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Research Article

Dengue-Virus Infection: Lung Involvement, Clinical Implications, and Associated Human Leukocyte Antigens

Attapon Cheepsattayakorn[1] and Ruangrong Cheepsattayakorn[2]

[1]10th Zonal Tuberculosis and Chest Disease Centre, Chiang Mai, Thailand, 10th Office of Disease Prevention and Control, Department of Disease Control, Ministry of Public Health, Thailand

[2]Department of Pathology, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand

Correspondence should be addressed to: Attapon Cheepsattayakorn; attaponche@yahoo.com

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Abstract

Four known dengue virus serotypes have been identified, DENV-1, DENV-2, DENV-3, and DENV-4. About 50 million-infected persons occurs each year. Adult primary infections with DENV-1 and DENV-3 usually result in dengue fever while some outbreak with DENV-2 infections have been predominantly subclinical. Dengue pulmonary complications include pulmonary infiltration, pleural effusion, non-cardiogenic pulmonary edema and respiratory failure while massive hemoptysis can occur. Several human leukocyte antigens class I and II alleles are associated with the development of dengue disease.

Keywords: Dengue, Lung, HLA

Introduction

This disease is caused by dengue virus (DENV) that belongs to the family Flaviviridae, genus Flavivirus, and is transmitted to humans by Aedes mosquitoes, mainly Aedes aegypti[Martina et al., 2009]. Four serotypes of viruses have been identified ; DENV-1, DENV-2, DENV- 3, and DENV-4 [Martina et al., 2009]. An estimated 50 million-infected people occur each year and more than 2.5 billion people are being at risk of infection [Guha-Sapir et al., 2005], but the simultaneous worldwide distribution of the risk of dengue virus infection and its public health burden are poorly understood [Bhatt et al., 2013]. Epidemic with high incidences of dengue hemorrhagic fever have been linked to

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primary infection with DENV-1 followed by infection with DENV-2 or DENV-3, whereas it indicated that the longer the interval between primary and secondary infections, the higher the risk of developing severe disease [Guzmaʹn et al., 2003-Ong et al., 2007]. The relationship between DENV-2 and dengue severity is controversial [Diʹaz-Quijano et al., 2012]. However, adult dengue infections are frequently accompanied by a tendency for severe hemorrhage [UNICEF, UNDP, World Bank, accessed January 8, 2014] and can be life-threatening when infections occur in patients withchronic diseases such as asthma and diabetes [Kouri et al., 1987-Lee et al., 2006]. The aim of this study is to review the clinical implications and associated human leukocyte antigens including lung pathological mechanisms and involvement in dengue disease.

Associated Human Leukocyte Antigens, Lung Involvement and Clinical Implications

Lungs of dengue cases, particularly with severe disease, present with mononuclear inflammatory infiltrates, hyperplasia of alveolar macrophages, and hyaline membrane formation with concomitant hypertrophy of type II pneumocytes [Poʹvoa et al., 2014]. Dengue virus antigens with virus replication are also identified in type II pneumocytes and pulmonary vascular endothelium [Poʹvoa et al., 2014]. These pulmonary pathological features can contribute to pulmonary edema, pulmonary hemorrhage, adult respiratory distress syndrome, and pulmonary tissue damages [Poʹvoa et al., 2014]. Several human leukocyte antigens (HLA) class I alleles, female sex, AB blood group, a single-nucleotide polymorphism in the tumor necrosis factor gene, and a promoter variant of the DC-SIGN receptor gene are the host factors that increase the risk of severe dengue disease [Stephens et al., 2002-Kalayanarooj et al., 2007]. Notably, the first outbreak in the Americas occurred in 1981, which coincided with the introduction of the possibly more virulent DENV-2 Southeast Asian genotype whereas the less virulent indigenous DENV-2 genotype was already circulating in the region [Kouri et al., 1987, Rico-Hesse et al., 1990-Rodriguez-Roche et al., 2005]. Age has been demonstrated to influence the disease outcome following a secondary infection with heterologous DENV [Guzmaʹn et al., 2002]. In Asia, the risk of severe disease is greater in children than in adults, in contrast to the Americas [Cologna et al., 2003, Leitmeyer et al., 1999]. Nevertheless, the finding that dengue hemorrhagic fever or dengue shock syndrome is noted primarily in a relative small percentage of secondary DENV infections and to a much lesser extent in primary infections although with virulent strains it indicates that host factors must be critical determinants of severe DENV disease development [Martina *et al.,* 2009]. There is evidence that DENV antigen is present in the pulmonary vascular endothelium [Jessie *et al*., 2004], whereas liver is the organ commonly involved in human DENV infections including mouse model [Paes *et al*., 2005, Seneviratne *et al*., 2006].

Glucose-6-phosphate dehydrogenase deficiency which is highly prevalence among the African population [Nkhoma *et al*., 2009] can cause abnormal cellular redox, therefore affecting the production of hydrogen peroxide, superoxide, and nitric oxide indicating oxidative stress [Wu *et al*., 2008]. Viral proliferation and virulence by increasing viral receptors on target cells or increasing viral particles is known to be affected by oxidative stress [Wu *et al*., 2008], therefore, glucose-6-phosphate dehydrogenase deficiency may contribute to the increased replication of DENV in monocytes [Nkhoma *et al*., 2009]. Several HLA class I alleles *(-A*01*, *-A*0207*, *-A*24*, *-B*07*, *-B*46*, *-B*51*) [Stephens *et al*., 2002, Loke *et al*., 2002, Zivna *et al*., 2002] and HLA class II alleles *(-DQ*1*, *-DR*1*, *-DR*4*) [LaFleur *et al*., 2002, Polizel *et al*., 2004] are associated with the development of

dengue hemorrhagic fever. Additionally, a recent study demonstrated that there was significantly higher frequency of *HLA-A*33* allele in dengue fever patients, *HLA-A*0211* allele in dengue hemorrhagic fever cases compared to healthy controls and dengue fever cases, respectively [Alagarasu *et al*., 2013]. The frequency of *HLA-B*18* and *HLA-Cw*07* alleles were significantly higher in DENV-infected cases compared to controls [Alagarasu *et al*., 2013]. The combined frequency of *HLA-Cw*07* with *HLA-DRB1*07/*15* genotype was significantly higher in dengue hemorrhagic fever cases as compared to dengue fever cases and controls, but the frequency of combination of *HLA-Cw*07* allele without *HLA-DRB1*07* allele was significantly higher in dengue fever cases compared to controls [Alagarasu *et al*., 2013]. This study result indicates that *HLA-A*33* allele may be associated with the development of dengue fever, whereas *HLA-B*18* and *HLA-Cw*07* alleles may be associated with symptomatic dengue infection requiring hospitalization [Alagarasu *et al*., 2013]. A previous study demonstrated that *HLA-A*0207* and *HLA-B*51* alleles were associated with dengue hemorrhagic fever in patients having secondary DENV-1 or DENV-2 infection only and children with *HLA-A*24* allele were more likely to develop dengue hemorrhagic fever [Malavige *et al*., 2004]. After secondary dengue infections, *HLA-B*44*, *-B*62*, *-B*76*, and *-B*77* alleles revealed that they protect against development of clinical disease [Malavige *et al*., 2004].

Rathakrishnan and colleagues conducted a study in 504 Chinese and Indian Malaysian populations, who aged 14 and above, which demonstrated that *HLA-A*24*, *HLA-A*33*, and *HLA-B*57* alleles were positively associated with patients with warning signs of dengue disease or severe dengue disease [Rathkrishnan *et al*., 2014]. *HLA-A*03* allele may be protective in both Chinese and Indian Malays, whereas *HLA-A*33* allele may be a predictive marker for the development of severe dengue disease [Rathkrishnan *et al*., 2014]. Cardozo *et al* demonstrated the results of their study of susceptibility of dengue virus serotype 3 among 95 patients that *HLA-DQA1*05:01* and *HLA-DRB1*11* alleles could be possible resistance factors to dengue virus serotype 3 infection, whereas *HLA-DQB1*06:11* and *HLA-DRB1*15* alleles may act as susceptible factors [Cardozo *et al*., 2014]. Alencar and colleagues conducted a study of a cohort of dengue patients in Brazil and demonstrated that *HLA-B*44*, *HLA-B*50*, *HLA-DR*16* alleles were associated with increased susceptibility to dengue hemorrhagic fever, particularly serotype 3, whereas *HLA-B*07* and *HLA-DR*13* alleles were associated with resistance to secondary dengue infection with DENV-3 [Alencar *et al*., 2013]. Monteiro *et al* conducted a retrospectively case (dengue hemorrhagic fever)-control (dengue fever) study among Brazilians during 2002-2008 and revealed that *HLA-A**01 allele was associated with increased susceptibility to dengue hemorrhagic fever, whereas *HLA-A*31* allele was associated with resistance to the development of dengue hemorrhagic fever [Monteiro *et al*., 2012]. Brown and colleagues conducted a study among Jamaicans and demonstrated that *HLA-A*24* and *HLA-DRbeta5*01/02* alleles were associated with increased susceptibility to dengue infection, whereas *HLA-A*23*, *HLA-CW*04*, *HLA-DQbeta*02*, *HLA-DQbeta*03*, and *HLA-DQbeta*06* alleles were associated with protection to dengue infection [Brown *et al*., 2011]. A previous study in Sri Lanka demonstrated that *HLA-A*31* allele was associated with dengue shock syndrome during secondary dengue infection, while *HLA-A*24* and *HLA-DRB1*12* alleles were associated with the development of dengue hemorrhagic fever during primary dengue infection [Malavige *et al*., 2011].

Appanna *et al*'s study demonstrated that *HLA-B*18* and *HLA—B*53* alleles were increased in patients with dengue hemorrhagic fever, whereas *HLA-A*03*

allele was decreased [Appanna *et al*., 2010]. Falcoʹn-Lezama and colleagues conducted a study among Mexican patients with dengue fever (23) and dengue hemorrhagic fever (16) in comparison to 34 healthy controls, and revealed that *HLA-DQB1*0202* and *HLA-DQB1*0302* alleles were associated with the development of dengue fever and dengue hemorrhagic fever, respectively [Falcoʹn-Lezama *et al*., 2009]. A study in 228 ethnic Thais with dengue fever and 142 patients with dengue hemorrhagic fever, which was further classified by disease severity according to the World Health Organization (WHO) criteria, aged 3-14 years, demonstrated that *HLA-B*48*, *HLA-B*57*, and *HLA-DPB1*0501* alleles were associated with the development of secondary dengue hemorrhagic fever [Vejbaesya *et al*., 2009]. Lan and colleagues conducted a study in Vietnam by gathering 211 patients with dengue hemorrhagic fever and 418 patients with dengue shock syndrome during 2002-2005, and revealed that *HLA-A*24* allele was associated with the development of dengue hemorrhagic fever and dengue shock syndrome, whereas *HLA-DRB1*0901* allele had protective effect against the dengue shock syndrome caused by DENV-2 [Lan *et al*., 2008]. Sierra *et al* demonstrated that *HLA-DRB1* polymorphism was associated with protective effect against the development of dengue hemorrhagic fever [Sierra *et al*., 2007].

Clinical findings in early febrile stage include fever, headache, malaise, rash, body pain, and later develop pleural effusion [UNICEF, UNDP, World Bank, accessed January 8, 2014, Likitnukul *et al*., 2004], both lower lobes infiltration [Likitnukul *et al*., 2004], bilateral perihilar edema [Ali *et al*., 2010], ascites, bleeding, thrombocytopenia (platelet < 100,000 per mm^3), hematocrit > 20%, and clinical warning signs such as restlessness, severe and continuous abdominal pain, persistent vomiting and a sudden reduction in body temperature associated with profuse perspiration, adynamia (vigor or loss of strength) and sometimes fainting which can be indicative of shock due to plasma extravasation [UNICEF, UNDP, World Bank, accessed January 8, 2014]. Wang and colleagues conducted a study in 661 Taiwanese patients diagnosed with dengue fever according to the clinical presentations and laboratory examination results and revealed that pleural effusion was the most common chest roentgenographic presentations (31.4% of the total chest roentgenograms and 57.4% of the abnormal chest roentgenograms), followed by pulmonary infiltration only (23.3% of the total chest roentgenograms and 42.6% of the abnormal chestroentgenograms), while small pleural effusion (less than 2 intercostal spaces) was the predominate type among the chest roentgenograms presented with pleural effusion and in all abnormal chest roentgenograms [Wang *et al*., 2007].

Additionally, pulmonary infiltration only and small pleural effusion were the major presentations in dengue hemorrhagic fever patients with abnormal chest roentgenographic features [Wang *et al*., 2007]. A previous study conducted in 100 patients in Yemen with seropositivity of dengue confirmed by reverse-transcriptase polymerase-chain-reaction method, demonstrate the chest presentations as the following : 1) adult respiratory distress syndrome in patients with dengue fever, dengue hemorrhagic fever, and dengue shock syndrome was 0%, 19.4%, and 53.3%, respectively; 2) pulmonary hemorrhage in patients with dengue fever, dengue hemorrhagic fever, and dengue shock syndrome was 0%, 21.4%, and 6.6%, respectively; 3) unilateral pneumonitis in patients with dengue fever, dengue hemorrhagic fever, and dengue shock syndrome was 0%, 0%, and 0%, respectively; 4) bilateral pneumonitis in patients with dengue fever, dengue hemorrhagic fever, and dengue shock syndrome was 0%, 9.5%, and 6.6%,

respectively; 5) pleural effusion in patients with dengue fever, dengue hemorrhagic fever, and dengue shock syndrome was 0%, 7.14%, and 0%, respectively ; 6) more than one presentation in patients with dengue fever, dengue hemorrhagic fever, and dengue shock syndrome was 0%, 38.1%, and 33.3%, respectively [Mohamed *et al*., 2013].

Asghar *et al* conducted a study of pulmonary manifestations in 76 confirmed dengue-hemorrhagic-fever patients, age ranking from 14 to 80 years, and demonstrated that right pleural effusion, bilateral pleural effusion, left pleural effusion, bilateral pneumonia, right sided pneumonia, and left sided pneumonia was 17.1%, 13.2%, 1.3%, 3.9%, 1.3%, and 0%, respectively [Asghar *et al*., 2011]. A study of chest computerized tomography (CT) in 29 Brazilian patients who fulfilled the World Health Organization case definition by diagnoses of dengue fever (9 patients) and severe dengue disease (20 patients) showed that abnormal CT findings were identified in 58.62% (12 with severe disease, 5 with dengue fever), pleural effusion in 55.17% (11 with severe disease, 5 with dengue fever, 13 with bilateral effusion, 3 with right-sided effusion), large pleural effusion in 4 patients with severe disease [Rodrigues *et al*., 2014]. Large pleural effusion was not identified in patients with dengue fever [Rodrigues *et al*., 2014]. Ground-glass opacity was the most common finding of lung parenchymal involvement that was noted in 8 patients (5 with severe disease, 3 with dengue fever) and followed by lung consolidation (6 patients (4 with severe disease, 2 with dengue fever)) [Rodrigues *et al*., 2014]. Interlobar septal thickening and pulmonary nodules with no specific distribution were detected in 2 patients (1 with severe disease, 1 with dengue fever, and 2 with severe disease, respectively) [Rodrigues *et al*., 2014]. One case with dengue fever and another case with severe disease demonstrated mild interlobar septal thickening that located predominantly in the upper lobes and lower lung zone, respectively [Rodrigues *et al*., 2014]. Only one case with intermediately severe disease demonstrated peribronchovascular interstitial thickening in the middle and lower zones [Rodrigues *et al*., 2014]. No patient with dengue fever showed pulmonary nodules [Rodrigues *et al*., 2014]. There was no specific axial distribution [Rodrigues *et al*., 2014]. The chest extent of disease tended to be greater in patients with severe disease than in those with dengue fever, but this difference was not statistically significant [Rodrigues *et al*., 2014]. Transudative pleural effusions that were mostly detected in dengue patients are largely due to imbalances in oncotic and hydrostatic pressures in the thoracic cavity because these effusions are ultrafiltrates of plasma [Wang *et al*., 2007]. Generally, the identification of a transudative pleural effusion indicates that the pleural membranes are not diseased and that pleural fluid accumulation is caused by systemic (non-pleural, non-lung) factors affecting the formation and absorption of pleural fluid [Wang *et al*., 2007]. Dengue disease must be excluded from two syndromes related to hantavirus, hemorrhagic fever with renal syndrome (HFRS) in Eurasia and hantavirus pulmonary syndrome (HPS) in the Americas [Duchin *et al*., 1994-Vapalahti *et al*., 2003]. HPS is typically characterized by acute noncardiogenic pulmonary edema and circulatory shock, whereas fever, hemorrhagia, and acute renal failure are hallmark findings in HFRS [Rasmuson *et al*., 2011].

Laboratory diagnosis of DENV infection includes virus isolation, serodiagnostic tests (MAC-ELISA, IgG ELISA, IgG : IgM ratio, neutralization assay), nucleic acid amplification tests (real-time PCR, reverse-transcriptase PCR, nucleic acid-sequence based amplification assay (NASBA)), and antigen detection (NS1 antigen and antibody detection) [UNICEF, UNDP, World Bank, accessed January 8, 2014]. DENV

complications include massive hemorrhage or hemoptysis, disseminated intravascular coagulation, non-cardiogenic pulmonary edema, respiratory failure, and finally develop multiple organ failure [UNICEF, UNDP, World Bank, accessed January 8, 2014]. The chest roentgenographic presentations are significantly correlated with the laboratory findings, particularly white blood cell counts, platelet counts, activated partial thromboplastin time, and serum alanine aminotransferase and albumin levels [Wang *et al*., 2007].

In uncomplicated dengue cases, treatment is only supportive, but in cases with prolonged or recurrent dengue shock, intravenous fluids should be administered carefully according to dosage and age to prevent pulmonary edema [UNICEF, UNDP, World Bank, accessed January 8, 2014]. DENV control and prevention strategies include vector control and vaccine development [UNICEF, UNDP, World Bank, accessed January 8, 2014]. Current approaches to vaccine development involve using deoxyribonucleic acid vaccine, chimeric viruses using yellow fever vaccine, subunit vaccine, inactivated viruses, attenuated viruses, and attenuated dengue viruses as backbones[Guirakhoo *et al*., 2006-Edelman *et al*., 2003]. An Acambis/Sanofi Pasteur yellow fever-dengue chimeric vaccine is in advanced Phase II testing in children in Thailand [UNICEF, UNDP, World Bank, accessed January 8, 2014]. A possible licensed vaccine will be available in less than 10 years [UNICEF, UNDP, World Bank, accessed January 8, 2014].

Conclusions

Presently, dengue is a global health threat and is tropically endemic or epidemic. Better use of currently available measures and interventions should be made while we wait for novel diagnostics, novel vaccines, and novel antivirals. Recently, several partnerships such as the Asia-Pacific Dengue Prevention Partnership and the Innovative Vector Control Consortium have come into existence and receive funding from the Bill and Melinda Gates Foundation, regional Development Banks and the private sector. These partnerships are collaborating with the WHO and national governmental organizations to develop novel tools and strategies to improve diagnostics, clinical therapies, and successful novel vaccines. The most common chest presentation is pleural effusion. To date, the number of known HLA alleles with susceptible effects on the development of dengue infection or severe disease are more than the number of known HLA alleles with protective effects, thus, the development of novel protective measures against dengue virus infection are urgently needed worldwide, particularly in the tropical regions. The summary of associated HLA alleles and chest roentgenographic presentations in dengue disease is demonstrated in table 1.

Table 1: Associated Human Leukocyte Antigen Alleles and Chest Roentgenographic Presentations in Pulmonary Dengue Infection or Disease

Known HLA Alleles	Influence	Reference	Chest Roentgenographic Presentations	Reference
HLA-A*01, HLA-A*0207, HLA-A*24, HLA-B*07, HLA-B*46, HLA-B*51, HLA-DQ*1, HLA-DR*1, HLA-DR*4, HLA-A*0211, HLA-Cw*07 **(in combination with *HLA-DRB1*07/*15* genotype)**	**Susceptible to development of dengue hemorrhagic fever**	LaFleur *et al*., 2002; Polizel *et al*., 2004; Alagarasu *et al*., 2013	unilateral/bilateral pleural effusion, pulmonary infiltrates, adult respiratory distress syndrome, pulmonary hemorrhage, unilateral/bilateral pneumonitis, ground-glass opacity, interlobar septal thickening, pulmonary nodules, peribronchovascular interstitial thickening	Wang *et al*., 2007; Asghar *et al*., 2011 (chest roentgenographic & CT findings); Mohamed *et al*., 2013; Rodrigues *et al*., 2014 (chest CT findings)
HLA-A*33, HLA-HLA-Cw*07	**Susceptible to development of dengue fever**	Alagarasu *et al*., 2013		
HLA-B*18, HLA-Cw*07	**Susceptible to development of symptomatic dengue infection**	Alagarasu *et al*., 2013		
HLA-A*24, HLA-A*33, HLA-B*57	**Susceptible to development of severe dengue disease**	Rathakrishnan *et al*., 2014		
HLA-A*03	**Protective to development of dengue disease**	Rathakrishnan *et al*., 2014		
HLA-A*33	**Predictive marker for development of severe dengue disease**	Rathakrishnan *et al*., 2014		
HLA-DQB1*06:11, HLA-DRB1*15	**Susceptible to development of dengue virus serotype 3 infection/disease**	Cardozo *et al*., 2014		
HLA-DQA1*05:01, HLA-DRB1*11	**Protective to development of dengue virus serotype 3 infection/disease**	Cardozo *et al*., 2014		

HLA-B*44, HLA-B*50, HLA-DR*16	**Susceptible to development of dengue virus serotype 3 infection/disease**	Alencar *et el*., 2013		
HLA-B*07, HLA-DR*13	**Protective to development of dengue virus serotype 3 infection/disease**	Alencar *et el*., 2013		
HLA-A*01	**Susceptible to development of dengue hemorrhagic fever**	Monteiro *et al*., 2012		
HLA-A*31	**Protective to development of dengue hemorrhagic fever**	Monteiro *et al*., 2012		
HLA-A*24, HLA-DRbeta5*01/02	**Susceptible to development of dengue infection**	Brown *et al*., 2011		
HLA-A*23, HLA-CW*04, HLA-DQbeta*02, HLA-DQbeta*03, HLA-DQbeta*06	**Protective to development of dengue infection**	Brown *et al*., 2011		
HLA-A*31	**Susceptible to development of dengue shock syndrome during secondary dengue infection**	Malavige *et al*., 2011		
HLA-A*24, HLA-DRB1*12	**Susceptible to development of hemorrhagic fever during primary dengue infection**	Malavige *et al*., 2011		
HLA-B*18, HLA-B*53	**Susceptible to development of hemorrhagic fever**	Appanna *et al*., 2010		
HLA-A*03	**Protective to development of hemorrhagic fever**	Appanna *et al*., 2010		

HLA-DQB1*0202	**Susceptible to development of dengue fever**	Falco′n-Lezama *et al*., 2009		
HLA-DQB1*0302	**Susceptible to development of dengue hemorrhagic fever**	Falco′n-Lezama *et al*., 2009		
HLA-B*48, HLA-B*57, HLA-DPB1*0501	**Susceptible to development of secondary dengue hemorrhagic fever**	Vejbaesya *et al*., 2009		
HLA-A*24	**Susceptible to development of dengue hemorrhagic fever and dengue shock syndrome**	Lan *et al*., 2008		
HLA-DRB1*0901	**Protective to development of dengue shock syndrome infected with serotype 2**	Lan *et al*., 2008		
HLA-DRB1	**Protective to development of dengue hemorrhagic fever infected with serotype 2**	Sierra *et al*., 2007		

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