Bronchial Asthma: Risk Condition for Dengue Severe Disease?

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ABBREVIATIONS

ADE: Antibody Dependent Enhancement; DF: Dengue Fever; DHF: Dengue Hemorrhagic Fever; DEN: Dengue; PBMC: Peripheral Blood Mononuclear Cells

Dengue is a tropical infectious disease caused by 1 of 4 dengue virus serotypes (DEN-1 to DEN-4). Immunity to a given dengue virus serotype provides protection against re infection with that same serotype (homotypic infection). However, subsequent infection with other serotype (heterotypic infection) markedly increases the risk for severe dengue disease, characterized by systemic plasma leakage that can cause hypovolemic shock, severe haemorrhagic manifestations or organs complications [1]. During the heterotypic secondary infection non neutralizing cross-reacting antibodies react with the virus and facilitate the viral entry to target cells via the Fcy receptors, phenomenon known as antibody dependent enhancement (ADE) [2].

The preceding dengue classification [3]. (Dengue fever (DF), and Dengue hemorrhagic fever / dengue shock syndrome (DHF/ DSS)) was re-evaluated in 2009 by World Health Organization re-evaluated and proposed two main clinical pictures: DF and severe dengue (SD), and introduced a new concept -the warning signs- [4]. in order to favor the early identification of patients more predisposed to develop complications [5].

Identification of host risk factors associated with a severe presentation can lead also to opportunte medical intervention to prevent death. Among them, white skin color and comorbidities as sickle cell anemia, hypertension, diabetes mellitus and bronchial asthma, were firstly reported as associated with a higher risk of DHF/DSS in Cuban DHF outbreaks [6].

Bronchial asthma is a frequent disease in Cuba. In this commentary we analyse the bronchial asthma as risk factor for the severest form of dengue virus infection in Cuban population. In 1981, dengue 2 (Asian origin) infected approximately 25% of Cuban the population causing in a large DHF/DSS epidemic. During this outbreak was recognized for the first time the bronchial asthma as host risk factor for dengue severity, which was confirmed afterwards in several other dengue Cuban outbreaks (1997: dengue 2 in the municipality of Santiago de Cuba; 2001: dengue 3 in Havana city; 2006: dengue 4 in Havana [7-10] (Table 1). It was also showed in an epidemiological survey made in Havana City after the dengue 3 epidemic (2001) [11]. that 90% of those individuals who suffered DHF had medical antecedents of allergy (Alvarez, personal communication).

Association of bronchial asthma or allergy with severe dengue was later studied by numerous groups [12-17].

Figueirêdo et al found significant association between DHF and reported allergy treated with steroids (OR=2.94; 1.01–8.54) while Teixeira et al. found association between DHF and skin allergy (OR = 1.8; 95% CI 1.1-3.2) after adjusting for skin color, both in Brazilian population. Alternatively, Pang et al., found in Singapore that Dengue patients with pre-existing asthma had 2.14 times higher risk than dengue patients without asthma.

However, other studies did not find this association. Mahmood et al. [16]. In a well-designed study looking for the comorbidities influence in the risk for dengue severe outcome in Pakistan population, did not find any relationship between DHF and bronchial asthma. The very high incidence of allergic diseases in Pakistan in general, and particularly in the Punjab province with the maximum incidence of allergic rhinitis and asthma (44.86%) [18]. Could have influenced in the lack of the association between asthma and dengue reported by these authors.

On the other hand, our report also differed of Alvarado et al., report [17]. which employed a different approach to the Cuban studies. They looked, in a wide study, for differences in dengue clinical presentation and risk for severe dengue in asthmatic patients from Puerto Rico, found no differences in dengue symptoms in those patients, while Cuban studies searched for the frequency of bronchial asthma as medical antecedent in the total of severe dengue cases. Which elements could be implied in the association of an infectious disease as dengue and a non-transmissible disease like asthma? Which possible mechanisms could explain this association? Different host factors related to the immune response could be involved in the association.

Allergic asthma is a complex and chronic inflammatory disorder characterized by bronchial inflammation and airway
obstruction, triggered by inhaled allergens that ultimately promote the activation of the Th2-like T cells and the development of Th2-mediated chronic inflammation. Th2 cells mediate these functions by producing various cytokines such as IL-4, IL-5, and IL-13 [19].

Events so early as the mosquito bite and virus inoculation could be involved in the association of asthma or allergy and dengue after mosquito injection. It has been shown that *Aedes aegypti* salivary gland extracts can modulate anti-viral and Th1/Th2 cytokine responses to virus infection, reducing IFN type I expression and up regulating significantly IL-4 expression [20]. Impaired IFN type I releasing shown in asthmatic patients [21]. Could favors the early spreading of the virus after mosquito inoculation. Besides, the ADE mechanism could lead to early dengue viral dissemination in asthmatic patients. Previous *in vitro* study demonstrated that PBMC collected from asthmatic patients and co-cultured with dengue 2 virus and anti-dengue 1 antibodies showed a significant virus enhancing activity compared with a control group [22]. Mast cells, tissue resident cells that are the main effector cell type of allergic reactions, are highly prevalent in the skin and may be among the first immune cells infected with DENV [23]. Being particularly favored their infection in the presence of pre-existing antibodies from an earlier infection [24]. Mast cell secretory granules contain many different inflammatory mediators including b-hexosaminidase, histamine, proteases and TNF, which are the causative agents of allergic reactions and bronchial inflammation in asthma [25]. Interesting, dengue infected mast cells trigger activation of endothelial cells [26]. Critical event in the pathogenesis of dengue severe disease. In fact, levels of certain mast cell proteins are elevated in patients with DHF compared to those with milder dengue fever [27]. Supporting the role of mast cells in dengue infection, it was reported that treatments of animals using drugs that inhibits the release of mast cells mediators by inhibiting degranulation such as ketotifen (clinically employed for the treatment of asthma) was effective at limiting DENV-induced vascular leakage [28]. Also in this line, in a study of characterization of the host transcriptomic response to DENV infection using the same mice model, ketotifen reduced the aberrant host responses that drive DENV disease severity [29]. Altered host immune responses have been considered as the major factor responsible for dengue pathogenesis. The process of plasma leakage, shock and hemorrhagic manifestations initiated by enhancing infection with DENV virus with the help of opsonizing antibodies, causes an exacerbated immune response which trigger memory Th1 cell activation resulting in cascades of releasing of pro-inflammatory cytokines and chemical mediators recognized as critical element contributing to severe dengue [30].

### Table 1: Bronchial asthma as risk factor for DHF/DSS in Cuban epidemics.

<table>
<thead>
<tr>
<th>DHF Outbreaks</th>
<th>DHF epidemic, 1981 (Children)</th>
<th>DHF epidemic, 1997 (Adults)</th>
<th>DHF epidemic, 2001–02 (Adults)</th>
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</thead>
<tbody>
<tr>
<td>Cases</td>
<td>Fatal cases</td>
<td>DSS</td>
<td>Fatal cases</td>
</tr>
<tr>
<td>Asthma prevalence</td>
<td>23%*</td>
<td>25%*</td>
<td>8.3%</td>
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<td></td>
<td></td>
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<td>16.5%*</td>
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<td>22.2%*</td>
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Significantly different compared to general population.

Data from Bravo et al., 1987; Valdes et al., 1999; González Cortiñas et al., 1999; Gonzalez, et al., 2005.

Exaggerated immune response, but induced by Th2 and T helper 17 (Th17) cells, which serve a major role in allergic diseases [19]. Our group demonstrated in an *in vitro* model culturing PBMC from dengue immune individuals with dengue virus, that a pro-inflammatory Th1 response -mediated by TNFα and IFNγ- is predominant in heterologous dengue virus challenge, compared with homologous [31]. The anti-inflammatory cytokines –IL-10 and TGFβ- were less expressed in PBMC during heterotypic challenge. Furthermore, the study of genetic polymorphism of those cytokines genes in DHF and DF patients showed that high producer genotypes of TNFα and IFNγ genes and low producer genotypes or haplotypes of anti-inflammatory cytokines IL-10 and TGFβ were associated to severe disease outcome [32]. IL-10 and TGFβ have been recognized as critical regulatory mediators synthesized by Treg cells, a sub-population of CD4+ T cells that control the cellular immune response through the inhibition of the proliferation and activities of effecting factors secreted by other T cells [33]. An impaired function of these cells seems to be implicated in the development of a dengue severe disease [34]. Those results support that the equilibrium between regulatory and pro-inflammatory functions seems to determine the outcome of dengue infection. Pro-inflammatory cytokines play also an important role in asthma pathogenesis. TNF-α is expressed in mast cells [35]. And is present in higher concentrations in bronchoalveolar fluid from patients with asthma [36]. But also higher TNF-α and lower IL-10 serum levels have been reported to be associated with a higher frequency of bronchial asthma [37].Persistently increased production of TNF-α in response to lipopolysaccharide-stimulated blood mononuclear cells at birth and at 3 months of age is a predictor for the development of childhood asthma [37]. Different studies suggests that individuals with TNF-α high producer genotypes have increased asthma risk in the case of whites, suggesting that interactions between different ethnicities and genetic variants may contribute to asthma risk [38]. Likewise, white skin color and European ancestry have been associated to severity in dengue infection [39,40]. Alternatively, IL-10 is a potent regulator of inflammatory responses and plays a critical role in controlling allergic airway inflammation [41]. Immune tolerance to allergens has been demonstrated to be mediated by Treg cells [41]. Its impaired expansion is hypothesized lead to the development of allergy and asthma [42]. Other chronic diseases identified as risk factors for severe dengue infection, like diabetes mellitus and hypertension, could share similar pathogenic mechanisms that may influence dengue clinical evolution. For example, some common pathogenic mechanism involved in those comorbidities and dengue could be the ability to activate NLRP3 inflammasome, implicated in translating inflammatory or metabolic danger signals into metabolic diseases like diabetes mellitus, airway
hyper responsiveness [43]. Hypertension [44], and also dengue infection pathogenesis [45]. Additionally, Tregs cells impairment, involved in autoimmune diseases such as type 1diabetes, and in vascular dysfunction of systemic hypertension through the regulation of arterial blood pressure and microvascular function [46]. These cells, also critical in allergic disease control, regulate immune responses to pathogens like dengue. Considering that, it is explainable that bronchial asthma, diabetes and hypertension could be confluent as risk factors for severe dengue. Here we offer several possible explanations to the increased frequency of bronchial asthma patients among severe dengue cases, first reported in Cuban epidemics. Notably, the pathogenesis of both diseases converges in a deregulated immune response. Ongoing studies will allow the complete elucidation of the involving mechanisms and will contribute to the understanding of the immune-pathogenesis of dengue disease, of value for clinical management and vaccine design.

REFERENCES


