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# OCULAR MANIFESTATIONS OF DENGUE: A COMPREHENSIVE REVIEW OF PATHOPHYSIOLOGY AND CLINICAL OUTCOMES

***João Pedro Batista Amaralo***
http://lattes.cnpq.br/6416579593830961

***Julia Araujo Risso***
https://wwws.cnpq.br/cvlattesweb/PKG_MENU.menu?f_cod=4484BD9F67295C-F283E8E05F75AE8CCF#

***Isabella Peixoto dos Santos***
http://lattes.cnpq.br/4791743372358340

***Rodrigo Herman Costa de Araújo***
http://lattes.cnpq.br/2231929028920065

***Henrique Dall Agnol Gonçalves***
http://lattes.cnpq.br/9467658052830973

***Mariana Mayumi Itikawa***
http://lattes.cnpq.br/5069544518155282

***Karla Leticia Santos da Silva Costa***
http://lattes.cnpq.br/4791743372358340

***Henrique Neves Ravenna Picazo*** http://lattes.cnpq.br/4791743372358340

***Breno de Amaral Gandini***
http://lattes.cnpq.br/8200270326480280

***Clarisse Rigon Mallaco***
http://lattes.cnpq.br/4791743372358340

***Mauricio Lopes da Silva Netto***
http://lattes.cnpq.br/4791743372358340

**Abstract: INTRODUCTION** Dengue fever, a mosquito-borne disease caused by the dengue virus, affects millions worldwide, particularly in tropical regions. It manifests with a wide range of symptoms, including severe ocular complications such as uveitis, retinitis, and maculopathy, which can significantly impact patients' quality of life. Understanding the pathophysiology, prevalence, and diagnostic approaches to these ocular manifestations is crucial for improving patient outcomes. **OBJETIVE** To provide a comprehensive review of the pathophysiology, clinical presentation, and management of ocular manifestations in dengue fever, highlighting the importance of early diagnosis and intervention in improving patient outcomes. **METHODS** This is a narrative review which included studies in the MEDLINE – PubMed (National Library of Medicine, National Institutes of Health), COCHRANE, EMBASE and Google Scholar databases, using as descriptors: "Dengue Fever" AND "Ocular Complications" AND "Uveitis" AND "Retinitis" AND "Maculopathy" AND "Optic Neuropathy" in the last years.[2] **RESULTS AND DISCUSSION** Ocular manifestations of dengue include various conditions like anterior and posterior uveitis, retinal hemorrhages, and optic neuropathy, often linked to the severity of systemic infection. The pathophysiological mechanisms involve direct viral invasion, immune-mediated inflammation, and vascular damage. Advanced diagnostic tools like OCT and FA are essential for accurate assessment, while treatment primarily involves corticosteroids and supportive care. Risk factors for severe ocular involvement include severe dengue and secondary infections. Long-term visual outcomes vary, with early intervention being critical for preventing permanent damage. Geographic and demographic variations, as well as co-infections, further influence

the clinical presentation and management of ocular dengue. **CONCLUSION** Dengue-related ocular complications represent a significant yet often overlooked aspect of the disease, necessitating comprehensive clinical awareness and timely management. Preventive measures, advanced diagnostics, and targeted therapies are vital for mitigating these complications and improving patient outcomes. Future research should focus on elucidating the underlying mechanisms and developing novel therapeutic strategies to enhance the care of dengue patients with ocular involvement.
**Keywords:** Dengue; Ocular Manifestations; Retinal Hemorrhages; Vision Impairment

## INTRODUCTION

Dengue fever, caused by the dengue virus (DENV), is a mosquito-borne tropical disease prevalent in many parts of the world, especially in tropical and subtropical regions[1]. The virus is primarily transmitted by Aedes aegypti mosquitoes. Dengue has a significant global impact, with an estimated 390 million infections annually, of which about 96 million manifest clinically[2]. The disease presents with a wide spectrum of symptoms, ranging from mild febrile illness to severe dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS), both of which can be fatal without proper medical intervention[3]. The clinical presentation of dengue varies widely among individuals. Common symptoms include high fever, severe headache, retro-orbital pain, myalgia, arthralgia, and rash. The disease progresses through three phases: febrile, critical, and recovery[4]. The critical phase, which occurs around the time of defervescence, is associated with increased vascular permeability, leading to plasma leakage, hemorrhagic manifestations, and organ impairment in severe cases. The recovery phase is characterized by reabsorption of leaked fluids and gradual improvement of clinical symptoms[1,2].

Dengue pathophysiology involves a complex interplay between the virus and the host's immune response[4]. Upon infection, DENV targets dendritic cells and macrophages, initiating a robust immune response. This response includes the production of pro-inflammatory cytokines and chemokines, which contribute to the systemic symptoms of dengue. Severe dengue is often associated with immune enhancement phenomena, such as antibody-dependent enhancement (ADE), where pre-existing non-neutralizing antibodies from a previous infection with a different DENV serotype exacerbate the infection[5].Understanding the impact of dengue on ocular health necessitates a brief review of the eye's anatomy and physiology. The eye is a complex organ composed of the cornea, lens, retina, choroid, and optic nerve, each with distinct functions. The retina is particularly susceptible to vascular and inflammatory insults due to its rich blood supply and immune privilege status. Any disruption in the ocular microenvironment, such as from viral infections, can lead to significant visual impairment[6].The ocular involvement in dengue was first reported in the early 20th century, with sporadic cases of retinal hemorrhages and uveitis described in dengue epidemics. Over the past few decades, there has been a growing recognition of the spectrum of ocular manifestations associated with dengue, ranging from mild transient conditions to severe and potentially blinding complications. Early studies laid the groundwork for understanding the pathophysiology and clinical spectrum of dengue-related ocular diseases[7].

Dengue can affect various parts of the eye, leading to a wide range of ocular manifestations[8]. These include anterior uveitis, intermediate uveitis, posterior uveitis, panuveitis, retinal

vasculitis, retinal hemorrhages, maculopathy, optic neuritis, and oculomotor nerve palsies. The pathogenesis of these conditions involves direct viral invasion, immune-mediated damage, and vascular changes induced by the systemic effects of dengue[9].The prevalence of ocular complications in dengue varies across studies, with estimates ranging from 10% to 50% among hospitalized patients. Factors influencing these variations include the study population, severity of dengue, diagnostic criteria, and geographic location. Recent studies suggest that ocular involvement may be underreported, particularly in resource-limited settings where access to ophthalmologic evaluation is limited[10].

Ocular complications from dengue can have a profound impact on patients' quality of life, causing visual impairment and blindness in severe cases[11]. Visual loss, even if temporary, can affect daily activities, work productivity, and psychological well-being. The long-term visual prognosis depends on the severity of the ocular involvement and the timeliness of intervention. Patients with persistent visual deficits may require ongoing ophthalmic care and rehabilitation[12]. Diagnosis of ocular involvement in dengue relies on a combination of clinical examination and imaging techniques. Fundoscopy, optical coherence tomography (OCT), fluorescein angiography (FA), and indocyanine green angiography (ICGA) are commonly used to evaluate retinal and choroidal changes. Laboratory tests, including serology and polymerase chain reaction (PCR), confirm dengue infection and help differentiate it from other viral infections with similar ocular manifestations[13].

Despite the increasing recognition of ocular manifestations in dengue, there remains a lack of comprehensive reviews synthesizing the current understanding of their pathophysiology, clinical presentation, and management[14]. This review aims to fill this gap by providing an in-depth analysis of ocular changes during and after dengue infection, highlighting the need for heightened awareness among healthcare providers and researchers. By consolidating existing knowledge and identifying areas for further research, this review seeks to contribute to the improved diagnosis, treatment, and prevention of dengue-related ocular complications[15].

## OBJETIVES

To provide a comprehensive review of the pathophysiology, clinical presentation, and management of ocular manifestations in dengue fever, highlighting the importance of early diagnosis and intervention in improving patient outcomes.

### SECUNDARY OBJETIVES

1. To analyze the spectrum of ocular complications associated with dengue and correlate these with the severity of the systemic infection.
2. To evaluate the diagnostic accuracy of current methods used in detecting ocular involvement in dengue patients.
3. To review treatment strategies and their effectiveness in managing dengue-related ocular conditions.
4. To identify risk factors and demographic variations influencing the prevalence and severity of ocular manifestations.
5. To assess the long-term visual outcomes and impact on patients' quality of life.

## METHODS

This is a narrative review, in which the main aspects of the pathophysiology, clinical presentation, and management of ocular manifestations in dengue fever, highlighting the importance of early diagnosis and intervention in improving patient outcomes were analyzed. The beginning of the study

was carried out with theoretical training using the following databases: PubMed, sciELO and Medline, using as descriptors: "Dengue Fever" AND "Ocular Complications" AND "Uveitis" AND "Retinitis" AND "Maculopathy" AND "Optic Neuropathy" in the last years. As it is a narrative review, this study does not have any risks.

Databases: This review included studies in the MEDLINE – PubMed (National Library of Medicine, National Institutes of Health), COCHRANE, EMBASE and Google Scholar databases.

The inclusion criteria applied in the analytical review were human intervention studies, experimental studies, cohort studies, case-control studies, cross-sectional studies and literature reviews, editorials, case reports, and poster presentations. Also, only studies writing in English and Portuguese were included.

## RESULTS AND DISCUSSION

Dengue fever's ocular manifestations encompass a diverse array of conditions, including uveitis, retinitis, maculopathy, and optic neuropathy[16]. Anterior uveitis presents with redness, pain, and photophobia, while posterior uveitis can cause floaters and blurred vision. Retinal involvement often manifests as retinal hemorrhages, cotton wool spots, and macular edema. Dengue maculopathy, characterized by yellowish-white retinal lesions, has been frequently reported in endemic areas. Optic neuropathy, although rare, can lead to significant visual loss and is often associated with severe systemic[17]. The pathophysiology of ocular manifestations in dengue involves direct viral invasion, immune-mediated inflammation, and vascular compromise[18]. Dengue virus can invade ocular tissues, as evidenced by the detection of viral RNA in ocular fluids. Immune responses, particularly T-cell mediated and cytokine-driven inflammation, play a crucial role in the development of uveitis and retinitis. Vascular endothelial damage and increased permeability contribute to retinal hemorrhages and macular edema. The interplay between these mechanisms underscores the complexity of dengue-related ocular pathology[19]. Several risk factors have been identified for the development of ocular complications in dengue patients. Severe dengue, characterized by plasma leakage, hemorrhage, and organ impairment, is a significant risk factor. Additionally, secondary dengue infection, involving a different serotype from the initial infection, is associated with an increased risk of severe ocular involvement due to immune enhancement mechanisms. Other risk factors include the presence of comorbidities such as diabetes and hypertension, which exacerbate vascular and inflammatory responses[20].

The severity of ocular manifestations often correlates with the severity of systemic dengue. Patients with severe dengue, including DHF and DSS, are more likely to develop sight-threatening ocular complications[21]. Retinal hemorrhages and maculopathy are commonly observed in these patients, reflecting the systemic vasculopathy and coagulopathy associated with severe dengue. Early recognition and management of systemic severity can thus play a crucial role in preventing or mitigating ocular complications[22]. Diagnostic accuracy for dengue-related ocular complications is critical for timely and appropriate management[23]. Fundoscopy remains the primary tool for initial evaluation, but advanced imaging modalities like OCT and FA provide detailed insights into retinal and choroidal changes. OCT is particularly useful for assessing macular edema and structural changes in the retina, while FA and ICGA help delineate vascular abnormalities. Combining these

diagnostic methods enhances the accuracy and comprehensiveness of ocular assessments in dengue patients[24].

Treatment of dengue-related ocular manifestations is primarily supportive, focusing on managing inflammation and preventing complications[25]. Corticosteroids are commonly used to control uveitis and macular edema, but their use must be carefully balanced against the risk of exacerbating systemic dengue. Antiviral therapies, though not yet standard for ocular dengue, hold potential based on emerging evidence from other viral uveitides. Intravitreal injections of anti-VEGF agents have shown promise in managing severe macular edema and retinal vascular leakage[26]. The long-term visual outcomes of dengue-related ocular complications vary depending on the severity and timely management of the condition[27]. While many patients recover with minimal or no visual impairment, others may suffer from persistent visual deficits, including chronic uveitis, retinal scarring, and optic atrophy. Follow-up studies indicate that early intervention, particularly in severe cases, significantly improves the prognosis and reduces the risk of long-term complications[28].

Ocular complications from dengue significantly impact patients' quality of life, affecting their ability to perform daily tasks and diminishing their overall well-being. Visual impairment, even if temporary, can lead to loss of independence and productivity[29]. Chronic ocular conditions may require long-term treatment and monitoring, imposing a financial and emotional burden on patients and their families. Psychological support and rehabilitation services are crucial components of comprehensive care for these patients[30]. Preventing ocular complications in dengue patients involves both public health measures to reduce dengue transmission and clinical strategies for early detection and management. Public health efforts, including vector control and vaccination programs, are essential in reducing the incidence of dengue[31]. Clinically, healthcare providers should maintain a high index of suspicion for ocular involvement in dengue patients, particularly those with severe or secondary infections. Regular ophthalmologic evaluations and prompt treatment of ocular symptoms can prevent severe complications and improve outcomes[32].

Future research should focus on elucidating the molecular mechanisms underlying dengue-related ocular complications, identifying biomarkers for early detection, and developing targeted therapies[33]. Studies investigating the role of genetic predisposition and immune response variations could provide insights into individual susceptibility to ocular manifestations[33]. Additionally, clinical trials assessing the efficacy and safety of antiviral and immunomodulatory treatments for ocular dengue are needed to establish evidence-based management guidelines[34]. Ocular manifestations of dengue exhibit geographic and demographic variations, influenced by factors such as endemicity, healthcare infrastructure, and genetic predispositions[35]. In regions with high dengue endemicity, such as Southeast Asia and Latin America, the prevalence and severity of ocular complications are notably highe[r35]. Demographic factors, including age, gender, and comorbidities, also play a role in the variability of ocular presentations. Understanding these variations is crucial for developing region-specific management and prevention strategies[36].

Co-infections with other arboviruses, such as Zika and Chikungunya, complicate the clinical picture of dengue and its ocular manifestations[37]. Co-infections can exacerbate inflammatory responses and increase the risk of severe ocular involvement[38]. For instance, Zika virus is known to cause congenital ocular

abnormalities, and its co-infection with dengue may lead to more complex and severe ocular pathology. Detailed studies on the interplay between these viruses are essential for comprehensive clinical management[39]. The onset and duration of ocular manifestations in dengue patients vary widely, with some symptoms appearing during the acute phase of infection and others developing weeks to months later[40]. Acute-phase manifestations, such as uveitis and retinal hemorrhages, are typically linked to systemic inflammatory responses, while late-onset complications, such as optic neuropathy, may result from prolonged immune-mediated damage. Understanding the temporal patterns of ocular involvement aids in timely diagnosis and intervention[41].

The immune response to dengue plays a pivotal role in the development of ocular complications. Studies have shown that both innate and adaptive immune mechanisms contribute to ocular inflammation and tissue damage[42]. T-cell mediated responses and the release of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), are implicated in the pathogenesis of dengue-related uveitis and retinitis. Further research into the immunological pathways involved could lead to novel therapeutic targets[43]. Genetic factors may influence susceptibility to ocular complications in dengue patients. Polymorphisms in genes related to immune response, such as those encoding cytokines and their receptors, could affect the severity and nature of ocular involvement. Familial clustering of severe dengue cases with ocular complications suggests a potential genetic component[44]. Identifying genetic markers associated with increased risk could enable personalized risk assessment and tailored preventive strategies[45].

Detailed case studies and clinical reports provide valuable insights into the clinical spectrum and management of dengue-related ocular complications[46]. Case reports highlight rare and severe manifestations, such as bilateral optic neuropathy and exudative retinal detachment, and document the outcomes of various treatment approaches. Reviewing these reports helps clinicians recognize atypical presentations and informs evidence-based management practices[47]. Comparing the ocular manifestations of dengue with those caused by other viral infections, such as herpes simplex virus (HSV) and cytomegalovirus (CMV), can highlight unique and overlapping features. While HSV and CMV primarily cause anterior segment inflammation, dengue predominantly affects the posterior segment[48]. Understanding these distinctions aids in differential diagnosis and appropriate management. Additionally, lessons learned from the treatment of other viral uveitides can inform therapeutic strategies for dengue-related ocular diseases[49].

The economic burden of managing dengue-related ocular complications is significant, encompassing direct medical costs, such as hospitalizations and treatments, and indirect costs, such as lost productivity and long-term care. In resource-limited settings, the economic impact is exacerbated by the lack of access to advanced diagnostic and therapeutic services[50]. Economic analyses underscore the need for cost-effective public health interventions and the allocation of resources for comprehensive dengue management[51]. Patient compliance with treatment regimens for dengue-related ocular complications is critical for successful outcomes[51]. Non-compliance can lead to suboptimal treatment, prolonged inflammation, and permanent visual impairment[52]. Factors influencing compliance include patient education, access to healthcare, and socioeconomic status.

Studies assessing compliance rates and associated outcomes can identify barriers to effective treatment and inform strategies to enhance adherence[53,54,55].

The psychosocial impacts of vision impairment due to dengue are profound, affecting patients' mental health, social interactions, and overall quality of life[56]. Vision loss can lead to anxiety, depression, and social isolation[57]. Addressing these psychosocial aspects through counseling, support groups, and rehabilitation services is essential for holistic patient care. Integrating psychosocial support into the management of dengue-related ocular complications can improve patient outcomes and quality of life[58,59,60].

## CONCLUSION

In conclusion, dengue fever's ocular manifestations represent a significant and often under-recognized aspect of the disease's clinical spectrum. This review highlights the diverse range of ocular complications associated with dengue, including uveitis, retinitis, maculopathy, and optic neuropathy. The pathophysiological mechanisms involve direct viral invasion, immune-mediated inflammation, and vascular compromise. Identifying risk factors, such as severe dengue and secondary infection, is crucial for early recognition and intervention.

The correlation between the severity of systemic dengue and ocular involvement underscores the importance of comprehensive clinical management. Advanced diagnostic tools, such as OCT and FA, enhance the accuracy of ocular assessments, while treatment strategies, including corticosteroids and anti-VEGF agents, offer promising outcomes. Long-term follow-up and supportive care are essential to mitigate the impact on patients' quality of life.

Preventive measures, including public health efforts to reduce dengue transmission and regular ophthalmologic evaluations for at-risk patients, are vital. Future research should focus on elucidating molecular mechanisms, exploring genetic predispositions, and developing targeted therapies. By consolidating current knowledge and addressing gaps in the literature, this review aims to contribute to the improved diagnosis, treatment, and prevention of dengue-related ocular complications, ultimately enhancing patient care and outcomes.

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