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Original Article

TNF-α 308 (rs1800629) and INF-γ +874 polymorphisms in dengue progression: genotype-specific trends amidst allelic non-association in West Africa

Fadilatou Tassembedo[1], Aziz Sidi Aristide Tapsoba[1,2*], Shoukrat Ohuwa Toyin Bello[3], Olawoumi Fabrice Kouta[1], Mousso Savadogo[1], Rogomenoma Alice Ouedraogo[1,4], Dénise P. Ilboudo[1,5*], Lassina Traore[1], Fiffou Yougbare[6], Bolni Marius Nagalo[7,8], Florencia Wendkuuni Djigma[1*], Potiandi Serge Diagbouga[9], Jacques Simpore[1,3]

[1] Université Joseph KI-ZERBO, Laboratoire de Biologie Moléculaire et de Génétique (LABIOGENE), PO Box 7021, Ouagadougou 03, Burkina Faso
[2] Centre Hospitalier Régional de Koudougou (CHR/KDG) BP 300, Burkina Faso
[3] Centre de Recherche Biomoléculaire Pietro Annigoni (CERBA), PO Box 364, Ouagadougou 01, Burkina Faso
[4] Université NAZI Boni, Centre Universitaire de Gaoua, PO Box 1091 Bobo-Dioulasso 01, Burkina Faso
[5] Université Yembila Abdoulaye Toguyeni, BP 54 Fada N'Gourma, Burkina Faso
[6] Centre National de Transfusion Sanguine de Ouagadougou, Burkina Faso
[7] Department of Pathology, UAMS, Little Rock, AR 72205, USA
[8] The Winthrop P. Rockefeller Cancer Institute, UAMS, Little Rock, AR 72205, USA
[9] Biomedical Research Laboratory (LaReBio), Biomedical and Public Health Department, Institute for Research in Health Sciences (IRSS/CNRST), 03 BP 7192, Ouaga 03, Burkina Faso

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Abstract

Dengue, transmitted by Aedes mosquitoes, represents a significant global health challenge due to its complex host-pathogen interactions and varying disease severity. Genetic factors are known to influence the clinical outcome of dengue infections. This study aimed to investigate the potential role of TNF-α gene polymorphism 308 (rs1800629) and INF-γ +874 (rs62559044) in the progression of dengue virus infection. Conducted in the Central region of Burkina Faso, this study included 246 participants, comprising 117 controls and 129 dengue-positive patients. Genotyping of the TNF-α 308 (rs1800629) and INF-γ +874 A/T (rs62559044) polymorphisms was performed using restriction fragment length polymorphism (RFLP) and Amplification Refractory Mutation System PCR (ARMS-PCR) techniques, respectively. Our analysis revealed no significant correlation between lymphocyte count and dengue severity (P = 0.95). Although we did not find an association between the alleles of the SNPs TNF-α 308 (rs1800629) and INF-γ +874 (rs6255904) studied with either DF or severe DS, we cannot conclude the same for their respective genotypes Thus, the AA and GG genotypes of TNF-α are associated with the contraction of DF and DS, respectively; the former is even associated with the progression of DF to the severe form of the disease. For INF-γ AA genotypes are more associated with progression to severe dengue and the AT heterozygote could be associated with a possibility of preventing progression to DS forms. . The A allele frequencies was higher frequency in DF than in DS pour TNF-α 308 , but this difference lacked statistical significance (P > 0.005). With INF-γ tTT genotype was more prevalent in DS, whereas the AT genotype frequencies differed between DF (23.96%) and DS (19.35%). Our results reveal through the allelic levels of TNF-α 308 and INF-γ +874; that the latter would not play a significant role in the progression of dengue virus infection to severe forms. However, previous studies through a clear mechanism show a strong association between the concentrations of these cytokines and the pathogenesis of dengue. This underlines the need for further investigations to elucidate the genetic determinants of the severity of dengue. In particular, a proteomic study coupled with sequencing on a representative population of the West African region would be a great asset in understanding the involvement of the genes of these cytokines in the pathogenesis of dengue.

Keywords: Dengue, Genetic, Polymorphisms, Cytokine, Disease progression.

1. Introduction

Dengue fever, also known as tropical flu, is a re-emerging viral disease transmitted to humans by mosquitoes of the *Aedes genus*. Dengue has been a significant public health problem for several decades, especially in tropical and subtropical regions where its incidence is highest [2]. Each year, around 390 million people are infected with the dengue virus (DENV), with 96 million developing cli-

* Corresponding author.
E-mail address: florencia.djigma@gmail.com (F. W. Djigma); denise.ilboudo@gmail.com (D. P. Ilboudo); aristap87@gmail.com (A. S. A. Tapsoba).
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nical manifestations, leading to 500,000 hospitalizations and 25,000 deaths annually [3]. The first case of dengue in Burkina Faso was reported in 1925 [4]. The country experienced its first dengue epidemic in 2016, with 2,526 suspected cases, including 1,561 probable cases and 20 deaths [5]. By 2023, Burkina Faso had reported 79,867 suspected cases, of which 34,687 were probable, resulting in 349 deaths.

Dengue fever is caused by an 11 Kb positive-sense single-stranded RNA virus belonging to the Flavivirus genus [6, 7]. Five genetically related and antigenically distinct serotypes of the virus have been identified: DENV 1, 2, 3, 4, and 5 [8, 9]. Of these, only DENV 1, 2, 3, and 4 have the potential to cause a range of symptoms from self-limiting fevers to fatal states. Infection with any of the four viral serotypes confers protective immunity against reinfection with the same serotype, while subsequent infections with other serotypes can result in severe dengue [8-10].

Although a vaccine has been approved and authorized by the WHO for use in areas with recurrent epidemics, there is still no specific treatment for the virus. The current vaccine is only partially effective against the four serotypes [11]. The outcome of dengue infection is influenced by complex interactions between viral factors, host genetic characteristics and the host immunological status. Genetic polymorphisms involved in the host immune response can significantly affect disease progression. The main target cells of DENV are circulating monocytes, tissue macrophages, and dendritic cells . New virions produced locally migrate to lymph nodes, presenting DENV to T lymphocytes. TCD8 cells can control viral infection through mechanisms including direct cytotoxicity and production of pro-inflammatory cytokines such as *IFN-γ* and *TNF-α* [12, 13]. It is hypothesized that antibodies involved in the reaction do not eliminate the virus but facilitate its phagocytosis, reducing the secretion of pro-inflammatory cytokines (*IFN-γ*, *TNF-α*) and nitric oxide, thus increasing the viral load and causing the release of vasoactive mediators leading to capillary leak [1]. Pro-inflammatory cytokines tend to increase in dengue virus infection [12]. Infection to DENV induces both innate and adaptative immune response in all type of population. However, it's important to explore all the aspects of dengue pathogenesis to understand role of immune systeme in mediated disease severity. In recent years, there has been growing interest in studying the contribution of genetic variants of *TNF-α 308* and *IFN-γ +874* to genetic susceptibility or resistance to dengue fever (DENV) and its progression towards severe forms of the diseases [14, 15]. Understanding how the *TNF-α 308* gene and *INF-γ +874* influence genetic susceptibility or resistance to dengue virus (DENV) infection is particularly crucial in low-resource areas like Burkina Faso, where healthcare infrastructure is limited and the burden of infectious diseases is high. This study aims to analyze genetic variations in pro-inflammatory cytokines, including *TNF-α 308* (rs1800629) and *INF-γ +874* (rs62559044), to provide essential information on their role in dengue virus infection within the Burkinabé population. This knowledge could significantly contribute to improving patient care in resource-limited settings. The objective of this study was to examine the genetic variations of *TNF-α 308* (rs1800629) and *INF-γ +874* (rs62559044) in individuals infected or not with dengue virus, determine the frequency of these genetic variations in the Burkinabé population, and evaluate their association with dengue virus infection.

2. Material and methods

2.1. Ethics approval and consent to participate

The study was approved by the Health Research Ethics Committee of the Burkina Faso Ministry of Health: N°2022-02-034 dated February 02, 2022, and written informed consent was obtained from participants prior to blood sampling.

2.2. Type and study population

This case-control study, with both descriptive and analytical aims, involved patients of all ages, including children and blood donors from various professions and social categories in Ouagadougou. Blood samples from dengue cases were collected in the laboratories of the Hospital Saint Camille de Ouagadougou (HOSCO) and the Pietro Annigoni Biomolecular Research Center (CERBA) from October 2021 to June 2022. Blood samples from volunteers with no known history of dengue, received during the collection period, served as controls. Patients with well-documented pre-existing pathologies were excluded from this study. For severe cases of dengue fever we refer to the clinical pictures of the patients, namely shock, bleeding and also to biological assessments such as plasma leakage and severe thrombocytopenia

2.3. Samples and data collection

A questionnaire was used to collect socio-demographic, anthropometric, and clinical data from each participant, followed by blood sample collection. The samples were centrifuged at 3500 rpm for 15 minutes, then aliquoted with individual codes and stored at -20°C until use.

2.4. Serological diagnosis

Dengue infection was initially confirmed by testing serum samples from patients using an enzyme-linked immunosorbent assay. The SD BIOLINE Dengue Duo Rapid Test, an in vitro immunochromatographic assay, was used for screening dengue virus infection in human serum, plasma, or whole blood. Subsequently, RT-PCR was performed to confirm the infection and identify the circulating virus type.

2.5. Molecular diagnosis

2.5.1. Extraction, quantification, and purity control of genomic DNA

Genomic DNA was extracted using the FAVORGEN Mini kit, following the manufacturer's protocol. The extracted genomic DNA was quantified and checked for purity using the Bio Drop device.

2.5.2. Amplification

The genetic variations of *TNF-α 308* rs 1800629 were analyzed by PCR-RFLP, a method involving PCR amplification followed by restriction enzyme analysis of the fragments. The GeneAmp PCR System 9700 amplifier was used, following the PCR protocol provided by the manufacturer. The PCR Mix for amplification consisted of 4 µL of master mix, 0.5 µL of each primer, 15 µL of PCR water, and 5 µL of pure DNA. For rs 62559044 polymorphism of the *IFN-γ +874* gene, genotyping was performed

Table 1. Primers and amplification program of TNF-α 308 gene (rs1800629) and IFN-α +874 (rs62559044) genes polymorphisms.

Gene	Polymorphisms	Primers / Sequences	Size (bp)	PCR cycle
TNF-α 308	rs1800629	*F: 5'AGG CAA TAG GTT TTG AGG GCC AT 3'* *A: 5'TCC TCC CTG CTC CGA TTC CG 3'*	107	1 cycle (94°Cat 5mins); 35 cycles (94°C at 40", 60°C at 40"; 72°C at 40") and 1 cycle (72°C at 5 min)
IFN-γ+874	rs62559044	*F(T): 5'TTCTTACAACACAAAATCAAATCT 3'* *F(A): 5'TTCTTACAACACAAAATCAAATCA3'* *A: 5' TCAACAAAGCTGATACTCCA3'*	264	1 cycle (95°Cat 5min); 30 cycles (95°C at 30"; 57.1°C at 30"; 72°C at 30") and 1 cycle 72°C at 5 min

using the Amplification Refractory Mutation System PCR (ARMS-PCR) method. PCR was conducted using 5X FIREPOL® master mix (Solis BioDyne, Estonia). For each sample, two tubes were used: one for the A allele and another for the T allele. The reaction mixture consisted of 1 µL of each primer, 1 µL of genomic DNA (approximately 100 ng/mL), 10 µL of 5X FIREPOL® master mix, and 7 µL of H2O. The A allele tube contained a forward primer for the A allele and the reverse primer, while the T allele tube contained a forward primer for the T allele and the reverse primer. The primers used and application program are shown in Table 1.

2.5.3. Enzymatic digestion

The different genotypes of the amplified polymorphisms rs 1800629 and rs 62559044 were digested by the restriction enzymes NcoI FAST for thirty minutes at 37 °C in a water bath. The enzymatic digestion of each sample was carried out in a total reaction volume of 25 µL, containing enzymatic buffer, pure water and the PCR product. Digestion of the gene by the restriction enzyme NcoI FAST produced three genotypes of different sizes: the AA genotype at 107 bp, the GA genotype at 107 + 87 bp and the GG genotype at 87 bp (Fig. 1). Note that for INF-γ we did not perform any digestion. The different genotypes were identified according to the presence or absence of the allele band. Thus, for the AA and TT homozygotes at 264 bp, we have a single band which appears respectively for A and for T. As for the AT heterozygote, we have a band in A and another in T. (Fig. 2).

2.5.4. Electrophoresis

The amplified and digested products were electrophoresed on 2% agarose gel stained with ethidium bromide, using a volume of 18 µL per sample. The DNA bands were visualized under UV illumination at 132 nm using a transilluminator (Vilber, copyright © 2004-2019 Vilber Lourmat). The results were documented and analyzed (see Fig.1 and Fig.2).

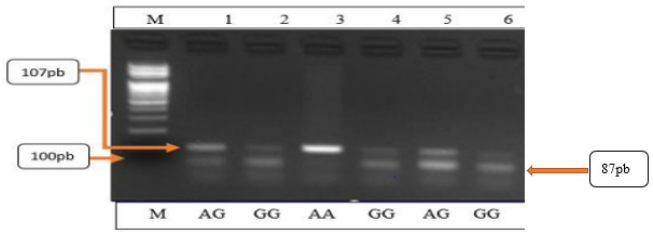

Fig. 1. Electrophoretic migration of the TNF-α 308 A/G gene. Legend: M: molecular weight marker; 1-6: Wells with PCR products.

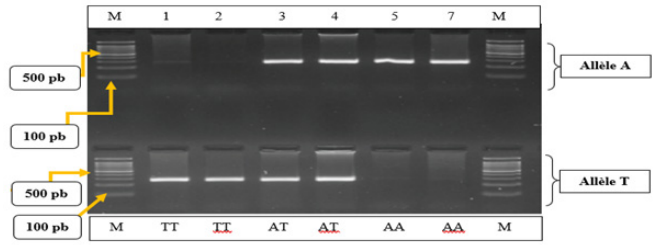

Fig. 2. Electrophoretic migration of the IFN-γ +874-A/T gene.

2.6. Data statistical analysis

Data were entered into Excel and analyzed using R software. The chi-square (χ^2) test was used to compare frequencies. Odds Ratios (OR) and 95% Confidence Intervals (CI) were calculated to measure the strength of association. Results were considered statistically significant if the P value was less than 0.05.

3. Results

3.1. Socio-demographic characteristics

In our study population, a higher number of women were infected with DENV compared to men. The criteria for severe dengue (DS) included clinical symptoms and

Table 2. Sociodemographic data of the population studied.

Variables	D.F. *n* (%)	DS *n* (%)	DF+DS *n* (%)	Witnesses *n* (%)	Total *n* (%)	OR	95% IC	*P-value*
Gender, n (%)								
Man	41 (41.84)	15 (48.39)	56 (43.41)	50 (42.74)	106 (43.09)	-	-	-
Women	57 (58.16)	16 (51.61)	73 (56.59)	67(57.26)	140 (56.91)	1.303	[0.579-2.932]	*0.5397*
Age (years)								
0-19	14 (14.29)	2 (6.45)	16 (12.40)	11 (9.40)	27 (10.98)	-	-	-
20-39	19(19.39)	9(29.03)	28(21.71)	22(18.80)	50(20.33)	0.309	[0.028-1.844]	*0.1621*
≥40	65(66.33)	20(64.52)	85(65.89)	84(71.79)	169(68.70)	0.301	[0.056-1.619)	*0.2775*

signs such as plasma leakage (characterized by an elevation in hematocrit), severe thrombocytopenia, abdominal pain with vomiting, and splenomegaly. Among the participants, 25.58% were classified as severe dengue cases, with no significant difference between men and women. The age group most affected by DENV infection was those over 40 years old (Table 2).

3.2. Serological characteristics of the study population

Table 3 presents the proportions of dengue fever (DF) and severe dengue (DS) infections, distinguishing between primary DENV infections and those with previous exposure. Primary DENV infections accounted for 46.94% of DF cases and 12.90% of DS cases. Among severe dengue cases, 45.16% had at least one previous infection during the acute phase. Antibody serology indicated that 42.86% of the population was either experiencing a secondary infection with another type of DENV or was in a recovery phase.

3.3. Relationship between DENV infection and biological parameters (lymphocyte, platelet and hematocrit)

All analyzed samples were subjected to a complete blood count (CBC) to assess lymphocyte, platelet, and hematocrit levels. These parameters were measured to evaluate their potential involvement in the severity of dengue disease. No statistically significant difference was observed in lymphocyte counts between dengue patients and controls, with a p-value greater than 0.05 (Fig.3). However, a statistically significant difference in platelet and hematocrit levels was found between patients with DENV infection and controls, with p-values less than 0.05 (Fig.4 and Fig.5)

3.4. Genotypic frequencies

The *TNF-α 308* polymorphism (rs1800629) in our study population included homozygous wild-type (GG), homozygous mutated (AA), and heterozygous (AG) genotypes (Fig. 1). The genotypic frequencies of the *TNF-α 308* polymorphism were analyzed in both dengue fever (DF) and severe dengue fever (DS) cases. The AA mutated genotype exhibited a higher frequency in DF cases compared to controls (see Table 4). The *INFγ+874* polymorphism was statistically significantly associated with dengue infection and its progression to the severe form. The TT genotype showed a strong association with severe dengue (DS), with a frequency of 25.20% in DS cases compared to dengue fever (DF) cases, and this association was statistically significant (p-value < 0.05) (Table 4). Conversely, the AT genotype was more frequent in DF cases (23.96%) compared to DS cases (19.35%), suggesting a potential protective effect against progression to severe dengue, also supported by a statistically significant p-value (< 0.05).

3.5. Implication of *TNF-α 308* gene polymorphisms and the *INFγ+874* gene in the pathogenesis of dengue

To evaluate the involvement of gene polymorphisms in the pathogenesis of dengue, we analyzed the different genotypes of the *TNF-α 308* (rs1800629) gene, comparing mutated (AA and AG) and wild-type (GG) genotypes. Also the GA vs GG genotype showed a higher frequency in controls than in dengue patients. Additionally, the AA vs GG genotype was more frequent in patients with dengue fever (DF) compared to controls. The mutated genotypes

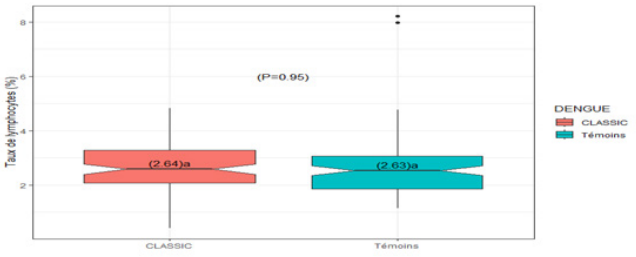

Fig. 3. Representative graph of lymphocyte levels.

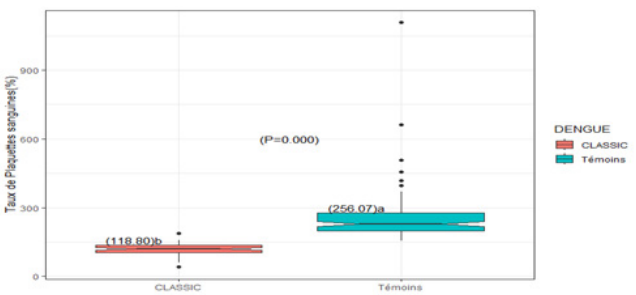

Fig. 4. Representative graph of platelet count.

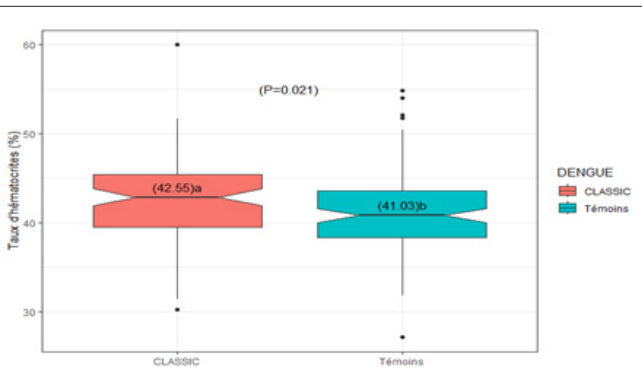

Fig. 5. Representative graph of hematocrit level.

Table 3. Serological data specific to DENV infection in the study population.

DENV serological markers	Witnesses		Dengue (DF)		Severe Dengue (DS)		Total	
	N	%	N	%	N	%	N	%
AgNS1 (+)	0	0	61	62.24	17	54.84	78	31.71
Ac IgM (-) / IgG (-)	117	100	46	46.94	04	12.90	167	67.89
Ac IgM (-) / IgG (+)	0	0	42	42.86	14	45.16	56	22.76
Ac IgM (+) / IgG (-)	0	0	01	01.02	07	22.58	08	03.25
Ac IgM (+) / IgG (+)	0	0	09	09.18	06	19.35	15	06.10
TOTAL	117	100	98	100	31	100	246	100

Table 4. Frequency of TNF-α 308 and INFγ+874 genotypes.

SNP	Genotypes	DF / Witnesses n (%)	DS/Witnesses n (%)	Witnesses n (%)	DS/DF n (%)
TNF- α 308 **(rs1800629)**	GA	37(38.54)	6(19.35)	59(51.30)	43(33.86)
	AA	40(41.67)	12(38.71)	34(29.57)	52(40.94)
	GG	19(19.79)	13(41.94)	22(19.13)	32(25.20)
	HWE p-value	0.0846	0.0008	0.8503	0.0005
INF-γ+874 **(rs62559044)**	AA	52(54.17)	14(4.16)	63(53.85)	66(51.97)
	AT	23(23.96)	6(19.35)	36(30.77)	29(22.83)
	TT	21(21.88)	11(35.48)	18(15.38)	32(25.20)
	HWE p-value	*0.000007377*	*0.0007927*	*0.004132*	*0.00000001043*

Table 5. Implication of the rs1800629, rs62559044 polymorphism of the *TNF-α 308* and *INFγ+874 genes* in dengue.

SNP	Genotypes and alleles	DF n (%)	DS n (%)	Witnesses n (%)	OR	IC (95%)	*P-value*
TNFα-308 **(rs1800629) G/A**	**AA vs. GG**	40(67.80)	12(48.00)	34(60.71)	1,085	[0.536-2.186]	0.817
	GA vs. GG	37(66.07)	6(31.58)	59(72.84)	0.520	[0.262-1.018]	0.053
	GA+AA vs. GG	77(80.21)	18(58.06)	93(80.87)	0.659	[0.346- 1,237]	0.190
	G (%)	75(39.06)	32(51.62)	103(61.29)	0.898	[0.626- 1,287]	0.556
	A (%)	117(60.94)	30(48.38)	127(38.71)	-	-	-
INF-γ+874 **(rs62559044) A/T**	**AT vs. AA**	23(30.67)	6(30.00)	36(36.36)	1,297	[0.712- 2,378]	0.389
	TT vs. AA	21(28.77)	11(44.00)	18(22,22)	0.593	[0.297- 1,156]	0.121
	TT+AT vs. AA	75(78.13)	20(64.52)	99(84.62)	0.9277	[0.559- 1,537]	0.769
	A (%)	127(66.15)	34(54.84)	162(69.23)	-	-	-
	T %)	46(33.85)	19(45.16)	56(30.77)	0.857	[0.562-1.302]	0.467

(AA and AG) showed higher frequencies in controls and DF patients but were reduced in severe dengue (DS) patients. The prevalence of the A allele was higher in DF patients. For the *INFγ+874* (rs62559044) gene, the prevalence of A and T alleles was higher in controls than in DS patients, but this difference was not statistically significant ($P > 0.05$). The combined TT+AT vs AA genotypes had different proportions in DF and DS compared to controls (Table 5). The TT vs AA genotype had a higher proportion in DS patients than in those with DF, indicating a possible association with disease severity.

4. Discussion

The objective of this study was to evaluate the involvement of *TNF-α 308* (rs1800629) and *INFγ+874* (rs62559044) gene polymorphisms in the progression of dengue virus infection towards severe forms of the disease. Effective control of dengue requires a thorough understanding of the immune response. It is therefore appropriate to combine genetics and immunology to understand the mechanisms by which our body protects itself from these viral infections. By studying the genetic factors that influence the immune response to the dengue virus, researchers can identify variations in sensitivity and severity of the disease in different populations [16]. Among the factors involved in the pathogenesis of dengue fever is the host genetic variation related to the expression of cytokines that may contribute to the susceptibility and severity of dengue fever. Therefore, our study on dengue and some host genetic polymorphisms is positioned as a crucial strategy to understand the role of mechanisms in dengue pathogenesis [17]. Previous knowledge therefore supports the hypothesis that genetic polymorphisms in genes related to the innate immune response could contribute to altering cytokine production, thereby modifying the immune response against dengue virus (DENV) and influencing disease outcome and severity [18].

Dengue virus infection leads to endothelial cell production. The majority of DENV-infected cells produce interferons (IFNs). Activation of dendritic cells (DCs) in particular leads to significant production of IFN-α/β and TNF-α, as well as a strong pro-inflammatory response to limit viral dissemination. In addition to IFNs, numerous pro-inflammatory cytokines appear to be important in DENV pathogenicity. These also participate in the activation of natural killer (NK) cells, which in turn produce large amounts of IFN-γ, allowing the control of viral replication and the activation of subsequent adaptive immunity. NK cells also appear to be cytotoxic to DENV-infected cells (Fig 6). An increase in MHC-I molecules on the surface of infected cells could constitute an escape mechanism

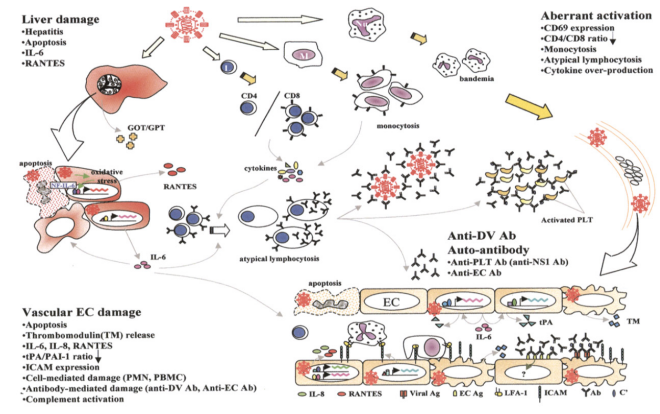

Fig. 6. Summary of the dengue pathogenesis hypothesis [1]

for NK cells. Tumor necrosis factor alpha (TNF-α) gene is a pro-inflammatory cytokine present in chromosome 6, MHC III. It is mainly secreted by different immune cells including macrophages, lymphocytes, neutrophils, mast cells and endothelial cells. This factor plays a major role in biological cascades enabling recruitment and activation of polymorphonuclear leukocytes, macrophages and lymphocytes at the site of infection after TLR engagement in the presence of pathogens. A variety of single nucleotide polymorphisms (SNPs) have been found in the promoter region of the TNF-α gene. Among these, the SNP at -308 in position (G/A) is the most prominent gene polymorphism, which is associated with altered levels of pro-inflammatory mediators and the progression of many communicable diseases such as tuberculosis, leprosy, dengue fever. Another important cytokine in human immunity is interferon gamma (IFN-γ), which is produced by activating T cells, natural killer cells, and macrophages. Its production plays a critical role in macrophage activation and promotes cell proliferation, adhesion, and apoptosis. There is a +874 T/A SNP located at the 5' end of a CA repeat in the first intron of human IFN-γ that may be associated with DF disease [19]

The immunopathogenesis of DHF/DSS is initiated by aberrant immune activation caused by dengue virus. Immune deviation is necessary but not sufficient to trigger subsequent endothelial cell dysfunction and coagulation. This immunological basis reconciles the epidemiological data on the association between secondary infection and DHF/DSS. Immune memory or immune enhancement during secondary infection can stimulate immune deviation, high-affinity autoantibodies, and cytokine overproduction. The ADE hypothesis can be interpreted at its origin that subneutralizing antibodies promote dengue virus entry, thereby increasing viral load. This immunopathogenesis of DHF/DSS may explain the specific features of clinical, pathological, and epidemiological observations of dengue virus infection. DHF/DSS [20].

The study highlights the importance of considering host genetics, and more specifically the +874 T/A polymorphisms of the IFN-γ and TNF-α gene, when assessing the risk of severe forms of dengue.

Elevated levels of TNF-α were first identified as being associated with dengue haemorrhagic fever (DHF) syndrome in 1991 [1]. However, our study found no significant difference between the genotypes examined and the risk of developing the severe form of the disease (p-value > 0.05). This finding aligns with research by Anbalagan et al., which reported consistent levels of *TNF-α* in patients with dengue fever (DF) and severe dengue syndrome (DS) [15]. In contrast, a study by Tran et al. in Vietnam showed a correlation between *TNF-α* levels and dengue severity in infected patients [14].

We observed a higher frequency of the AA mutated genotype in DF patients (41.67%) compared to controls (29.57%). Similarly, the frequency of the GA genotype of the *TNF-α 308* polymorphism (rs1800629) was higher in healthy controls (51.30%) than in DF and DS patients, though this did not reach statistical significance (P = 0.805). Sam and al. also reported a decrease in the frequency of AA and GA genotypes in patients with DS, suggesting that the GA genotype may confer protection against dengue virus (DENV) disease severity [21].

Our results contrast with those of a study by Sánchez-Leyva et al. in a Mexican population, which found an association between the GA genotype and increased susceptibility to severe forms of the disease [22]. Conversely, the GG genotype was associated with an increased risk of developing severe dengue (19.79% in DF cases and 41.49% in DS cases, with a p-value < 0.005). A study by Santos et al. in northern Brazil showed a higher frequency of the GG genotype in patients compared to the control group, although this difference was not statistically significant [14].

Our study found no significant association between the alleles studied and disease severity, although we did observe an increased frequency of the A allele (60.94%) among DF patients compared to the G allele (39.06%) (P = 0.55). Santos et al. also suggested a possible correlation between the presence of the A allele of the *TNF-α 308* gene and protection against severe dengue syndrome [14].

The study of genetic variations in the IFN-γ 874 T/A gene revealed that the allele mutated A was no significant link with the severity of dengue fever, consistent with the conclusions of Fernandez and al. [23]. Looking at the genotypes, we notice that AA would be in the dynamics of favoring the development or even the evolution towards the severe form of dengue, while AT would prevent it. This is in agreement with recent studies which have shown a strong link between INF and DS.

However, other research indicates that IFN-γ may influence vascular permeability and thus contribute to the pathogenesis of dengue disease [24]. A study by Patro et al. suggests that the IFN-γ gene may serve as a predictor of disease severity [10]. Our results show that individuals carrying the AA genotype of the IFN-γ +874 gene are more likely to have increased susceptibility to dengue fever (DF) and severe dengue syndrome (DS) compared to those with the TT and AT genotypes. Additionally, we observed a higher frequency of the AT genotype among controls compared to dengue patients, with a statistically significant difference between these genetic groups (p-value < 0.05). The AT genotype appears to confer resistance to severe dengue. A study by Feitosa et al. found an increased prevalence of the AT genotype and a low occurrence of the TT genotype among controls compared to the dengue-positive and dengue-negative patient group [25].

These observations suggest that for the two SNPs studied, the A alleles could play a role in being associated with a possible possibility of developing DF or even the DS form; while the G and T alleles could play a protective role against the severe form of the disease respectively for the SNPs TNF-308 and INF-874.

This study demonstrates that there is no significant association between the TNF-α 308 and IFN-γ+874 gene alleles in the progression of dengue virus infection to severe forms. However, the AA genotype of the IFN-γ+874 gene increases the risk of dengue, while the AT genotype seems to confer protection against the disease. The present study nevertheless admits limitations that could be lifted by extending the study population to the sub-regions, also by relating the studied polymorphisms with the nature and concentration of cytokines in order to lay the foundations for a probable idea of early diagnostic markers. Studies of the gene sequences could allow to discover the different possible mutations in order to better support their role in the pathogenesis of dengue virus infection.

Abbreviation

Ag: Antigen**; Ab** : Antibody ; **ARMS-PCR** : Amplification Refractory Mutation System PCR; **DENV**: Dengue virus; **DF**: Dengue Fever; **DS**: Severe Dengue; **IFN-γ**: gamma-interferon; **PCR**: Polymerase Chain Reaction; **RFLP**: Restriction Fragment Length Polymorphism; **rs**: restriction sequence; **TNF-α**: Tumor necrosis factor α

Conflict of interests

Author's has no conflicts with any step of the article preparation.

Consent for publications

The author read and approved the final manuscript for publication.

Ethics approval and consent to participate

We have obtain authorization to ethic committee to health at Burkina Faso

Informed consent

Author's declare that patients has gived ther consentment in this study.

Availability of data and material

The data that support the findings of this study are available from corresponding author's upon reasonable request

Authors' contributions

We can assure you that everyone mentioned at the beginning of this article actually participated in its design. Some contributed to the technical aspects of the article, while others kindly enriched it with amendments. Everyone contributed to the best of their skills and knowledge.

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