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Review

Take a look at the eyes in Systemic Lupus Erythematosus: A novel point of view

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ABSTRACT

Systemic Lupus Erythematosus (SLE) is a connective tissue disease that involves multiple organs. Ocular structures and visual pathways can be affected in SLE because of disease-related eye involvement or drug toxicity. All the part of the eye may be interested with an external, anterior involvement, responsible of the dry eye disease, or posterior (retina) and neuro-ophtalmic manifestations. Retinopathy in SLE is suggestive of high disease activity being a marker of poor visual outcome and prognosis for survival. The early diagnosis is thus the key to a better management and successful treatment. Antimalarial drugs are the cornerstone of SLE treatment and recently the American Academy of Ophthalmology updated the recommendations for hydroxychloroquine retinal toxicity screening which includes the standard automated visual fields and the spectral domain optical coherent tomography. More recently new imaging techniques have been investigated to assess retinal function and reveal subclinical eye involvement. In this review we focalize on the evidence of eye manifestations in SLE, the eye drug toxicity related to antimalarial agents and steroids, and the methods employed for the eye screening. Moreover, the future perspectives on new techniques, such as the optical coherence tomography angiography, are dissected giving new insights on evaluation of microvasculature of the retina and choroid in SLE.

1. Introduction

1.1. Systemic Lupus Erythematosus

Systemic Lupus Erythematosus (SLE) is a connective tissue disease that involves multiple organs [1]. The pathogenesis of SLE is multifactorial with various genetic, epigenetic, immunoregulatory, environmental and infectious factors contributing to susceptibility, onset, progression and prognosis. The immune system dysregulation affects cellular and humoral compartment involving both adaptive and innate immunity to mount an autoimmune response against self chromatin antigens [2]. The pathogenic process is characterized by a sequence of events, which take long time before ending into overt clinical manifestations. Autoantibodies are key mediators in determining the clinical manifestations and may display their pathogenic effects by complement-mediated inflammation, cell apoptosis, immune complexes mediated damage in the presence of additional local factors [3]. Antiphospholipid antibodies (aPL) may be associated to SLE or be independent in a syndrome [4]. Kidney involvement is one of the most serious manifestations of SLE patients and it is relatively common (50–80%). Usually appears in the first three years from onset [5].

2. Ocular manifestations in SLE

2.1. SLE-associated eye involvement

Ocular manifestations in SLE can occur in up 1/3rd of SLE patients and vary from patient to patient [6]. They can correlate to the systemic disease activity or be a complication of systemic or topical therapy [7]. The assessment of the visual disturbance is included in the context of SLE disease activity scores such as the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2 K) [8], the British Isles Lupus Assessment Group Index (BILAG 2004) [9], the Systemic Lupus International Collaborating Clinics/American College of Rheumatology

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(SLICC/ACR) damage index [10]. SLE can affect multiple ocular structures including the periorbita, adnexa, eye and optic nerve [11].

2.1.1. External ocular structures

The orbit and periorbita are rarely involved in SLE. Findings can include itching, pain, edema, proptosis, enophthalmos, chemosis, decreased vision, and extraocular muscle limitation of movement. These findings can be caused by periorbital edema, vasculitis, myositis and panniculitis [12]. Orbital inflammation and vasculitis result in vision loss due to ischemic injury in the optic nerve [7]. Orbital myositis may be misdiagnosed as bacterial cellulitis [6]. It is characterized by pain, globe restriction, periorbital swelling and proptosis [13]. Creatine kinase, aldolase and myglobin levels are often elevetad [7]. Orbital panniculitis may occur independently or be often associated with discoid lupus [14]. These lesions appear as nodules adherent to the overlying skin. Periocular skin can also be affected with scaly and atrophic lesions associated with discoid rash [15].

2.1.2. Anterior ocular structures

Keratoconjunctivitis sicca, also known as dry eye disease (DED), represents the most common manifestation and is a complex condition that affects the ocular surface causing alterations in the quality and/or quantity of the tear film with ocular distresses [7]; [16]. In SLE patients, DED is often associated with secondary Sjögren's syndrome (SS) [11] [17];. The symptoms varies from itching, mild irritation, foreign body sensation and redness to severe pain [6]. Consequence of DED are corneal scarring, ulceration, filamentary keratitis and decreased visual acuity [18]. Other corneal manifestations are peripheral ulcerative keratitis (PUK), often indicated active disease, peripheral corneal infiltration, interstitial keratitis, and endothelitis [6]. Scleritis has an incidence of 2% and it is a vision-threatening ocular manifestation requiring prompt treatment [19]; [20]. Scleritis may present as anterior diffuse scleritis or anterior nodular scleritis. Rarely it manifests as necrotizing scleritis or posterior scleritis [7]; [21]. Episcleritis may also be seen in SLE with milder symptoms and redness due to injection of the superficial blood vessels. It is usually self limiting and does not require treatment [22]; [20]). Nongranulomatous anterior uveitis has also been reported and the prevalence varies from 0.1% to 4.8% [22] [23];.

2.1.3. Posterior ocular structures

The incidence of retinal involvement in SLE is 7–29% and is the second most common ocular manifestation after DED representing the most associated with visual loss [7] [24];. The incidence of retinopathy is decreased since the introduction of steroids in the treatment of SLE. It tends to be bilateral although it can be asymmetric. The major pathology of lupus retinopathy is attributed to a vasculopathy rather than a true vasculitis, most commonly, immune complex-mediated microangiopathy, with complement activation though immune complex deposition and vascular damage [25]. Microangiopathy is similar to diabetic and hypertensive retinopathy and should be considered the mild form of lupus retinopathy while severe vaso-occlusive retinopathy is a rare and severe form associated with reduced vision and visual field defects [11]. Retinopathy is first evidenced by small intraretinal hemorrhages, cotton wool spots, arteriolar narrowing with capillary and venous dilatation, and vascular tortuosity [15]. It can be characterized also by retinal edema, exudates and microaneurysms and be associated with visual acuity deterioration [7]. Central retinal artery and/or vein occlusion can lead to neovascularization and be related to aPL antibodies or syndrome [24]; [7]. Retinal vasculitis, a subset of retinal vasculopathy, is characterized by inflammation of the retinal arterioles or venules and has poor visual outcomes presenting in an acute onset fashion. A large proportion of these patients have aPL antibodies [26]. Retinopathy in SLE is suggestive of high disease activity and correlate with central nervous system (CNS) and kidney involvement during the course of SLE being a marker of poor prognosis for survival [7]; [27]. The early diagnosis is thus the key to successful treatment and better prognosis.

Lupus choroidopathy can occur either independently or with lupus retinopathy [28]; [29]. It is generally seen in patients who have highly disease activity including CNS vasculitis and nephropathy. The common manifestations include single or multiple areas of serous or exudative retinal detachment, detachment of the retinal pigment epithelium (RPE) or retinal pigment epitheliopathy [29]. The posterior segments findings, particularly the retinal signs, often reflect the severity of systemic inflammation and may indicate inadequate control of systemic disease [22]; [30].

2.1.4. Neuro-ophthalmic

Neuro-ophtalmic manifestations have a prevalence of 3.6% in adult SLE patients. Findings are highly variable with the most common presentation being optic neuritis followed by myasthenia gravis, visual field defects and optic disc oedema [11]. Optic neuropathy can be the presenting feature of SLE, occurring in 1% of patients [16]; [31]. Optic neuritis is usually an ischemic process that can cause subsequent demyelinization and axonal necrosis. The initial visual loss can be severe but respond to corticosteroids [16]; [12]. Presentation can vary based on the location of pathology; patients may present with painless or painful progressive visual loss, with or without pain on eye movement, optic disc swelling or pallor on examination [32]; [31]. Visual prognosis is generally moderate to poor [32]; [31]. Oculomotor abnormalities are more common in SLE patients being reported in up to 29% of patients. They are caused by ischemic microvascular disease, sixth nerve palsies or internuclear ophthalmoplegia [7]. Other rare manifestations are nystagmus, pseudotumor cerebri, pupillary abnormalities, light-near dissociation, blepharospasm, transient mononuclear visual loss, and cortical blindness [16].

2.2. Drug-associated ocular toxicity

Ocular manifestations may also represent toxic effects of treatments. Treatment strategies for SLE include hydroxychloroquine (HCQ) or chloroquine (CQ) and systemic corticosteroids that are both correlated with the possible risk of visual impairment [33]; [34] [35];. Antimalarials and corticosteroids can be considered the cornerstone of the medical management of SLE. CQ/HCQ is effective in cutaneous disease, arthritis, management of nephritis and prevents SLE flares [36]. Numerous other benefits, along with being inexpensive, include protection against the occurrence of diabetes, thrombotic events, dyslipidemia, improvement of pregnancy outcome, and reduction of overall damage in SLE. Moreover, HCQ appears to have a protective effect on survival in SLE patients [37,38,39].

2.2.1. Chloroquine and hydroxychloroquine eye toxicity

Retinal toxicity from CQ and its analogue HCQ has been recognized for many years. Most studies on the incidence of CQ or HCQ retinopathy defined the toxicity by severe field loss or bull's-eye change in the fundus, so the true incidence of retinopathy was underreported. Moreover, the incidence was often underestimated because it was calculated from a mix of patients treated with the drugs for different period of time with only few patients on long-term treatment. The incidence of retinal toxicity varies from 0% to 4% [40] with a report published by Melles and Marmor reporting an overall incidence of HCQ toxicity near 7.5% among 2361 patients using the drug for > 5 years [41]. This study suggested that HCQ (and probably CQ) toxicity is not so rare among long-term drug users. The frequency of retinal toxicity has been reduced when CQ has been replaced by HCQ. Many authors suggest that CQ is more toxic than HCQ but older literature does not give details about dose/weight and duration of each treatment. The higher toxicity of CQ in clinical use may be an artifact of common prescription practices biased by the available CQ tablet size (250 mg). Almost any patient taking 1 tablet of CQ will receive > 2.3 mg/Kg. Thus it is not clear whether this conclusion is true or is an artifact of

convenient dose levels that have never been compared [42]. HCQ is used widely for the treatment of SLE and other autoimmune diseases, thus it is important to know the prevalence and risk factors for retinopathy. The mechanism of CQ and HCQ toxicity is not well understood. High experimental doses have acute effects on the metabolism of retinal cells, but it is not clear how short effects relate to the slow and chronic damage that characterizes the clinical state of toxicity. Melanin bearing cells in the posterior segment including the RPE may act as a sink for the accumulation of HCQ that appears to bind melanophores. The accumulation of HCQ may lead to the toxicity of photoreceptors. In the clinical practice the primary damage is to photoreceptors and as the outer nuclear layer degenerates there is secondarily disruption of the RPE [43]. No anatomic features of the retina and RPE are known to correlate specifically with the parafoveal or extramacular pattern of damage as CQ and HCQ toxicity develops. The macular localization of the disease suggests that light absorption or possibly cone metabolism may play a role, but that is speculation. The clinical picture of HCQ and CQ toxicity had been characterized on fundus examination as a bilateral bull's-eye maculopathy, an irregular central zone of pigmentation surrounded by a ring zone of depigmentation in the parafoveal RPE. This finding is infrequent in Asian patients who show a damage with a peripheral extramacular distribution [44]; [45]; [46] [47]; [48]. This lesion produces a corresponding ring scotoma. However, this pattern should no longer be seen because screening tests detect toxicity long before RPE damage is visible by imaging of fundus examination. Visual acuity is excellent until severe stages of damage and most patients who develop HCQ toxicity have no visual symptoms at all; only a few patients may notice paracentral scotomas [49]. If drug exposure continues the area of functional disturbance expands, the RPE becomes involved and the maculopathy can encroach on the foveal center with eventual loss of visual acuity [41]; [43]. Cystoid macular edema sometimes may develop [50] and advanced cases show widespread RPE and retinal atrophy with loss of visual acuity, peripheral vision and night vision. HCQ and CQ retinopathy can progress even after the drugs are stopped although the progression and the risk to vision are functions of the severity of retinopathy at the time it is detected [51]; [50]. This late progression of damage after stopping the drugs is related to the reservoir of the drug because of clearance from the body does take many months. Only in the final severe stage the lesions appear visible on ophthalmoscopic exam.

Antimalarial agents may also affect the anterior eye; CQ and less frequently HCQ can cause intraepithelial deposits in the cornea that can be observed within the first 2–3 weeks of treatment and are usually reversible on drug discontinuation without any residual corneal damage regardless of the duration of therapy [42]. They can also disappear despite the continuation of therapy and are usually not a reason to stop the treatment because that they are not a direct marker for retinal damage and are not associated with visual loss [52]. Difficulty with accommodation may occur soon after administration of CQ and also with HCQ; these symptoms may disappear despite the continuation of therapy or after reduction of the dose [52].

2.2.2. Glucocorticoid eye toxicity

Chronic corticosteroid therapy is associated with an increased risk of developing cataracts and glaucoma [53]; [54]; [55,56]. In a recent study on SLE patients cataracts were observed in 29% of patients while glaucoma in 3% of cases. The development of cataracts was associated with age, disease duration, and cumulative steroid dose. An association between these two conditions was observed [57]. Posterior subcapsular cataract is considered to be irreversible and there is no evidence that reducing the dose or stopping treatment might halt its progression [58]. Although no corticosteroid dose has been reported to be safe, the incidence of glaucoma appears to increase for dosage over 7.5 mg/day, chronic dosages below 5 mg/day are sufficient for the development of posterior subcapsular cataract [59]. Risk factors for glaucoma development are age, ethnic background, family history of glaucoma, diabetes mellitus, systemic hypertension, hypothyroidism, myopia and uveitis. Secondary open-angle glaucoma caused by steroids may result in visual field loss of blindness and is generally reversible when the therapy is stopped [58].

3. Screening for eye involvement and drug toxicity

Toxicity is a serious ophthalmologic concern because it is not treatable. Nonetheless, visual function can be preserved if damage is recognized before there are changes in the RPE [51]. The aim of the screening for CQ/HCQ retinopathy is not to stop a valuable drug at the first borderline abnormality, but to recognize definitive signs of toxicity at an early stage to prevent a loss of visual acuity. A proper screening should avoid the classic bull's-eye retinopathy. The American Academy of Ophthalmology (AAO) in 2011 published the recommendations for HCQ retinal toxicity screening [40] and these have been updated recently in 2016 [49]. Despite these guideline and increased availability of testing, overall adherence to the guidelines, particularly in long-term HCQ users has been reported to be poor [60]. Nika et al. [61] demonstrated that a third of high-risk patients did not receive appropriate diagnostic testing or lacked regular eye care [61]. Additionally, Browning et al. [62] showed poor documentation of patient height, weight, daily and cumulative dose that would be helpful in risk stratification [62]. The study by Melles RB et al. [41] showed that real weight was better than ideal weight for calculating dose and lower risk for toxicity was achieved with HCQ doses ≤ 5 mg/Kg real weight in accordance with the 2016 AAO revised recommendations [49]; [41]. There are no similar data for CQ but dose comparison in older literature suggest using ≤ 2.3 mg/Kg real weight. The risk of toxicity is dependent on daily dose (> 5 mg/Kg) and duration of use (> 5 years) that is linked to dosage. At recommended doses the risk of CQ/HCQ toxicity up to 5 years is $< 1\%$ and up to 10 years is $< 2\%$, but it rises to almost 20% after 20 years. Other major risk factors are concomitant renal disease or use of tamoxifen. HCQ and CQ are cleared to a large degree by the kidney, so that renal disease, relatively common in SLE patients, may increase the circulating level of the drug and the risk of toxicity [41]; [63]. Therefore, patients with renal disease can have unpredictably high blood drug levels, and both dosage and screening frequency may need to be adjusted. Other factors that contribute to toxicity in a less extent are age, liver disease and genetic factors as abnormalities in the gene ATP-binding cassette, sub-family A, member 4, (ABCA4) [64] and polymorphism in the cytochrome P540 gene [65]; [66]. Moreover, patients with underlying retinal disease may be at higher risk for toxicity, although there are no specific data to confirm this.

A baseline fundus examination, within the first year of starting the drug, should be performed to rule out preexisting maculopathy. Therefore, an annual screening after 5 years of treatment should be performed for patients on acceptable doses and without major risk factors. More frequent screening may be considered for patients with major risk factors. The rationale for screening is that when retinopathy is recognized early, before RPE damage, there is only mild and limited progression after discontinuing the drugs and the fovea is not threatened. Therefore, screening may not prevent damage but may avoid that vision is affected [51]. The early recognition of definitive findings in a typical pattern should be verified with more than one test or by repeat testing. Primary screening test includes standard automated visual fields and SD OCT. Automated visual field is a subjective functional screening test covering the central macula (called the Humphrey 10–2 field because it spans 10° on either side of the fovea). It is very sensitive for revealing early change in reliable patients. Wider test patterns (24–2 or 30–2) are needed for Asian patients in whom toxicity often manifests beyond the macula. The field machine prints out a grey scale of sensitivity and a pattern deviation plot that is a statistical analysis of deviation from average sensitivity [43]. Visual fields can vary markedly between visits and some patients respond more reliably than others.

The most frequent regions of the retina showing early damage are inferotemporal with a corresponding superonasal field defect. Uncertain visual field changes should trigger retesting for consistency or evaluation with other objective tests, such as multifocal electroretinography (mfERG), spectral domain optical coherent tomography (SD OCT), and fundus autofluorescence (FAF).

The second primary screening technique is SD OCT, a non-invasive imaging objective and structural test that uses light waves to take in vivo cross-section pictures of the retina. Each of the retina's distinctive layers can be recognized and measured accurately within at least 10–15 μm providing an invaluable tool for diagnosis and follow-up of macular hole, pucker, edema, age-related macular degeneration, glaucoma, central serous retinopathy, diabetic retinopathy and preretinal membranes. SD OCT allows assessment of the morphological features of the optic nerve and may enable determination of visual disturbances even in the early stages of optic nerve diseases [67]. OCT is also useful in detecting subclinical retinal impairment or neuronal loss as thinning of the retinal nerve fiber layer [68].

Localized thinning of the photoreceptor layers in the parafovea is highly specific evidence of CQ/HCQ toxicity, assuming that no other retinal conditions are present. Initial damage can be recognized as distinctive focal interruption of the photoreceptor outer segment structural lines [43]; [69]; [70]. Outer retinal thickness remains normal until these focal signs develop, so that screening should aim at recognition of previously unrecognized areas of retinopathy. SD OCT may not be as sensitive as visual field or mfERG but it is definitive when regional thinning is present in a typical pattern. Disruption of the RPE can be observed in the late and severe stage [44]. Unless toxic changes are advanced, at least one objective test should confirm subjective findings before toxicity is diagnosed.

An additional objective functional screening test is mfERG that generates local electroretinogram responses topographically across the posterior pole and can objectively document parafoveal or extramacular electroretinogram depression in early retinopathy. The mfERG is similar in sensitivity to visual fields and can provide objective confirmation of suspected field loss [71]. It requires proper well-calibrated equipment and experienced personnel to perform and interpret well and is available usually in large clinical centers. Another objective structural screening test is the FAF that shows damage topographically highlighting region of cellular dysfunction [44]. It can reveal early parafoveal or extramacular photoreceptor damage as an area of increased autofluorescence that may precede thinning on SD OCT [43]. Late RPE loss appears as a dark area of reduced autofluorescence.

Other tests not recommended for screening of drug toxicity are: fundus examination because damage is detectable in the late stage of toxicity and the bull's-eye implies RPE loss, fluorescein angiography that recognize RPE defects in the late stage, time-domain OCT which has a low resolution to detect early changes or Amsler grid testing that is not consistent for reliable screening of subtle scotomas [49].

A baseline eye examination and follow-up eye examinations should be performed also in patients with high risk of glaucoma or cataract who are treated with systemic low-dose glucocorticoid according with the 2010 European League Against Rheumatism (EULAR) recommendations for monitoring adverse events [54]; [72].

4. Future perspectives

4.1. Subclinical retinal abnormalities

Antimalarial drugs are under investigation in several clinical trials with a focus on genetic polymorphism and early detection of retinopathy (Table 1). Furthermore, HCQ has been reported to be a potential therapeutic treatment in other autoimmune diseases such as vasculitis for its anti-thrombotic properties [73]. In the last years the interest to discover subclinical alterations in tissue targets of disease is growing up. Motarjemizadeh Q et al. [74] demonstrated a retinal toxicity in a

Table 1
Ongoing clinical trials on retinopathy/ophthalmological diseases in patients on antimalarials.

Trial (official title)	Study population	Outcome measures	Time perspective/ allocation	Study Type	Status	NCT
Comparison of Complement Factors and Genetic Polymorphisms of AMD Between Patients With Systemic Lupus Erythematosus (SLE) With and Without Retinal "Pseudo-drusen-like" Deposits: Case-control Study (PLAMD)	SLE patients treated or not with antimalarial drugs. Case patients: with "pseudo-drusen-like" deposit Control patients: without "pseudo-drusen-like" deposit	complement factors and genetic polymorphisms of AMD (Age related macular degeneration)	Prospective	Observational (case-control)	Recruiting	03504540
Study of Anti-Malarials in Incomplete Lupus Erythematosus (SMILE)	SLE patients	SLICC score. Ophthalmologic toxicity	Randomized (parallel assignment)	Interventional	Phase 2	03030118
Incidence and Risk Factor Evaluation for Toxic Maculopathy Associated With Hydroxychloroquine and Chloroquine	Patients who treated with HCQ (Hydroxychloroquine) or CQ (Chloroquine) for autoimmune diseases including SLE	Incidence of toxic maculopathy associated with HCQ or CQ	Prospective	Observational (cohort)	Recruiting	02550964
Evaluation and Prediction of Relapse Risk After Glucocorticoid Withdrawal in Patients With Stable Systemic Lupus Erythematosus: An Open-labeled Multi-centric Randomized Controlled Study From China	SLE patients on HCQ/GC treatment	SELENA-SLEDAI score, PGA, BILAG evaluation including ophthalmological status	Randomized (parallel assignment)	Interventional	Recruiting	02842814
Studying the Performance of OCT C-scan in the Screening for Retinopathy Related to Synthetic Antimalarials	Patients treated with synthetic antimalarials for at least 5 years	Concordance between OCT – SD and multifocal electroretinogram	Single Group Assignment	Interventional	Recruiting	02719002
Cytochrome P450 and ATP-Binding Cassette C C (ABCC) Variants in Egyptian Patients Receiving Hydroxychloroquine and Their Association With Efficacy and Toxicity	All patients received HCQ treatment	HCQ ocular toxicity in Egyptian patients	Cross-sectional	Observational (case-only)	Not yet recruiting	03180190

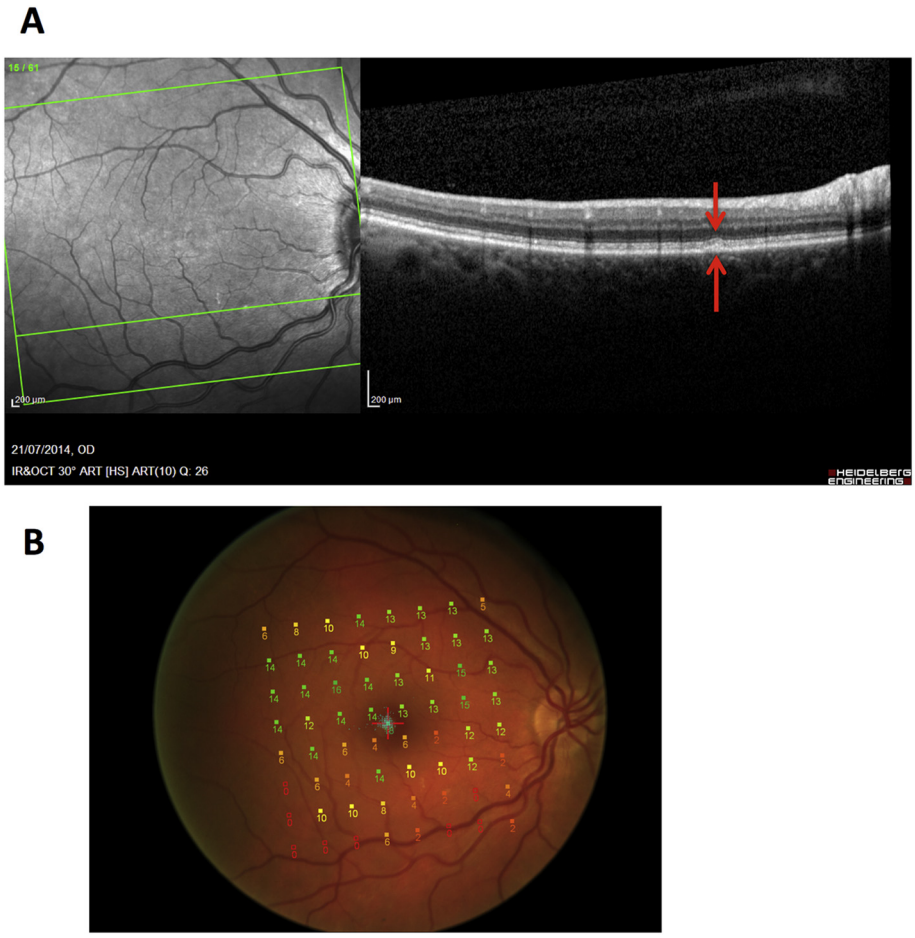

Fig. 1. Structural and functional eye abnormalities in a SLE patient.
A. Spectral-domain optical coherence tomography shows retinal pigment epithelium alteration (red arrows) in the context of diffuse inferior retinal thinning. B. Representative image of a posterior pole fundus perimetry shows reduction of differential light sensitivity in the inferior hemifield at 6–8 degrees of eccentricity.

study carried on sixty patients affected by rheumatoid arthritis on HCQ therapy only after six months of treatment by standard automated visual field [74]. In another study SD OCT was demonstrated to be useful in the early diagnosis and in monitoring the progression of retinal changes in patients receiving long-term HCQ therapy when compared with fundoscopy and visual field. In particular, authors detected a significant thinning of the macular ganglion cell-inner plexiform layer in the absence of clinically evident HCQ-related retinopathy in a cohort of ninety patients treated with HCQ for at least 5 years compared to healthy controls [75]. We recently carried out an analysis of subclinical retinal involvement in forty-two SLE and thirty-six Sjögren patients compared with seventy-six healthy controls. We performed a thorough examination of retinal complications by the mean of different ophthalmological investigations (fundoscopy, automated visual field, SD OCT, and microperimetry). Indeed, we observed a functional eye impairment in SLE, possibly associated with renal involvement while corticosteroids seemed to exert a protective role [76]. Fig. 1 shows representative images of a SD OCT and fundus perimetry of a SLE patients treated with HCQ revealing alterations of RPE and correlated functional abnormalities evidenced by a reduction of light sensitivity [76].

4.2. Novel tools for ophthalmological assessment

Recent ophthalmic imaging technologies are capable of identifying early changes in retinal and choroidal morphology and circulation [77].

Microperimetry is a procedure to assess retinal sensitivity while fundus is directly examined. It utilizes fundus imaging and motion tracking to ensure precise stimulation of a certain location of the retina. These instruments allow for registration of fundus imaging with the visual field map, and make it possible to compare retinal morphology to visual function. Fundus perimetry relates retinal sensitivity testing with morphology and is therefore a powerful tool in evaluating macular disease [78]. Microperimetry was used to assess retinal sensitivity in several studies in recent years; it is a psychophysical method which is rapid, safe and non-invasive [79] and showed good repeatability [80]. The main advantage of these automated microperimeters is that they can be used to evaluate visual sensitivity in patients with eccentric and/or unsteady fixation; another advantage is that they can be used to quantify the location and stability of fixation, measurements that are relevant in the evaluation of disease progression. It is used to investigate retinal sensitivity and fixation in patients with age-related macular degeneration [81], retinal vein occlusion [82], birdshot chorioretinopathy [83], cystoid macular edema [84] or epiretinal membrane [85]. It is also an accurate tool for detecting early macular hyposensitivity caused by CQ and HCQ [86]. However, in a recent study on nineteen pediatric patients taking HCQ compared with twenty-one healthy controls microperimetry was not more revealing early retinal toxicity than 10-2 visual field and SD OCT [87].

Optical coherence tomography angiography (OCT-A) is a non-invasive technique for imaging the microvasculature of the retina and choroid. OCT-A technology uses laser light reflectance of the surface of moving red blood cells to accurately depict vessels through different segmented areas of the eye, thus eliminating the need for intravascular dyes [88]. The OCT scan of a patient's retina consists in multiple individual A-scans, which compiled into a B-scan provides cross-sectional structural information. With OCT-A technology, the same tissue area is repeatedly imaged and differences analyzed between scans, thus allowing one to detect zones containing high flow and zones with slower, or no flow at all, which will be similar among scans [89]. The result is

an image (3 mm^2 to 12 mm^2) that is segmented, by standard, into four zones: the superficial retinal plexus, the deep retinal plexus, the outer retina and the choriocapillaris. Applied to the optic disc it includes its full depth [90]. OCT-A has been reported to be useful in the diagnosis and understanding of many retinal conditions as diabetic retinopathy, choroidal neovascular membranes, dry and wet age-related macular degeneration and vascular occlusions with good sensitivity and specificity for detection [91]; [92]. It may quantify foveal avascular zone, nonperfused areas [93] and be useful to follow-up structural changes after intravitreal injections [94]. It has been reported as a useful tool for evaluating optic disc perfusion in glaucomatous eyes, since attenuated peripapillary and macular vessel density was detectable in pre-perimetric glaucoma patients. It was also showed that OCT-A could potentially be used to diagnose glaucoma at earlier stages [95]. Recently the importance of OCT-A in uveitis has been explored and its role on monitoring progression and response to treatment as well as predicting visual complication [96]. Specifically in inflammatory conditions, OCT-A has the advantage of acquiring three-dimensional data, and potentially improving the understanding of the pathophysiology of these diseases as well as their follow-up and management. In recent studies on small cohorts of patients with Behcet's uveitis, OCT-A was found to be an alternative noninvasive method to monitor macular ischemia and the pathologic vasculature changes in this condition [97]; [98]; [99]. Authors presented in 2017 the first case of paracentral acute middle maculopathy as a manifestation of primary antiphospholipid syndrome (APS) with multimodal imaging, including OCT-A, which allowed a comprehensive assessment of retinal ischemia [100]. Recently, we demonstrated a reduced retinal microvascular density by OCT-A in SLE patients compared with healthy controls, in particular in those patients with kidney involvement. Vessel density correlated with age, visual acuity, disease activity and damage accrual. HCQ might have a protective role in preserving the miscovascular structures that needs to be further investigated [101].

5. Conclusions

This review aimed at dissecting the ocular involvement in SLE. Eye involvement may be disease-related or drug-induced. Moreover, it can be clinically manifest or hidden by the treatment, isolated or associated to kidney/SNC involvement and aPL antibodies. Therefore, a proper screening should be performed early and regularly according to AAO and EULAR recommendations. In this context new imaging techniques are needed to explore the correlation between structural and functional changes that may be revealed early compared with those identified by fundoscopy. OCT-A technology in a non-invasive manner might reveal new insights on vascular remodeling and defect of perfusion in a tissue target of the disease.

Competing interests

The authors declare they have no competing interests.

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