD, with a possible recessive mode of inheritance (41). Both HLA-linked and HLA-unlinked factors are responsible for familial HD, and only a subset of cases is determined by specific HLA antigens: HLA-A1, B5, B8, B18 and W35 (41). Immunodeficiency might play an etiological role in very rare cases of familial HD, as suggested by the report of decreased induced lymphocyte DNA synthesis and decreased CD4+/CD8+ ratio in HD cases and family members of patients with HD (42).

There is a threefold to sevenfold increased risk of HD for the siblings of young adults with HD, and siblings of the same sex as the affected person have a risk double than that of siblings of the opposite sex (43). The risk for identical twins of HD patients to develop HD themselves is 99-fold (44). A long time interval between cases in the same family is very uncommon. There is an increased concordance of histological subtypes between affected relatives (41). Genetic susceptibility might be involved in the male predominance, which is particularly marked before 10 years of age, but
no study has suggested this hypothesis so far.

Our team reported the first case of familial HD in Indian children(45). Two siblings aged 14 and 7 years presented on the same day with a history of cervical lymphadenopathy for 4 years and 12 months respectively and were diagnosed as MC-HD. Both tumors showed positive immunohistochemical staining for EBV latent membrane protein-1.

Conclusion

Epidemiological features of childhood HD vary greatly among countries with different socio-economic level. Both the development of HD at a younger age and the male predominance in underprivileged populations could be at least partly explained by the hypothesis of an etiologic role of EBV in the genesis of HD, as there is an increased male susceptibility to viral and bacterial infection in childhood, which is more marked in the first five years of life. In India, as in other developing countries where EBV primary infection occurs at an early age, EBV genome is almost universally found in HD tumor cells. Low socio-economic status may generate malnutrition, which could lead to impaired immunity after initial exposure, and so to EBV-associated HD.

Genetic predisposition to HD rarely occurs, and etiological factors other than EBV are responsible for the development of EBV-negative tumors. Much is still to be proven in order to understand the various mechanisms leading to HD. The current challenge in childhood HD remains to improve patients’ survival at the cost of minimal late complications.

REFERENCES


