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Short Communication

IL1B rs1143634 (+3953) variant associated with severe dengue in Brazilian children

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ABSTRACT

Several variants involved in the expression of proteins related to immunopathological mechanisms have been associated with dengue, but few specifically related to severe dengue. In addition, children are a group with a high incidence and mortality rate due to dengue. Several immunopathological processes developed specifically in children affected with severe dengue partially explain this risk condition. This case-control retrospective study aimed to examine the association of variants in *CD209*, *NFKBIA*, *IL12B*, and *IL1B* genes with severe dengue. These genes encode proteins involved in one of the main pathways of the immune response against dengue virus infection. The study population included affected children and householding controls from Brazil. Genotyping was performed with Real-Time TaqMan assays, and the association analysis was performed with conditional logistic regressions. We found the *IL1B* rs1143634 genotypes carrying the T allele to be associated with susceptibility to severe dengue in children. The lower circulating levels of IL-1β associated with carrying the T allele of the *IL1B* rs1143634 suggest a role of this cytokine in the impairment of the immune response and plasma leakage, and, consequently, in the development of severe dengue.

Keywords: SNPs, Severe dengue, *IL1B*, Association

INTRODUCTION

Dengue is the most important arthropod-transmitted human viral disease, caused by four dengue virus serotypes (DENV-1, DENV-2, DENV-3, or DENV-4), and is a global health problem.[1] The more recent global estimation, based on data between 1990 and 2013, showed that symptomatic cases reach 58.4 million (23.6 million–121.9 million), and 576,900 (330,000–701,200) dengue deaths.[2] In Brazil, 487,763 dengue cases were confirmed in 2015, representing 87% of the total cases in the Americas.[3] Noteworthy is the higher risk of children with dengue shock syndrome (DSS) in Southeast Asian populations, and the risk of hemorrhagic forms in Salvadorian population.[4,5] Moreover, about 53% of dengue deaths occurred in children up to 15 years of age during 2007–2008 in Brazil.[6] Furthermore, symptoms of severe dengue in children, such as continuous severe abdominal pain or tenderness, are highly predictive of relevant plasma leakage, hepatomegaly, and shock.[7,8]

Immunopathological processes partially explains the higher risk condition of children. It has been reported that in children with Dengue Hemorrhagic Fever (DHF), the dysfunction of immune cells, complement, and cytokines increases viral load and tissue damage.[9] This immune dysfunction leads to worsening of the clinical picture in severe pediatric dengue cases, which have lower serum levels of T helper (Th)1 cytokines (IL-1β, IL-2, IL-12, TNF-α, and IFN-γ) and a concomitant increase in inflammatory mediators (IL-6, IL-8, and IL-10).[10]

Pro-inflammatory cytokine expression due to DENV infection is induced by several pathways, including binding of DENV with to the dendritic cell (DC)-specific ICAM-3 grabbing non-integrin (DC-SIGN), encoded by the CD209 gene. The DENV-CD209 interaction induces endosome formation, allowing DENV to enter the DC.[11] Within the endosome, the Toll-like receptor-3 recognizes DENV RNA triggering activation of the NF-κB pathway. Upon NFKBIA degradation, which releases the NF-kB, it translocates to the nucleus, inducing the transcription of several pro-inflammatory cytokine genes.[12] Some of these cytokines are IL-1β and IL-12 that promote the DENV clearance by several immune responses, including IL-1β-induced IFNα/β production and STING signaling, and the expression of IFNγ and IL-12 during activation of Th1 response.[13-15] Furthermore, other studies have correlated the over-expression of pro-inflammatory cytokines with the exacerbated activation of immunity, consequently inducing extravasation and tissue damage in severe dengue.[16,17] Also, DENV protease interaction with NF-κB inhibitor results in endothelial cell apoptosis and hemorrhage development.[12] The high frequency of severe dengue and its symptoms among children, especially those infected by the first time, suggests a genetic basis for the severe dengue. MICB and PLCE1 variants have been associated with susceptibility to severe dengue (not dengue hemorrhagic fever) in more than one population.[18] However, the background genetic contribution to explain their possible effects on NF-κB pathway related to severe dengue has not been explored.

This study aimed to examine the associations of single nucleotide polymorphisms (SNPs) in *CD209*, *NFKBIA*, *IL12B*, and *IL1B* genes, related to the activation of of the mostly T helper (Th)1-induced response, in a sample of Brazilian children with severe dengue and their household contacts. We suggest possible relationships between the evaluated SNPs and severe dengue that possibly result from the immune response to DENV infection.

METHODS

Study design

A case-control retrospective study included a sample of the Rio de Janeiro city population (Rio de Janeiro state, Brazil) with 88 children with severe dengue recruited during the 2007-2008 outbreak. Cases were affected children admitted in Instituto Fernández Figueira – FIOCRUZ, Instituto de Puericultura e Pediatria Martagão Gesteira, Hospital Municipal Jesus, and Hospital da Criança. Forty-nine patients (56%) were confirmed IgM+ serologically using specific ELISA, and all patients were IgG+ when blood was collected during recruitment in 2010 (2 years later of infection). All dengue cases were diagnosed according to the WHO-2009 criteria and were classified with dengue shock syndrome (DSS).[19] We reviewed medical records of recruited dengue cases, and we found at least one or more defining criteria of severe dengue, according to the last published Dengue guidelines (2016): shock or respiratory distress due to plasma leakage, severe bleeding, or severe organ impairment (myocarditis, hepatitis, encephalitis).1 Severe dengue cases had symptoms related to shock (slow capillary filling, hypotension), severe bleeding or fluid leakage related symptoms (hemorrhagic manifestations, constant vomits, persistent abdominal pain, pleural or pericardial effusion or ascites), and symptoms related to hepatitis (high levels of AST and ALT). Patients with either hematological, neoplastic, or autoimmune diseases, transplanted, or HIV positive were excluded from the study.

The control group included 335 children' household members or neighbors (four individuals for each dengue case), excluding relatives and siblings. Controls were healthy or with previous mild dengue (60% IgG positive and 5% undetermined), matched by age with severe dengue cases. Candidate controls with severe dengue history were excluded from the study. More information about the sample features is available in Xavier-Carvalho et al.[20]

Genotyping

Genomic DNA extraction from the whole blood cells was performed by the salting-out method. The DNA quality was assessed using a Nanodrop 2000c (Thermo Scientific) following the manufacturer's instructions. SNPs selected for this study were candidate genes in the immune response, some of them associated with dengue or other inflammatory diseases. For instance, rs7248637 in the *CD209* gene was associated with susceptibility to dengue; rs8904 in the *NFKBIA* gene has been associated with severe pain and osteoarthritis; rs1143634 in the *IL1B* gene was associated with chronic periodontitis and HIV-1 infection; rs3212227 and rs2569253 in the *IL12B* gene have been associated with asthma, HCV infection, and rhinitis.[21-28] Then, the genotyping included one SNP in *CD209*, *NFKBIA*, *IL1B* genes and two SNPs in *IL12B* gene, using allelic discrimination by Real-Time TaqMan assays (Applied Biosystems) in the StepOne Plus Real-Time PCR System. Amplification reactions (5 µl) containing 20 ng/µl DNA, 2.5 µl 2X TaqMan® Master Mix, and 0.25 µl 20X of SNP specific probe (Thermo Fisher Scientific) as follows: C_29710787_10 (rs7248637 *CD209*), C_145670_10 (rs8904 *NFKBIA*), C_9546517_10 (rs1143634 *IL1B*), C_2084293_10

(rs3212227 *IL12B*), and C_2569253_10 (rs2569253 *IL12B*).

Genetic analysis

Genetic ancestry was previously estimated for this sample by Ornellas et al, using 28 Ancestry Informative Markers validated for the Brazilian population.[29,30] Association analysis excluded the SNPs that did not meet Hardy-Weinberg Equilibrium (HWE, χ2-tests). Allelic, genotypic, and allele carrier association analyses were performed by conditional mixed-effects multiple logistic regressions. Due to the cohabiting dependence among participants, it was treated as an aleatory component. Confounding variables (e.g., Age, European, Amerindian, African ancestries, and gender relative frequencies) were included in models, and p-values were corrected for multiple comparisons by FDR. All analyses were carried out with the R software v.3.6.3.

Ethics approval and consent to participate

The ethical approval and all the methods and procedures of this study were approved by the research ethics committee (CAAE 3723.0.000.009–08) of the Instituto Nacional de Infectologia Evandro Chagas/FIOCRUZ. Patients, controls, and their legal guardians were informed of the study and gave their written informed consent.

RESULTS

Population's summary

The sample included 88 cases of severe dengue and 335 household controls, and its description is in Table 1. The groups of cases and controls had a similar mean age, approximately ten years (p=0.957). The cases were matched by gender (43 males and 45 females), and there was a small, non-significant (p=0.339), gender imbalance in the control group (183 males and 152 females) (Table 1). Regarding the genetic ancestry variable, European ancestry was higher in the case group when compared to the control group (p=0.005, Table 1), while African ancestry was higher in the control group than in the case group (p=0.004, Table 1). Overall, European ancestry was the highest, followed by African and Native American ancestry. The proportion of genetic ancestry and gender were included as confounding variables in the model fits.

Table 1. Characteristics of the study subjects from Rio de Janeiro sample (Brazil).

Variables	Rio de Janeiro (n=423)		
	Control group (n=335)	Severe dengue cases (n=88)	P value*
	N (%)	N (%)	
Age (years)	10 (4)	10 (4.25)	0.957
Gender			
Male	183 (43.3)	43 (10.2)	0.339
Female	152 (35.9)	45 (10.6)	
Genetic ancestry			
European	0.52 (0.37)	0.57 (0.29)	0.005
Native American	0.08 (0.15)	0.08 (0.17)	0.49
African	0.34 (0.33)	0.24 (0.27)	0.004

Data were represented as absolute numbers (frequency) for gender and median (interquartile range) for age and genetic ancestry.
*Comparisons between severe dengue cases and control group were performed using Fisher exact test for gender and Mann-Whitney test for quantitative variables.

Table 2. Hardy-Weinberg Equilibrium analysis for SNPs studied in the Rio de Janeiro sample (Brazil).

Gene	SNP	Chiq	P value
CD209	rs7248637	0.0756669907	0.7421
NFKBIA	rs8904	0.0799871209	0.8292
IL12B	rs3212227	0.0206195327	0.9145
IL12B	rs2569253	4.8927364964	0.0295
IL1B	rs1143634	0.5603939939	0.4210

Significant p value <0.05.

Genetic associations

Association analysis was performed with four SNPs rs7248637 (*CD209*), rs8904 (*NFKBIA*), rs1143634 (*IL1B*), and rs3212227 (*IL12B*). The allele frequencies of these SNPs were within Hardy-Weinberg equilibrium, HWE (p value >0.05, Table 2), and had few missing values (<1%) in both groups. SNP rs2569253 was excluded from further analysis because it did not meet the HWE assumption. We found the *IL1B* rs1143634 CT genotype and carrying the T allele (genotypes CT, TT) associated with severe dengue susceptibility [aOR (CI)

=2.35 (1.28-4.33), FDR=0.0244; and aOR (CI) =2.09 (1.16-3.78), FDR=0.0576 Table 3] in the sample of children from Rio de Janeiro. We found no associations of other SNPs analyzed: rs7248637 (*CD209*), rs8904 (*NFKBIA*), or rs3212227 (*IL12B*).

Table 3. Allele/genotype logistic multiple conditional regression analysis in Rio de Janeiro sample (Brazil).

Gene-SNP (Position)	Frequency (%)		Severe dengue cases vs. Control group	
Genotypes/Alleles	**Control group (n=335)**	**Severe dengue cases (n=88)**	**aOR (CI 95%)***	**FDR**
CD209-rs7248637 (+898)				
GG	208 (62.09)	56 (63.64)	Reference	
GA	113 (33.73)	30 (34.09)	0.9 (0.49-1.65)	0.8564
AA	14 (4.18)	2 (2.27)	0.34 (0.04-2.74)	0.3116
GA+AA	127 (37.91)	32 (36.36)	0.83 (0.46-1.51)	0.5432
G	529 (78.96)	142 (80.68)	Reference	
A	141 (21.04)	34 (19.32)	0.8 (0.49-1.33)	0.5313
NFKBIA-rs8904 (+2643)				
CC	103 (31.12)	31 (35.23)	Reference	
CT	161 (48.64)	40 (45.45)	0.67 (0.35-1.26)	0.2872
TT	67 (20.24)	17 (19.32)	0.89 (0.41-1.94)	0.8564
CT+TT	228 (68.88)	57 (64.77)	0.74 (0.42-1.3)	0.5432
C	367 (55.44)	102 (57.95)	Reference	
T	295 (44.56)	74 (42.05)	0.89 (0.61-1.31)	0.5509
IL12B-rs3212227 (+1188)				
CC	109 (32.93)	25 (28.74)	Reference	
AC	163 (49.24)	39 (44.83)	1.06 (0.57-1.97)	0.8564
AA	59 (17.82)	23 (26.44)	1.65 (0.77-3.5)	0.2872
AC+AA	222 (67.07)	62 (71.26)	1.21 (0.68-2.16)	0.5432
C	381 (57.55)	89 (51.15)	Reference	
A	281 (42.45)	85 (48.85)	1.26 (0.86-1.84)	0.4706
IL1B-rs1143634 (+3953)				
CC	233 (69.55)	52 (59.09)	Reference	
CT	95 (28.36)	34 (38.64)	2.35 (1.28-4.33)	0.0244
TT	7 (2.09)	2 (2.27)	0.39 (0.04-4.25)	0.8564
CT+TT	102 (30.45)	36 (40.91)	2.09 (1.16-3.78)	0.0576
C	561 (83.73)	138 (78.41)	Reference	
T	109 (16.27)	38 (21.59)	1.53 (0.95-2.46)	0.3164

*aOR: Adjusted Odds-ratio, model adjusted by gender and ancestry. FDR in bold indicate significant associations (FDR<0.05).

DISCUSSION

Epidemiological and immunopathological studies have shown that children have a high risk of developing severe dengue, and this evidence is consistent with gene expression studies. Transcripts belonging to pathways associated with apoptosis, cytokine signaling, more particularly IFN, and NF-κB were less abundant in children's patients with DSS. Which explains the missing host-defense profile at the time of decompensation in patients with DSS. This attenuated response might be related to intrinsic host-genetic influences on gene expression.[31]

Several variants in the *IL1B* gene were associated with inflammatory-related diseases, including dengue.[32,33] Specifically, the T allele of the rs1143634 (+3953 C/T) on the fifth exon was related to low secretion of IL-1β by peripheral blood monocytes stimulated with lipopolysaccharide taken from healthy individuals, suggesting that low IL-1β levels could be a condition of dengue risk in these Brazilian population.[32] Moreover, other SNP rs1143627 (-31 C/T) in the *IL1B* gene was associated with susceptibility to DSS. The −31C allele turns the region of a TATA box less efficient to bind with relevant transcription factors, leading to *IL1B* down-regulated expression.[34] This study supports that low IL-1β levels are associated with DSS (severe dengue).

Pro-inflammatory cytokine expression is critical to the response to DENV infections. For instance, DENV-2 induces both IL-1β production and STING signaling, resulting in IFNα/β production that restricts DENV-2 infection.[13] Moreover, IL1B mRNA expression and IL-1β blood levels were high in children during the onset of DHF.[35] Also, IL-1β, IL-6, and TGF-β released by activated NLPR3 inflammasome induce both Th17 and the secretion of IL-17.[36] Indeed, increased levels of serum IL-17 in children (<14 years) with severe dengue were

detected and related to both with reducing T-lymphocytes cytotoxic function and with the promotion of vascular leakage.[37]

It seems that in the studied Rio de Janeiro children sample, the association analysis points to the genetic variant in *IL1B* gene leading to a reduced immunity observed through lower IL-1β expression levels. This statement is according to the modulation of a few cytokines from high levels in the DENV-infection onset until low levels after the defervescence phase. At this moment, the patient could develop symptoms of DSS and expression of low circulating levels of IL-1β.[10,38]

Although we found the association with the variant in *IL1B* gene, it is clear that other variants in the same gene can alter its expression, so they also should be evaluated. On the other hand, the size of the analyzed sample is small, so possibly we could not detect lower-risk associations with the other analyzed SNPs. Studies with other gene variants related to immunopathological processes might be made up to understand the contribution of genetic background in the risk of severe dengue.

In summary, we found the association with severe dengue of genotypes including T allele of *IL1B* rs1143634, in a Brazilian children sample. Moreover, this finding suggests that the genetic base of IL-1β may have a role in the impairment of the immune response, the fluid leakage, and the development of severe dengue. Association studies in other populations, and functional analyses with the associated SNP in this study might be conducted to reveal their use as prognostic biomarker.

CONCLUSION

The lower circulating levels of IL-1β associated with carrying the T allele of the *IL1B* rs1143634 suggest a role of this cytokine in the impairment of the immune response and plasma leakage, and, consequently, in the development of severe dengue.

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