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Choroidal impairment and macular thinning in patients with systemic sclerosis: The acute study

Francesca Ingegnoli [a,*], Roberta Gualtierotti [a], Luisa Pierro [b], Claudia Del Turco [b], Elisabetta Miserocchi [c], Tommaso Schioppo [a], Pier Luigi Meroni [a], on behalf of the, ACUTE study group
Co-authors of the ACUTE (**A**ssessement of **C**horoidal and mac**U**lar **T**hickness in syst**E**mic sclerosis) study group (in alphabetical order):Marco Gagliardi [1], Giulio Modorati [2], Giuseppe Querques [1]

[1] Department of Ophthalmology, San Raffaele Scientific Institute, Vita-Salute University, Via Olgettina 60, Milano, Italy
[2] Ocular immunology and Uveitis Service, San Raffaele Scientific Institute, Vita-Salute University, Via Olgettina 60, Milano, Italy

[a] Division of Rheumatology, Istituto Gaetano Pini, Department of Clinical Sciences & Community Health, University of Milano, Piazza cardinal Ferrari 1, Milano, Italy
[b] Department of Ophthalmology, San Raffaele Scientific Institute, Vita-Salute University, Via Olgettina 60, Milano, Italy
[c] Ocular immunology and Uveitis Service, San Raffaele Scientific Institute, Vita-Salute University, Via Olgettina 60, Milano, Italy

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ABSTRACT

Raynaud's phenomenon (RP) is a reversible vasospastic response of the extremities to cold or emotion, and can be the first manifestation or may be present before the development of an overt systemic sclerosis (SSc). The disturbance of the balance between vasodilation and vasoconstriction is not limited to the peripheral microcirculation of the skin, but it is also observed in other organs, such as the choroidal plexus of the eye.
We aimed to examine the choroidal thickness (CT), the macular thickness and ganglion cell complex (GCC) average in thirty consecutive patients, without visual symptoms, classified as primary RP (pRP), RP secondary to suspected SSc, and overt SSc. All the patients underwent rheumatologic and ophthalmologic examination, capillaroscopy, test for anti-nuclear antibodies, anti-dsDNA, and anti-extractable nuclear antigens. Ophthalmologic examination included: best corrected visual acuity; slit lamp biomicroscopy; intraocular pressure measurements, fundus examination, and Spectral Domain-Optical Coherence Tomography (SD-OCT) with enhanced depth imaging scan system. Twenty-seven healthy subjects similar for gender and age were analyzed. In pRP, CT was significantly thinner than controls in the outer nasal and temporal regions. In secondary RP, the inner and outer nasal areas were significantly thinner than controls. In SSc, the central, inner inferior, inner nasal, inner superior, outer temporal, outer inferior, and outer nasal regions were significantly thinner than controls. A decreasing trend of central foveal thickness was noted. All the patients had GCC average significantly lower than controls. A thinning of choroidal and macular thickness, as well as of GCC was observed in patients with pRP and becomes more severe and extensive in RP secondary to suspected SSc and overt SSc.
To our knowledge, this is the first study to analyze the choroidal features using SD-OCT in RP. These data may be clinically useful in suggesting an early involvement of ocular microcirculation with significant reduction of choroidal perfusion.

Introduction

Raynaud's phenomenon (RP) is an exaggerated vasospastic response of the extremities to cold or emotion. RP can be either primary (pRP), a benign idiopathic condition that does not progress into any further disease, or secondary to many non-rheumatic and rheumatic conditions (Herrick, 2012). Among the latter, RP occurs in almost all patients with systemic sclerosis (SSc), and it usually predates the onset of systemic clinical signs of tissue fibrosis (Herrick, 2012).

It is generally accepted that SSc is characterized by prominent vascular involvement that is not limited to the peripheral microcirculation of the skin, but is also observed in the heart, lungs, kidneys, gastro-intestinal tract and eyes (Matucci-Cerinic et al., 2013). Many ocular manifestations have been described involving both anterior and posterior segment, as well as the orbit, and the extra-ocular muscles, although most of these are small case series or case reports (Tailor et al., 2009).

* Corresponding author at: Division of Rheumatology, Piazza Cardinal Ferrari, 1 20122 Milano, Italy.
E-mail addresses: francesca.ingegnoli@unimi.it (F. Ingegnoli), roberta.gualtierotti@unimi.it (R. Gualtierotti), pierro.luisa@hsr.it (L. Pierro), c.delturco@studenti.unisr.it (C. Del Turco), miserocchi.elisabetta@hsr.it (E. Miserocchi), invidendus@gmail.com (T. Schioppo), pierluigi.meroni@unimi.it (P.L. Meroni), marco.gagliardi@studenti.unisr.it (M. Gagliardi), modorati.giulio@hsr.it (G. Modorati), giuseppe.querques@hsr.it (G. Querques).

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In particular, histological studies in patients with SSc have demonstrated that choroidal vessels are grossly affected and present endothelial cell damage, basement membrane thickening and absence of pericytes (Farkas et al., 1972), which overall can contribute to the impaired choroidal circulation shown by fundus fluorescein angiography, an invasive technique (Serup et al., 1987). In addition, abnormal neurogenic control of choroidal vascular tone has been reported in SSc patients. Ocular vasospasm may induce optic nerve damage, thus contributing to normal-tension glaucoma which is reported to have an increased prevalence in SSc (Allanore et al., 2004). Moreover, in patients with SSc, normal-tension glaucoma has been related to the observation of nail bed hemorrhages observed by capillaroscopy, whereas other nailfold capillary abnormalities, such as giant capillaries or avascular areas, are not related to retinal vascular changes observed in the ocular fundi (Bozic et al., 2010; Park et al., 2011; Ushiyama et al., 2003). In the early phase of the disease, these eye abnormalities are generally overlooked in a regular eye examination because they are not necessarily associated with impaired visual acuity.

Against this background, we designed the ACUTE (**A**ssessement of **C**horoidal and mac**U**lar **T**hickness in syst**E**mic sclerosis) study in which a cohort of patients with RP at the first rheumatologic evaluation were studied. Our specific objectives were to examine the choroidal and macular thickness (CT and MT) and ganglion cell complex (GCC) average by Spectral Domain-Optical Coherence Tomography (SD-OCT), and to determine whether these parameters differ between patients with pRP, RP suspected secondary to SSc, overt SSc and healthy controls.

Materials and methods

Patient selection

Between February 2011 and May 2012, 30 consecutive adults with RP at the first rheumatologic evaluation and without visual symptoms were recruited at the Rheumatology Division of the University of Milano (Milano, Italy). In order to eliminate myopic patients that present a thin choroidal thickness (Flores-Moreno et al., 2014), enrolled patients with RP had to have an axial length of 24 ± 0.5 mm.

RP was defined as an episodic, reversible vasospastic ischemia of the digits upon exposure to cold and/or in association with emotional stress, and characterized by blanching, possibly followed by cyanosis and post-ischemic red flushing upon rewarming. The episodes may have involved biphasic or triphasic color changes, and could have been accompanied by varying degrees of paresthesia, numbness or pain (Herrick, 2012).

The study was approved by the ethics committee, and informed consent was obtained from all patients.

Ophthalmologic assessment

Enrolled patients underwent a complete ocular examination at San Raffaele Scientific Institute, Milano, Italy. The ocular examination in both eyes included: best-corrected visual acuity, slit lamp biomicroscopy, intraocular pressure measurements, fundus examination, and SD-OCT. All patients were examined to rule out the presence of any ocular disease.

CT was assessed using the Zeiss Cirrus high definition (HD)-OCT with enhanced depth imaging (EDI) scan system. The scans were conducted in the macular region by using horizontal and vertical sections of the HD 5 line raster analysis. A single expert grader, blind to patients' subgroup identity, manually measured CT, by using the caliper tool of the software, from the external limit of Bruch's membrane to the innermost layer of the sclera, at 9 points (in the subfoveal, superior, inferior, nasal and temporal regions at intervals of 0.5 mm up to 1 mm from the fovea). The measures of MT in the central point, named foveal thickness (FT), and GCC average were obtained automatically by using the Macular Cube 518 × 128 analysis.

Twenty-seven healthy subjects of the same ethnic group, and similar to the patients' group for gender and age were analyzed as control group. Their SD-OCT features were analyzed as mentioned in the above paragraph. Inclusion criteria for healthy subjects were an unremarkable ophthalmologic pathological history, best corrected visual acuity of 20/20 or better, spherical refraction between +2.0 to −2.0 diopters, axial length ≤24 mm, normal optic nerve with no neuro-retinal rim alterations, cup-to-disk greater than 0.2, normal anterior chamber with open angle, normal macular region, normal vessels and a normal SD-OCT scan.

Rheumatologic assessment

Patients underwent complete clinical examination to rule out any underlying cause of secondary RP (i.e. connective tissue diseases, current drug use, exposure to toxic agents, history of use of vibrating tools, thoracic outlet syndrome).

Serum was collected at the time of clinical assessment and stored at −80 °C until assayed. The samples were tested for: anti-nuclear antibodies (ANA) by indirect immunofluorescence on HEp2 cells, considering positive those samples with a dilution higher than 1:80, anti-dsDNA by ELISA, anti-extractable nuclear antigens (anti-ENA) by ELISA (Phadia, Freiburg, Germany) and DotBlot (EUROLINE Systemic Sclerosis and Myositis profile IgG EUROIMMUN AG Luebeck, Germany).

Nailfold capillaroscopy was performed using a video-capillaroscopy equipment (Videocap, DS-Medica, Milan, Italy) with optic probe 200×. Images were captured, coded, and stored through a Videocap software (Ingegnoli et al., 2009, 2013a, 2013b).

Based on this set of diagnostic examination and investigation, patients with RP were classified as: pRP (i.e. normal capillaroscopy, negative ANA and anti-ENA, in the absence of any symptoms/signs suggestive of connective tissue diseases); RP secondary to suspected SSc (i.e. abnormal capillaroscopy or positive ANA with or without anti-ENA positivity, and without any symptoms/signs suggestive for SSc); SSc (van den Hoogen et al., 2013).

Data analysis

One-way ANOVA in rank transformation was used to analyze differences in means between the subgroups. Multiple post hoc pairwise comparisons were then performed, taking into account the appropriate significance level for each comparison (Bonferroni method).

Results

Of the 30 patients enrolled (90% females), 8 (16 eyes) were classified as pRP (median age 52.5 yrs), 12 (24 eyes) as SSc (median age 56.5 yrs), and 10 (20 eyes) as RP secondary to suspected SSc (median age 54 yrs). ANAs were positive in nearly all patients with SSc (91.6%). At enrollment, only 2 patients were receiving calcium channel blockers for RP.

Slit lamp biomicroscopy was within normal range in all patients, as well as the mean best-corrected visual acuity and the mean intraocular pressure measurement (mean 14 mm Hg).

Analysis of the choroidal thickness

The choroidoscleral boundary was clearly identified in 101/104 (97.1%) of eyes imaged with Cirrus EDI-HD-OCT. The mean subfoveal CT was 313.2 μm (range 267–348) in healthy subjects, 273.9 μm (range 229.8–306) in pRP, 275.1 μm (range 254–310.5) in RP suspected secondary to SSc, 250.5 μm (range 189.8–314.3) in SSc. Mean, median and interquartile range of CT values in different subgroups are summarized in Fig. 1.

Differences among CT mean values were analyzed by one-way ANOVA. Significant differences between subgroups, with decreases of values from healthy controls to SSc, were observed for the central CT ($p = 0.01$), the inner nasal ($p = 0.001$), superior ($p = 0.02$) and inferior ($p = 0.03$) areas, as well as for the outer nasal ($p < 0.001$), temporal