Familial Hodgkin Lymphoma

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ABSTRACT

Hodgkin Lymphoma (HL) is a lymphoid tumour that represents about 1% of all neoplasms occurring worldwide. HL is the most treatable of childhood malignancies. The etiology of HL is unknown. However, increase risk has been reported in males, with autoimmune diseases, poor socioeconomic status, increased family size, Ebstein Barr Virus (EBV) exposure, congental or acquired immunodeficiency and those with a family history of HL. Familial HL is rare. The risk of developing HL is increased six times in the siblings of the affected patients. Both genetic and environmental factors have been postulated in the pathogenesis. No case of familial HL has been reported in the literature from Pakistan. We report two families with familial HL occurring in siblings that have been successfully treated and are on our follow-up.

Key Words: Hodgkins lymphoma. Childhood cancer. Familial cancers.

INTRODUCTION

Formally known as Hodgkin disease, Hodgkin lymphoma (HL) is a highly curable malignancy. It is a malignancy of the germinal-center B cells that affects the reticuloendothelial and lymphatic systems. It accounts for 9% of all childhood cancers. with more than 65,000 new cases of HL diagnosed globally per annum. Clues about the etiology of HL have been suggested by the bimodal age distribution, higher risk in males, poor socioeconomic status, and in smaller families; and by the occurrence of Epstein-Barr Virus (EBV) in HL tumor cells. Children and adolescents with HL have a five-year survival of 94 percent since 2002 compared with 81 percent survival in the early 1970s. Five-year survival rates with modern therapies are now approaching more than 95%.

HL shows distinct behaviour in the developing countries. In developed nations, HL is more common in adolescents, males, higher socioeconomic status and nodular sclerosis histology and shows little association with EBV. However, in developing world, it is predominant in 5-10 years, males, lower socioeconomic status, EBV positivity and mixed cellularity histology. Familial clustering of HL has been described in literature, but it is rare. Familial cases can be justified by genetic or enviromental factors or by an interaction between the two. Awareness of risk among healthy family members may help us to recognize the symptoms early and thus facilitate treatment. Hereby, we report two families with HL in the siblings.

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Received: November 02, 2016; Accepted: July 21, 2017.

CASE REPORT

Case 1: An 8-year male child presented in August 2008 with complaints of fever and left-side neck swelling for one month. There was no history of tuberculosis contact. He was vaccinated according to EPI schedule, and developmentally normal child, born to consanguineously related parents, and eldest among 7 siblings belonging to poor socioeconomic status. He was conscious, well thriving child with stable vital signs. On examination, there was bilateral cervical lymphadenopathy, largest lymph node measured 3 x 3 cm with no overlying skin discoloration or discharging sinus. There was no visceromegaly. Rest of systemic examination was unremarkable. His baseline workup revealed anemia (Haemoglobin 7.5 g/dl) and raised Lactate Dehydrogenase (LDH) 2400u/l. Liver and renal function tests were normal. Hepatitis B surface antigen and Anti-HCV screening was negative. Excisional biopsy of the cervical lymph node showed mixed cellularity HL that was positive for CD15 and CD30. CT scan neck, chest and abdomen showed bilateral cervical, axillary and abdominal lymphadenopathy with no focal lesion in the liver, kidney and spleen. Bilateral bone marrow aspiration and biopsy was positive for involvement by Reed Sternberg cells. He was diagnosed as HL mixed cellularity, stage 4B. He was treated as per United Kingdom Children's Cancer Study Group (UKCCSG) Hodgkin Disease Protocol 2000, followed by radiation therapy. He achieved complete response and is on regular follow-up since then. He is now 16 years old and thriving well. In May 2016, his 4 years old younger brother presented with complaints of bilateral neck swelling and fever. He was febrile, and weighed 15Kg. He had bilateral cervical and axillary lymphadenopathy with largest node measuring 2 x 1 cm. His baseline full blood counts, liver and renal function tests, hepatitis B and C screening were normal. LDH was 1500 u/l CT scan neck, chest and abdomen showed lymphadenopathy above and below the diaphragm with no focal lesions in
the liver, kidney and spleen. Bilateral bone marrow aspiration biopsy was normal. He was diagnosed as HL, mixed cellularity, stage 3B. He was started treatment according to EuroNet Paediatric HL treatment protocol. He received 2 cycles of OPEA and 4 cycles of COPDAC and his early and end of treatment response assessment showed complete response. Currently, both siblings are on our regular follow-up.

**Case 2:** A female child, aged 9 years presented to us in 2007 with complaints of neck swelling and fever for 9 months. At presentation she was febrile, pale, with right cervical lymphadenopathy measuring 2 x 3 cm. Baseline hemoglobin was 8 g/dl, total leucocyte count (TLC), 5000/ul, platelets, 250,000 ml, and LDH, 1240u/L. Excisional biopsy of cervical lymph nodes showed Reed Sternberg cells with CD15 and CD30 positivity. Bilateral bone marrow aspiration biopsy was normal. CT scan neck, chest and abdomen showed cervical axillary, inguinal, and abdominal lymphadenopathy. She was diagnosed as HL mixed cellularity, stage 3B. She was treated as per UKCCSG Hodgkin Disease Protocol 2000 and achieved complete remission. Later on, in 2014, her younger brother, who was also 9 years old, presented to us with complaints of fever and neck swelling for 6 months. He had right cervical and axillary lymphadenopathy. He was diagnosed as HL mixed cellularity, stage 2B on excisional lymph node biopsy of cervical lymph node. He was treated as per protocol of EuroNet Paediatric Hodgkin’s Lymphoma Group. He was treated with 2 cycles of OPE and 2 cycles of COPDAC chemotherapy. He achieved complete remission and is on regular follow-up since then.

**DISCUSSION**

Pediatric HL is the most curable of childhood malignancies with cure rate of more than 90%. The exact etiology is unknown. However, risk has been associated with socioeconomic status, family size, EBV exposure, immunodeficiency and family history of HL. Family history of lymphoid neoplasm (LN) is a strong and consistently observed risk factor, although it has been only marginally examined in pediatric/adolescent patients. A study, analyzing Swedish cancer registry and compared with matched healthy cohort, revealed that HL was fourth in list of cancers with high familial incidence, just after cancer affecting eye or testis. According to a larger study, conducted in five Nordic countries, the overall life-time cumulative risk of HL in 1st Degree relatives is 0.6%, which is 3.3% more than that in the general population. The risk is more, if HL was diagnosed at a younger age, with lymphocyte rich histology and in siblings than in parents or children. The risk is highest, if more than one family member are involved or in identical twins. There is scarce data available from developing countries as few case reports are available.

Both genetic and environmental factors are involved in the pathogenesis. Children within the same family usually have the same socioeconomic status, family size, and have similar chances of exposure to EBV. Increased incidence in sibling as compared to parents/children suggests recessive pattern of inheritance. Heritable genetic risk variants have only recently begun to be discovered. No specific gene has been identified, but linkage analysis in HL families shows specific focus on HLA chromosome 6. Several studies identify the role of genetic variants that promote B cell survival and growth with increased risk of lymphoma. Positive association between GSTT1 deletion and risk of HL have been reported. Risk estimation in susceptible individuals is important for early recognition of symptoms as earlier diagnosis yields better prognosis.

**REFERENCES**


