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Epidemiology of Hodgkin's Lymphoma

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1. Introduction

Hodgkin's lymphoma (HL), formerly called Hodgkin's disease, is a malignant tumor of the lymphatic system (Schnitzer, 2009). It was first recorded by Thomas Hodgkin in 1832, when he described seven patients suffering from enlargement of lymph nodes and spleen as a new disease entity (Thomas et al, 2002).

Understanding of its pathogenesis remains unclear (Mueller, 1991). The cellular origin of this lymphoma was failed to be clearly identified by molecular biology studies. The characteristic Reed Sternberg cell is thought to be derived from the histiocytes, granulocytes and reticulum cells (Lee et al, 1993). But other studies suggest that these cells represent immature lymphoid cells (Diehl et al, 1990).

Hodgkin's lymphoma was described microscopically for the first time by Langhans in 1872 (Langhans, 1872). Jackson and Parker (1947) described the first histological classification of Hodgkin's lymphoma in 1947, later on this classification was revised at Rye in 1966 and in 1994 the Rye classification was incorporated into the revised European-American lymphoma classification (REAL). Accordingly, Hodgkin's lymphoma was classified into nodular lymphocyte predominant, nodular sclerosing, mixed cellularity, lymphocyte depletion and lymphocyte - rich classical disease (Cartwright and Watkins, 2004).

2. Incidence

The incidence of Hodgkin's lymphoma shows marked heterogeneity with respect to age, gender, race, geographic area, social class and histological subtype (Burke, 1992). Hodgkin's lymphoma is listed as a rare disease by the office of rare diseases (ORD) of the National Institutes of Health (NIH). This means that it affects less than 200,000 people in the US population. About 8000 new cases of Hodgkin's lymphoma occur each year in the United States. 1500 people in the US die from Hodgkin's lymphoma each year. It is more common in Caucasians (Lee et al, 1993). Asians have lower incidence than other races (Glaser and Hsu, 2002). The annual incidence of Hodgkin's lymphoma appears stable over the past several decades. Incidence in the United Kingdom is about 2.4 per 100,000 per year. Worldwide prevalence rates vary, with more than 5.5 per 100,000 in Yemen and Lebanon and less than 1 per 100,000 in China and Japan. At least some of this variation appears to relate to the degree of industrialization (Hoffbrand et al, 2011).

3. Age

The incidence of Hodgkin's lymphoma has increased among adolescents and young adults in the Nordic countries in the past few decades, whereas it has decreased strikingly among those aged 40 years or more (Hjalgrim et al, 2001). In developing countries, Hodgkin's lymphoma appears more during childhood and its incidence decreases with age, while in developed countries, young children are rarely affected by Hodgkin's lymphoma in contrast with young adults where incidence increase with age (Thomas et al, 2002). It has a bimodal age distribution in both sexes, peaking in young adults (aged 15-34 y) and older individuals (>55years) (IARC, 1997). In the United States, Nodular sclerosing subtype predominates in young adults, while Mixed cellularity subtype is more common in children (aged 0-14 y) and older individuals (Grufferman and Delzell, 1984; IARC, 1997 & Muller and Grufferman, 1999). From 2004-2008, the median age at diagnosis for Hodgkin's lymphoma was 38 years of age and approximately 12.3% were diagnosed under age 20 years and 27.7% above 55 years of age.

There are two peaks in the age-specific incidence of Hodgkin's lymphoma. For males there is one in men aged 30-34 and another in older men aged 75-79 years. For women the two peaks occur in women aged 20-24 and 70-79 (Yung and Linch, 2003).

Hodgkin's lymphoma is the third most common cancer in people aged 15-29 years, and the sixth most commonly diagnosed cancer in children under 14 years (Yung and Linch, 2003 & Hoffbrand et al, 2011).

The bimodal incidence curve has been postulated to represent two etiology processes. The first hypothesis suggests an infectious cause of the disease in young adults and other environmental causes for older age groups (Cole et al, 1968).

Low childhood rates and high young adulthood rates were found in the USA and West Europe. The Baltic States and central and Eastern European countries had higher childhood rates than those seen in the United States and Europe, but had similar rates in young adults. The pattern in Latin America and other developed countries is more, whilst the rates in Asia remain low (Cartwright and Watkins, 2004).

A significant increase in the incidence of Hodgkin's lymphoma in adolescents and young adults was observed in Nordic countries (Langhans, 1872), India (Reed, 1902) and North America in the period between 1960 and 1997 (Cartwright and Watkins, 2004). Also, decrease rates has been reported in older adults.

Hodgkin's lymphoma is most common in children and young adults, between the ages of 15 and 40.

The mortality rates are low (0.4 per 100000 per year in the United Kingdom) due to the excellent response to treatment. Mortality increases with age and in Countries with less access to treatment (Hoffbrand et al, 2011).

4. Male : Female ratio

Overall male to female ratio is 1.4:1 (Hoffbrand et al, 2011). It is the third most commonly diagnosed cancer in people aged 15-29 years. There is a slight overall male predominance in the incidence of Hodgkin's lymphoma, which is most marked in the childhood form (Spitz et

al, 1989). In adolescents, the incidence between males and females are roughly equal. Data from Norway showed that a sex ratio of 1:1 is seen in the 15-34 age group which increase to 2:1 in the 50 and over group (MacMahon, 1966). Hodgkin's lymphoma is nearly twice as common in males. It is higher in males than females and higher in whites than other races (Shenoy et al, 2011). Men are affected by Hodgkin's lymphoma slightly more than women among all subtypes except for the nodular sclerosing subtype (Thomas et al, 2002). The observed male predominance is particularly evident in children, in whom 85% of the cases are in males.

5. Season

May studies have revealed peaks in the early months of the years especially in February and March (Douglas, 1998; Neilly et al, 1995; & Newell et al, 1985).

6. Race

Both Blacks and Asians had lower incidence rates than whites, which may suggest genetic resistance possibly related to HLA type. Hodgkin's lymphoma is relatively rare in Japan (age-adjusted incidence of 0.3 per 100.000 males) and China (age-adjusted incidence of 0.2 per 100.000 males) in comparison to North America and Europe. Within the European Union the highest rates are in Austria and Greece and the lowest rates are in Spain and Slovakia, (Glaser and Hsu, 2002 & Shenoy et al, 2011).

7. Relation to infections

Hodgkin's lymphoma is a complex of related conditions that are part mediated by infectious diseases, immune deficits and genetic susceptibilities. The descriptive epidemiology of Hodgkin's lymphoma suggests an infectious disease process underlying its aetiology in children and young adults (MacMahon, 1966). There is a relationship between Hodgkin's lymphoma and Epstein-Barr virus (EBV) infection (Evans and Gutensohn, 1984; Mueller et al, 1989 & Swerdlow, 2003). The mechanisms underlying this association are unknown and the virus has never been isolated from or identified in most of Hodgkin's lymphoma tissue (Cartwright and Watkins, 2004 & Gruffeman and Delzell, 1984).

Patients with a history of infectious mononucleosis due to Epstein-Barr virus may have an increased risk of Hodgkin's lymphoma (Alexander et al, 2000; Hjalgrim et al, 2000 & Mueller and Grufferman, 1999).

EBV is the main candidate suggested as the infection causing Hodgkin's lymphoma for several years. However EBV genome has been found only within the tumor in about 20-40% of Hodgkin's lymphoma cases with a prior diagnosis of infectious mononucleosis (Landgren and Caporaso 2007). Several studies suggest that EBV may be a transforming agent in Hodgkin's lymphoma. Patients with a history of EBV infection are at a 2-3 fold higher risk for development of Hodgkin's lymphoma (Thomas et al, 2002). Mueller et al. (1989) analyzed EBV titers in pre-disease sera and found an enhanced level of EBV activation prior to onset of Hodgkin's lymphoma.

Many authors using novel molecular techniques found that EBV DNA is present in Hodgkin's lymphoma cases more frequently in developing countries than in developed countries (Glaser et al, 1997 & Zarate et al, 1995). In Western countries, about 50% of classical Hodgkin's lymphoma are EBV-positive (Brousset et al, 1991).

Reed-Sternberg cells in EBV positive patients show an expression pattern of EBV-encoded genes, termed type 2 latency, which resembles that found in endemic nasopharyngeal carcinoma or a subset of T-cell lymphomas (Thomas et al, 2002). Activated NFκB was found to be a characteristic feature of Reed-Sternberg cells (Bargou et al, 1996). This activation results in massive spontaneous apoptosis of Reed-Sternberg cells by downregulation of an antiapoptotic signaling network (Hinz et al, 2001). Many reports have noted geographic and familial clustering of Hodgkin's lymphoma (Smith et al, 1977; Vianna et al, 1971 & Vianna and Polan, 1973). Swedish investigators suggested that early exposure to viral infection may play a role in the pathogenesis of the disease (Chang et al, 2004).

EBV strain subtypes identified within Reed-Sternberg cells vary geographically. EBV type 1 is predominant in the United Kingdom, South America, Australia and Greece, whereas EBV type 2 is predominant in Egypt (Wrinreb et al, 1996). Mixed cellularity Hodgkin's lymphoma is more likely to be EBV-associated than nodular sclerosis subtype.

Many studies have found significant increase in risk of Hodgkin's lymphoma among patients with AIDS in the developed countries (Grulich et al, 1999 & Serraino et al, 2000). In contrast, these increased risk have not been observed in Africa (Chokunonga et al, 1999; Dolcetti et al, 2001 & Iazzi et al, 1998). In addition, other studies have demonstrated an increased incidence in HIV-positive intravenous drug users (Andrieu et al, 1993; Roithmann et al, 1990 & Rubio, 1994).

Also, Human Herpes virus 6 (HHV-6), HHV-7, HHV-8 and cytomegalovirus infections were demonstrated in Hodgkin's lymphoma patients (Gompels et al, 1993; Josephs et al, 1988 & Salahuddin et al, 1986).

Patients with HIV infection have a 15- fold increase risk to develop Hodgkin's lymphoma than the general population (Biggar et al, 2006). They usually present at a more advanced age with associated extranodal involvement and B symptoms (Glaser et al, 2003).

8. Socio-economic status

The childhood form of Hodgkin's lymphoma tends to increase with increasing family size and decreasing socio-economic status. The young adult form is associated with a higher socioeconomic status in industrialized countries. The risk decreases significantly with increased sibship size and birth order (Westergard et al, 1997). It has been suggested that the risk of Hodgkin's lymphoma may be correlated to higher social classes in children and young adults (Alexander et al, 1991a & Alexander et al, 1991b). Reports regarding the socio-economic status in older adults are conflicting (DeLong et al, 1984; Glaser et al, 2001 & Gutensohn, 1982).

9. Occupational exposures

It is not possible to conclude that a causal relationship exists between the various occupational exposures and risk of Hodgkin's lymphoma. Although one study reported that the physicians had a risk 80% higher than that of controls (Vianna et al, 1974), yet other studies did not found this increased risk (Grufferman et al, 1976; Matanoski et al, 1975 & Smith et al, 1974). Some studies reported an increased risk of Hodgkin's lymphoma in white men employed in woodworking or wood-related industries (Fonte et al, 1982; Milham and Hesser, 1967; Olsen and Sabroe, 1979 & Petersen and Milham, 1974). Conflicting results were

reported regarding the association between Hodgkin's lymphoma and benzene exposure, rubber and chemical industries (La Vecchia et al, 1989; Lagorio et al, 1994; Rushton and Alderson, 1983; Schnatter et al, 1993; Sorahan et al, 1989 & Vianna and Polan, 1979).

Smoking more than 14 cigarettes per day was associated with a 50% increased risk (Adami et al, 1998 & Paffenbarger et al, 1977).

10. Familial incidence and genetic susceptibility

There is 3 to 9 fold increased risk of developing Hodgkin's lymphoma in family members of these patients (Haim et al, 1982 & Mack et al, 1995). Razis et al. (1959) were the first to report a three fold risk in first-degree relatives of patients with Hodgkin's lymphoma.

Swedish Cancer registry reported that Hodgkin's lymphoma was the fourth in a list of cancers with high familial incidence (Lindeiof and Eklund, 2001). Many oncogenes and tumor-suppressor genes have been studied, but no consistent mutation pattern has been identified (Thomas et al, 2002). Translocation [t (2;14) (P13;q32.3)] involving the BcL 11 a gene was reported in classic Hodgkin's lymphoma (Martin-Subero et al, 2002).

Numerical and structural chromosomal alterations are frequent in Hodgkin's lymphoma patients but they lack any consistent pattern (Thomas et al, 2002). However, molecular clonal alterations such as gene amplifications or deletions reflect a distinct pattern of genetic instability.

Aggregation in families and persons with specific human leukocyte antigen (HLA) type indicates genetic susceptibility (Burke, 1992 & Maggioncalda et al, 2011). Several reports recorded aggregation and clustering of Hodgkin's lymphoma patients in the same families and races which may suggest a genetic predisposition or exposure to a certain etiologic agent.

The Antigens were found to be associated with Hodgkin's lymphoma: A1, B5 and B18 which might indicate that a disease susceptibility gene lies in or near the major histocompatibility region. These associations suggest that this disease is a result of genetic environmental interaction (Bodmer, 1973; Chakravarti et al, 1986; Robertson et al, 1987 & Svejgaard et al, 1975). Also, concordance of Hodgkin's lymphoma in first degree relatives and in parent-child pairs has been noted in many studies (Claser and Jarren, 1996) especially if they are of the same sex.

Familial Hodgkin's lymphoma lacked the classic bimodal age distribution and has a peak between 15 and 34 years. It represents about 4.5% of all new cases (Kerzin-Storarr et al, 1983).

Evidence of genetic susceptibility of this disease was supported by the finding that monozygotic twins have a 99-fold increased risk in contrast to dizygotic twins who have no increased risk to it (Mack et al, 1995). We found significant increase in the frequency of HLA DRB1*0403 and *1202 and DQ131*0604, *0201 and *0203 alleles which may confer susceptibility (Al-Tonbary et al, 2004). Similar results were reported by Klitz et al. (1994) who reported a significant association of HLA class II alleles with Hodgkin's lymphoma and Harty et al. (2002) who reported that the DRB1*1501 allele is related to the development of familial Hodgkin's lymphoma particularly the familial nodular sclerosis type. The association of Hodgkin's lymphoma with different HLA-DRB1 and -DRQ1 alleles may be explained by three possibilities, first one implies that genes determining Hodgkin's lymphoma are located close to the major histocompatibility loci, and are thus transmitted along with whatever HLA haplotypes in the family (Hafez et al, 1985). Second one is the

cross-tolerance to a self-component (Woda and Rappaport, 1981). The third possibility is that the immunogenic responsiveness to oncogenic viruses may be linked to genes coding for HLA antigens (Zimadahl et al, 1999). In conclusion, certain environmental factors in addition to HLA genotypes might play a role in the occurrence of Hodgkin's lymphoma indicating a genetic-environmental interaction.

		Age group of Hodgkin's Lymphoma							
Ethnic origin	Country	0-14 years		15-34 years		35-59 years		Above 60 years	
		M	F	M	F	M	F	M	F
European	Belarus	1.46	0.64	4.38	4.15	3.24	2.19	5.72	2.64
	Croatia	0.92	0.25	1.49	2.37	2.04	1.24	3.74	1.68
	Czech	0.94	0.52	3.83	4.26	3.40	1.92	5.92	3.79
	Denmark	0.53	0.21	4.00	2.88	3.58	1.40	4.43	2.41
	East Germany	0.56	0.51	3.59	3.58	2.67	1.58	5.24	3.15
	England and Wales	0.51	0.31	3.80	3.24	3.00	1.64	3.64	2.10
	Finland	0.43	0.50	3.11	2.73	2.96	1.73	4.42	2.56
	Netherlands	0.56	0.30	3.54	3.06	2.74	1.43	3.77	2.21
	Scotland	0.52	0.58	3.84	3.19	2.94	1.68	3.99	2.58
	Slovakia	0.89	0.71	2.58	2.95	2.58	1.53	4.29	1.76
North American/ Hispanic/ Australian	Australia-NSW	0.84	0.24	2.81	2.39	2.39	1.12	3.34	2.90
	Canada	0.69	0.47	4.24	4.38	3.35	1.89	3.95	2.71
	LA-Hispanic Whites	0.70	0.60	1.74	1.69	2.68	1.20	5.96	3.89
	LA-non-Hispanic Whites	0.42	0.15	5.17	4.88	4.10	2.34	4.15	2.91
	SEER-Whites	0.70	0.50	5.29	5.39	3.71	2.16	4.57	2.77
Asian	India - Bombay	0.82	0.19	0.76	0.39	1.51	0.94	3.48	1.96
	Hong Kong	0.42	0.03	0.47	0.39	0.67	0.24	1.77	0.62
	Japan-Osaka	0.09	0.10	0.27	0.35	0.52	0.17	2.25	0.61
	LA-Chinese	0.00	0.00	0.00	0.29	0.70	0.68	2.53	1.63
	LA-Filipino	0.78	0.78	1.25	1.22	2.34	0.62	2.49	1.45
	LA-Japanese	0.00	0.00	0.00	0.00	0.00	0.00	3.16	2.71
	LA-Korean	0.00	0.00	0.00	0.77	0.76	0.00	0.00	0.00
African	LA-Black	0.15	0.46	2.57	2.31	3.30	1.16	2.56	2.68
	SEER-Blacks	0.62	0.39	3.17	3.10	3.56	1.27	3.14	3.13
Israeli	Israel-all Jews	0.73	0.53	4.17	5.57	4.02	1.47	3.02	2.47
	Israel-non-Jews	1.40	0.56	3.02	1.57	3.27	0.20	1.20	6.01
	Israel-Jews born in America/Europe	0.91	0.00	4.16	6.51	4.12	1.55	2.62	3.11
	Israel-Jews born in Africa/Asia	0.00	0.00	0.87	1.38	4.04	1.98	3.81	0.88

Table 1. Age standardized (World) incidence rates /100 000/year for Hodgkin's lymphoma in males and females (IARC, 1997 and Cartwright & Watkins, 2004).

Region	Numbers per year	Incidence ASR	Deaths per year	Mortality ASR	Mortality to incidence ratio
WHO Africa region	5879	0.9	4893	0.8	0.9
WHO East Mediterranean region	7663	1.4	6004	1.2	0.9
Less developed regions	40137	0.7	23698	0.5	0.7
WHO South-East Asia region	11682	0.7	6276	0.4	0.6
WHO Western Pacific region	8476	0.4	3478	0.2	0.5
World	67887	1	30205	0.4	0.4
WHO Europe region	19342	2	5898	0.5	0.3
More developed regions	27750	2	6507	0.4	0.2
WHO Americas region	14802	1.5	3649	0.3	0.2

Table 2. Age-standardized incidence and mortality rates ranked by mortality to incidence ratio (case fatality ratio). Calculations are based on data from GLOBOCAN 2008.

11. Hormonal factors

Hormonal factors might have a role in the aetiology of this disease as evidenced by the male predominance in patients over 30 years and the higher risk in women aged less than 45 years at diagnosis (Cartwright and Watkins, 2004). In addition, prolonged use of human growth hormone was considered as a risk factor for Hodgkin's lymphoma.

12. Conclusion

Hodgkin's lymphoma is a malignant tumor of the lymphatic system. It arises from germinal center or post germinal center B cells. It has a unique cellular composition, containing a minority of neoplastic cell (Reed- Sternberg cells and their variants) in an inflammatory background. By 1902, the characteristic giant cells of Hodgkin's lymphoma were recognized by Sternberg and Reed.

The incidence of Hodgkin's lymphoma shows marked heterogeneity with respect to age, gender, race, geographic area, social class and histological subtype.

- About 3200 deaths were attributed to Hodgkin's lymphoma annually in the United States.
- About 8000 new cases of Hodgkin's lymphoma occur each year in the United States.
- It is nearly twice as common in males.
- It is more common in Caucasians
- There are 3 age periods: 0-14 years, 15-34 years and over 50 years.
- A significant peak in months of February and March were observed
- There is no direct person to person spread of Hodgkin's lymphoma

The descriptive epidemiology of Hodgkin's lymphoma suggests an infectious disease process underlying its aetiology in children and young adults. There is a relationship between Hodgkin's lymphoma and Epstein-Barr virus infection. The mechanisms underlying this association are unknown and the virus has never been isolated from or identified in Hodgkin's lymphoma tissue. Many studies have found significant increase in

risk of Hodgkin's lymphoma among patients with AIDS. Also human herpes virus 6 (HHV-6), 7,8 and CMV infections were demonstrated in patients with Hodgkin's lymphoma than in controls. Mixed cellularity subtype is more likely to be EBV-associated than nodular sclerosis subtype.

The higher the socioeconomic status of person, the greater the risk in the young adult disease. It is not possible to conclude that a causal relationship exists between the occupational exposures and risk of Hodgkin's lymphoma. Smoking more than 14 cigarettes per day was associated with a 50% increased risk. Increased incidence in males may suggest hormonal background. Several reports record aggregation of Hodgkin's lymphoma patients within the same family.

Several studies of HLA typing showed that some AGs were associated with Hodgkin's lymphoma. This association might indicate that a disease susceptibility gene lies in or near the major histocompatibility region. These associations suggest that this disease is a result of genetic environmental interaction.

13. References

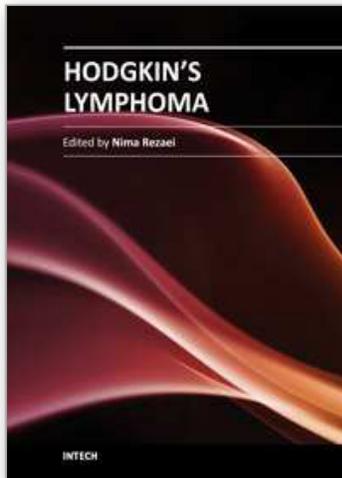
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