Mini Review

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Spondyloarthritis Associated Uveitis

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Abstract

Spondyloarthritis is a group of chronic inflammatory rheumatism characterized by common clinical, radiological and biological manifestations occurring on a predisposing genetic background dominated by the HLA-B27 antigen. Acute anterior uveitis is the most common extra-articular feature of spondyloarthritis. The objective of this review is to describe the prevalence, demographic characteristics, factors favouring the occurrence of uveitis in patients with spondyloarthritis, clinical manifestations, and there therapeutic management.

Key words: Uveitis • Spondyloarthritis

Introduction

Uveitis is the inflammation of the uvea: iris, ciliary body and / or choroid. However, the term uveitis is now synonymous with intraocular inflammation and covers conditions of various aetiologies [1]. Its annual incidence in Europe and North America is estimated at 17 to 24/100 000 inhabitants [2]; while its prevalence would be 115 cases per 100 000 inhabitants according to a recent North American study [3]. The clinical presentation of uveitis is particularly heterogeneous. Indeed, the classification of the International Uveitis Study Group, based on the anatomical location of intraocular inflammation, distinguishes four clinical forms of uveitis: anterior, intermediate, posterior and pan uveitis [4]. Rheumatologists may be advised to consult with patients with uveitis to identify systemic disease. Indeed, anterior uveitis in particular is an extra-articular manifestation of many forms of joint disease which include spondyloarthritis (SpA), juvenile idiopathic arthritis and Behçet's disease.

Epidemiology

The worldwide incidence of uveitis over 2 year's evolution in patients with spondyloarthritis (SpA) is 4.3% [5]. 33% of patients with SpA had uveitis [6]. In specific populations the prevalence of uveitis is variable. For example, in a South American series of SpA, the prevalence of uveitis was approximately 20% [6]. This disparity is partly related to the prevalence of the HLAB27 antigen in the population [7]. The first flare of uveitis associated with the B27 antigen occurs typically between the ages of 30 and 40 [7]. According to an Italian study, the prevalence changes according to the sex of the patient: the female prevalence is higher than the men. However, the data on sex differences in the prevalence of uveitis have not been fully elucidated in the literature. Uveitis occurs with varying frequency depending on the subtype of SpA. The relationship between psoriasis arthritis (PsA) and uveitis is strongest than that of psoriasis alone [6]. Likewise, for chronic inflammatory disease of the gastrointestinal tract with rheumatological manifestations compared to isolated intestinal damage [6].

The presence of uveitis is correlated positively with the presence of radiological sacroiliitis, HLA-B27, and disease's Duration of 10 years or more [6-9]. The association between HLA B27 and acute anterior uveitis dates back to 1973, very soon after the discovery of its link with ankylosing spondylitis and reactive arthritis. Genetic sequencing has shown that the HLA B27 antigen possesses about sixty subtypes corresponding to different proteins [10]. Thus, HLA B * 2705 is the most associated with the development of uveitis and remains very frequently found in most populations. The subtype HLAB * 2702 and B * 2704 (predominant in Asia) are also associated with spondyloarthropathies, while the subtypes HLA B * 2709 (Sardinia) and HLA B * 2706 (Southeast Asia) are poorly associated at the risk of developing uveitis [8]. These subtypes differ from each other by amino acid substitutions and may influence the selection of peptides presented to T lymphocytes [9]. Thus this great polymorphism of HLA antigens is at the origin of the theories of the "uveitogenic" peptide, which supposes that the HLA B27 molecule presents the peptides originating from the antigens expressed in the target tissues of spondyloarthropathies (eye and joints) and to activate the Pathogenic CD8 + T lymphocytes localized in these tissues. The HLA-B27 genotype is present in 50% of AAU cases in the West and between 18% and 88% worldwide due to considerable racial variations in the carriage of HLA-B27 [8]. In Japan and Korea, for example, they have fewer cases of anterior uveitis associated with SpA and fewer cases of HLA-B27 anterior uveitis without systemic disease. Anterior uveitis, like SpA, is polygenic, and in some breeds there may be additional contributing genetic susceptibility factors that may protect against or promote the disease [8,9,11]. According to a Caucasian study, the risk of developing uveitis for a relative of a patient who presented with B27 uveitis is 13%, compared with 1% for carriers of B27 in the general population [12]. The concordance rate in homozygous twins is 40% compared to 7% in dizygotic twins for uveitis, also suggesting that other non-HLA-B27 genes are involved in the development of uveitis [13].

Clinical particularities

Anterior uveitis is the most common SpA presentation [6]. It is often characterized by a sudden unilateral, recurrent, and not granulomatous onset. It can sometimes precede from a few months to several years the articular manifestations.

- **Anterior segment involvement:** Acute anterior uveitis manifests as a sudden drop in visual acuity, associated with a painful red eye. The patient often consults urgently. The ophthalmologic examination shows the visual acuity decrease, which can be profound and it's often proportional to the inflammatory intensity. There is usually a predominant conjunctival hyperemia around the cornea, in the form of a perkeratic ring, associated with photophobia, and sometimes blepharospasm. The fibrinous inflammatory reaction is rapid and intense, causing adhesions between the lens capsule and the iris, which are called iridocrystalline synechiae. The protein Tyndall clearly predominates over the cellular reaction. Hypopion can be observed in almost 10% of cases, indicating the most severe stage of inflammation [14]. A fibrin plug can be observed at the level of the pupil. Eye pressure may be normal or more frequently lowered. The average duration of inflammation is 4 to 6 weeks. Note that conjunctivitis next to acute anterior uveitis is also a clinical manifestation of spondyloarthritis. The ophthalmologist will differentiate between the two anatomical conditions after a slit lamp examination. The other forms are less frequent and are seen mainly in PsA and chronic inflammatory disease of the gastrointestinal tract where uveitis is likely to be associated with an insidious onset, a bilateral appearance, a chronic course and affects the posterior part of the segment [15]. Chronic inflammatory disease of the gastrointestinal tract, in particular, is very frequently associated with episcleritis and scleritis.

- **Posterior segment involvement:** Posterior segment involvement is rarer and usually occurs when the anterior involvement has become chronic due to lack of effective treatment. It can manifest as macular edema observed in 6 to 20% of cases, or more rarely hyalitis, papillary hyperemia or retinal vasculitis. Mini-foci of retinal necrosis are exceptionally observed in patients with Crohn's disease.

Differential diagnosis

The main condition that can mimic acute anterior uveitis type B27 is Behçet's disease. The attack occurs more frequently in men with an average age of 30 years with a geographical predominance around the Mediterranean basin or more precisely at the level of the "Silk Road". Pure anterior inflammation is rare (10% of cases) but it is also, like rheumatic uveitis, non-granulomatous. Hypopion is observed in almost 13% of cases [16]. Oral aphthosis is a mandatory associated sign. HLA B51 typing is not part of the diagnostic criteria. The visual prognosis is much more reserved than type B27 uveitis and the disease requires systemic therapeutic management combining corticosteroids, immunosuppressants or biological agents. It is conventional to say that the diagnosis of uveitis type B27 and Behçet's disease can be ruled out in the event of any granulomatous uveitis. In total, in the face of acute non-granulomatous anterior uveitis, If

SpA is known, no investigation is required. However, the problem arises if the patient is not followed up for spondyloarthritis, in which case, it is necessary to look for the presence of low back pain lasting more than 3 months or arthralgia in a subject under 45 years old. If present, HLA B 27 testing is required.

Evolution and prognosis

Uveitis associated to spondyloarthritis is acute (uveitis flare duration is less than three months), with an average duration of four to six weeks [17]. The damage is usually unilateral with a tendency to relapse. However, the eye initially affected is more often affected by relapses [18]. A trend of decreasing recurrence parallel to the duration of the course since the first uveitis outbreak has been observed [18]. The frequency of relapses varies from 0.6 to 3.3 relapses of uveitis per year depending on the studies [8], with an interval between relapses varying from two months to more than thirty-five years (average of fifteen to twenty-five months). As for the course of spondyloarthritis, the total duration of the disease may also be longer in those with uveitis to an average of 5 years [19]. A large French observational study of 902 cases of SpA found no association between uveitis and disease activity [20], although the presence of uveitis was associated with greater disease severity or disability in other reports [21]. It is possible that the combination of cases in the Canoui-Poitrine study included fewer cases of severe SpA than the other reports because the study population was not limited to tertiary referral centers, thus limiting referral bias [20]. The prognosis of HLA B27 uveitis is classically more reserved than that of UA not linked to this antigen of the major histocompatibility complex, in relation to the multiple recurrences and the intensity of the fibrinous reaction. Uveitis complicating psoriatic arthritis has a more severe prognosis and a less favourable response to the various therapeutic strategies currently available.

Complication

Switching to a chronic mode is associated with a high risk of inevitable long-term complications affecting the posterior segment, mainly macular edema type or leading to chronic glaucoma. The main complication remains the formation of iridocrystalline synechiae, which varies from 13 to 90% of cases [8]. The extent of synechiae remains limited given the acute nature of the uveitis which leads the patient to consult urgently with consequently the almost immediate start of anti-inflammatory and cycloplegic treatment. Cataracts are a common complication of chronic UA. Its constitution is favored by intraocular inflammation and corticosteroid treatment. It is seen in 7 to 28% of chronic uveitis [8,22]. The site of opacities is often cortical or posterior subcapsular. The risk of developing cataracts is proportional to the chronicity of the uveitis, iris involvement and corticosteroid therapy. Cataract surgery does not generally pose any particular problem in these patients as the inflammation has been durably controlled in the 3 month preceding and, in the weeks, following the operation. Ocular hypertension and secondary glaucoma Ocular hypertension should always be sought in any uveitis. In the acute phase, it is classic to observe a relative drop in eye pressure compared to the adelphe eye, linked to astonishment of the ciliary body. However, ocular hypertension may accompany the acute flare through trabeculitis or by obstruction of the trabecular meshwork by inflammatory cells. In chronic forms, the effect of goniosynechia is added. Screening for ocular hypertension is often the cause of a modification of the therapeutic strategy with the relative contraindication of topical corticosteroids and recourse to the systemic route.

Treatment

Consists of treating the acute uveitis flare and its complications as well as preventing recurrence

- **Treatment of uveitis flare:** It is always initiated locally, it can be combined with mydriatic eye drops (tropicamide, neo-synephrine, and atropine) which prevents the formation of iridocrystalline synechiae. It is more rarely associated with antihypertensive drugs if ocular hypertension [7]. In the absence of a response to well-conducted topical treatment, corticosteroid therapy will be administered in high doses, if no corneal epithelial damage. It will be started with a powerful corticosteroid, dexamethasone, at a rate of administration proportional to the severity of the inflammation of the anterior segment. It is accepted that any initial therapeutic insufficiency exposes to the risk of persistent inflammatory disease or of transition to chronicity. Thus, in the event of severe inflammation, hourly instillations may be recommended, relayed in the evening by a corticosteroid ointment. This frequency will be reduced as the eye inflammation subsides. A maintenance dose of one drop 3 times a day may be necessary to prevent a possible relapse. The average duration of treatment is between 4 and 6 weeks [7]. The clinical monitoring of local corticosteroid therapy should be brought closer, appreciating the Tyndall of the anterior chamber, at best thanks to the laser tyndallometer, which allows an accurate and objective quantitative assessment of the anterior inflammation. The measurement of the ocular pressure must be systematic because of the frequency of cortisoneic hypertonia [7]. In severe cases, especially if hypopion is observed, subconjunctival injections of dexamethasone may be given in the initial phase.

Systemic corticosteroid therapy is exceptional in purely anterior uveitis, but this solution is used in cases of resistance to well-conducted treatment [23].

- **Treatment and prevention of recurrence:** Cs DMARDs, including MTX, sulfasalazine or cyclosporine A, are indicated in cases of active persistence of ocular inflammation, recurrent flare-ups despite treatment with CS, or sight-threatening complications, particularly macular edema, so to avoid long-term complications of corticosteroid therapy. However, data on sulfasalazine and lefunomide for the treatment of AUA are very limited. For cyclosporine, its interest in posterior uveitis is well described by several articles showing comparable efficacy with corticosteroids. It provided both complete remission in more than 30% and a significant corticosteroid-sparing effect in at least 20% of the patients treated. But, the lack of data on the treatment of anterior uveitis, and its nephrotoxic and hypertensive effects, are the main limitations of the extensive use of cyclosporine for the management of AAU associated with SpA. As for the use of methotrexate associated with local corticosteroid therapy seems to be just an intermediate step before moving on to biological agents which appear to have replaced immunomodulators in the treatment of AUA [24]. TNF alpha is essential in the intraocular immune response and in the autoregulation of physiological apoptosis of ocular cells. Thus, the advent of anti-TNF alpha biotherapies has revolutionized the prevention of recurrence of uveitis linked to SpA. To compare the effectiveness of different anti-TNF alpha in the treatment of uveitis, a retrospective study of 46 patients treated with: etanercept, infliximab or adalimumab showed that the number of uveitis outbreaks per patient before starting treatment anti-TNF alpha was higher than after the start of treatment. Infliximab and adalimumab showed the greatest reductions [25]. In Swedish, biological register, on 1365 patients, Lie et al. found a four-fold increase in the risk of anterior uveitis in the first 2 years after starting treatment in patients who started etanercept versus adalimumab and a two-fold increase in etanercept compared to infliximab, but no statistical difference between adalimumab and infliximab [25]. This shows that the efficacy of infliximab and adalimumab is better than that of etanercept in reducing recurrence [23]. Recently 2 other anti-TNF agents, Golimumab, and certolizumab demonstrated efficacy in the control of recalcitrant uveitis secondary to spondyloarthritis and HLA B27, and may be indicated in cases of intolerance to infliximab [23,25]. In addition to TNFα, studies have implicated the importance of cytokines, IL-17 and IL-23, in the pathogenesis of axial SpA, leading to the possibility that they are a target in treatments for uveitis. IL-23 is currently under investigation for uveitis. It showed its effectiveness in a case report of a patient with PsA and uveitis, with improvement. It also showed control of uveitis in a patient with paediatric PsA who failed infliximab and adalimumab [25]. IL-22, a cytokine secreted by certain Th17 cells, is an integral part of PsA and RA disease and in uveitis, suggesting a potential future target for the treatment of uveitis [25]. Likewise, the JAK and tyrosine kinase pathways are being studied for their impact on uveitis. Tofacitinib (Xeljanz; Pfizer, New York City, NY, USA) which inhibits JAK 1-3 and tyrosine kinase 2, has shown some improvement in symptoms in patients with SpA, and may be a future tool in uveitis associated with SpA also filgotinib which is an inhibitor of JAK1, is currently being tested [25]. Cataract surgery on these eyes should be done with caution by following a few simple rules. Indeed, ocular inflammation should be controlled for more than 3 months before surgery and perioperative corticosteroid therapy, the modalities of which will be decided on a case-by-case basis, will allow the best possible recovery without postoperative relapse [23].

Conclusion

Uveitis secondary to spondyloarthritis is the most common extra-articular manifestation. It is seen particularly in males. The duration of the disease, HLA B 27 and radiological sacroiliitis are the main predictors of its onset. It is preferably an acute, anterior, unilateral and non-granulomatous, with a tendency to recurrence and the development of potential complications affecting the long-term visual prognosis. The treatment of the crisis is based on local corticosteroid therapy. As for the prevention of recurrence, this involves the introduction of DMARDs, but above all biotherapy, in particular Adalimumab and infliximab.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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