Journal of the Formosan Medical Association (2012) 111, 370–379

Available online at www.sciencedirect.com

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journal homepage: www.jfma-online.com

ORIGINAL ARTICLE

Clinical features and major histocompatibility complex genes as potential susceptibility factors in pediatric immune thrombocytopenia

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Received 8 March 2011; received in revised form 13 June 2011; accepted 22 June 2011

KEYWORDS
antecedent of preceding illness;
human leukocyte antigen;
ITP;
major histocompatibility complex;
pediatric immune thrombocytopenia;
pediatric immune thrombocytopenic purpura

Background/Purpose: Immune thrombocytopenia (ITP) is a heterogeneous autoimmune disorder with diverse response rates to treatments that include corticosteroids, intravenous immunoglobulins (IVIG), and splenectomy. The predisposing causes of this autoimmune disorder, one of which is immunogenetic susceptibility, have not been fully determined. We investigated whether clinical features and human leukocyte antigen (HLA) genotypes influence the occurrence, treatment response, and disease duration of childhood ITP in Taiwan.
Methods: We performed HLA genotyping of 70 Taiwanese children with ITP and of 70 healthy controls and compared the data. Demographic data were also collected and evaluated.
Results: The frequencies of heterozygous HLA-A11 and the HLA-Cw1 allele were both significantly decreased in the ITP group ($p = 0.0160$ and $p = 0.0089$, respectively), whereas the frequency of heterozygous HLA-DQ5 was significantly increased in the ITP group ($p = 0.0057$). Patients with HLA-DRB1*11 or -DRB1*15 were more likely to respond poorly to corticosteroids than IVIG ($p = 0.0446$ and $p = 0.0008$, respectively). In addition, we observed a positive association between HLA-A11 homozygosity and the development of persistent or chronic ITP [odds ratio (OR) = 6.3165, $p = 0.0479$]. The presence of HLA-DRB1*08 was, however, negatively correlated with the development of persistent or chronic ITP

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doi:10.1016/j.jfma.2011.06.025

(OR = 0.1729, $p = 0.0657$). Children with antecedent of preceding illness (API) and with a younger age of onset were more likely to experience a better treatment response and shorter course of ITP.
Conclusion: We suggest that API, age of onset, and particular HLA class I and class II alleles, may be involved in and influence the occurrence and disease duration of childhood ITP, as well as responses to different therapeutic approaches.

Introduction

Immune thrombocytopenia (ITP) is a heterogeneous disease characterized by increased platelet destruction and thrombocytopenia. Most researchers believe that this platelet destruction is immune mediated and may also involve the inhibition of platelet release by megakaryocytes. Autoantibodies against platelet antigens are the diagnostic hallmark of ITP; however, this mechanism may not account for all cases, as antiplatelet autoantibodies are detected in only 50%–70% of patients with ITP.[1–4] Failure to detect autoantibodies could be due to limited test sensitivity, undetected antigens, or additional mechanisms of platelet loss. Other contributing mechanisms for ITP have been proposed, such as complement-mediated lysis,[5] tolerance checkpoint defects, ineffective thrombopoiesis, direct T-cell cytotoxicity, and a combination of genetic susceptibility and environmental factors.[3]

The functional role of human leukocyte antigen (HLA), which is the human form of the major histocompatibility complex (MHC), is to present antigens to the immune system, and the genetic diversity of the HLA is postulated to have arisen as a host strategy to counter the antigenic diversity of infectious organisms. To identify potential susceptibility factors for ITP, several groups have focused on the identification of MHC genes; however, findings from these HLA association studies in ITP have produced inconsistent results. Nomura and colleagues[6] examined the clinical significance of HLA class II genes in more than 100 Japanese patients with ITP and showed that the frequency of the DRB1*0410 allele was significantly increased in patients with ITP compared with controls. Moreover, this allele was found significantly less frequently in patients who showed a good response to prednisolone. Stanworth and others[7] reported an association between the presence of HLA-A2 and ITP, particularly in female patients, with HLA-A2 also present at increased frequency in patients with chronic ITP that progressed to requiring splenectomy. Another study revealed strong associations between anti-glycoprotein autoantibodies and HLA class II alleles: antibodies against GPIIb-IIIa were associated with DRB1*0405 and DQB1*0401, and antibodies against GPIb-IX were associated with DRB1*0803 and DQB1*0601.[8] When factors influencing therapeutic responses to splenectomy were examined, a poor response was correlated with the presence of DRB1*0405, DQB1*0401, and anti–GPIIb-IIIa. Furthermore, some groups have reported weak associations, such as an increased frequency of HLA-Bw56 and HLA-DR2, in patients with ITP.[9,10]

Based on these previous studies and two additional aspects of ITP, we hypothesized that the HLA class I genes (in addition to the HLA class II genes) may play critical roles in childhood ITP. First, the platelet surface expresses HLA class I molecules (rather than HLA class II molecules), but platelet interactions with cytotoxic T cells, natural killer (NK) cells, and killer cell immunoglobulin-like receptors (KIRs) in patients with ITP are not well understood. Second, it is commonly accepted that childhood ITP is associated with infection, either viral or bacterial.[11] Thus, to investigate whether HLA classes I and II genotypes play a critical role in childhood ITP in Taiwan, we first identified demographic factors, laboratory parameters, and other clinical characteristics that may be linked to the course and treatment responses of childhood ITP. We performed HLA class I (HLA-A, -B, and -C) and class II (HLA-DQ and -DR) genotyping to explore the relationship between HLA susceptibility genes and the occurrence, treatment responses, and disease duration of childhood ITP in Taiwan.

Materials and methods

Participants

Patients were identified following a retrospective review of medical records at National Taiwan University Hospital and Shin Kong Wu Ho-Su Memorial Hospital from January 2007 to December 2009. For this study, 70 patients with ITP were enrolled who had attended pediatric hematology clinics, visited emergency departments, or been referred from other hospitals. For the control group, blood was collected from January 2007 to December 2009 from 70 healthy children (37 boys and 33 girls; mean age, 4.3 ± 3.8 years) who were in our vaccine study or were brought to our pediatric hematology clinic for blood typing. These children had no underlying diseases, and a hemogram showed no evidence of thrombocytopenia.

The diagnosis of primary ITP was established on the basis of history, physical examination, and a laboratory result showing isolated thrombocytopenia (peripheral blood platelet count $<100{,}000/mm^3$) in the absence of other disorders that may be associated with thrombocytopenia.[12] If a patient had atypical features or was not responding to therapy, a bone marrow aspirate was performed to exclude other diseases that result in thrombocytopenia. The age and season of onset, sex, antecedent of preceding illness (API), initial platelet count at diagnosis, treatment choice and response, and disease duration of the patients were also evaluated. API was defined as the occurrence of viral infection or immunization within 4 weeks prior to presenting with bleeding manifestations.[13] This study was approved by the Institutional Review Board of National Taiwan University Hospital and Shin Kong Wu Ho-Su Memorial Hospital. Informed written consent was obtained from the parents of each participant.