ORIGINAL ARTICLE

Study of SH2D1A gene mutation in paediatric patients with B-cell lymphoma

L. Koochakzadeh\textsuperscript{a}, S. Hosseinverdi\textsuperscript{a,b}, M. Hedayat\textsuperscript{c}, F. Farahani\textsuperscript{a}, A. Tofighi\textsuperscript{a}, M. Eghbali\textsuperscript{a}, A.Z. Bidoki\textsuperscript{d}, M. Izadyar\textsuperscript{a}, M.S. Rahiminejad\textsuperscript{a}, A. Ramyar\textsuperscript{a}, A. Aghamohammadi\textsuperscript{a,b}, N. Rezaei\textsuperscript{a,b,d,e,}\textsuperscript{*}

\textsuperscript{a} Pediatrics Center of Excellence, Children’s Medical Center, Tehran University of Medical Sciences, Tehran, Iran
\textsuperscript{b} Research Center for Immunodeficiencies, Children’s Medical Center, Tehran University of Medical Sciences, Tehran, Iran
\textsuperscript{c} Division of Immunology, Boston Children’s Hospital, Harvard Medical School, Boston, MA, USA
\textsuperscript{d} Molecular Immunology Research Center, and Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
\textsuperscript{e} Universal Scientific Education and Research Network (USERN), Tehran, Iran

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KEYWORDS

SH2D1A gene; Hypogammaglobulinaemia; Mutations; Lymphoma; X-linked lymphoproliferative disorder

Abstract

Background: X-linked lymphoproliferative disease (XLP) is an often fatal inherited immunodeficiency disorder characterised by fulminant infectious mononucleosis, acquired haemophagocytic lymphohistiocytosis, dysgammaglobulinaemia and malignant lymphoma. Given the paucity of data on the genetic stratification of XLP gene mutations in paediatric patients diagnosed with B-cell lymphoma, we sought to determine the existence of such association in the present study.

Methods: We studied 20 male subjects diagnosed with non-Hodgkin B-cell lymphoma.

Results: Eleven patients had laboratory evidence of EBV infection by serology and quantitative PCR. The SH2D1A gene analysis was negative in all patients.

Conclusions: This is the first study to analyse the SH2D1A gene mutations in Iranian paediatric patients diagnosed with lymphoma. Although we could not demonstrate such an association in our cohort of patients, larger, multi-centre studies are required to extend and confirm our early findings.

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Introduction

Primary immunodeficiencies (PIDs) are a heterogeneous group of disorders that predispose to recurrent severe infections, autoimmunity, and in certain diseases, cancers. The overall risk for developing malignancies in children with PIDs has been estimated to be 4–25%, with lymphomas...
accounting for up to 60% of all cancer types.\textsuperscript{1-3} X-linked lymphoproliferative disease (XLP) is a life-threatening inherited disorder characterised by severe dysregulation of the immune system, often, but not always, in response to Epstein–Barr virus (EBV) infection, manifesting as fulminant infectious mononucleosis and/or acquired haemophagocytic lymphohistiocytosis (HLH), dysgammaglobulinaemia, and a markedly increased risk of lymphoma.\textsuperscript{4-6} Most cases of XLP, particularly those with lymphoma, are caused by germ-line mutations in the Src homology 2-domain-containing gene 1A (SH2D1A) encoding the signalling lymphocytic activation molecule (SLAM)-associated protein (SAP).\textsuperscript{5,7} Lymphomas frequently develop as the initial presenting manifestation in XLP patients.\textsuperscript{7} Failure to properly diagnose XLP as the underlying genetic cause of lymphoma would have drastic consequences on patient management and survival. This study was performed to evaluate the use of SH2D1A mutation analysis to discern between these often clinically indistinguishable disorders in a cohort of Iranian paediatric patients presenting with B-cell lymphomas.

Methods

Twenty male subjects aged between 4 and 14 years, diagnosed with B-cell lymphoma, and no history of fulminant infectious mononucleosis or family history of PID, who were referred to the Oncology Clinic of the Children’s Medical Center Hospital, Tehran, Iran, were recruited in the present study. This study was approved by the Ethics Committee of Tehran University of Medical Sciences. Written informed consent was obtained from the parents or legal guardians prior to blood sampling. DNA samples were extracted from peripheral blood mononuclear cells using standard genomic DNA purification methods. Nucleotide sequences of all four exons and their flanking intronic sequences of the SH2D1A gene were amplified by polymerase chain reaction (PCR) followed by direct sequencing. The status of EBV infection was evaluated based on serological evidence of EBV-specific antibody responses and quantitative PCR, using standard method by amplification of 129 bp of latent membrane protein-1 (LMP-1) gene.

Results

Twenty male subjects diagnosed with non-Hodgkin B-cell lymphoma were enrolled in this study. The EBV serologic tests and quantitative PCR for EBV-DNA on peripheral blood were positive in 11 patients (44%). The results of SH2D1A gene analyses showed no mutation in all 20 male patients.

Discussion

SAP deficient patients are known to face an increased risk of lymphoma development, as high as 30%, as the initial manifestation of the disease.\textsuperscript{5,8} The majority are of B-cell origin, arising in extranodal sites, most commonly localised in the ileocecal region, with Burkitt's lymphoma comprising approximately 50–60% of total lymphomas.\textsuperscript{9} Up to one-third of XLP patients with lymphoma are EBV-seronegative, indicating that mechanisms other than malignant transformation of EBV-infected B cells, such as defective antitumor immunosurveillance, contribute to lymphomagenesis.\textsuperscript{5,7}

In the present study, genetic screening showed no SH2D1A gene mutations in male subjects diagnosed with B-cell lymphoma. Previously, Parolini et al. identified SH2D1A mutations only in the majority of patients presenting with fatal mononucleosis or family history of XLP, but in none of the 35 patients diagnosed with non-endemic Burkitt’s lymphoma (BL), Burkitt-type leukaemia, or Hodgkin’s lymphoma.\textsuperscript{9} In addition, a study of 60 BL cell lines and 12 BL tumour samples found no mutations in the SH2D1A gene.\textsuperscript{10} In contrast to our results, Sandlund et al. described five cases of XLP diagnosed among 158 male subjects (approximately 3.2%) presenting with B-cell non-Hodgkin lymphoma (NHL).\textsuperscript{11} Similarly, Brandau et al. reported three patients from two unrelated families presenting with early onset NHL with no laboratory or clinical signs of previous EBV infection.\textsuperscript{12}

XLP patients diagnosed with lymphomas may respond to initial standard chemotherapy; however, many die from relapse or infectious complications. Currently, haematopoietic stem cell transplantation is the only curative treatment for XLP, which has the best chance of success if performed as early as possible – before the onset of other disease manifestations. Although the results of our study could not detect any association between B-cell lymphoma and SH2D1A gene mutations, larger studies are required to make any firm conclusion and give evidence-based recommendations for specific diagnostic approaches in patients diagnosed with lymphoma.

Conflict of interest

The authors have no conflict of interest to declare.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the responsible Clinical Research Ethics Committee and in accordance with those of the World Medical Association and the Helsinki Declaration.

Confidentiality of data. The authors declare that they have followed the protocols of their work centre on the publication of patient data and that all the patients included in the study have received sufficient information and have given their informed consent in writing to participate in that study.

Right to privacy and informed consent. The authors have obtained the informed consent of the patients and/or subjects mentioned in the article. The author for correspondence is in possession of this document.

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References

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