Wide-field fluorescein angiography findings in active anterior scleritis

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Abstract

Aim

Describe the proportion of patients with wide-field fluorescein angiographic (WFFA) findings in patients with active anterior scleritis.

Methods

An observational, descriptive, cross-sectional study of the WFFA findings of patients with active anterior scleritis. Studies were performed with the Heidelberg Spectralis module (102º). Images were saved and assessed by two masked co-authors.

Results

Seventy-nine eyes from 39 patients, 31 (79%) females with mean age was 50.5 ± 13.98 years. WFFA findings were seen in 52% of eyes with active scleritis and in 16.6% of eyes without scleritis. Retinal vasculitis was detected in eyes with scleritis in 31.25%, mainly with peripheral vascular leakage (19.2%), and in eyes without scleritis in 10.4%. Systemic association was present in 51.3%, being the most prevalent ANCA associated vasculitis and rheumatoid arthritis.

Conclusions

One third of patients with active scleritis have WFFA evidence of retinal vasculitis. WFFA gives supplementary information for monitoring patients with scleritis.

Introduction

Anterior scleritis is a chronic, inflammatory scleral disease, with or without necrosis, which is a form of active vasculitis. It can be the first sign of an autoimmune disease and 50% are associated with Anti-Neutrophil Cytoplasmic Antibodies (ANCA) associated vasculitis (AAV), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and HLA-B27 spondyloarthropathies.\(^1\)\(^-\)\(^3\)

Retinal vasculitis (RV) is asymptomatic until there is visual loss. It can be present in all autoimmune diseases, mainly in RA, SLE and AAV, and it is associated with an increase in mortality.\(^1\)\(^,\)\(^4\) RV is an endothelial inflammation that leads to vascular occlusion and eventually to ischemia. Frequently ocular vasculitic processes are not confined to a one region, and can occur in retina, sclera, choroid, and/or periocular tissue, and can be the first sign of a systemic disease.\(^5\)\(^,\)\(^6\)

Retinal vascular involvement is secondary to the deposition of immune complexes that affect the periphery of the retina, usually with no symptoms or clinical signs. The gold standard for RV diagnosis is fluorescein angiography, and in recent years wide-field angiography (WFFA) has become important for
evaluation of the periphery of the retina. Conventional angiography takes images of the central retina (30–60°), with a montage of 90°, and WFFA of 102°.7,8

There are currently limited references on the association between active anterior scleritis and RV, including Behcet's disease, granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MAP), RA and Sjögren syndrome.9,10 Our aim was to describe the proportion of patients with wide-field fluorescein angiographic findings in cases of active anterior scleritis. And as a secondary outcome to determine which rheumatological disease and gender is more frequent.

**Methods**

An observational, descriptive, cross-sectional study of the WFFA findings of patients with active anterior scleritis was conducted at the Inflammatory Eye Disease Clinic at the Asociación para Evitar la Ceguera en México from March 2018 through February 2020. Institutional Review Board (IRB)/Ethics Committee approval was obtained, number UV-18-03, and was carried out following the principles of the Declaration of Helsinki.

Consecutive series of patients with a diagnosis of active anterior scleritis. The inclusion criteria were adult patients with a diagnosis of active anterior scleritis, associated or not with rheumatological diseases, such as RA and AAV. After the assessment of the inclusion criteria, relevant data on the current clinical course, rheumatological disease, treatment, and time since diagnosis were collected. Initial symptoms and signs, laterality, type of anterior scleritis (nodular, diffuse, necrotizing, or peripheral ulcerative keratitis),11 laboratory results were used to confirm systemic diagnosis (C-reactive protein, globular sedimentation rate, rheumatoid factor, anticyclic citrullinated peptide, ANCA, MPO, PR3, HLA-B27) and epidemiological information was retrieved from electronic medical records.

Exclusion criteria included retinal pathology (e.g.: diabetic retinopathy, age-related macular degeneration), posterior synechiae that made impossible to assess posterior pole, chronic renal insufficiency, uncontrolled systemic arterial hypertension, and/or diabetes; pregnant, breastfeeding, or puerperium patients; RV due to infectious, hematological, coagulopathy, or neoplastic etiology. Elimination criteria included patients in whom the study we could not do, such as for allergy to fluorescein.

WFFA findings were defined as described literature in central leakage (affection of macula alone), peripheral leakage (involving leakage outside of the vascular arcades), central and peripheral leakage (if < 50% retinal vasculature was involved) or diffuse leakage (> 50% of the retinal vasculature involved).12 Tortuosity, occlusions, AV shunts and cystoid macular edema were also recorded.

WFFA studies were performed with the Heidelberg Spectralis module (102°). With adequate dilation, fixation with external fixation device, the intravenous fluorescein injection was performed with arm patient extended. Using the joystick to align the illumination beam within the pupil in both eyes, starting in the side of active anterior scleritis and focusing on designated field of view, with pre-planned
photographic sequence: nine projections, starting in the posterior pole and then in the eight peripheral quadrants. Images were saved and assessed by two masked co-authors (RCK and LECR).

Information was separately emptied on a spreadsheet using Microsoft Excel (Excel 2016). Data was analyzed using SPSS version 23.0 (NY: IBM corp.). As for the statistical analysis for the descriptive variables, measures of central tendency and frequencies were carried out. Subsequently, for comparative analysis of systemic diseases, the antibody and angiographic findings were analyzed using chi-square and a value of p < 0.05 was considered being statistically significant. Concordance was performed with X test and inter-rater agreement was calculated with Cohen's kappa coefficient.

Results

We included 39 patients with bilateral disease in 23%, with a median of 52 years, 79% females (table 1), and with a mean best-corrected visual acuity (BCVA) of 0.1343 ± 0.2475 logMAR. Five (12%) patients had associated hypertension.

Ophthalmological diagnoses included 48 eyes: 26 eyes (54.1%) had diffuse anterior scleritis, 16 eyes (33.3%) had nodular anterior scleritis, and six eyes (12.5%) had necrotizing anterior scleritis. On fundoscopic evaluation we found optic nerve hyperemia (n = 2, 4.1%), macular edema (n = 2, 4.1%), peripheral vascular sheathing (n = 8, 8.3%) and serous retinal detachment (n = 1, 2.05%). A systemic association was observed in 51% of the patients, represented by AAV in 33.3% and RA in 17.9%.

There was a moderate level of agreement between the two masked researchers, with a Cohen´s kappa of 0.664, of the WFFA studies.

According to the classification, WFFA findings were seen in 31.25% of the patients. The most frequent was peripheral leakage in 19.2%; central and peripheral leakage was only seen in AAV (p < 0.001). WFFA findings were more frequent in anterior diffuse scleritis and were not statistically different, nor with rheumatologic diagnosis, gender, or age. (Fig. 1) Other angiographic findings included peripheral occlusion in one eye with AAV (2.05%), shunts in 7 eyes (8.9%), CME in 2 eyes (2.5%), and tortuosity in 19 eyes (24.3%). (Tables 2 and 3).

During the evaluation of contralateral eyes without scleritis, we observed that 16.6% of them presented at least one angiographic sign of RV, being peripheral vascular leakage the most frequent finding in 10.4%. (Table 3)(Fig. 2)

Discussion

This is the first study that systematically evaluates WFFA in active anterior scleritis, demonstrating concurrent RV in one third of the patients. WFFA can image peripheral retina and it may alter management decisions compared with standard-of care and clinical examination. Systemic vasculitis
have varied ocular manifestations, including conjunctivitis, episcleritis, scleritis, peripheral ulcerative keratitis (PUK), and uveitis.\textsuperscript{8,12}

New diagnostic tools like wide-field angiography allow us to obtain a more specific diagnosis of RV, but we should keep in mind that there is not always a clinical-angiographic correlation. Another advantage is that vascular changes are frequently found in the retina’s periphery, and standard field cameras (30–60º) often cannot capture them and can be missed. Therefore, we carried out a study to determine whether wide-field angiography (102º) allows us to find changes that suggest RV in patients with active anterior scleritis.

Retinal examination is required in all patients with scleritis, since RV at onset is asymptomatic. Is an extra-articular manifestation of rheumatic diseases and can be the first finding of systemic activity in a patient with non-specific rheumatologic presentation.\textsuperscript{4} Rheumatologists have attempted to include end-organ involvement information, to create a universal scoring system that could be used in the diagnosis, disease staging and treatment of these conditions.\textsuperscript{4}

The frequency of RV findings associated with rheumatologic diseases is reported up to 12\% with conventional angiography,\textsuperscript{13} and of 67.7\% with ultrawide-field angiography.\textsuperscript{14} The difference between these last two studies and ours is that their association refers to RV as an isolated finding, and not in combination with active anterior scleritis. Retinal vasculitis is usually related to an inflammatory breakdown of the retinal blood–brain barrier. Eyes with retinal vasculitis manifest focal, segmental, or diffuse vascular leakage.\textsuperscript{12} It is important to determine if there is endothelial dysfunction or if active inflammation is secondary to retinal blood vessel disruption, with focal leakage from the retinal vasculature, or obstruction of the vascular lumen.\textsuperscript{4} Peripheral vascular leakage correlates with patients requiring additional immunosuppression, and may alter management decisions versus standard-of-care treatment.\textsuperscript{4}

It is postulated that necrotizing scleritis represents a primary vasculitis of the deep episcleral vessels and in non-necrotizing scleritis, a delayed type of hypersensitivity reaction.\textsuperscript{15} In eyes with necrotizing scleritis, evidence shows endarteritis and periarteritis of the thickened choroidal vessels, particularly in relation to the scleral reaction.\textsuperscript{16}

We found peripheral vascular leakage in WFFA, demonstrating a clinically active retinal vasculitis. Additionally, we detected CME and vascular occlusion, complications of RV that would not have been identified without the imaging study.\textsuperscript{8,17}

Scleritis needs to be properly diagnosed to guarantee accurate and sufficient treatment in order to improve outcomes. Sclera is more vulnerable to inflammation because of the vascular circulations.\textsuperscript{11} A systemic association with active anterior scleritis was detected in 51.3\% of the eyes in our study, similar to what was previously reported in the literature.\textsuperscript{18} The most associated disease was AAV, a primary systemic vasculitis with small vessel involvement and it was the only with peripheral vascular occlusion.
on WFFA. Disease activity, including extension and subsequent damage from ischemia and necrosis, needs to be considered when establishing if organ-threatening vasculitis exists additionally to systemic disease.\textsuperscript{19} The second associated disease was rheumatoid arthritis. In RA, a subclinical vasculitis due to disease systemic activity, there is an increase in the amount of inflammatory and endothelial dysfunction markers, in and around the vessel wall. Which was also seen in choroid with an increase in choroidal thickness.\textsuperscript{20} A previous study described RV in 18\% of patients lacking clinical signs of RV.\textsuperscript{21} Also in rheumatoid subclinical vasculitis there is a decrease in blood supply, alongside with a thinned choroid layer, which can produce ischemia in the FAZ regions.\textsuperscript{22}

We observed venous tortuosity in all types of scleritis and in all diseases, and only 2 patients had systemic hypertension. Tortuosity is considered a risk factor in many retinal pathologies, and modifications in retinal vessels give clues about disease severity and changes in disease.\textsuperscript{23} In diabetes, increased vessel tortuosity is related to diabetes-driven hemodynamic changes such as disturbed blood flow, tissue hypoxia, endothelial dysfunction and increased levels of VEGF.\textsuperscript{24} It has been reported that in antiphospholipid syndrome, Human immunodeficiency virus, and RA are related to endothelial dysfunction. This endothelial phenomenon can occur at macrovascular and microvascular levels and has a prognostic value for cardiovascular events. For example, in RA, endothelial function improved in patients with disease activity that responded to treatment. \textsuperscript{25,26,27}

Ophthalmologists play a decisive role in diagnosis and treatment of patients with autoimmune diseases. We are involved in the assessment of patients that debut with ocular symptoms or who consult with a known diagnosis of autoimmune disease for an ophthalmological exam, to determine disease activity and extension. RV can be asymptomatic until vision is lost. It is diagnosed with a complete ophthalmological examination with a dilated fundus and a fluorescein angiography is needed. \textsuperscript{4} If we detect RV at the same time as scleritis, then retinal vessels are evidence of more than one site of inflammation. So, it will be important to establish if this will change clinical practice.\textsuperscript{12}

Our study has several strengths. We demonstrated in eyes with and without active anterior scleritis that RV can be present at the same time. The findings offer new, potentially useful information for this disease, having then WFFA a decisive role in the treatment to start or to escalate, and that in the short or long term, impact morbidity and mortality. It also has some limitations. The first one is the small number of patients. Second, it’s possible for a selection bias, as our institution is a tertiary referral center. And third, being a cross-sectional study, we do not know yet the improvement with the established treatment.

**Conclusions**

We found angiographic evidence associated with RV in 31.25\% of eyes with active anterior scleritis and in 10.4\% without scleritis. More studies are needed to determine the significance of these additional findings, as a sign of systemic activity and their relationship to treatment response, and as an indicator of disease progression. In summary, WFFA helps us detect retinal vasculitis in patients with active scleritis. The clinical significance of these findings as a marker of activity is not known, however angiographic
leakage is an indication of treatment, and with a second WFFA will be necessary to see improvement after treatment.

**Declarations**

**Ethics approval and consent to participate:** Institutional Review Board (IRB)/Ethics Committee approval was obtained, number UV-18-03.

**Consent for publication:** institutional consent form was approved and used.

**Availability of data and material:** The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Competing interests:** The authors declare that they have no competing interests

**Funding:** None

**Authors' contributions:**

JCRA design of the work AND acquisition data AND interpretation of data AND have drafted the work.

MZM acquisition data AND interpretation of data AND have drafted the work.

RSK design of the work AND acquisition data AND interpretation of data AND have drafted the work or substantively revised it.

CHT design of the work AND interpretation of data AND have drafted the work or substantively revised it AND to have approved the submitted version.

LECR design of the work AND acquisition data AND interpretation of data AND have drafted the work or substantively revised it AND to have approved the submitted version AND to have agreed both to be personally accountable for the author's own contributions.

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**References**


Tables

Tables 1 to 3 are available in the Supplementary Files section.

Figures

Figure 1
Female patient in her 40s, with a diagnosis of rheumatoid arthritis attending for anterior nodular scleritis in the right eye. Wide field angiography in late arteriovenous phase with presence of peripheral vascular leak and parietal staining in upper temporal, lower temporal and lower nasal quadrants (yellow arrow).

Figure 2

The following images are of the contralateral eye without scleritis of patient of Figure 1. Wide field angiography in late arteriovenous phase with presence of peripheral vascular leakage and parietal staining in lower and upper nasal quadrants (yellow arrow).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Tables.docx