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Non-infectious uveitis: A review of clinical, diagnostic and therapeutic approach to the disease

Uveíte não infeciosa: Uma revisão sobre abordagem clínica, diagnóstica e terapêutica da doença

Uveítis no infecciosa: Una revisión del enfoque clínico, diagnóstico y terapéutico de la enfermedad

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Abstract
The incidence of non-infectious uveitis (NIU) is influenced by genetic and environmental factors. This disease has a clinical picture similar to other eye pathologies, it becomes difficult to obtain accurate diagnosis. The research aims to review the clinical, diagnostic and therapeutic approach of NIU. To achieve this objective, there was a bibliographic review study based on therapeutic guidelines and scientific articles published in MedLINE from 2018 to 2023. The evidence presented based on the investigated literature gives us that before starting to the Therapy, it is necessary to perform the proper diagnosis and choose the best therapy that preserves anatomical structures and improves the patient's vision. In addition, it is worth mentioning that the base of NIU treatment remains immunosuppressants and corticosteroids, the latter known for having eye and systemic side effects. Currently to minimize these effects, therapy has been introduced with biological products, which provides better visual acuity, reduces intraocular inflammation, decreases the systemic dose of corticosteroids and minimizes adverse effects. However, its use requires caution as it has already been reported to occur demyelinating disorders in a small group of patients. NIU is always associated with a systemic or idiopathic autoimmune condition. Thus, for a good clinical, diagnostic and therapeutic approach, it is necessary that there is close collaboration between the ophthalmologist and doctors of other specialties (rheumatologist) to have an accurate diagnosis and discard other associated comorbidities, avoiding complications that cause blindness.
Keywords: Non-infectious uveitis; Diagnosis; Treatment.

Resumo
A incidência da uveíte não infecciosa (UNI) é influenciada por fatores genéticos e ambientais. Esta doença por apresentar um quadro clínico semelhante a outras patologias oculares, torna-se difícil de obter o diagnóstico preciso. A pesquisa tem como objetivo revisar a abordagem clínica, diagnóstica e terapêutica da UNI. Para alcançar esse objetivo, realizou-se um estudo de revisão bibliográfica com base em diretrizes terapêuticas e artigos científicos publicados no MedLINE no período entre 2018 a 2023. As evidências apresentadas com base na literatura investigada, dá-nos a entender que antes de iniciar a terapia, é necessário realizar o diagnóstico adequado e escolher a melhor terapia que preserve as estruturas anatômicas e melhore a visão do paciente. Além disso, vale realçar que a base do tratamento da UNI continuam a ser os imunossupressores e os corticosteroides, estes últimos conhecidos por apresentar efeitos colaterais oculares e sistêmicos. Atualmente para minimizar esses efeitos introduziu-se a terapia com produtos biológicos, que proporciona melhor acuidade visual, reduz a inflamação intraocular, diminui a dose

sistêmica de corticosteroide e minimiza os efeitos adversos. Entretanto, a sua utilização é preciso cautela, pois já foi relatado a ocorrência de distúrbios desmielinizantes em um pequeno grupo de pacientes. A UNI sempre é associada a uma condição autoimune sistêmica ou idiopática. Assim sendo, para uma boa abordagem clínica, diagnóstica e terapêutica, é necessário que exista estreita colaboração entre o oftalmologista e médicos de outras especialidades (reumatologista) de modo a ter um diagnóstico preciso e descartar outras comorbidades associadas, evitando complicações que causem a cegueira.
Palavras-chave: Uveíte não infecciosa; Diagnóstico; Tratamento.

Resumen
La incidencia de uveítis no infecciosa (UNI) está influenciada por factores genéticos y ambientales. Esta enfermedad presenta un cuadro clínico similar a otras patologías oculares, dificultando la obtención de un diagnóstico certero. La investigación tiene como objetivo revisar el abordaje clínico, diagnóstico y terapéutico de la UNI. Para lograr este objetivo se realizó un estudio de revisión bibliográfica con base en guías terapéuticas y artículos científicos publicados en MedLINE en el período comprendido entre 2018 y 2023. La evidencia presentada con base en la literatura investigada, nos da a entender que antes de iniciar la terapia, es Es necesario realizar el diagnóstico adecuado y elegir la mejor terapia que preserve las estructuras anatómicas y mejore la visión del paciente. Además, cabe destacar que la base del tratamiento de la UNI siguen siendo los inmunosupresores y los corticosteroides, estos últimos conocidos por tener efectos secundarios oculares y sistémicos. Actualmente, para minimizar estos efectos se ha introducido la terapia con productos biológicos, que proporciona una mejor agudeza visual, reduce la inflamación intraocular, reduce la dosis sistémica de corticoides y minimiza los efectos adversos. Sin embargo, su uso requiere precaución, ya que ya se ha informado de la aparición de trastornos desmielinizantes en un pequeño grupo de pacientes. UNI siempre se asocia con una enfermedad autoinmune sistémica o idiopática. Por tanto, para un buen abordaje clínico, diagnóstico y terapéutico, es necesario que exista una estrecha colaboración entre el oftalmólogo y médicos de otras especialidades (reumatólogo) para tener un diagnóstico certero y descartar otras comorbilidades asociadas, evitando complicaciones que provoquen ceguera.
Palabras clave: Uveítis no infecciosa; Diagnóstico; Tratamiento.

1. Introduction

Uveitis is considered a public health problem in several regions, and is often associated with complications that can lead to visual impairment (VI) and blindness. Depending on the degree of inflammation, uveitis can have a significant impact on reducing visual acuity (VA), causing changes in the iris, ciliary body, vitreous humor, retina, and choroid (Hasegawa et al., 2019).

The diseases that most contribute to the emergence of NIU are: Vogt-Koyanagi-Harada disease (VKH) and Behcet disease (BD). Some studies raise the hypothesis that the combination of certain genetic and environmental factors may be responsible for the appearance of many forms of NIU (Hou et al., 2020). The occurrence of NIU has been reported in children, young people and adults, with a significant impact on quality of life and representing a burden of around 5 to 10% of VI globally (Burek-Michalska & Turno-Kręcicka, 2020).

The clinical diagnosis of this disease has been a cause for concern for several professionals, taking into account that it presents a clinical picture similar to other ocular pathologies, a detailed ophthalmological and systemic investigation is always necessary to have the diagnosis confirmed and to carry out appropriate treatment (Rathinam et al., 2020).

Conventional treatment for NIU has been corticosteroids and immunosuppressants. However, the resistance and side effects of prolonged use of corticosteroids (can cause glaucoma and cataracts) have forced treatment with biological products to be added. Biological therapy has gradually been used in the treatment of NIU, in cases of refractory uveitis, intolerance or to reduce ocular and systemic adverse effects associated with chronic use of corticosteroids. The agent tumor necrosis factor inhibition (anti-TNF) therapy, targets inflammation at the molecular level with fewer side effects (Gupta et al., 2022).

It is crucial that treatment is adapted according to the severity of the disease, as severe ocular involvement can provide information about the therapeutic approach in each situation (Hysa et al., 2021). Furthermore, when choosing each type of therapy or route of administration be it systemic, periocular regional or intravitreal, it is necessary to evaluate the advantages and disadvantages of each case, and it is essential that the ophthalmologist knows the benefits and possible complications of

each therapy. (Couret et al., 2019; Shahab et al., 2019). This will allow the best therapeutic choice to be made that culminates in controlling inflammatory activity, reducing complications and preserving vision (Garweg, 2019; Wang et al., 2021)

Understanding clinical, diagnostic and therapeutic mechanisms can assist in the development of new therapeutic strategies, reducing avoidable blindness worldwide and preventing the harmful impact of this disease on society (Egwuagu et al., 2021). Due to the arguments presented above, it is justifiable to carry out this research, whose main objective is to review the NIU clinical, diagnostic and therapeutic approach.

2. Methodology

This is a narrative literature review that aims to review the clinical, diagnostic and therapeutic approach to NIU. To achieve this objective, searches were carried out in the Medical *Literature Analysis and Retrieval System Online* (MedLINE) database via PubMed, using the following key words: "Non-infectious uveitis", "treatment" and "diagnosis", with the support of Boolean operators " AND" and "OR", in addition to the use of the NIU clinical protocol and therapeutic guidelines. Articles published from 2018 to 2023 were included.

The research was carried out from September to December 2023, following all 10 steps in the research process, namely defining the title of the article; formulation of the research question; identification of key words; choosing the best databases to carry out research on the subject under study; application of time limits (last 5 years); combination of search terms with the support of Boolean operators; execution of research; adaptation of the search strategy using synonyms; selection of articles; organization of results and discussion (Watson, 2020).

The best reviews synthesize primary studies to draw broad theoretical conclusions about a given subject, linking theory to evidence and evidence to theory. The main goal of a literature review is to create solid scientific evidence on a topic in order to reach robust conclusions and implications (Siddaway et al., 2019).

This research is a narrative review as it does not require a rigid protocol to carry it out, being characterized by an arbitrary selection of articles and subjective perception of the contents (Cordeiro et al., 2007). Furthermore, in this review model, several authors maintain that there is no need to exhaust all data sources, nor to use a comprehensive search strategy, with the selection and interpretation of articles left to the researchers' discretion (Mattos, 2015). Furthermore, it allows the reader to acquire and update knowledge on a given subject, through the authors' personal interpretation and critical analysis (Rother, 2007). Thus, narrative review research in health enables a flexible and rigorous approach that allows for a clearer interpretation, analysis and understanding of the various topics that have been the subject of questioning (Sukhera, 2022).

3. Results and Discussion

3.1 Definition and clinical manifestations

3.1.1 Definition

Uveitis is defined as a disease characterized by inflammation of the uvea or uveal tract, a highly vascularized region responsible for nourishing the eyes, composed of the ciliary body, the iris, and the choroid (Bonnet & Brézin, 2020).

3.1.2 Clinical manifestations

Anterior uveitis (AU) can be unilateral or bilateral, presenting the following clinical manifestations: pain, blurred vision, ocular discomfort, red eye, cells in the anterior chamber with enlargement, loss of corneal sensitivity or reduced sensitivity. Another sign that can be seen is an atrophied iris, which will culminate in an irregular pupil. In terms of complications, cases of episcleritis or scleritis may occur. Furthermore, coin-shaped keratic precipitates may be found on the

cornea, leading to corneal endocarditis, iridocyclitis, increased intraocular pressure (IOP), as well as the formation of posterior synechiae (Gozzi et al., 2022).

Intermediate uveitis (IU) is generally painless and unilateral, and is often characterized by: myodesopsis, blurred vision, photophobia, red eye, reduced visual field (VF), contrast sensitivity and difficulty distinguishing colors (Abraham et al., 2021).

In turn, posterior uveitis (PU) presents with little or no pain, with frequent symptoms of vision loss, changes in VF, retinal whitening, glanulomatous precipitates at the vitreoretinal interface, chorioretinal lesions and vascular lining (Pichi et al. al., 2022)

Finally, pan-uveitis (PANU) can be unilateral or bilateral, with clinical signs in both the anterior and posterior segments, presence of inflammatory cells, multiple small serous detachments around the optic disc and folds of the retinal pigment epithelium (RPE), cells and enlargement in the anterior segment, cells and haze of the vitreous, chorioretinal lesions, retinal whitening, with the main symptom being a marked reduction in vision (Therssen et al., 2022).

3.2 Pathophysiology

The pathophysiology of NIU is still not well understood. However, there are several theories that attempt to explain the occurrence of this pathological condition, one assumes that in NIU the inflammation arises from an immune response triggered against antigens in the eye, being a process driven by T cells and mediated by B cells and other cells of the system. immune systems that spread inflammation. In turn, NIU caused by autoimmune diseases arises when an immune response is triggered against native intraocular antigens (Chang et al., 2021).

The main non-infectious diseases of uveitis are genetically associated with human leukocyte antigen (HLA) alleles, classified into major histocompatibility complex (MHC) class I and MHC class II. The MHC class I molecule participates in mediation by cells (CD8-positive cytotoxic T cells). While MHC class II molecules participate in humoral immunity (CD4-positive T helper cells) (Takeuchi et al., 2021).

3.3 Classification

The Standardization of Uveitis Nomenclature (SUN) Working Group (WG), classified uveitis based on anatomy, etiology and clinical activity. One of the main objectives of this classification was to create a certain specificity in the diagnosis to guarantee homogeneous groups of patients in scientific studies (Heiligenhaus et al., 2021).

3.3.1 Anatomical classification

In anatomical terms, uveitis can be classified into AU, IU, PU and PANU. AU, which is the most common, can be divided into iritis if the inflammation affects only the iris and iridocyclitis if it involves the iris and *pars plicata* (Gueudry & Muraine, 2018). In turn, IU is characterized by inflammation in the vitreous area, absence of inflammation in the retina and choroid (*pars plana*) (The Standardization of Uveitis Nomenclature [SUN] Working Group [WG], 2021a). PU presents with changes that involve the retina and choroid. Lastly is PANU, a complex inflammation that involves the entire structure of the uvea (SUN-WG, 2021b).

3.3.2 Clinical classification

Regarding clinical characteristics, it can be divided into acute, chronic and recurrent. It is considered acute when it presents with a sudden onset and with clinical manifestations that persist for a maximum period of 3 months, being chronic

when it exceeds a period of 3 months and/or with relapses in less than three months after stopping treatment, with the onset of many sometimes insidious and without symptoms. And finally recurrent, when there are repeated episodes separated by untreated inactive periods (Kalogeropoulos et al., 2023).

3.3.3 Etiological classification

In relation to etiology, they can be divided into infectious, where there is the presence of the infectious agent; and non-infectious, which are assumed to be immune-mediated, and can be further subdivided into those that are associated with a known systemic disease and those that have an unknown cause (idiopathic) (Burkholder & Jabs, 2021).

3.4 Diagnosis

The diagnosis of NIU is based on a clinical approach that begins with a detailed anamnesis, complete ophthalmological examination (VA, assessment of pupillary reflexes, anterior segment biomicroscopy, tonometry and fundoscopy), where typical clinical signs of uveitis must be observed. , such as the presence of keratic precipitates, cells in the aqueous and vitreous humor, aqueous flare, increased IOP, lens opacity, retinal changes (retinal edema and retinal ischemia), iris nodules, koeppe nodules and busacca nodules (Ministério da Saúde, 2020).

It may be necessary to perform fluorescein angiography and ocular ultrasound as complementary tests. Immune complex typing (HLA-B27), optical coherence tomography, radiography and magnetic resonance imaging may be necessary to investigate associated systemic diseases. Furthermore, it is essential to rule out infectious and neoplastic causes based on laboratory tests. If it is associated with other systemic diseases, the ophthalmologist must work in collaboration with other medical specialties (Bertrand et al., 2019).

3.5 Treatment

The choice of treatment for NIU is generally influenced by several factors, which include anatomical location (AU, IU, PU and PANU), presence of systemic disease, laterality (unilateral or bilateral), degree of inflammation and possibility of complications (blindness) (Balasubramaniam et al., 2022). NIU has been related to a systemic or idiopathic autoimmune condition, and its treatment involves the composition of a multidisciplinary team with different medical specialties, such as collaboration between the Ophthalmologist and the Rheumatologist, thus providing an ideal treatment. It is worth highlighting that before starting therapy, it is necessary to carry out an adequate diagnosis and choose the best therapy that preserves the anatomical structures and improves the patient's vision (Gamalero et al., 2019).

After excluding infectious etiology, local and systemic corticosteroids have been the drugs of choice, with timely treatment within 6 weeks being crucial. In case of high doses of corticosteroid administration, it is necessary to introduce and alternate with immunomodulators. If inflammation is not controlled, therapy can be complemented by treatment with biological products, which have been successful in 65-80% of cases and guarantee anatomical integrity (Garweg, 2019).

Generally in the treatment of NIU, corticosteroids have been the first line of treatment, being administered topically, commonly prednisolone acetate 1% or dexamethasone 0.1%, which respond well in isolated AU, due to the ease of penetration of the anterior segment of the eye. . Furthermore, in many cases it has been common to use corticosteroids combined with mydriatic and cycloplegic agents such as cyclopentolate 1% or atropine 1%, to prevent posterior synechiae and pigment deposition in the anterior lens capsule (Gamalero et al., 2019). Cycloplegics may experience ocular adverse effects such as allergic conjunctivitis and increased IOP, and systemic adverse effects such as drowsiness and disorientation (Balasubramaniam et al., 2022).

In turn, the therapy of choice for IU, PU and non-infectious PANU has been systemic corticosteroids such as methylprednisolone (30 mg/kg), as topical administration drugs alone do not allow good tissue penetration of the affected anatomical areas. Furthermore, the choice of route of administration may be conditioned by the recurrence of uveitis, duration, laterality, association with systemic inflammatory disease and the presence of contraindications. Furthermore, the use of immunosuppressants such as methotrexate, cyclosporine A or azathioprine are part of the therapeutic options in case of resistance to corticosteroids, dependence on corticosteroids in high doses (7 to 10 mg/day) or immediately in cases of Behçet's disease (Couret et al., 2019).

Several studies have reported resistance to corticosteroids and immunosuppressive agents in the treatment of pediatric uveitis, however, treatment using biological therapy, especially Adalimumab, has been shown to be effective in pediatric patients, providing better VA, reducing ocular inflammation, decreasing systemic dose of corticosteroid and minimizing side effects. Oh, et al (2019) demonstrated that Adalimumab can be effective by applying a standard dose of 20 mg subcutaneously every two weeks in children weighing less than 30 kg.

In 2019, the Food and Drug Administration accepted the use of the anti-TNF therapy adalimumab for the treatment of IU, PU and PANU. Furthermore, it has been proven that the anti-TNF drugs adalimumab and infliximab are effective in NIU, being second-line therapy for most forms of NIU, although they can be considered first-line therapy for uveitis associated with Behçet's disease and juvenile idiopathic arthritis (Thomas, 2019).

Biological therapy can be used to treat uveitis in children and adults. It has been reported in studies that most children treated with Adalimumab had a significant improvement in VA due to the effectiveness of the therapy (Smeller et al., 2022).

Many studies have proven that adalimumab is safe and effective in the treatment of NIU associated with various systemic diseases, as it controls inflammation and preserves ocular structures (Burek-Michalska & Turno-Kręcicka, 2020). The efficacy and safety of adalimumab is also defended by Hiyama, et al (2022), although there are differences in the efficacy of its use between patients with VKH disease and patients with Behçet's disease. However, there is a possibility of side effects such as infections and demyelinating disorders. In addition to adalimumab, there are other biologics that can also be used in refractory uveitis, which include anti-CD20 inhibitors (rituximab), interleukin-6R inhibitor (tocilizumab), interleukin-1R inhibitor (anakinra) and interleukin-2 inhibitor (daclizumab) (Gupta et al., 2022). Tosi, et al (2019) demonstrated that golimumab and Certolizumab pegol can be effective and safe treatment options for treating NIU, even in cases where other anti-TNF medications have failed. However, Jin, et al (2022) emphasize that it is necessary to be cautious when generalizing this conclusion, as it is necessary to carry out multicenter studies in order to produce data that support efficacy and safety.

The success of NIU treatment is confirmed by controlling the degree of inflammation and preserving ocular structures and vision (Wang et al., 2021). In cases where this does not occur, it may be due to several factors that include damage to the retina and choroid, as well as macular changes (Couret et al., 2019). If there is macular edema due to uveitis, administration of systemic immunosuppression or intravitreal steroids is recommended (Balasubramaniam et al., 2022).

4. Final Considerations

This research highlighted the need for a good diagnostic and therapeutic approach at NIU. It was found that to this day, the mainstays of treatment for this pathology are immunosuppressants and corticosteroids, the latter known to have several adverse effects both in topical and systemic administration, and a gradual reduction in therapy is recommended. Isolated AU responds well to topical therapy with corticosteroids and cycloplegics to prevent posterior synechiae. The other anatomical forms: IU, PU and PANU, do not respond well to topical treatment, due to the drugs' low tissue penetration capacity. Biological therapy has recently been introduced, which is considered safe and effective for the treatment of any form

of NIU. However, its use requires caution, as the occurrence of demyelinating disorders has already been reported in a small group of patients.

Therefore, for a good clinical, diagnostic and therapeutic approach to this disease, it is necessary that there is close collaboration between the ophthalmologist and doctors from other specialties in order to have an accurate diagnosis and rule out other associated comorbidities, avoiding complications that can lead to blindness.

It is expected that future research will be conducted to improve understanding of the pathophysiology and use of biological products in NIU treatment.

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