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Article

Symptomatologic Profile and Associated Factors Observed in Patients with Dengue

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Abstract: Background/Objectives: Dengue is an arbovirus caused by a virus. It is an endemic infectious and occurs in warmer climates. It is not uncommon for the disease to be asymptomatic. However, the severe form can also be triggered and require intensive care. In this sense, patients present a wide variety of symptoms, which can trigger comorbidities such as arthritis, hematologic diseases, liver diseases, kidney diseases, autoimmune diseases, and, mainly, diabetes and hypertension. Among the symptoms, the presence of fever, myalgia, headache, nausea, vomiting, leukopenia, petechiae, retroorbital pain, arthralgia, rashes, skin eruptions, cardiovascular symptoms, respiratory symptoms and, depending on the severity, the presence of hemorrhages may occur. **Methods:** 235 patients' anonymized records from a secondary hospital were analyzed. Ethics approval was obtained and no patients' consent was needed. Statistical analysis used frequency distributions and Chi-square tests, with SPSS software. **Results**: Similar to other studies, our results show that dengue can lead to complications. Furthermore, there was no significant difference in the distribution of the proportion of symptoms between patients with positive and negative serology. However, there was a significant association between age group and symptoms of fever and myalgia, with the occurrence of fever decreasing with increasing age and myalgia being more frequent in adults and less frequent in those <10 years old. **Conclusions**: Dengue can lead to complications, with fever becoming less common and muscle pain increasing as people age. Climate change could spread dengue to new areas. To address this, we need better vaccines and more effective mosquito control.

Keywords: Dengue; DENV 1, 2, 3 e 4; *Aedes* spp; Hematologic Diseases; Leukopenia; Cardiovascular Symptoms; Hypertension.

1. Introduction

Dengue fever is a disease caused by a virus that belongs to the Flaviviridae family. This virus is spread to humans primarily through the bite of female mosquitoes, including Aedes aegypti and, less commonly, Aedes albopictus, among other species. The virus has four main serotypes: DENV 1, 2, 3, and 4. Infection with one serotype confers lifelong immunity against that specific serotype, but re-

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infection with a different serotype can occur. Secondary infection with another serotype increases the risk of developing severe forms of dengue fever [1–3].

During dengue virus infection and replication, several mammalian cell receptor molecules are known to mediate virus binding and entry, including DC-SIGN/L-SIGN [4], heparan sulfate, mannose receptor, laminin receptor, and dopamine receptor. Initially, viral particles bind to these receptors and enter the cell through a process of clathrin-mediated endocytosis [5]. Within the host cell, the virus fuses with the endosome membrane, releasing its viral genome into the cytoplasm. The viral genome is then translated into a single polypeptide, which is cleaved into ten different proteins [6,7]. The structural proteins and newly synthesized viral RNA protrude from the endoplasmic reticulum, where viral particle assembly occurs. Maturation of immature viral particles occurs in the trans-Golgi network, transforming them into complete infectious forms. Subsequently, fully developed viruses are released from the host cell, where they can infect new cells and continue the viral replication cycle [8–10].

This disease has been considered a public health problem in Brazil and in numerous other countries, as the numbers have grown exponentially in recent years [11]. Infection by dengue viruses is influenced by environmental factors such as wind speed, atmospheric pressure, relative air humidity, and temperature, which interfere with the dynamics of vectors, the development of the agent, and the interactions between vectors and humans [12–14]. The epidemiological survey indicates that DENV infection spreads to approximately two-fifths of the world's population, infecting nearly 390 million people annually, resulting in 500,000 hospitalizations and 20,000 deaths. Furthermore, the distribution is mainly in the Eastern Mediterranean, Southeast Asia, Africa, the Western Pacific, and South America due to environmental factors. According to the World Health Organization (WHO), the number of cases has increased year after year (505,430 in 2000 to 5.2 million in 2019), with deaths more than quadrupling from 2000 to 2015 (934 and 4,032 deaths, respectively). Due to the increase in the number of cases, there has consequently been a substantial increase in public and private spending on the disease in affected countries in order to control vectors and recover patients [15,16].

Dengue fever can cause a serious condition characterized by the presence of serious plasma leakage, manifested by hypovolemic shock, accumulation of fluid outside the vessels with respiratory difficulty and/or increased concentration of blood cells, and hemorrhage [17,18]. In addition, it can present with severe bleeding in the gastrointestinal or vaginal tract requiring medical intervention, such as administration of intravenous fluids or blood transfusion. Finally, it can be accompanied by severe organ involvement, which can include significant elevation of liver enzymes (aspartate aminotransferase or alanine aminotransferase ≥1,000 U/L), altered state of consciousness and/or diagnosis of encephalitis, encephalopathy or meningitis, in addition to cardiac involvement or involvement of other organs such as myocarditis, cholecystitis and pancreatitis [19–21].

The symptoms include fever, intense muscle pain, a positive result in the lasso test, decreased white blood cells (leukopenia), and small red spots on the skin (petechiae). In this phase, dengue is classified as classic or without warning signs and can be treated with hydration and appropriate medications. It commonly disappears in a few days. In some cases, other more specific symptoms can be observed later, mainly if the fever subsides around the fifth day. In this phase, the main symptoms are dehydration, loss of appetite, intense vomiting, abdominal pain, and bleeding in the mucous membranes. This phase of dengue is considered a severe condition, and a strategic medical approach should be initiated. In severe dengue, the most worrying scenario is the intense systemic inflammation process, and the consequences may include intense bleeding and blood pressure alterations related to the shock associated with dengue, the main cause of death [22–30]. Although the symptoms of dengue are well known, our daily clinical practice has shown that patients with or suspected of having dengue have shown a change in the symptom profile depending on their age group. Furthermore, due to the severity of the disease, many patients with symptoms but without diagnostic confirmation by serology have been treated as having dengue. On the other hand, patients with confirmed serological diagnosis have presented a different symptom profile than usual. In other words, analyzing whether there is a difference in the symptom profile between patients with and

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without positive serology, as well as whether factors such as sex and age group influence the symptom profile, makes sense in the current context. Furthermore, due to the alarming increase in dengue cases in Brazil and many other countries, increasing knowledge about this disease and its various aspects is urgent. This study aimed to analyze the symptom profile and associated factors of patients diagnosed with dengue.

2. Materials and Methods

2.1. Study Design and Case Study

The sample for this study consisted of 235 patients of both sexes treated at the Medical Specialties Outpatient Clinic or admitted to the Hospital Beneficente Unimar (HBU) - UNIMAR in the city of Marília - São Paulo. Data were collected from anonymized medical records.

2.2. Ethical Aspects

The study only started after approval from the Research Ethics Committee (CEP) of Unimar. Since this is a retrospective study based on medical records, there was no need to sign the Free and Informed Consent Form.

2.3. Statistical Analysis

Qualitative variables were described by absolute (N) and relative (%) frequency distribution. Pearson's Chi-square test, Fisher's exact test or linear association Chi-square test were used to analyze the associations between qualitative variables. The significance level adopted was 5%, and the data were analyzed using SPSS software (version 27.0).

3. Results and Discussion

Dengue fever is a global concern, affecting about half of the world's population and impacting people of all ages, including the very young. Research indicates that individuals with formal education below university level face a higher risk of contracting dengue fever compared to those with higher education. This association may be attributed to lower health literacy among people with less education, both young and old, which makes it difficult for them to understand the risks of dengue fever and the protective measures needed [31–33]. The results of this study show that the largest proportion of the sample is made up of adults (20 to 59 years old) and elderly subjects (>59 years old), but without significant differences in relation to sex (Table 1).

Table 1. Characteristics of the sample in relation to the distribution of absolute (N) and relative (%) frequencies by sex and age group.

Age	Sexo				Total		p-value
	Female		Male				
	N	%	N	%	N	%	
<10 years	3	2.4%	6	5.5%	9	3.8%	0.777
10-19 years	10	7.9%	3	2.8%	13	5.5%	
20-59 years	52	41.3%	43	39.4%	95	40.4%	
>59 years	61	48.4%	57	52.3%	118	50.2%	
Total	126	100.0%	109	100.0%	235	100.0%	

The p-value was calculated using the Chi-square test for linear association.

Older individuals are more susceptible to viral infections and often face more severe outcomes. This is because the frailty associated with aging, which is characterized by the decline in physiological and functional reserves, affects several tissues and organs [34]. The evaluation of elderly patients

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with viral infections is complex due to the high prevalence of multiple comorbidities and the frequently present sensory or cognitive impairment. These patients often present with common geriatric syndromes, such as falls or delirium, rather than the more typical features of viral illnesses seen in younger individuals [35,36]. Additionally, depending on the age group, the places people frequent may increase their vulnerability to viral infections. For example, exposure to outdoor environments may occur for educational purposes, business visits, health care for children or older people, and travel to endemic areas [37]. The mosquito that transmits the disease is predominantly associated with urban areas, which makes urban populations more susceptible to infection. In addition, as age advances, the immune system weakens, increasing vulnerability to viral diseases [38].

The most frequent comorbidities were hypertension and diabetes (Table 2).

Table 2. Absolute (N) and relative (%) frequency distribution of the presence of comorbidities in the sample (n=235).

Comorbidities	N	%
Arthritis	4	1.7
Diabetes	56	23.8
Hematological Diseases	2	0.9
Liver Diseases	12	5.1
Chronic Kidney Disease	1	0.4
Hypertension	89	37.9
Autoimmune Diseases	17	7.2

Available evidence indicates that age, sex, and genetic predisposition can negatively influence the clinical manifestation of the infection, as well as the presence of pre-existing clinical conditions. Studies have shown that people with diabetes mellitus have a four times greater risk of developing severe forms of the disease, while those with hypertension and cardiovascular problems have a two times greater risk [39,40]

Patients with poor glycemic control (HbA1c >7%) are at higher risk of severe complications of dengue compared to diabetics with better glycemic control. In this sense, hyperglycemia can lead to suppression of the immune response, including reduced cytokine production, impaired phagocytosis, and immune cell dysfunction, in addition to increasing the risk of compromise of the natural barrier due to neuropathy, facilitating viral invasion. Furthermore, platelet activity is often increased in type 1 and type 2 diabetic patients, which may interact with neutrophils to promote the activation and release of platelet factor (CXCL4), known to inhibit the interferon pathway and increase dengue virus replication. There is also the possibility that patients with diabetes mellitus infected with the dengue virus are more likely to develop severe forms of the disease. Studies have indicated that blood glucose can facilitate the replication of the dengue virus and promote its transmission by mosquitoes through signaling pathways such as protein kinase B (AKT) and target of rapamycin (TOR)[41–45]. Diabetes is a condition characterized by a chronic inflammatory state that affects the endothelial permeability of blood vessels. This can damage both small and large blood vessels, compromising blood circulation in terms of irrigation and nutrition to the body, as well as venous return. These changes can contribute to increased accumulation of interstitial fluid, preventing the body from "cleaning itself" during severe cases of dengue fever, facilitating the development of severe shock [46–49].

Obesity, which is usually directly associated with the presence of diabetes, is strongly linked to the severity of dengue, adversely influencing several physiological systems [50]. In addition to being a risk factor for several medical conditions, obesity is recognized as a negative prognosis for several infectious diseases. Compromised immunity in obese individuals increases susceptibility to postoperative infections and serious viral infections. The greater vulnerability to infectious disease in obese individuals is likely associated with dysfunction of innate and adaptive immune responses,

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vitamin D deficiency, and elevated levels of circulating total cholesterol and low-density lipoprotein, which harm the body's homeostasis. In addition, obesity influences the expression of harmful cytokines, promoting a pro-inflammatory profile instead of an anti-inflammatory one [51–53].

Likewise, cardiac pathologies such as arterial hypertension and any abnormality on echocardiography were associated with adverse outcomes in patients infected with dengue as well [54]. A similar mechanism may explain why patients with dengue fever and hypertension (or diabetes associated with hypertension) have a 1.6- to 2.16-fold increased risk of developing right heart failure. Individuals with hypertension often have elevated levels of C-reactive protein in their blood, which increases capillary permeability and the risk of clotting disorders [55–58].

Hypertension is a condition characterized by a pro-inflammatory state that results in significant increases in interleukin-6 and C-reactive protein levels in affected individuals. This condition can lead to dysfunction in the vascular endothelium, which may predispose to complications during severe cases of dengue fever [59–63].

Chronic kidney disease poses a significant risk for patients who develop severe dengue fever, as it can predispose them to acute kidney injury. This scenario can be triggered by hemorrhagic shock, rhabdomyolysis, and glomerulonephritis, conditions that can be exacerbated by viral infection [64,65].

Respiratory symptoms are correlated with higher mortality in dengue infection, and conditions such as asthma may contribute to the worsening of the disease. This is due to the release of cytokines and inflammatory cells associated with asthma, which can intensify vascular leakage and increase the risk of developing severe dengue, potentially resulting in fatal complications [66,67]. However, it was not possible to assess these symptoms in this study.

Tables 3 to 6 show the symptoms the patients included in this study presented. The most frequent symptoms were fever, followed by myalgia and headache, but the frequency distribution of symptoms was similar between genders (Table 3).

Table 3. Analysis of the distribution of absolute (N) and relative (%) frequency of symptoms in total and by gender.

Symptoms	Sex				Total		p-value
	Female		male				
	N	%	N	%	N	%	
Fever	87	69.0%	69	63.3%	156	66.4%	0.353
Myalgia	84	66.7%	68	62.4%	152	64.7%	0.493
Headache	62	49.2%	56	51.4%	118	50.2%	0.740
Nausea	50	39.7%	33	30.3%	83	35.3%	0.132
Vomiting	43	34.1%	27	24.8%	70	29.8%	0.118
Leukopenia	15	11.9%	13	11.9%	28	11.9%	0.996
Petechiae	16	12.7%	8	7.3%	24	10.2%	0.176
Retroorbital Pain	14	11.1%	10	9.2%	24	10.2%	0.625
Severe Arthralgia	15	11.9%	7	6.4%	22	9.4%	0.150
Back Pain	5	4.0%	5	4.6%	10	4.3%	0.815
Rash	5	4.0%	4	3.7%	9	3.8%	0.905
Lace Test	1	0.8%	1	0.9%	2	0.9%	0.918

The p-value was calculated using Fisher's exact test for association. * indicates a significant association for p-value ≤ 0.050.

A significant association between age group and symptoms of fever and myalgia was observed. The frequency of fever decreased with increasing age. Myalgia was more frequent in adults and less frequent in those <10 years old (Table 4).

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Table 4. Analysis of the distribution of absolute (N) and relative (%) frequency of symptoms by age group.

Symptom	Age								p-value
	<10 years		10-19 years		20-59 years		>59 years		
	N	%	N	%	N	%	N	%	
Fever	9	100.0%	11	84.6%	69	72.6%	67	56.8%	0.003*
Myalgia	4	44.4%	7	53.8%	72	75.8%	69	58.5%	0.019*
Headache	5	55.6%	7	53.8%	56	58.9%	50	42.4%	0.107
Rash	0	0.0%	0	0.0%	7	7.4%	2	1.7%	0.198
Vomiting	3	33.3%	5	38.5%	32	33.7%	30	25.4%	0.446
Nausea	2	22.2%	4	30.8%	34	35.8%	43	36.4%	0.890
Back Pain	1	11.1%	1	7.7%	4	4.2%	4	3.4%	0.323
Severe Arthralgia	2	22.2%	0	0.0%	9	9.5%	11	9.3%	0.373
Petechiae	1	11.1%	2	15.4%	11	11.6%	10	8.5%	0.630
Leukopenia	0	0.0%	1	7.7%	10	10.5%	17	14.4%	0.697
Lace Test	0	0.0%	1	7.7%	1	1.1%	0	0.0%	0.123
Retroorbital Pain	0	0.0%	1	7.7%	16	16.8%	7	5.9%	0.052

The p-value was calculated using Fisher's exact test for association. * indicates a significant association for p-value ≤ 0.050.

Although the sample contained 235 patients who were referred for Dengue treatment, serological testing was performed on 126 patients, with a positive result in 74 (58.7%). Among the patients who underwent serological testing, no significant difference was observed in the distribution of the proportion of symptoms between patients with positive and negative serology (Table 5).

Table 5. Analysis of the distribution of absolute (N) and relative (%) frequency of symptoms for patients with positive and negative serology.

Symptom	Result				p-valor
	Positive		Negative		
	N	%	N	%	
Febre	49	66.2%	30	57.7%	0.330
Mialgia	45	60.8%	38	73.1%	0.153
Cefaleia	41	55.4%	25	48.1%	0.417
Exantema	1	1.4%	4	7.7%	0.073
Vômito	19	25.7%	20	38.5%	0.126
Náuseas	32	43.2%	17	32.7%	0.232
Dor Nas Costas	5	6.8%	1	1.9%	0.210
Artralgia Intensa	6	8.1%	4	7.7%	0.932
Petéquias	9	12.2%	5	9.6%	0.654
Leucopenia	8	10.8%	9	17.3%	0.293
Prova Do Laço	0	0.0%	1	1.9%	0.231
Dor Retroorbital	7	9.5%	5	9.6%	0.977

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The p-value was calculated using the Pearson's Chi-square test for linear association.

In Table 6, the association analysis was performed, including patients who did not undergo serology testing but who received therapeutic guidance for suspected dengue. No difference was observed in the distribution of the proportion of symptoms among patients without testing, positive testing, and negative testing, which indicates that the symptoms are similar regardless of the serology results or even the absence of testing.

Table 6. Analysis of the distribution of absolute (N) and relative (%) frequency of symptoms for patients with positive and negative serology and absent testing.

Symptoms	Results						p-value
	Without exam		Positive		Negative		
	N	%	N	%	N	%	
Fever	77	70.6%	49	66.2%	30	57.7%	0.111
Myalgia	69	63.3%	45	60.8%	38	73.1%	0.313
Headache	52	47.7%	41	55.4%	25	48.1%	0.790
Rash	4	3.7%	1	1.4%	4	7.7%	0.349
Vomiting	31	28.4%	19	25.7%	20	38.5%	0.282
Nausea	34	31.2%	32	43.2%	17	32.7%	0.590
Back Pain	4	3.7%	5	6.8%	1	1.9%	0.815
Severe Arthralgia	12	11.0%	6	8.1%	4	7.7%	0.452
Petechiae	10	9.2%	9	12.2%	5	9.6%	0.823
Leukopenia	11	10.1%	8	10.8%	9	17.3%	0.224
Lace Test	1	0.9%	0	0.0%	1	1.9%	0.664
Retroorbital Pain	12	11.0%	7	9.5%	5	9.6%	0.749

The p-value was calculated using the Chi-square test for linear association.

As can be seen in Tables 3 to 6, dengue infection can manifest a variety of symptoms or even be symptom-free and is mostly divided into three distinct phases: febrile, critical, and recovery. During the febrile phase, which usually lasts about a week, symptoms include high fever, flu-like symptoms, headache, vomiting, and joint pain. The critical phase, in turn, is characterized by an increased risk of serious complications, such as plasma leakage and possible internal bleeding. Within the critical phase, dengue hemorrhagic fever is marked by abnormal vascular permeability, which can lead to sudden hypovolemic shock, known as dengue shock syndrome. Finally, in the recovery phase, symptoms tend to diminish as vascular permeability is re-established gradually and the patient recovers [68–71].

4. Conclusions and Future Perspectives

Similar to other studies, our results show that dengue can lead to complications. Furthermore, there was no significant difference in the distribution of the proportion of symptoms between patients with positive and negative serology. However, there was a significant association between age group and symptoms of fever and myalgia, with the occurrence of fever decreasing with increasing age and myalgia being more frequent in adults and less frequent in those <10 years old.

Dengue fever is a mosquito-borne infection that has taken hold in almost all tropical countries of the world. Given global warming, climate change, and misinformation, it is highly likely that this range of dengue fever will expand beyond its current limits. Preventive measures such as vaccination, mosquito control, and public health campaigns play a crucial role in reducing the impact of dengue fever in endemic regions. Conventional vaccine approaches such as live attenuated vaccines,

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recombinant subunit vaccines, inactivated virus vaccines, viral vector vaccines, and DNA and mRNA vaccines have been developed to prevent transmission of all dengue serotypes in humans. These strategies work primarily by promoting defense against DENV virions or envelope proteins displayed on the surface of the virus that causes the disease. However, such defense measures require ongoing studies to avoid side effects in all age groups, including people with comorbidities. In addition, new studies must be conducted to identify new sites for vaccine action, such as new proteins, new cellular receptors, not only on the membrane but also in the intracellular environment, and mediators that are essential for survival in the body. Furthermore, with new locations around the world affected by the virus, technological innovations must also address the packaging and greater durability of vaccines to reach new locations that are affected by the virus.

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