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# The frequency of choroidal neovascularization from causes other than age-related macular degeneration in the Department of Ophthalmology and Ocular Oncology at the University Hospital in Krakow

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## ABSTRACT

**The aim of the study** was to assess the frequency of choroidal neovascularization (CNV) from causes other than age-related macular degeneration (AMD). Diseases complicated by CNV were diagnosed using multimodal imaging of the fundus in patients with retinal diseases.

**Materials and methods:** In this retrospective study, we assessed the medical records of 70 patients (48 women and 22 men) diagnosed with CNV secondary to causes other than AMD between July and December 2019. All patients underwent standard ophthalmologic examination, along with color fundus photography, fundus autofluorescence, swept-source optical coherence tomography, and fluorescein angiography.

**Results:** Based on a comprehensive analysis, the most common retinal disease in patients with CNV included myopia (22 patients [31%]), punctate inner choroidopathy (14 patients [20%]), idiopathic CNV (10 patients [14%]), central serous chorioretinopathy (8 patients [11.5%]), angioid streaks [8 patients [11.5%]), adult-onset foveomacular vitelliform dystrophy (6 patients [9%]), as well as Stargardt disease and fundus flavimaculatus (2 patient [3%]).

**Conclusions:** Among retinal diseases other than AMD, pathological myopia is the one most often complicated by CNV. The differential diagnosis should include other less common diseases that may be complicated by CNV. Multimodal retinal imaging is now increasingly available and should be used to facilitate the diagnostic workup and to guide therapeutic decision-making.

**KEY WORDS:** choroidal neovascularization, fluorescein angiography, fundus autofluorescence, optical coherence tomography.

## INTRODUCTION

Choroidal neovascularization (CNV) is a disease characterized by an abnormal growth of vessels from the choriocapillaris through the Bruch's membrane into the space beneath the retinal pigment epithelium (RPE) or beneath the neurosensory retina [1].

The most common causes of CNV in adults are neovascular age-related macular degeneration (AMD) and pathological myopia [2, 3]. Less frequent causes include angioid streaks, chorioretinitis (e.g., punctate inner choroidopathy [PIC], multifocal retinitis, serpiginous choroiditis), inherited retinal or macular disorders (e.g., Stargardt disease/fundus flavimaculatus, adult-onset foveomacular vitelliform dystrophy [AOFVD]), intraocular tumors (e.g., choroidal melanoma, choroidal hemangioma), uveitis, central serous chorioretinopathy (CSC), and trauma [1,4-6]. Choroidal neovascularization is defined as idiopathic if no apparent cause of CNV can be detected [1]. Importantly, CNV in the course of diseases other than AMD and pathological myopia is rare and typically affects younger patients (aged < 50 years) [1, 7].

Clinically, CNV occurs in a broad spectrum of retinal and choroidal diseases and differs in terms of morphology, size, location, and disease course. The use of modern imaging modalities in ophthalmology allows clinicians to determine

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the exact cause underlying the growth of pathological blood vessels, which is important for prognosis and management of patients.

The aim of the study was to assess the incidence of CNV from causes other than AMD and to present different diagnostic modalities applied in each of the analyzed clinical entities.

## MATERIAL AND METHODS

This was a retrospective analysis of medical history of 70 patients (48 women and 22 men) who were diagnosed with CNV in the course of retinal diseases other than AMD in the Department of Ophthalmology and Ocular Oncology at the University Hospital in Kraków, between July and December 2019. The diagnosis was established on the basis of ophthalmoscopy, color fundus photography (Topcon ImageNet Camera, Topcon, Japan), swept-source optical coherence tomography (DRI OCT Atlantis, Topcon, Japan), as well as fundus autofluorescence (FAF) and fluorescein angiography (FA) (both Spectralis, Heidelberg Engineering, Germany) in all recruited patients.

## RESULTS

The study included 48 women (68.5%) and 22 men (31.3%) with CNV. The mean age of patients was 47.5 ±9.1 years (range, 33-62 years). A comprehensive analysis of imaging results revealed the following concomitant conditions: myopia in 22 patients (31%), PIC in 14 (20%), idiopathic CNV in 10 (14%); CSC in 8 (11.5%), angioid streaks in 8 (11.5%), AOFVD in 6 (9%), as well as Stargardt disease and fundus flavimaculatus in 2 patient (3%).

Color fundus photography, SS-OCT, FA, and FAF revealed characteristic imaging features depending on a given condition complicated by CNV. These representative features are described in detail below.

### Pathological myopia

Pathological myopia is the second most common cause of CNV following AMD [2]. The disorder is more common in women than in men [8]. It is diagnosed on the basis of characteristic findings on ophthalmoscopy, including multiple foci of chorioretinal atrophy, and yellow-appearing lacquer cracks representing breaks in the RPE–Bruch's membrane–choriocapillaris complex [8, 9]. In pathological myopia CNV is typically found subfoveally or very close to the center of the fovea. It can also develop in lacquer cracks. An important feature of the fundus accompanying the presence of myopic CNV is peripapillary RPE atrophy. Color fundus photography of a highly myopic eye is presented in Figure 1A. On SS-OCT, an area of moderate hyperreflectivity is seen beneath the neurosensory retina corresponding to CNV (Figure 1B), which may be accompanied by subretinal fluid and intraretinal edema and choroidal thinning [10]. In 90% of cases, FA shows mild hyperfluorescence of myopic CNV in early phases, with minimal leakage outside the border of the lesion in the late phase (Figure 1C). Lack of intensive leakage on FA sometimes makes it difficult to differentiate active and inactive forms of that form of CNV. In such cases OCT angiography might help to evaluate the membrane's vasculature. Finally, FAF shows areas of RPE atrophy around the optic disc that appear hypoautofluorescent (Figure 1D).

### Punctate inner choroidopathy

Punctate inner choroidopathy is a rare idiopathic ocular inflammatory disease affecting the choroid and the retina. The disease may have viral or autoimmune etiology and most commonly affects young women with myopia [4, 11, 12]. It often affects both eyes, although not symmetrically. Initially, patients present with symptoms in one eye, but imaging tests reveal bilateral lesions. Topographically, these inflammatory foci develop in the posterior pole of the fundus at the level of the RPE and the choriocapillaris [11]. They have white-yellow appearance and a diameter of 100 to 300 μm. The lesions progress to atrophic chorioretinal scars that become more pigmented with time. When grayish CNV appears in the course of PIC, these inflammatory foci are still present, which is characteristic and makes the diagnosis easier (Figure 1E) [4, 11]. On SS-OCT, a focal elevation of the RPE with hyperreflectivity is seen, often without concomitant neurosensory retinal edema (Figure 1F). Fluorescein angiography shows early localized hyperfluorescence corresponding to CNV and progressing over time, with leakage of the CNV lesion on late images. Atrophic scars appear hypofluorescent (Figure 1G) [12]. On FAF, inflammatory foci are hypoautofluorescent, inactive CNV lesions appear hypoautofluorescent, while active lesions show isofluorescence (Figure 1H).

### Central serous chorioretinopathy

Central serous chorioretinopathy is an ocular disease that leads to central vision impairment, mostly affecting young men [13, 14]. Typical fundus findings include minor lesions corresponding to RPE atrophy and changes in the macular pigment profile. Acute CSC is defined as an acute-onset, dome-shaped serous detachment of the neuroretina, while chronic CSC is characterized by serous detachment of the retina, with either small or more extensive areas of serous detachment of the RPE, together with atrophic changes to the outer retina and RPE developing secondary to choroidal vasculopathy (Figure 2A). In patients with CSC complicated by CNV, SS-OCT reveals neurosensory retinal detachment of the macula with flat RPE detachment (called the double-layer sign; Figure 2B). Fluorescein angiography is notable for a hyperfluorescent halo corresponding to window defects in the areas of RPE atrophy as well as fluorescein leakage of CNV lesions (Figure 2C). Importantly, in acute CSC, hyperfluorescence may be due to pooling of fluorescein dye into the subneurosensory retinal or subretinal pigment epithelial space. Autofluorescence reveals numerous changes referring to alterations of the RPE: areas of hypoautofluorescence in the presence of RPE atrophy or geographic hyperautofluorescence shapes that correspond to the areas of subretinal fluid (gravitational tracks). Finally, on FAF, areas of CNV do not

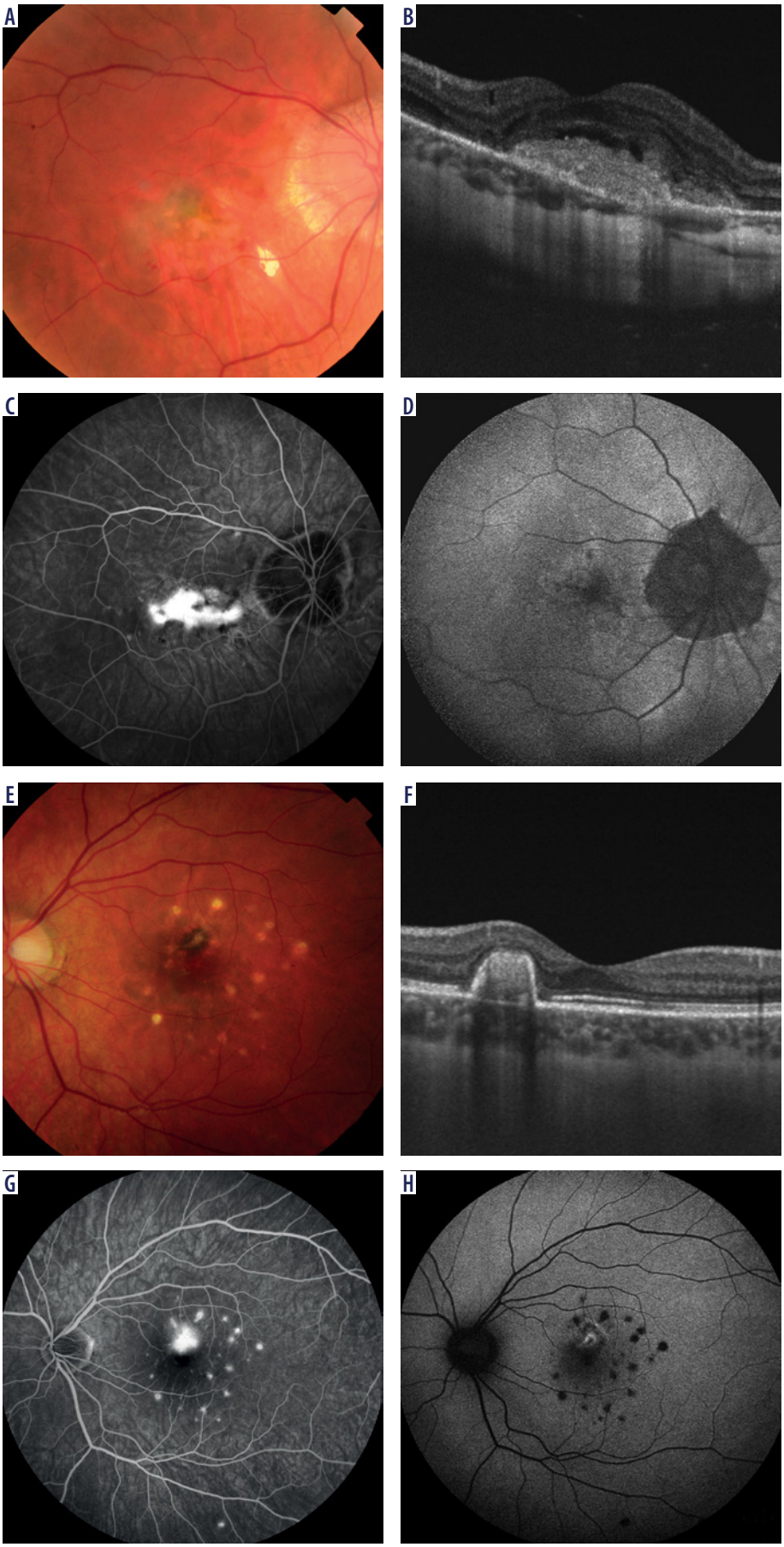


**Figure 1.** Pathological myopia – color fundus photography (A), swept-source optical coherence tomography (B), fluorescein angiography (C), fundus autofluorescence (D). Punctate inner choroidopathy – color fundus photography (E), swept-source optical coherence tomography (F), fluorescein angiography (G), fundus autofluorescence (H)

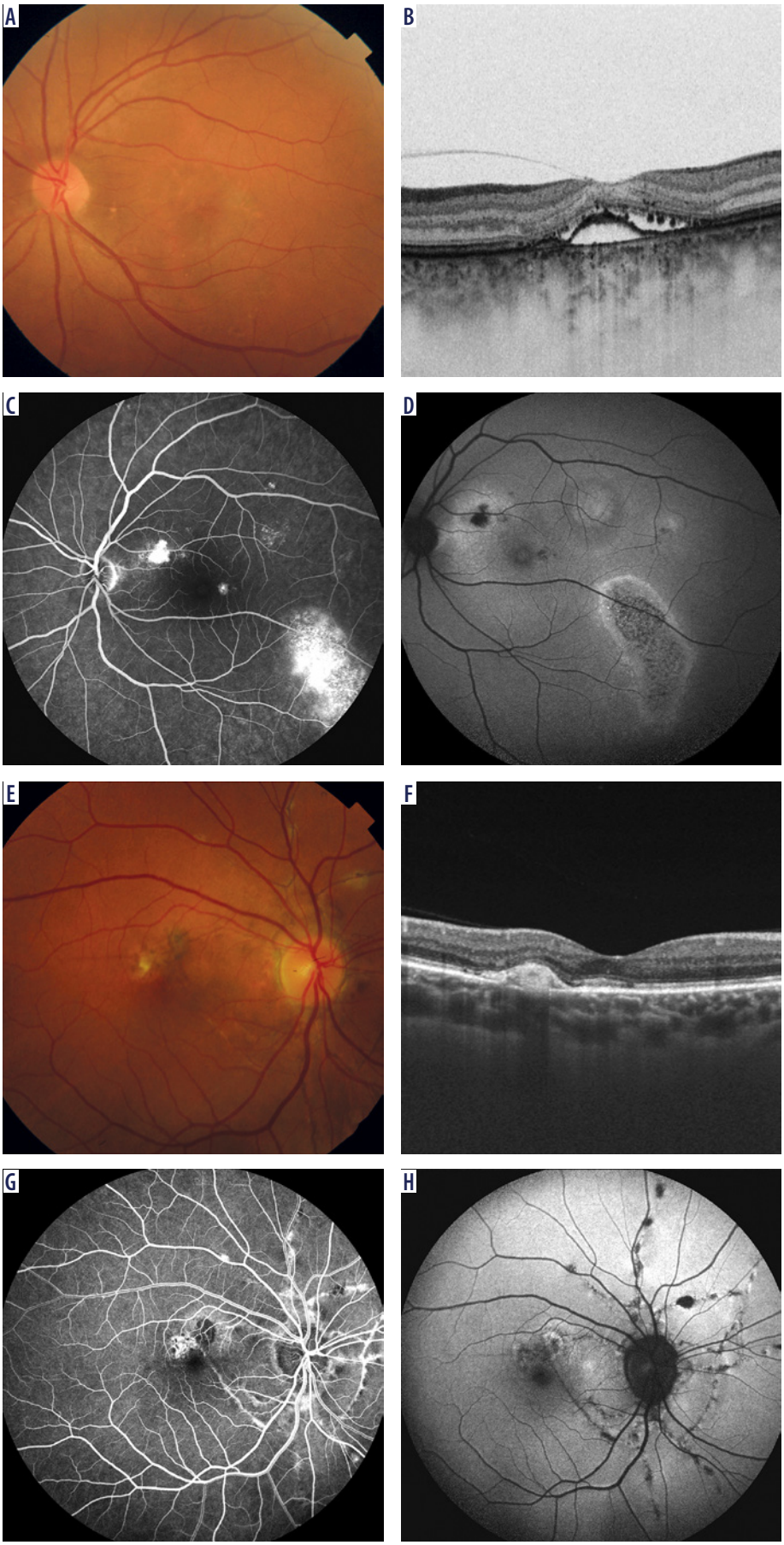


**Figure 2.** Central serous chorioretinopathy – color fundus photography (A), swept-source optical coherence tomography (B), fluorescein angiography (C), fundus autofluorescence (D). Angioid strakes – color fundus photography (E), swept-source optical coherence tomography (F), fluorescein angiography (G), fundus autofluorescence (H)

show increased autofluorescence; however, it is observed for long-lasting lesions at the level of the RPE (Figure 2D). To detect CNV in CSC SS-OCT, FA, indocyanine green angiography and OCT angiography should be performed.

**Angioid streaks**

The term "angioid streaks" refers to breaks in a thickened Bruch's membrane accompanied by RPE atrophy. The diagnosis is facilitated by the characteristic fundus appearance on clinical examination. Ophthalmoscopy reveals linear grey lesions underneath normal retinal vessels. These lesions form a peripapillary ring from which numerous streaks radiate in a circumferential pattern to the periphery. They are often accompanied by optic disc drusen and the *peau d'orange* (orange skin) pattern of diffuse mottling of the pigment epithelium, usually in the temporal part (Figure 2E) [4]. An SS-OCT scan of CNV shows an elevation of the RPE with hyperreflectivity, sometimes with the presence of subretinal fluid (Figure 2F). On FA, the streaks appear hyperfluorescent due to window defects in the RPE. A variable amount of hypofluorescence due to RPE hyperplasia is also seen (Figure 2G) [4]. Finally, on FAF imaging, angioid streaks appear as irregular hypoautofluorescent lines radiating from the optic disc (Figure 2H) [10].

**Adult-onset foveomacular vitelliform dystrophy**

Adult-onset foveomacular vitelliform dystrophy is characterized by bilateral, round or oval-shaped, yellowish deposits that are one-third to one-half of the optic disk diameter in size and are found in the macular area at the level of the RPE, often centered by a pigmented spot [4, 15-17]. These lesions are most likely caused by lipofuscin accumulation in the RPE due to reduced phagocytic function of these cells [17]. The disease onset is typically between 30 and 50 years of age [17]. Ophthalmoscopic examination reveals the characteristic finding of yellow lipofuscin accumulation in the macula (Figure 3A, E). If AOFVD is complicated by CNV, examination of the lesions in the other eye can be helpful. The characteristic SS-OCT findings of hyperautofluorescent deposit material as well as accumulation of highly reflective material between the neurosensory retina and RPE allows clinicians to establish the correct diagnosis (Figure 3B) [10, 18]. In eyes with CNV, SS-OCT reveals irregular RPE elevation, subretinal fluid, and intraretinal edema (Figure 3F). Hyperreflectivity corresponding to subretinal hemorrhage is also possible [10]. It was reported that SS-OCT might serve as a standard diagnostic tool in patients with AOFVD [17]. On FA, CNV lesions appear increasingly hyperfluorescent as the study progresses, with CNV leakage in the late phase (Figure 3G). The other eye appears hypofluorescent due to the masking effect of lipofuscin autofluorescence (Figure 3C). Finally, FAF imaging reveals strong hyperautofluorescence in eyes without CNV (Figure 3D), while no areas of hyperautofluorescence are seen in eyes complicated by CNV due to the presence of intraretinal edema or subretinal fluid (Figure 3H).

**Stargardt disease and fundus flavimaculatus**

Stargardt disease (juvenile macular dystrophy) and fundus flavimaculatus are characterized by abnormal lipofuscin accumulation in the RPE, a feature that also confers a vermillion fundus appearance [4]. A typical manifestation includes fundus flecks, that is, dot-like yellow-white lesions at the level of the RPE in the posterior pole (Figure 4A), usually with a central distribution with variable mid-periphery involvement. On SS-OCT, highly reflective material is observed at the level of the RPE and beneath the neurosensory retina, corresponding to areas of lipofuscin accumulation (Figure 4B). Fluorescein angiography reveals areas of hyperfluorescence due to window defects. Another common finding is the "dark choroid", in which the retinal circulation appears to be highlighted against a hypofluorescent choroid. Newly developed lesions show early hypofluorescence as a result of blockage of fluorescence, followed by late hyperfluorescence due to staining. Well-established lesions result in a window defect while CNV shows hyperfluorescence leakage of dye during the late phase (Figure 4C) [4]. The lesions are usually bilateral and symmetrical. On FAF, newly developed lesions appear hyperautofluorescent while older ones appear hypoautofluorescent (Figure 4D) [17].

**Idiopathic choroidal neovascularization**

Diagnosis of idiopathic CNV is made when other possible causes of CNV have been excluded (diagnostics by exclusion). Depending on the type, severity, and activity of CNV in the macula, ophthalmoscopy reveals yellowish-green pigmentation or greyish tissue in the deep retinal layers, with concomitant neurosensory retinal detachment (Figure 4E). Other possible findings include macular edema, serous RPE detachment, RPE tears, intra- and subretinal hemorrhage, and ultimately, fibrous tissue [4]. On SS-OCT, CNV lesions appear as areas of moderate or strong reflectivity, with concomitant thickening and fragmentation of the RPE as well as the presence of subretinal fluid and edema (Figure 4F). Moreover, SS-OCT allows an assessment of CNV localization: beneath the RPE, above the RPE or in the neurosensory retina. With FA, the extent, type, size, and site of CNV lesions can be determined (Figure 4G). However, if the type of CNV lesions cannot be established, the following tests can be useful: FAF (Figure 4H), indocyanine green angiography, SS-OCT angiography of the macula.

## DISCUSSION

Our study in patients with CNV due to causes other than AMD revealed the following underlying conditions: pathological myopia, PIC, idiopathic CNV, CSC, angioid streaks, AOFVD, as well as Stargardt disease and fundus flavimaculatus.

Our results are in line with the data reported in other studies [1, 2]. In a multicenter retrospective study, Carneiro *et al.* [2] assessed 21 eyes with CNV and reported angioid streaks in 9 eyes, chorioretinitis in 5, CSC in 3, and idiopathic CNV in 4. They assessed the efficacy of intravitreal injections

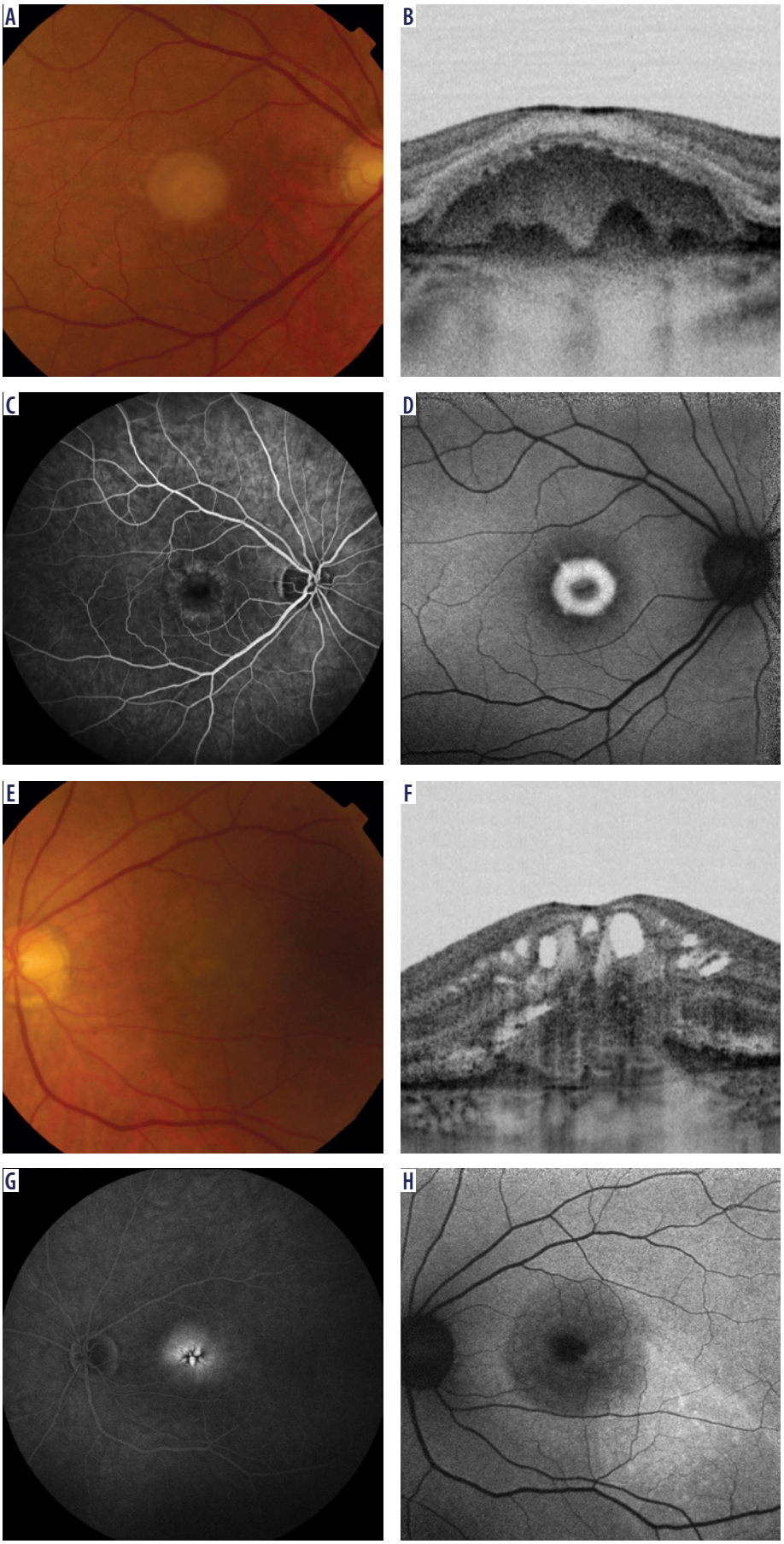


**Figure 3.** Adult-onset foveomacular vitelliform dystrophy – color fundus photography (A, E), swept-source optical coherence tomography (B, F), fluorescein angiography (C, G), fundus autofluorescence (D, H)

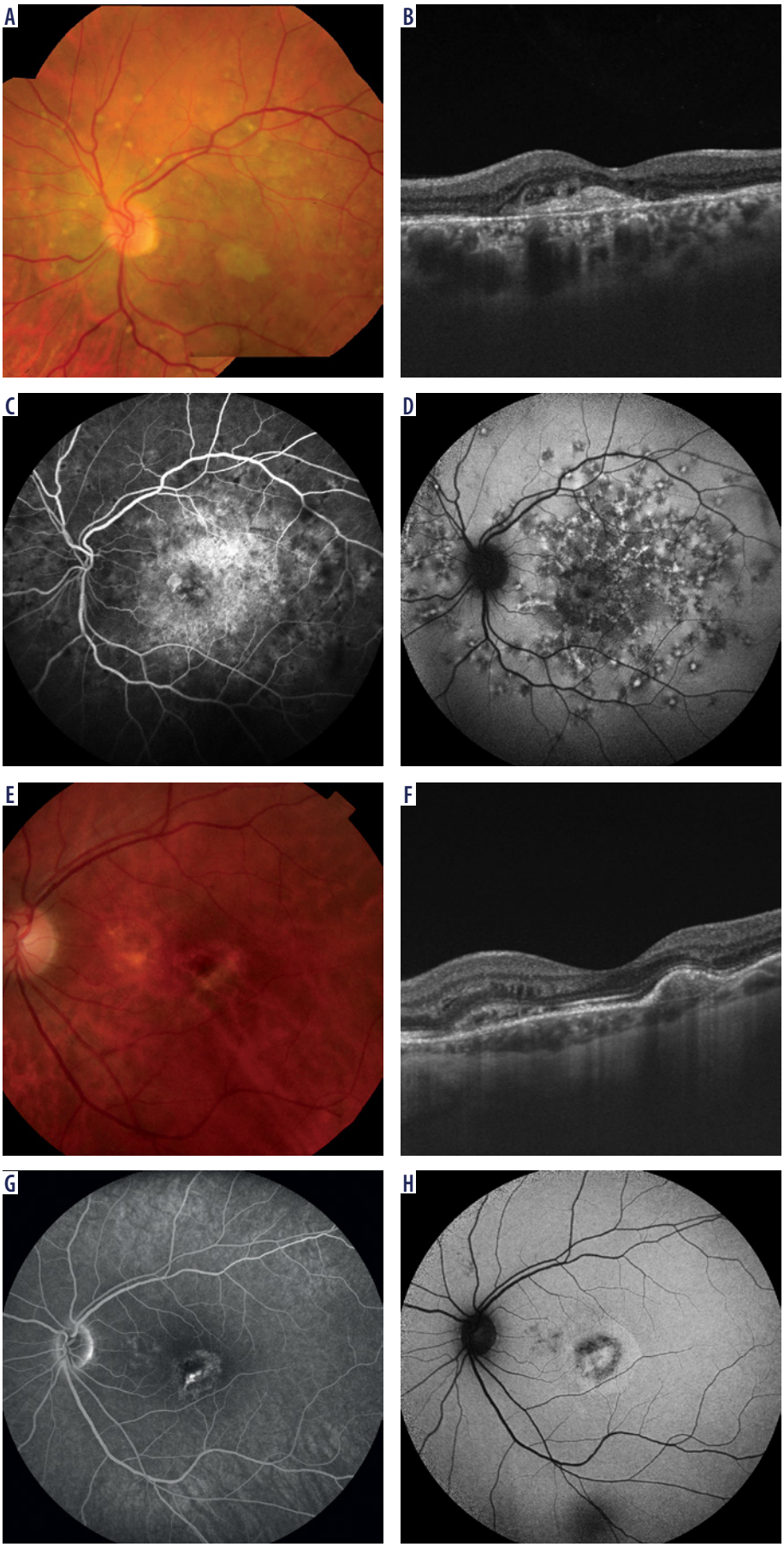


**Figure 4.** Stargardt disease and fundus flavimaculatus – color fundus photography (A), swept-source optical coherence tomography (B), fluorescein angiography (C), fundus autofluorescence (D). Idiopathic CNV – color fundus photography (E), swept-source optical coherence tomography (F), fluorescein angiography (G), fundus autofluorescence (H)

of ranibizumab in patients with CNV due to pathological myopia [2]. Lai *et al.* [1] reported that the most common cause of CNV in adults is neovascular AMD and high myopia, but the condition may also develop secondary to choroiditis, CSC, angioid streaks, trauma, as well as retinal and macular tumors or dystrophies, or occur without an apparent underlying cause or without clinical evidence of a predisposing abnormality [1].

Choroidal neovascularization secondary to pathological myopia is a common complication, affecting from 5% to 10% of patients with degenerative myopia, of whom 15% present with bilateral lesions [7]. Punctate inner choroidopathy, which is less common than pathological myopia, is associated with CNV in 17% to 40% of patients [9]. On the basis of SS-OCT angiography of 363 eyes with CSC, Shiragami *et al.* [19] detected CNV in 15.6% of patients with acute CSC and 21.8% of those with chronic CSC. Bousquaet *et al.* [20] detected CNV in 35.6% of patients with chronic CSC with flat irregular RPE detachment. Moreover, it was reported that CNV occurs in 70% of patients with angioid streaks [22]. In a study by Da Pozzo *et al.* [22], CNV was observed in 11.7% of patients with AOFVD during a 6-year follow-up. In the case of Stargardt disease and fundus flavimaculatus, CNV is rare but has a severe course [23].

In our study, we assessed the incidence of CNV in patients with diseases of the posterior eye other than AMD. Of note, most of our patients were women and the most common cause of CNV was myopia. This is in line with literature data reporting that 67% of patients with CNV secondary to pathological myopia are women, which is probably related to estrogen receptor expression in CNV [8].

Our study confirms that CNV is a common complication of various diseases, not only AMD. Since the treatment of abnormalities underlying CNV may vary, it is important to determine the exact cause. A quick diagnosis is also critical to prevent vision loss. Another key issue is the clinical assessment of the other eye, which in many cases helps identify the underlying cause. Optical coherence tomography reveals typical CNV lesions that are common for various diseases complicated by CNV. Therefore, SS-OCT alone is not sufficient to establish the diagnosis. However, the differential diagnosis of CNV is possible with the use of modern multimodal imaging techniques. Similar to other pathologies, it is necessary to carefully analyze all imaging findings to identify the causative factor. A proper diagnosis allows clinicians to monitor disease progression and decide on the management strategy. Depending on the cause, CNV demonstrates differences in response to therapy as well as patient prognosis; therefore, an individualized approach to each patient and therapeutic decision-making is needed. The most important limitation of our study is the relatively short period of retrospective analysis.

## CONCLUSIONS

In summary, our material proves that among retinal diseases other than AMD, pathological myopia is the one most often complicated by CNV. However, the differential diagnosis should include other less common diseases that may be complicated by CNV. Multimodal retinal imaging is now increasingly available and should be used to facilitate the diagnostic workup and to guide therapeutic decision-making.

## DISCLOSURE

The authors declare no conflict of interest.

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