CHOROIDAL NEOVASCULARIZATION IN CAUCASIAN PATIENTS WITH LONGSTANDING CENTRAL SEROUS CHORIORETINOPATHY

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Purpose: To report the frequency of choroidal neovascularization (CNV) in Caucasian patients with chronic central serous chorioretinopathy (CSC).

Methods: Retrospective consecutive series of 272 eyes (136 patients) who were diagnosed as having chronic CSC based on clinical and multimodal fundus imaging findings and documented disease activity for at least 6 months. The CNVs were mainly determined by indocyanine-green angiography.

Results: Patients were evaluated and followed for a maximum of 6 years, with an average follow-up of 14 ± 12 months. Distinct CNV was identified in 41 eyes (34 patients). Based on fluorescein angiography, 37 eyes showed occult with no classic CNV, 3 eyes showed predominantly classic and 1 eye had a disciform CNV. Furthermore, indocyanine-green angiography revealed polypoidal choroidal vasculopathy lesions, in 27 of the 37 eyes, classified as occult CNV on fluorescein angiography. In total, 17.6% of our patients with chronic CSC were found to have CNV that upon indocyanine-green angiography were recognized as being polypoidal choroidal vasculopathy.

Conclusion: In our series of Caucasian patients, we found a significant correlation between chronic CSC and CNV, in which the majority of patients with CNV were found to have polypoidal choroidal vasculopathy. Our findings suggest that indocyanine-green angiography is an indispensable tool in the investigation of chronic CSC.

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Central serous chorioretinopathy (CSC) is a common disease characterized by idiopathic neurosensory retinal detachment, often associated with one or more serous pigment epithelial detachment in the macular or paramacular area. It generally affects men aged between 20 and 45 with a 6:1 predominance, but it can also occur in patients aged 50 years and older.1,2

Although the underlying pathophysiological mechanisms are not completely understood, a very strong correlation between CSC and endogenous or exogenous hypercortisolism has been observed.3,4 The clinical presentation may vary widely, although visual symptoms are generally mild, unspecific, and transitory. It is typically a self-limited disorder that tends to resolve in 3 to 6 months, but recurrences can occur in 50% of cases. The terminology “chronic” applies to the CSC cases with a persistent leakage in the macular area and also to more aggressive forms of this condition, characterized by diffuse chronic accumulation of subretinal fluid or patchy retinal pigment epithelium (RPE) atrophy with pigmentary changes, indicating long-standing disease.1,2,5,6 Chronic CSC may predispose to the development of choroidal neovascularization (CNV).7–17 The prevalence of CNV in chronic CSC cases has been estimated by different authors to be around 4% to 8%.1,8,9

Long-standing CSC can show subtle signs that may suggest the presence of an occult CNV such as an indistinct late leakage on fluorescein angiography (FA)
or the presence of fibrin or lipid deposition, as well as the presence of PED. Diagnosis of occult CNV associated with chronic CSC, especially in patients older than 50 years, can therefore be difficult. It is for this reason that ICG angiography is considered the gold standard for diagnosis occult CNV.1,18,19

Polypoidal choroidal vasculopathy (PCV) is known to be a variant of CNV. It is characterized, using indocyanine-green angiography (ICGA), as a branching vascular network arising from the inner choroid and with characteristic polypoidal or aneurismatic dilations at the border of the network of vessels.20–22

First described by Yannuzzi et al20 and by Kleinert et al21 as posterior uveal bleeding syndrome, PCV is often idiopathic,22 but it has also been associated with other diagnoses such as tilted disc syndrome, choroidal nevi, and sickle cell retinopathy.23–26 The prevalence of PCV has been reported as being higher in African American and Asian people compared with the Caucasian population,27 and seems therefore to have a predilection for pigmented individuals.28

Differentiating PCV from occult CNV can be difficult using only on FA or ophthalmic examination, and ICGA is considered as the most sensitive tool to diagnose the presence of PCV.28,29 To better characterize CSC associated with CNV and the potential role of PCV herein, we performed a retrospective analysis of multimodal imaging, FA, ICGA, and optical coherence tomography (OCT) of patients diagnosed as having long-standing CSC.30

Methods

We retrospectively reviewed clinical and multimodal fundus imaging data from all eyes noted to have long-standing CSC (i.e., persistent and/or chronic CSC) between January 2008 and January 2013. Patients were seen at the Retina Center of the Eye Clinic, University of Cagliari, the only certified referral center for medical retinal diseases on the island of Sardinia, Italy. This retrospective study followed the guidelines of the Declaration of Helsinki and was approved by a local Institutional Review Board.

Fundus color photography, red-free, infrared, and autofluorescence pictures as well as fluorescein and ICGA with OCT were obtained of each patient. Near-infrared reflectance using a light stimulus of 815 nm, blue autofluorescence using a light stimulus of 488 nm, and angiographic studies (fluorescein and indocyanine green) were obtained with the HRA (Heidelberg Engineering, Heidelberg, Germany). Optical coherence tomography examinations were obtained with Stratus OCT (Carl Zeiss, Dublin, CA), Cirrus HD-OCT (Carl Zeiss), and SLO Heidelberg Spectralis OCT (Heidelberg Engineering).

All subjects during the follow-up underwent OCT-assisted enhanced depth imaging using spectral domain optical coherence tomography (Heidelberg Spectralis HRA + OCT) to determine subfoveal choroidal thickness, measuring from Bruch membrane to the inner scleral border.

All patients had at least 1 documented episode of retinal elevation with ≥6 consecutive months in duration and were followed for a minimum of 1 year. For inclusion in this study, patients were classified as having a chronic form of CSC or so-called “long-standing,” after the common accepted definition of a localized or widespread sensory retinal detachment associated with areas of RPE atrophy and pigment mottling, displaying signs of recurrent or long-standing disease on FA such as the presence of one or multiple focal leaks, often teardrop or long-necked, in many cases with diffuse decompensation of the RPE evident as an indistinct hyperfluorescence with subtle leakages. The presence of these typical signs as well gravitational tracks, retinal precipitates, and absence of drusen were helpful to distinguish between CSC and AMD. The presence of patchy areas of choroidal hyperpermeability, filling delay, and venous dilatations or multiple presumed small occult retinal pigment epithelium detachments confirmed by ICGA were characteristic for CSC.5,16,31–33

Exclusion criteria included age-related maculopathy; pathologic myopia (defined as a spherical equivalent of −6 diopters or more or retinal abnormalities consistent with pathologic myopia, such as lacquer cracks); angiod streaks; traumatic choroidal rupture; peripapillary changes with atrophic or pigmented “punched out” chorioretinal lesions, central focal laser, or any history of uveitis.

For each patient, the following information was collected: duration of the symptomatology or clinical history, area of disease-related RPE changes, and previous peripheral argon laser treatment for retinal breaks or lattice.

Results

A total of 272 eyes (136 patients) with long-standing CSC were included (98 men and 38 women with a ratio of 2.6:1). The mean average ± SD age was 54.7 ± 11.3 at the time of characterization of CSC; 52 patients were aged 50 or younger, and 84 patients were older than 50 years. The mean average ± SD follow-up time was 14 ± 12 months, a range of 12 months to 60 months. All patients showed clinical and specific FA and ICGA features of long-standing CSC such as multiple RPE atrophies, RPE hyperpigmentation, atrophic descending
tracks, and choroidal patchy areas of hyperfluorescence. In our cohort, 41 eyes (15.1%) of 34 patients with chronic CSC showed the presence of CNV on both FA and ICGA. Of those, 37 eyes had occult with no classic component, 3 eyes had predominantly classic CNV, and 1 eye had a fibrotic CNV lesion. In addition, ICGA revealed the presence of PCV in 27 of the 37 eyes diagnosed as occult lesions and in this subgroup, 3 patients had bilateral involvement. In all these patients, characteristic PCV was defined as one or multiple hyperfluorescent aneurysmatic lesions at the border of the branching vascular choroidal network clearly visible shortly after the ICGA injection (Figure 1).

In 100% of the eyes diagnosed with PCV, an OCT scan guided by simultaneous ICGA was able to demonstrate one or multiple RPE detachments (Figure 1, Figure 3C and Figure 5, E–G). The OCT-assisted enhanced depth imaging scan in those patients had a mean average ± SD of 376 ± 67 μm in choroidal thickness.

In our series of 136 patients with classic features of chronic CSC, 25% had CNV lesions. As final data, in the whole group of 41 eyes, which showed the characteristic features of CNV on FA, we found 27 eyes with PCV (17.6% of patients) on the basis of ICGA. Two cases representative for this group are presented below.

Case 3

A 57-year-old man with an ocular history of CSC for 3 years was referred for a second opinion to our clinic, complaining of a slight reduction of visual acuity in the right eye for the last 2 years. At the time of presentation, his visual acuity was 20/40 in the right eye and 20/20 in the left eye. The fundus autofluorescence showed signs of chronic CSC in both eyes (Figure 2, A and B). Fluorescein angiography revealed some leakage in the macula of right eye (Figure 2, C and D). Early and late frame ICGA show the inner choroidal vessels dilatation and the hyperfluorescent patchy areas of choroidal staining and highlight the late staining of the PCV (see the white line). Early and late frame FA show similar finding of right eye with diffuse pigment epithelial decompensation at the posterior pole. OCT scan confirms the PCV seen on ICGA (white line in H).
Fig. 2. Case 3. A and B. Fundus autofluorescence of both eyes shows the presence of descending tracts usually characteristic of chronic CSC. C and D. Mid-phase FA reveals various spots of hyperfluorescence corresponding to the leaking area in right eye and leakage temporally to the macula in the left eye (Black line indicates the OCT scan in G). E and F. Late phase ICGA shows different spots of choroidal staining in both eyes. G. OCT scan of right eye demonstrates the presence of subretinal fluid in the macular area.
C and D) and 2 areas of hyperfluorescence in the posterior pole of left eye, while ICGA revealed different foci of choroidal staining in both eyes (Figure 2, E and F). Optical coherence tomography scan confirmed subretinal fluid underneath the fovea (Figure 2G). After 1 year, the patient complained of a further reduction in visual acuity (20/50) and metamorphopsia in right eye. Fluorescein angiography showed a new hyperfluorescent spot involving the fovea in right eye (Figure 3A). Indocyanine-green angiography revealed a hyperfluorescent spot corresponding to a polypoidal lesion (Figure 3B). Optical coherence tomography confirmed subretinal fluid accumulation in the macular area and the presence of a small RPE detachment corresponding to the PCV lesion observed on ICGA (Figure 3C).

Case 12

A 65-year-old man with an ocular history of CSC for 4 years was referred to our clinic for a persistent visual decrease in the left eye for the last 2 years. At the time of presentation, his visual acuity was 20/25 in the right eye and 20/200 in left eye. Fluorescein angiography revealed a mottled hyperfluorescence in right eye (Figure 4, A and B), and ICGA showed diffuse choroidal staining at the posterior pole (Figure 4, C and D). Optical coherence tomography demonstrated increased reflectivity at the level of the RPE/choriocapillaris complex corresponding to areas of RPE changes in the macula and at the posterior pole (Figure 4, E and F). Fluorescein angiography of the left eye showed various spots of leakage and an area of hypoﬂuorescence that corresponds to lipid exudation observed ophthalmoscopically at the posterior pole (Figure 5, A and B). Indocyanine-green angiography allowed the detection of 3 different hyperfluorescent lesions corresponding to PCV lesions (Figure 5, C and D). Optical coherence tomography (areas of scans indicated by black lines in D) revealed the presence of cystoid retinal changes at the posterior pole, similar to those described by other authors.35

In addition, 3 sharp protrusions of the RPE line were observed on OCT corresponding to the polyp lesions seen on ICGA (Figure 5, E–G).

Discussion

Central serous chorioretinopathy is a relatively common chorioretinal disease that usually spontaneously resolves and rarely leads to chronic manifestations.6,36 Multimodal imaging may assist the diagnosis and identification of the disease as well as its secondary complications. Although focal leakage at
the level of the RPE is highlighted on FA, ICGA reveals widespread fundus involvement with several regions of choroidal hyperpermeability that is believed to be a hallmark of CSC pathophysiology and is frequently identified in chronic cases. More recently, fundus autofluorescence has been shown to be a valuable investigative tool and has led to new insights about CSC disease. In addition, OCT, especially in the enhanced depth imaging mode, has become an important tool to confirm and add further insight in the diagnosis and management of CSC.

It has been speculated that decompensation of RPE and the consequent damage of Bruch membrane in patients with a long history of CSC may trigger the development of CNV. Yannuzzi et al proposed that PCV could mimic the presence of CSC. As he states, for the diagnosis of CSC, ICGA should demonstrate the characteristic patchy choroidal hyperpermeability. This was the case for all patients in our series.

Other authors have proposed that the pathophysiological response of the long-standing process of CSC may result in chronic leakage coming from the choroidal vessels and the occurrence of a chronic inflammation involving the choriocapillaris. This process may alter the choroidal milieu and induce the formation of PCV lesions.

Additionally, Sasahara et al hypothesized a fundamental correlation between CSC and PCV based on the characteristic choroidal vascular hyperpermeability typically observed in both entities, assuming that inner choroidal abnormalities in chronic CSC might predispose the development of PCV.

Koizumi et al investigated the correlation between PCV and choroidal hyperpermeability highlighting the fact that many patients who showed both entities had a history of CSC and a thicker choroid.

Furthermore, Fung et al indicated that patients older than 50 years with no evidence of AMD were shown with multimodal imaging to in fact be long-standing

Fig. 4. Case 12. Right eye: A and B. Early and late frame of FA show different areas of hyperfluorescence at the posterior pole. C and D. Early frame ICGA highlights the choroidal vessel dilation and that choroidal staining is visible in the late phase of the examination. E and F. OCT scans reveal the RPE alterations without the presence of subretinal fluid (scan in E and F indicated by the black line in A).
forms of CSC, and in their series, the presence of PCV was observed.

In summary, we found a high incidence of CNV (25%) in a large series of Caucasian patients with chronic CSC. Interestingly, the majority of eyes that developed CNV demonstrated PCV lesions (27 of 41 eyes). Polypoidal choroidal vasculopathy is not a common diagnosis in the spectrum of age-related macular degeneration in Caucasian populations, which has been estimated at around 4% in European countries and around 9.8% in Italy. In our series, PCV were found in 27 eyes (17.6% of patients) of a consecutive series of 136 patients with clinical signs of chronic CSC. This discrepancy in the prevalence of PCV in our series indicates a strong correlation with patients affected by long-standing CSC. This study has obvious limitations imposed by its retrospective data analysis and considering that many of our patients did not have ICGA at manifestation of CSC. In fact, we cannot exclude the presence of PCV lesions before the advent of CSC disease. Nonetheless, the primary diagnosis of chronic CSC has been obtained during the clinical course of the disease and has been confirmed by clinical and multimodal imaging features, including typical findings in fundus autofluorescence, FA, and ICGA. We conclude that the presence of CSC with PCV lesions may be more common than expected. Therefore, ICGA is a valuable investigative tool in the management of CSC, not only for the primary diagnosis but also for the identification and characterization of secondary complications, such as CNV and PCV, and should be considered early on in the course of the disease.

Key words: chronic central serous chorioretinopathy, indocyanine-green angiography, polypoidal choroidal vasculopathy.

References
