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A systematic review and a prospective cross-sectional observational study

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Prevalence of Cilioretinal Arteries: A systematic review and a prospective cross-sectional observational study

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4Department of Mechatronics, Optics and Mechanical Engineering, Faculty of Mechanical Engineering, Budapest University of Technology and Economics, Budapest, Hungary
5Centre for Public Health, Queen’s University Belfast, Belfast, UK
6Research Unit of Ophthalmology, Department of Clinical Research, University of Southern Denmark, Odense, Denmark

ABSTRACT.

Purpose . To review studies focusing on cilioretinal arteries (CLRA) in order to assess the overall prevalence and establish the prevalence of CLRA in a Hungarian Caucasian population.

Methods #1 . Systematic literature review of published studies with at least 100 participants.

Methods #2 . Non-mydriatic digital colour photographs were taken of 1000 consecutively enrolled healthy Caucasian young adult volunteers. Images were graded by two trained independent observers. Number and location of identified cilioretinal arteries were recorded and statistically analysed.

Results #1 . Prevalence of CLRA ranges from 6.9% to 49.5%. Detection with fluorescein angiography yields the highest values followed by fundus photography and ophthalmoscopy. Unilateral presence of CLRA is between 70.30% and 93.65%, and temporal location is between 80.77% and 100%.

Results #2. We found at least one CLRA in 36.5% of the participants and in 22.75% of all the examined eyes. Cilioretinal arteries (CLRA) were unilateral in 75.34% and bilateral in 24.66%. Of all the identified CLRA, 96.16% were originating from the temporal rim of the optic disc. We identified at least one temporal CLRA supplying the macula in 28% of the participants and 16.95% of the examined eyes.

Conclusion . Prevalence of CLRA varies depending on identification method. Unilateral presence is unequivocally more frequent similarly to temporal location. From a risk of bias standpoint, high-quality studies are rare. Our data on the distribution pattern of CLRA are similar to that in the international literature. Based on our findings, we assume that slightly more than one-third of the Hungarian Caucasian population has a CLRA.


No conflicting relationship exists for any author.

Introduction

Cilioretinal arteries were first described by Müller (1856) in 1856; then, in 1876 Nettleship (Nettleship 1876) provided histological evidence. Cilioretinal artery (CLRA) is the most common congenital anomaly of the retinal circulation. It is so common that some authors question whether it is appropriate to label them as anomalies (Mann 1957; Awan 1977). The usual appearance of a cilioretinal artery is a bent or hooked vessel at the rim of the optic disc resembling a ‘walking stick’ (Lorentzen 1970). Identification of these vessels is possible with ophthalmoscopy or fundus photography. Oftentimes arteries that are evidently distinct from the central retinal artery have a partial hook only or none at all (Justice & Lehmann 1976). Distinction between arteries of cilioretinal or central retinal origin with certainty is only possible with fluorescein angiography (Hayreh 1963), an invasive imaging technique during which the fluorescein dye fills the cilioretinal arteries at the time it reaches the choroid, before the arterial phase of the angiogram. Cilioretinal arteries belong to the posterior ciliary artery system. They arise...
either directly from the choroid or from one of the posterior ciliary arteries, providing additional or alternative blood supply to the retina. Usual location is the edge of the optic nerve head, most commonly on the temporal side. The size and length varies, often they contribute significantly to the macular circulation, and in some rare cases, they can supply the entire retina (Barroso et al. 1991; Hegde et al. 2006; Hayreh 2011).

Prevalence of cilioretinal arteries has a wide range as reported by previous studies (Mehra 1965; Justice & Lehmann 1976).

To the best of our knowledge, there has not been any investigation on the prevalence of cilioretinal arteries among Hungarians before and data on European Caucasians are also limited.

The aim of our study was to assess the overall prevalence of cilioretinal arteries in previously reported studies with more than 100 patients published and determine the prevalence of cilioretinal arteries in a Hungarian Caucasian population by using non-myrdian fundus photographs.

**Patients and methods**

**Methods #1: Systematic literature review**

This systematic review was performed at the Department of Ophthalmology, Semmelweis University, Budapest, Hungary, and was verified to meet the requirements of the 'Synthesis Without Meta-analysis' (SWiM) guidelines (Campbell et al. 2020) upon completion. SWiM is intended to complement and be used as an extension to the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) (Moher et al. 2009) reporting guidelines. The SWiM checklist is included in Table S1.

**Eligibility criteria for considering studies for this review**

We restricted our analysis to prospective or retrospective observational studies, randomized clinical trials, secondary analyses of clinical trials having results of number of cilioretinal arteries in the studied population and having at least 100 participants. Primary outcome was prevalence of cilioretinal arteries, secondary outcome was distribution of cilioretinal arteries (i.e. unilateral or bilateral appearance, temporal or nasal location).

**Search methods for identifying studies**

We performed a systematic search of PubMed/MEDLINE and EMBASE for records published up to January 2020 in English and German language. The search included relevant terms in Boolean combinations (Table S2). We also performed manual bibliography search of identified studies, review articles and book chapters to find additional relevant studies. For the management of the identified records, the EndNote X9 (Clarivate Analytics, Philadelphia, US) software was used.

**Study selection**

Two investigators (MS and AM) reviewed all identified studies for inclusion independently. Decision-making to include studies was hierarchical, starting with study title, followed by abstract and then full-text review. Disagreements were resolved by discussion between the two investigators.

**Data collection and risk of bias assessment**

Data regarding the number of patients and eyes, number or patients and eyes having cilioretinal arteries, unilateral and bilateral, and temporal and nasal presence were extracted and recorded by two investigators (MS and AM). The risk of bias of eligible studies was evaluated using the Agency for Healthcare Research and Quality (AHRQ) checklist for Cross-Sectional Studies, the recommended tool for evaluating cross-sectional studies (Zeng et al. 2015). The AHRQ checklist consists of 11 items of which we excluded item number 5 and 9–11 as those were not relevant for this type of investigations. Disagreements were resolved by discussion between the two investigators.

**Data synthesis and analysis**

Percentage of patients and eyes having cilioretinal arteries were calculated as per-person and per-eye prevalence. Uni- and bilateral proportions were recounted in relation to the total number of patients having cilioretinal arteries if original data were available. Data for temporal and nasal distribution were also recounted wherever it was necessary in relation to the total number of eyes having cilioretinal arteries. Subgroups among papers were defined based on the technique used to identify cilioretinal arteries. Following synthesis, a qualitative analysis of the data was performed.

**Methods #2: Prospective observational study**

This prospective cross-sectional observational study was carried out at the Department of Ophthalmology, Semmelweis University, Budapest, Hungary. The research was conducted in accordance with the tenets of the Declaration of Helsinki and the ‘The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies’ guideline. (von Elm et al. 2007) The STROBE checklist is included in Table S3. Based on the decision of the Scientific and Research Ethics Committee of the Medical Research Council, the study protocol was approved by the Medical Research Council of the Ministry of Health. (approval no.: 8504-I/2014/EKU, ClinicalTrials.gov ID: NCT02089893). Written informed consent was obtained from each participant before enrolment.

Two thousand eyes of 1000 healthy Caucasian young adult volunteers (age: 18–40 years, mean ± SD: 23.25 ± 2.32 years; 360 (36%) male, 640 (64%) female) were included in the study. Participants were consecutively enrolled between 2014 and 2018 and were predominantly medical students of Semmelweis University attending ophthalmology courses held by the Department. Exclusion criteria were optical media opacities that would have disturbed imaging. Personal data of the participants were anonymized before evaluation. Non-myrdian, 45-degree, digital colour fundus photographs were taken with the Nidek AFC-210 (Nidek Co. Ltd, Hamagori, Japan) fundus camera of both eyes of each participant. An initial quality check excluded fundus photographs of unacceptable quality from the study. Each set of pictures was graded by two independent, masked and trained observers. The two observers had the option to mark their readings as ‘uncertain’. In cases of discrepancy between the observers or the presence of uncertainty marking a senior retinal
specialist (MS and AP), as a third observer also reviewed the images and made the final decision. Additionally, one out of eight (12.5%) of the matching and non-uncertain readings was randomly selected to be reviewed by the senior retinal specialists for quality assurance reasons.

Similarly to previous studies on this topic, cilioretinal arteries were defined as retinal artery branches non-contiguous with the central retinal artery, forming a near-180° hook as they emerge from underneath the retinal pigment epithelium at the rim of the optic disc (Jackson 1911; Liu et al. 2011; Tuncer et al. 2013). Presence, number and location of the identified cilioretinal arteries were recorded.

Location of the cilioretinal artery was defined with respect to the centre of the optic nerve head, upper/lower temporal and upper/lower nasal locations were distinguished (Fig. 1). In cases of temporal location, macular circulatory supply was also evaluated. Macular supply was defined by our research team as the cilioretinal artery reaching a circle centred on the fovea with a radius of fovea-optic disc rim distance minus one-disc diameter (Fig. 2).

**Statistical analysis**

Statistical analysis was done using Excel Analysis ToolPak (Microsoft Excel for Office 365 MSO 16.0.11231.20122 64-bit, Microsoft Corp., Redmond, Washington, US) and R system (software version 3.5.0, the R Foundation for Statistical Computing, Vienna, Austria, available at: http://www.R-project.org). Confidence limits were calculated using the Wilson method which may provide more reliable coverage than the alternatives, especially when the sample size is small or the probability of success is close to 0 or 1 (Wilson 1927). Phi coefficient was applied for measuring the association between two binary variables, and the probability value of the binary variables (i.e. gender) was calculated via chi-squared test. Additionally, point-biserial correlation coefficient was applied for the correlation between two variables considered dichotomous and continuous (i.e. age). The probability value for such variables was calculated with two-tailed unpaired t-test.

A p-value of <0.05 was considered statistically significant.

**Results**

**Literature review: Search findings**

This systematic search of electronic databases identified 539 records. Bibliography search identified an additional five reports. Finally, 19 studies (Elschnig 1897; Jackson 1911; Bullwinkel 1954; Mehra 1965; Lorentzen 1970; Jain et al. 1972; Justice & Lehmann 1976; Erkkild & Laatikainen 1979; Shihab et al. 1985; Jonas et al. 1988; Lindenmuth et al. 1988; Nipken & Schmidt 1996; Taarnhoj et al. 2005; Liu et al. 2011; Tuncer et al. 2013; Baneke et al. 2018; Ebraheem et al. 2018b; Snyder et al. 2018; Bavinger et al. 2019) involving 15 611 patients were selected for full-text review and were included in this analysis (Fig. 3).

**Literature review: Study characteristics and risk of bias**

The reported prevalence of cilioretinal arteries ranges from 6.9% to 49.5% (Mehra 1965; Justice & Lehmann 1976). Detailed summary tabulation of data provided by previous relevant studies recruiting at least 100 subjects can be seen in Table 1. While compiling the summary, we used original data from the papers and recounted percentages on a unified basis wherever necessary to make results across studies comparable.

In the studies included in this review, we could find three different imaging techniques for the identification of cilioretinal arteries, namely ophthalmoscopy, fundus photography and fluorescein angiography. The earliest publication reporting on prevalence by Elschnig (1897) used histology in addition to ophthalmoscopy, but the distribution between those two methods is unclear from the paper.

There was a general trend between papers based on the technique. Studies which used ophthalmoscopy had the lowest values for both per-person and per-eye prevalence, studies using fundus photography had generally higher values, and studies with fluorescein angiography had the highest results.

In all of the included studies, unilateral presence and temporal location were more frequent. Unilateral presence of cilioretinal arteries was found to be between 70.30% and 93.65% while temporal location was between 80.77% and 100%.

Evaluation of risk of bias within studies showed that papers published after the year 1980 became generally more transparent. Summary of relevant risk of bias parameters can be found in Table 2.

**Prevalence and distribution pattern of cilioretinal arteries in a Hungarian Caucasian population**

The per-person prevalence of cilioretinal arteries (defined as one or more
cilioretinal artery present in either eye of the participants) in our prospective observational study was 36.50% (95% confidence interval [CI]: 33.57–39.53%, n = 365). Age had no impact on the presence of cilioretinal arteries (point-biserial correlation coefficient = 0.0134, t-test p = 0.0975). In males and females, per-person prevalence values were 36.67% (95% CI: 31.85–41.76%, n = 132) and 36.41% (95% CI: 32.77–40.20%, n = 233), respectively, with no significant difference between them ($\chi^2$, p = 0.9346).

The per-eye prevalence of cilioretinal arteries (defined as one or more cilioretinal arteries present in any eye in the entire study population) was 22.75% (95% CI: 20.97–24.64%, n = 455).

Of the total number of patients with cilioretinal arteries, 75.34% (95% CI: 70.67–79.49%, n = 275) were unilateral, and 24.66% (95% CI: 20.51–29.33%, n = 90) were bilateral. Values for unilateral and bilateral presence of cilioretinal arteries for males and females were 71.21% (95% CI: 62.97–78.25%, n = 94) and 28.79% (95% CI: 21.75–37.03%, n = 38) versus 77.68% (95% CI: 71.91–82.56%, n = 181) and 22.32% (95% CI: 17.44–28.09%, n = 52), respectively. Bilateral presence was more frequent in men, but this difference was not significant ($\chi^2$, p = 0.1973). Of the total number of participants having bilateral cilioretinal arteries in 76.67% (95% CI: 66.95–84.20%, n = 69), mirror symmetry (i.e. one or more cilioretinal artery in the same quadrant in both eyes) was observed.

Of the total number of cilioretinal arteries identified, 50.48% (95% CI: 46.20–54.75%, n = 263) were in right eyes and 49.52% (95% CI: 45.25–53.80%, n = 258) were in left eyes. Difference between right and left eyes was not significant ($\chi^2$, p = 0.8281), and gender had no impact on right or left presence of cilioretinal arteries ($\chi^2$, p = 0.6060 for right and p = 0.6466 for left eyes).

Of the total number of cilioretinal arteries, 96.16% (95% CI: 94.15–97.50%, n = 501) were located at the temporal and 3.84% (95% CI: 2.50–5.85%, n = 20) at the nasal side of the optic disc.

Detailed results of the locations and distributions of cilioretinal arteries can be seen in Table 3.

Presence of cilioretinal arteries in lower location was more frequent than in the upper location on both temporal and nasal sides (see Table 3.).

Macular supply was observed in a high percentage of temporal cilioretinal arteries, in 76.05% (95% CI: 72.12–79.58%, n = 381) of the total and in 78.84% (95% CI: 70.20–82.18%, n = 149) and 74.36% (95% CI: 66.56–76.50%, n = 232) of the upper and lower temporally located ones, respectively. The per-person prevalence of cilioretinal arteries supplying the macula (defined as one or more cilioretinal artery supplying the macula present in either eye of the participants) was 28.00% (95% CI: 25.31–30.86%, n = 280), and the per-eye prevalence of cilioretinal arteries supplying the macula (defined as one or more cilioretinal artery supplying the macula present in any eye in the entire study population) was 16.95% (95% CI: 15.37–18.66%, n = 339). Bilateral macula-supplying cilioretinal artery was found in 5.90% (95% CI: 4.60–7.54%, n = 59) of the study population. Gender had no impact on the presence of bilateral macula-supplying cilioretinal arteries ($\chi^2$, p = 0.1073).

We calculated the total number of cilioretinal arteries in a given eye as well. In our study population, the maximum number of cilioretinal arteries in one eye was three. Of the total number of eyes having cilioretinal arteries, we found 1 cilioretinal artery in 86.81% (95% CI: 83.39–89.62%,

![Fig. 2. Macular supply grading examples. A: Cilioretinal artery (green arrow) graded with macular supply. B: Cilioretinal artery (green arrow) graded without macular supply. White dotted line: the line between the centre of the fovea and the optic disc rim, 1 DD: one-disc diameter distance, circle with white dashed line: defined area to reach for the cilioretinal artery to be graded as having macular supply, and R: radius of the circle (fovea-to-optic disc rim distance minus 1 DD).](image)
Prevalence and distribution pattern of cilioretinal arteries in a Hungarian Caucasian population: Grading statistics

Two masked observers graded all images independently. Of the thousand gradings, there was discrepancy between graders in 30.40% (95% CI: 27.63%–33.32%, n = 304) and 12.50% (95% CI: 10.59%–14.69%, n = 125) of eyes were marked as ‘uncertain’ requiring arbitration grading. A total of 33.30% (95% CI: 30.45%–36.28%, n = 333) of the readings needed to be re-evaluated due to discrepancy or uncertainty. Note that in our reading process we had 12 captured data points per reading (i.e. number of cilioretinal arteries in upper temporal, lower temporal, upper nasal, lower nasal quadrants; presence of macular supply in upper temporal, lower temporal quadrants; for both eyes) making the reading and the resulting dataset complex. Due to the high number of data points, differences between readings were expected and we considered any difference a discrepancy. Of the discordant cases, 42.76% (95% CI: 37.33%–48.38%, n = 130) had discrepancy in one data point, and 38.82% (95% CI: 33.51%–44.40%, n = 118), 8.22% (95% CI: 5.63%–11.86%, n = 25) and 10.20% (95% CI: 7.28%–14.11%, n = 31) had discrepancies in 2, 3 and more than 3 data points, respectively. For further quality assurance reasons, random checks were carried out on one out of eight (n = 84) of the matching and non-uncertain readings (n = 667). In 94.05% of the cases, no further correction was required; the remaining 5.95% (95% CI: 2.57%–13.19%, n = 5) of the random checks third observer needed to correct the results.

Discussion

The clinical significance of the presence of cilioretinal arteries lies in two potential situations: first, a patent temporal cilioretinal artery that provides macular supply can preserve the macular circulation and save central vision during a complete central retinal artery occlusion (Brown & Shields 1979; Hayreh & Zimmerman 2005; Hayreh 2011; Angeli et al. 2019). Second, during an isolated occlusion of a cilioretinal artery vision in the supplied area will be damaged, if the artery contributed to the macular circulation central vision can severely be affected (Hayreh 2011; Pichi et al. 2019). In extremely rare cases where the same eye has more than one cilioretinal artery, more can be occluded simultaneously (Pincus 1975).

Findings on cilioretinal arteries in age-related macular degeneration (AMD) are controversial. In a recent report, a secondary analysis of the Age-Related Eye Disease Study (AREDS) Snyder and co-workers reported that cilioretinal arteries may have a possible hemodynamic contribution to the pathogenesis of neovascular AMD. They observed that the presence of a cilioretinal artery was associated with a lower risk of developing choroidal neovascularization but had no effect on the development of geographic atrophy (Snyder et al. 2018). The former finding was however not corroborated by the more recent report, the secondary analysis of the Comparison of Age-Related Macular Degeneration Treatment Trials (CATT) by Bavinger et al. Their analysis did not find a protective association between cilioretinal arteries and the incidence of choroidal neovascularization and confirmed that there was no association with geographic atrophy (Bavinger et al. 2019). Another recent research by Ebraheem et al. (2018b) found a negative correlation between presence of cilioretinal arteries and the volume of subretinal fluid in neovascular AMD giving another piece of possible evidence for the hemodynamic theory. The same workgroup, contrary to the previously mentioned ones, described a moderate correlation between the presence of cilioretinal arteries and macular atrophy in another report (Ebraheem et al. 2018a).

In 2015, Hayreh gave an overview about cilioretinal arteries in his book, including most of the historically significant publications, highlighting some the most important features (Hayreh 2015).

In a study based on the review of stereo fundus photographs and
Table 1. Summary of studies reporting on the prevalence of cilioretinal arteries.

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Year</th>
<th>Technique</th>
<th>Subjects</th>
<th>Eyes</th>
<th>Unilateral (%)</th>
<th>Bilateral (%)</th>
<th>Temporal (%)</th>
<th>Nasal (%)</th>
<th>Country of origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elschnig</td>
<td>1897</td>
<td>O + HIS</td>
<td>170</td>
<td>340</td>
<td>about 7%</td>
<td></td>
<td></td>
<td></td>
<td>Austria</td>
</tr>
<tr>
<td>Jackson</td>
<td>1911</td>
<td>O</td>
<td>500</td>
<td>1000</td>
<td>29.60%</td>
<td>19.10%</td>
<td>70.95%</td>
<td>29.05%</td>
<td>USA</td>
</tr>
<tr>
<td>Bullwinkel</td>
<td>1954</td>
<td>O</td>
<td>500</td>
<td>1000</td>
<td>16.00%</td>
<td></td>
<td></td>
<td></td>
<td>USA</td>
</tr>
<tr>
<td>Mehra</td>
<td>1965</td>
<td>FP</td>
<td>1448</td>
<td>2996</td>
<td>6.91%</td>
<td>4.04%</td>
<td>83.00%</td>
<td>17.00%</td>
<td>India</td>
</tr>
<tr>
<td>Lorentzen</td>
<td>1970</td>
<td>O</td>
<td>172</td>
<td>344</td>
<td>26.16%</td>
<td>15.12%</td>
<td>84.44%</td>
<td>15.56%</td>
<td>USA</td>
</tr>
<tr>
<td>Jain et al.</td>
<td>1976</td>
<td>FP + FA</td>
<td>1000</td>
<td>2000</td>
<td>49.50%</td>
<td>32.10%</td>
<td>70.51%</td>
<td>29.49%</td>
<td>USA</td>
</tr>
<tr>
<td>Justice, Lehman</td>
<td>1976</td>
<td>FP</td>
<td>122</td>
<td>244</td>
<td>23.77%</td>
<td>14.34%</td>
<td>79.31%</td>
<td>20.69%</td>
<td>USA</td>
</tr>
<tr>
<td>Erkkila, et al.</td>
<td>1985</td>
<td>FP</td>
<td>100</td>
<td>200</td>
<td>34.00%</td>
<td>22.00%</td>
<td>70.59%</td>
<td>29.41%</td>
<td>Finland</td>
</tr>
<tr>
<td>Jonas et al.</td>
<td>1989</td>
<td>FP</td>
<td>105</td>
<td>163</td>
<td>26.99%</td>
<td></td>
<td></td>
<td></td>
<td>Germany</td>
</tr>
<tr>
<td>Nipken, Schmidt</td>
<td>1996</td>
<td>O</td>
<td>140</td>
<td>280</td>
<td>38.57%</td>
<td>23.21%</td>
<td>79.63%</td>
<td>20.37%</td>
<td>Germany</td>
</tr>
<tr>
<td>Taarnhøj et al.</td>
<td>2005</td>
<td>FP</td>
<td>224</td>
<td>448</td>
<td>45.10%</td>
<td>28.80%</td>
<td>72.28%</td>
<td>27.72%</td>
<td>Denmark</td>
</tr>
<tr>
<td>Liu et al.</td>
<td>2011</td>
<td>FP</td>
<td>2500</td>
<td>5000</td>
<td>35.04%</td>
<td>18.46%</td>
<td>93.04%</td>
<td>6.96%</td>
<td>China</td>
</tr>
<tr>
<td>Tuncer et al.</td>
<td>2013</td>
<td>FP</td>
<td>1100</td>
<td>2200</td>
<td>29.09%</td>
<td>17.18%</td>
<td>93.65%</td>
<td>6.35%</td>
<td>USA</td>
</tr>
<tr>
<td>Erkkila, et al.</td>
<td>2018</td>
<td>FA</td>
<td>500</td>
<td>1000</td>
<td>38.20%</td>
<td>26.00%</td>
<td>93.08%</td>
<td>6.92%</td>
<td>Turkey</td>
</tr>
<tr>
<td>Baneke et al.</td>
<td>2018</td>
<td>FA</td>
<td>1530</td>
<td>3406</td>
<td>45.03%</td>
<td>28.01%</td>
<td>75.62%</td>
<td>24.38%</td>
<td>USA</td>
</tr>
<tr>
<td>Erkki, et al.</td>
<td>2018</td>
<td>FA</td>
<td>3647</td>
<td>6966</td>
<td>35.29%</td>
<td>21.98%</td>
<td>76.30%</td>
<td>23.70%</td>
<td>USA</td>
</tr>
<tr>
<td>Bavinger et al.</td>
<td>2019</td>
<td>FA</td>
<td>350</td>
<td>694</td>
<td>35.86%</td>
<td>20.17%</td>
<td>78.26%</td>
<td>21.74%</td>
<td>USA</td>
</tr>
</tbody>
</table>

CLRA = cilioretinal artery, FP = fundus photography, FA = fluorescein angiography, HIS = histology, N/A = not applicable, O = ophthalmoscopy, UK = United Kingdom, UN = unknown, USA = United States of America.

a Using the original data from the reports, uni- and bilateral proportions were recounted in relation to the total number of patients having CLRA to make results across studies comparable.
b Recounted using original data where both eyes were gradable.
c Only temporal CLRAs extending into the macular region were graded.
d Recounted using original data.

Table 2. Summary of risk of bias of included studies.

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Source defined</th>
<th>Eligibility criteria</th>
<th>Time period</th>
<th>Consecutive recruitment</th>
<th>Quality assurance</th>
<th>Exclusions explained</th>
<th>Confounding described</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elschnig</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Unclear</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Jonas et al.</td>
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<td>Justice, Lehman</td>
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<td>Liu et al.</td>
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</table>

Evaluation conducted using the relevant items of the Agency for Healthcare Research and Quality checklist. Source defined: define the source of information (survey, record review). Eligibility criteria: list inclusion and exclusion criteria for subjects or refer to previous publications. Time period: indicate time period used for identifying patients. Consecutive recruitment: indicate whether or not subjects were consecutive if not population based. Quality assurance: describe any assessments undertaken for quality assurance purposes (e.g. test/retest of primary outcome measurements). Exclusions explained: explain any patient exclusions from analysis. Confounding described: describe how confounding was assessed and/or controlled.
Table 3. Locations and distribution of cilioretinal arteries.

<table>
<thead>
<tr>
<th></th>
<th>Temporal</th>
<th>Lower temporal</th>
<th>Nasal</th>
<th>Upper nasal</th>
<th>Lower nasal</th>
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<tbody>
<tr>
<td></td>
<td>Upper temporal</td>
<td>Lower temporal</td>
<td>Nasal</td>
<td>Upper nasal</td>
<td>Lower nasal</td>
</tr>
<tr>
<td></td>
<td>96.16% (95% CI: 94.15%–97.50%, ( n = 501 ))</td>
<td>62.28% (95% CI: 57.95%–66.41%, ( n = 312 ))</td>
<td>3.84% (95% CI: 2.50%–5.85%, ( n = 20 ))</td>
<td>30.00% (95% CI: 14.55%–51.90%, ( n = 6 ))</td>
<td>70.00% (95% CI: 48.10%–85.45%, ( n = 14 ))</td>
</tr>
<tr>
<td>Macular supply</td>
<td>76.05% (95% CI: 72.12%–79.58%, ( n = 381 ))</td>
<td>74.36% (95% CI: 66.56%–76.50%, ( n = 232 ))</td>
<td>78.84% (95% CI: 70.20%–82.18%, ( n = 149 ))</td>
<td>70.00% (95% CI: 66.41%–72.12%, ( n = 189 ))</td>
<td>5.85%–10.00% (95% CI: 5.85%–10.00%, ( n = 6 ))</td>
</tr>
</tbody>
</table>

Upper/lower temporal distributions are calculated from total temporal numbers, and Upper/lower nasal distributions are calculated from total nasal numbers. Macular supply percentages are calculated from each respective temporal category, that is total, upper, and lower.

An interesting observation in our study was that cilioretinal arteries were much more common in the two lower quadrants, by almost double on the temporal (62.28% versus 32.72%) and more than double on the nasal (70% versus 30%) side of the optic disc. The reason for this phenomenon remains to be explained and contradicts the results of Collier (Collier 1957), who found cilioretinal arteries to be more common in the upper quadrants. Note that we categorized the origin of the cilioretinal arteries with respect of the centre of the optic disc only, regardless of the actual supplied area (i.e. in a few cases we observed that a cilioretinal artery originated from the lower temporal side of the optic disc but supplied the upper macula and vice versa).

Factors influencing the presence or absence, the number and distribution pattern of cilioretinal arteries are not so well understood. A Danish study by Taarnhøj et al. including 112 twin pairs examined the heritability of cilioretinal arteries. They found that the layout of the arterial blood supply of the retina, as represented by the presence or absence of cilioretinal arteries, was influenced by heritability in 71.4% and they found a random environmental effect in 28.6%. Their results suggest that the presence or absence of cilioretinal arteries in healthy persons is influenced by genetic factors. The per-person prevalence of cilioretinal arteries in their studied population was 45.1% (Taarnhøj et al. 2005). Another study, built upon the former, conducted in the United Kingdom by Baneke et al. examined a much larger twin sample of 862 twin pairs. According to their results, heritability for cilioretinal arteries in either eye was 49.4% and 32.9% for both eyes, a considerably lower result than that of the Danish study. The possible reasons for such a large difference are explained in detail in the paper. They conclude that cilioretinal arteries are moderately heritable and individual environmental factors explain a considerable proportion of the variance. The per-person prevalence in their study was very similar, 45.0% (Baneke et al. 2018).

There have only been six studies reporting on the prevalence of cilioretinal arteries involving at least thousand subjects (Mehra 1965; Justice & Lehmann 1976; Liu et al. 2011; Tuncer et al. 2013; Baneke et al. 2018; Snyder et al. 2018). These projects originated from the USA, UK, China, Turkey, India and Germany with only four (Liu et al. 2011; Tuncer et al. 2013; Baneke et al. 2018; Snyder et al. 2018) of them published in the last 25 years. Our knowledge regarding the prevalence of cilioretinal arteries in the European population is therefore severely limited and no data exists regarding Central or Eastern Europe. Additionally, our risk of bias assessment revealed that of the publications included in our systematic review there are only a few of high quality and none of those were originally designed to be epidemiological studies.

Based on our systematic review, authors use ophthalmoscopy, fundus photography and fluorescein angiography for the identification of cilioretinal arteries with fundus photography being the most popular option most likely due to its ease of use, the archiving possibility and non-invasive manner. In the studies, we analysed the prevalence results were highest where fluorescein angiography was used, with the exception of the paper by Ebraheem et al. (2018b) in which the lower values can be explained by selection bias. The differing results among the three techniques suggest that prevalence values might be underestimated in studies.
using fundus photography and ophthalmoscopy. However, there is one major limitation to this assessment. In our review, we identified only four studies that used fluorescein angiography (Justice & Lehmann 1976; Tuncer et al. 2013; Ebraheem et al. 2018b; Bavinger et al. 2019) and such a low number makes conclusions uncertain.

Additionally, another limitation of our review is that the protocol was not formally registered; therefore, the objectives and methods were not publicly and explicitly prespecified. To overcome this limitation, we challenged our review against the SWiM (Campbell et al. 2020) guidelines published in 2020. Lastly, another limitation of our review is the arbitrary chosen inclusion criterion for minimal number of participants. This latter prevented us from conducting a meta-analysis of the data and may have caused exclusion of studies with valuable results.

A limitation of our observational study is that it recruited young adults only by design; therefore, age impacts for the presence of cilioretinal arteries cannot be judged with certainty. However, cilioretinal arteries are generally considered congenital rather than acquired (Brown & Tasman 1983; Hayreh 2015) and their appearance or disappearance was not observed over time. The reason for selecting such a narrow age group was simply practical since young adults usually have clear optical media and better cooperation making the imaging with non-mydriatic cameras easier.

Other limitations of our study include the arbitrarily chosen number or participants and the non-equal distribution of males and females. In our study population, we had 1.78 times more women than men (640 versus 360). This difference is attributable to our subject recruiting method as we selected predominantly medical students consecutively from our university having a female/male gender ratio of 1.54 during the time of recruitment. (Semmelweis University, Budapest, Dean’s Office (2019): Semmelweis University student attendance records (Years: 2014–2018), Verbal communication).

Additionally, we evaluated the presence or absence of cilioretinal arteries based on fundus photographs. The method allowing identification of cilioretinal arteries with complete certainty is fluorescein angiography (Hayreh 1963) as mentioned earlier. In conclusion, prevalence of cilioretinal arteries ranges from 6.9% to 49.5% depending on the identification method, with fluorescein angiography having the highest values followed by fundus photography and ophthalmoscopy. Unilateral presence is unequivocally more frequent by a large margin similarly to temporal location. High-quality papers are rare.

Based on the data from our prospective cross-sectional study, we estimate that slightly more than one-third of the Caucasian population in Hungary has at least one cilioretinal artery. The high majority of these vessels are at the temporal side of the optic disc, and approximately three-fourth of those are contributing to the macular circulation. Numbers and distribution patterns are similar in men and women and align well with previous findings of the international literature.

Data on prevalence and patterns can be helpful for future studies further exploring the link between cilioretinal arteries and the development of age-related macular degeneration and for risk assessment of patients prone to artery occlusion.

References


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MS involved in study design, regulatory administrations, study coordination, image reading supervision, literature research and review, risk of bias assessment, drafting and final approval of the manuscript. AM involved in patient interaction, image acquisition, initial image quality check, image reading, literature research and review, risk of bias assessment and final approval of the manuscript. OA involved in patient interaction, image acquisition, initial image quality check, image reading and final approval of the manuscript. EG involved in patient interaction, image acquisition, initial image quality check, image reading and final approval of the manuscript. ZZN involved in critical revision and final approval of the manuscript. BVN involved in database management, statistics, final approval of the manuscript. BJ involved in patient interaction, image acquisition, database management and final approval of the manuscript. DB involved in database management, statistics, critical revision and final approval of the manuscript.

Additional Supporting Information may be found in the online version of this article:
Table S1. SWiM checklist.
Table S2. Search query strings on the selected databases.
Table S3. STROBE checklist.