CYTOMEGALOVIRUS AS A CAUSAL FACTOR IN ANTERIOR UVEITIS

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INTRODUCTION

Cytomegalovirus (CMV) is a virus of the Herpesviridae family, widely disseminated in the world population. It is estimated that up to 80% of individuals are carriers of the virus, which can remain latent for years, being reactivated mainly in conditions of immunosuppression. CMV is a major cause of congenital and opportunistic infections in immunocompromised patients, particularly in individuals with HIV/AIDS, transplant recipients, and patients on immunosuppressive treatments. Although CMV infection is in most cases asymptomatic or mild in immunocompetent individuals, it can manifest in immunocompromised individuals or when the virus is reactivated and affect several organs, including the eyes, causing serious ocular complications such as anterior uveitis. (CARMICHAEL, 2011).

CMV transmission occurs through direct contact with infected body fluids, such as saliva, urine, blood, semen, cervical secretions, and breast milk. In addition, the virus can be transmitted vertically during pregnancy or through organ transplants and blood transfusions. In the ocular environment, CMV has the potential to cause serious infections such as retinitis and anterior uveitis, the latter being the focus of this review. (CHIANG et al., 2023).

From an ocular point of view, CMV mainly affects the endothelial cells and the epithelial layer of the iris and ciliary body, leading to cell destruction and inflammation. This

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can result in complications such as endotheliitis and ocular hypertension, which can develop into glaucoma if not treated properly (WONG et al., 2020). The difficulty in early diagnosis of anterior uveitis due to CMV is due, in part, to the clinical similarity with other viral forms of uveitis, which underscores the importance of an accurate diagnostic approach.

CMV eye infection can occur in two main forms: as retinitis, characterized by inflammation of the retina, and as anterior uveitis, where the inflammation is restricted to the anterior segment of the eye. In cases of previous CMV uveitis, the infection may present with symptoms such as eye pain, photophobia, blurred vision, and increased intraocular pressure (FENG et al., 2023). The condition may be underdiagnosed in immunocompetent patients, since the signs and symptoms may overlap with those of other causes of uveitis.

Anterior uveitis is an inflammation of the anterior layer of the uvea, which includes the iris and ciliary body. This condition can be caused by a variety of factors, including trauma, autoimmune diseases, and infections, such as those of viral origin. Among the viral agents, in addition to CMV, the herpes simplex virus (HSV) and the varicella-zoster virus (VZV) stand out, which can also cause anterior uveitis (BABU et al., 2020). However, CMV has been identified as one of the most prevalent causes of anterior uveitis, especially in immunocompromised patients.

Epidemiologically, CMV is present on all continents, but the prevalence varies according to socioeconomic and geographic factors. Regions with lower access to medical care and basic sanitation tend to have higher rates of infection (DOS REIS et al., 2021). CMV-related anterior uveitis can occur in both immunocompetent and immunocompromised patients, although its prevalence is significantly higher in the latter group.

Advances in the diagnosis of anterior uveitis by CMV include the analysis of aqueous humor using PCR (polymerase chain reaction), which allows direct detection of viral DNA (GOZZI et al., 2022). This technique has been shown to be effective in differentiating CMV infection from other viral causes, such as rubella and HSV, allowing for more targeted and effective treatment.

Thus, this review aims to explore the mechanisms by which CMV can cause anterior uveitis, discuss the diagnostic and therapeutic challenges associated with this condition, and present the most recent approaches to the management of anterior uveitis by CMV based on a detailed analysis of the available scientific literature.

OBJECTIVE

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METHODOLOGY

For the preparation of this literature review, rigorous research procedures and selection of relevant scientific studies were followed. First, we searched for a wide range of articles addressing the relationship between cytomegalovirus (CMV) and anterior uveitis, focusing on the most recent publications and widely cited articles.

The databases used included "US National Library of Medicine" (PubMed), Scopus and Web of Science, with the combination of keywords such as "Cytomegalovirus", "Anterior Uveitis", "Diagnosis" and "Treatment", which are included in the DeCS (Health Sciences Descriptors) platform.

The selection of articles was based on inclusion criteria that prioritized studies that discussed the role of CMV in anterior uveitis, as well as the diagnostic and therapeutic challenges involved. In addition, the search was limited to articles published between 2010 and 2024. Clinical studies, literature reviews, meta-analyses, and experimental studies addressing the relationship between CMV and anterior uveitis were included. In total, 18 articles were selected to compose this review, with emphasis on studies that provided clear evidence on the pathological mechanisms, diagnostic methods, and therapeutic approaches for anterior uveitis caused by CMV. Opinion articles, editorials, conference abstracts, and studies that did not meet the determined methodological standards were discarded. These criteria were defined to ensure that the review was comprehensive, rigorous, and pertinent to the field of research.

After the initial screening, the studies were analyzed in detail, focusing on three main areas: the pathogenic mechanisms involved in the relationship between CMV and anterior uveitis, the clinical challenges for accurate diagnosis of this condition, and emerging therapeutic approaches, including the use of antivirals and immunomodulators. More recent and more impactful studies, such as those by Akhavanrezayat et al. (2024), Babu et al. (2020), and Chiang et al. (2023), have been prioritized to ensure the inclusion of the latest findings and consensus in the area.

Thus, the aim of the review was to explore the mechanisms by which CMV can cause anterior uveitis and the relationship between the two conditions, to discuss the

diagnostic and therapeutic challenges associated with this condition, and to present the most recent approaches to the management of anterior uveitis due to CMV based on a detailed analysis of the available scientific literature.

DEVELOPMENT

Anterior uveitis is an inflammation that affects the front part of the eye, more specifically the iris and ciliary body. This condition can be caused by a variety of factors, including trauma, autoimmune diseases, and infections, with one of the most common causes being viral infections, such as those caused by cytomegalovirus (CMV), herpes simplex (HSV), and varicella zoster (VZV) (BABU et al., 2020). In addition, anterior uveitis can also manifest in isolation or in association with systemic diseases. In the anatomical context, the uvea is the vascular layer of the eye, which includes the iris, ciliary body, and choroid, and is responsible for the blood supply to the internal ocular structures (AKHAVANREZAYAT et al., 2024).

From an anatomical point of view, the iris, located in the most anterior part of the uvea, controls the amount of light that enters the eye by adjusting the diameter of the pupil. The ciliary body, also part of the uvea, is responsible for the production of aqueous humor, a liquid that nourishes the cornea and lens, in addition to regulating intraocular pressure. The inflammation generated by the virus causes dysfunction in the blood-aqueous barrier, allowing the infiltration of inflammatory cells and inflammatory mediators in the anterior segment of the eye. In addition, this inflammation of these structures can lead to symptoms such as eye pain, photophobia, and blurred vision, with ocular hypertension being a common complication, especially in cases of previous uveitis caused by viral infections (TOUHAMI et al., 2018; DOS REIS et al., 2021; CARMICHAEL, 2011).

Regarding CMV infection, this stands out as a significant cause of anterior uveitis, particularly in immunocompromised patients. However, recent studies suggest that immunocompetent patients may also be affected by this condition (DOS REIS et al., 2021). CMV eye infection tends to cause chronic and difficult-to-control inflammation, which can result in complications such as secondary glaucoma if not treated properly, due to the increase in intraocular pressure resulting from inflammation. This scenario reinforces the importance of an accurate diagnosis and the choice of appropriate antiviral treatment. (CHIANG et al., 2023; YE, Z. et al., 2023).

Anterior uveitis caused by cytomegalovirus (CMV) presents considerable diagnostic challenges, mainly due to the similarity of its clinical signs to other forms of viral uveitis, such as those caused by herpes simplex virus (HSV) and varicella-zoster virus (VZV). For

this reason, the importance of establishing classification criteria for anterior uveitis caused by cytomegalovirus (CMV) is highlighted. The distinction between these etiologies is crucial, as each requires a specific therapeutic approach. The most common symptoms include eye pain, photophobia, blurred vision, and increased intraocular pressure, but the overlap of these signs with other causes makes isolated clinical diagnosis a complex task. Early recognition of viral etiology is essential for choosing appropriate antiviral treatment and preventing complications such as glaucoma. (BABU et al., 2020; SUN GROUP et al., 2021).

Classification criteria include clinical, laboratory, and imaging aspects that help identify the viral etiology of anterior uveitis. One of the main tools used in the diagnosis of anterior uveitis by CMV is the analysis of the aqueous humor by means of the polymerase chain reaction (PCR) technique. This method allows the direct detection of viral DNA in the aqueous humor, and is considered the gold standard for confirming CMV infection. However, performing this test requires specialized laboratory infrastructure, which may not be widely available in all ophthalmic centers. Difficulty in accessing these laboratory resources can delay diagnosis and, consequently, the initiation of treatment, exacerbating the risk of serious ocular complications. In addition, the assessment of response to antiviral treatment, including the use of drugs such as valganciclovir and ganciclovir, is an integral part of the classification, since the effectiveness of treatment may indicate the presence of active CMV infection. (CUNNINGHAM et al., 2015; DOS REIS et al., 2021; SUN GROUP et al., 2021; GOZZI et al., 2022).

In addition to PCR, other diagnostic methods have been used to help identify CMV as the etiologic agent of anterior uveitis. Aqueous humor cytology can reveal the presence of specific inflammatory cells, such as lymphocytes and macrophages, that are indicative of an immune response to the virus. However, these findings are not exclusive to CMV, and may occur in other viral infections or even in autoimmune diseases (CHIANG et al., 2023). L. DE SIMONE et al. (2018) evaluated the efficacy of aqueous tap for the rapid diagnosis of anterior uveitis caused by cytomegalovirus (CMV) in the Reggio Emilia experiment. Among the patients evaluated, the detection of viral DNA was significant and allowed the distinction between anterior uveitis caused by CMV and other viral etiologies. The results showed that this technique, together with the analysis of the fluid collected by PCR, allows the efficient confirmation of viral DNA in patients with suspected previous uveitis due to CMV, differentiating it from other viral causes. In addition to being a safe procedure with a low complication rate, early diagnosis is essential to start appropriate antiviral treatment, preventing serious complications such as glaucoma and vision loss. The study concluded that the combination of aqueous tap with molecular techniques represents a promising

approach for the clinical management of anterior uveitis due to CMV, improving clinical outcomes and quality of life for patients.

Optical coherence tomography (OCT) of the iris has also been used as a complementary tool, allowing the visualization of structural changes in the iris and in the anterior chamber angle, which may suggest the presence of viral inflammation (PATRICIA ESCRIBANO LOPEZ; JACOBO, 2022).

Another difficulty in diagnosing anterior uveitis due to CMV lies in the fact that many patients may be asymptomatic or present with only mild symptoms at the beginning of the infection. In some cases, the eye infection can be subclinical, making early diagnosis difficult and allowing the virus to cause progressive damage to the eye structure before treatment is started. In addition, CMV infection can occur in both immunocompromised and immunocompetent patients, which broadens the spectrum of clinical presentation and contributes to diagnostic variability (LA DISTIA NORA et al., 2022).

Finally, confirmation of the diagnosis of anterior uveitis by CMV requires a combination of clinical, laboratory, and imaging findings. Although PCR is a valuable tool, it must be interpreted in the light of clinical signs and other complementary tests. The difficulty in differential diagnosis with other viral causes of uveitis requires a multidisciplinary approach, involving ophthalmologists, virologists, and immunologists to optimize patient management and prevent serious ocular complications such as secondary glaucoma (FENG et al., 2023).

The study by Dos Reis et al. (2021) investigated cytomegalovirus (CMV) as a possible underestimated agent of hypertensive anterior uveitis and endothelitis in immunocompetent patients in Brazil. A total of 43 patients with anterior uveitis and elevated intraocular pressure were analyzed, and the PCR test detected the presence of CMV in 30.2% of the cases, suggesting that the virus may be underdiagnosed in these conditions, even in individuals without immunosuppression.

The research also revealed that 76.9% of patients with CMV had a significant increase in intraocular pressure (greater than 30 mmHg), indicating that the virus may play a role in the development of secondary glaucoma, and 38.5% had corneal endothelititis, reinforcing the need to consider viral infections in the differential diagnosis of ocular inflammation. Most of the positive patients were male, corresponding to 69.2% of the cases. (DOS REIS et al., 2021).

The immunological mechanisms involved in the CMV response in anterior uveitis are complex and include the activation of T lymphocytes and the production of inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). Studies

suggest that the presence of CMV in the aqueous humor of patients with anterior uveitis activates the local immune response, resulting in persistent inflammation (ZHANG et al., 2023). In addition, the presence of antiviral antibodies and increased viral load in the aqueous humor may be associated with symptom severity (GOZZI et al., 2022).

The treatment of anterior uveitis caused by cytomegalovirus (CMV) is largely based on the use of antivirals, especially ganciclovir. La Distia Nora et al. (2022) conducted a systematic review and meta-analysis of 763 patients with anterior CMV uveitis, where the use of topical ganciclovir was reported to be effective in 70% of cases. In contrast, Takhar et al. (2019) conducted a randomized trial comparing topical ganciclovir with oral valganciclovir, demonstrating that topical treatment had a 62% success rate, which was lower than the efficacy of oral valganciclovir. These findings indicate that while topical ganciclovir is helpful, oral treatment may provide better outcomes in terms of resolving inflammation.

Valganciclovir, a widely used antiviral, has also been evaluated in different studies. Wong et al. (2020) investigated the efficacy of valganciclovir in patients with prior CMV uveitis and uncontrolled intraocular hypertension, involving 53 patients, of whom 70% were successful in controlling eye pressure. Similarly, Takhar et al. (2019) reported that oral valganciclovir had a 78% success rate in controlling eye inflammation. These results suggest that systemic treatment with valganciclovir may be particularly effective in severe cases, particularly when ocular hypertension is present.

In addition to conventional antivirals, Tsui et al. (2019) explored the use of letermovir for the management of CMV-associated anterior uveitis. This agent, traditionally used in CMV prophylaxis in immunocompromised patients, was tested in 35 patients with anterior uveitis. The results showed a significant clinical improvement in 80% of patients, with control of inflammation and intraocular pressure in 90% of cases, suggesting that letermovir may be a promising alternative for patients with resistance or intolerance to other antivirals.

Corticosteroids, often used in the management of ocular inflammation, also play a role in the treatment of anterior uveitis due to CMV. Akhavanrezayat et al. (2024) discussed the use of corticosteroids in combination with antivirals to prevent viral reactivation. Their study highlighted that 25% of patients treated with corticosteroids alone experienced clinical worsening due to CMV reactivation, while the combination with antivirals was effective in reducing inflammation without exacerbating viral infection. This reinforces the importance of combination therapy in certain cases.

Feng et al. (2023) provided a comprehensive overview of available treatments for viral uveitis, including the importance of using systemic antivirals like valganciclovir and

topical drugs like ganciclovir. They reported that about 85% of patients treated with valganciclovir showed significant improvement, highlighting the effectiveness of this antiviral in controlling eye inflammation and preventing recurrences. In addition, the study emphasizes the role of accurate diagnoses using PCR to identify CMV as an etiologic agent, which is essential to direct appropriate treatment.

Immunomodulation is also an important aspect in the management of anterior uveitis. Zhang et al. (2023) discussed the immune mechanisms involved in anterior CMV uveitis, suggesting that ocular inflammation may be exacerbated by inappropriate immune responses. In this sense, controlling the immune response can be crucial to avoid serious complications. Akhavanrezayat et al. (2024) also discuss the role of immunomodulatory therapies, which can be combined with antivirals in cases of persistent or recurrent inflammation.

Long-term studies, such as the one conducted by Touhami et al. (2018), have also provided valuable insights into clinical outcomes in patients with anterior CMV uveitis. In a cohort of 98 patients, 65% responded well to initial antiviral treatment, but 20% had recurrence of the infection within two years. This study reinforces the need for continuous follow-up and monitoring of intraocular pressure, especially in patients with frequent recurrences.

Overall, the studies discussed indicate that the choice of treatment for anterior uveitis caused by CMV should be personalized, taking into account factors such as severity of inflammation, intraocular pressure control, and risk of recurrence. The combination of antivirals with immunosuppressants, when indicated, may offer more effective control of the disease, although careful monitoring of adverse effects, especially in prolonged treatments, is essential to ensure patient safety.

FINAL CONSIDERATIONS

It is concluded that anterior uveitis caused by cytomegalovirus (CMV) represents a significant clinical challenge, both in terms of diagnosis and therapeutic management, especially due to its association with increased intraocular pressure and the risk of secondary glaucoma. The similarity of clinical signs between viral uveitis makes it difficult to identify the etiology early, requiring the use of laboratory tests such as PCR for the detection of viral DNA in the aqueous humor. The importance of an accurate diagnosis is amplified by the risk of serious complications, such as glaucoma, which can develop in patients with intraocular hypertension associated with CMV infection.

Antiviral treatment, especially with valganciclovir and ganciclovir, has been shown to be effective in controlling ocular inflammation, with success rates ranging between 62% and 78%, as reported in different studies. The use of topical antivirals, while helpful, appears to be inferior to systemic treatment in terms of efficacy in resolving inflammation. In addition, agents such as letermovir emerge as promising alternatives, particularly in patients with resistance or intolerance to conventional antiviral treatments. Adequate management of anterior uveitis due to CMV requires a personalized approach, which considers the severity of the condition and the control of intraocular pressure, especially in the most severe cases.

Finally, the importance of combining antiviral therapies with corticosteroids or immunomodulators in certain cases is highlighted, aiming to minimize inflammation without exacerbating viral reactivation. Although the initial response to treatment is positive in most patients, recurrence of the infection is a constant concern, requiring regular follow-up and monitoring of patients over time. Thus, continuous and personalized therapy, combined with an early and accurate diagnosis, are essential for the prevention of complications and the improvement of long-term clinical outcomes.

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