Cureus

Open Access Original Article

DOI: 10.7759/cureus.138

Epidemiology of Angioid Streaks-Associated Choroidal Neovascular Membranes in the United Kingdom

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Abstract

Background: The purpose of this study is to determine the incidence of angioid streak-associated choroidal neovascular membranes (CNV) in the UK and provide other epidemiological data, clinical characteristics, therapies used, and short-term outcomes following treatment of this condition.

Procedure: This is a prospective multicenter cohort study. Patients newly diagnosed of angioid streaks-associated CNV were identified prospectively over a 14-month period (January 2009-March 2010) by active surveillance through the British Ophthalmic Surveillance Unit (BOSU). Questionnaire-based data was obtained from reporting ophthalmologists at baseline and 12 months. The main outcome measure was incidence of angioid-streak associated CNV. Secondary outcomes included clinical characteristics, treatments used, and visual outcomes.

Results: Forty-four cases of angioid streak-associated CNV were reported to BOSU, giving an annual incidence of 0.057 (95% CI: 0.040-0.074) per 100,000 population. Affected patients had a mean age of 47 years (range: 24-62 years), presented with a mean (SD) LogMAR visual acuity (VA) of 0.53 (0.51) (Snellen equivalent 6/18), and had most often subfoveal CNV. At one year, the mean LogMAR visual acuity had declined to 0.73 (0.59) (Snellen equivalent 6/36). Visual acuity improved > two Snellen lines in six cases (21%) and deteriorated > two lines in 13 cases (41%). Treatments used included anti-VEGF in 25 eyes (83%), photodynamic therapy (PDT) in two (7%), and observation in three (10%).

Conclusions: This study represents the first population-based prospective study evaluating the incidence of angioid streak-associated CNV in the UK. Despite new treatments for CNV, the visual outcome of patients with this disorder remains guarded.

Categories: Ophthalmology
Keywords: epidemiological data, laser, ranibizumab, anti-vegf, bevacizumab, cnv, photodynamic therapy, pseudoxanthoma elasticum, angioid streaks, choroidal neovascular membrane

Received 03/06/2013
Review began 03/08/2013
Published 09/01/2013

Introduction

Angioid streaks (AS) are irregular, radiating, orange-red jagged lines that extend from around the optic nerve head into the mid-peripheral retina, including the macula. Early on in the course of the disease, AS appear as well-defined orange lines; as the disease progresses, they became less well-defined and more pigmented. They represent crackline dehiscences in Bruch's membrane [1]. AS can be associated to systemic diseases, most commonly pseudoxanthoma elasticum, Ehlers-Danlos, Paget disease, sickle cell disease, or they may be idiopathic [2]. Rarely, they may be associated with abetalipoproteinemia [2-3].

Choroidal neovascular membranes (CNVs) may develop in up to 86% of patients with AS; when left untreated, they undergo progressive scarring leading to visual loss, often to levels of < 20/200 [1, 4-7]. The age at presentation of patients with AS-associated CNVs varies between 11 to 85 years with a mean age of 44 to 59 years [1, 8-14]. Due to the brittle nature of Bruch's membrane in these patients, acute visual loss can occur also following minor trauma as a result of choroidal rupture and sub-macular haemorrhage [15-16]. Bilateral visual loss is not uncommon, and it has been reported to occur in 42 to 71% of patients [6, 17]; legal blindness has been reported in about 50% of patients due to the occurrence of bilateral CNV [1].

How to cite this article
Abdelkader E, Scott N W, Lois N (September 01, 2013) Epidemiology of Angioid Streaks-Associated Choroidal Neovascular Membranes in the United Kingdom. Cureus 5(9): e138. DOI 10.7759/cureus.138

The management of patients with AS-associated CNV is challenging. Several treatment modalities have been used, including laser photocoagulation [18-19], photodynamic therapy (PDT) [20-21], transpupillary thermotherapy [8, 22], feeder vessel occlusion [11], and surgical removal of the CNV or macular translocation [23-24]. Poor visual outcomes are often obtained with these treatments, and a high recurrence rate is observed. Intravitreal injection of anti-VEGF (vascular endothelial growth factor) has been recently used with promising results [13, 25-29]. However, due to the rarity of this condition, no prospective randomised clinical trial (RCT) is available to evaluate the outcomes and complications of these treatments.

The purpose of this study was to prospectively estimate the incidence of AS-associated CNV in the general population in the UK and to gain knowledge on the aetiology, clinical characteristics, management, and response to treatment of this group of patients.

Abbreviations

CNV= choroidal neovascular membrane

UK= United Kingdom

BOSU= British Ophthalmology Surveillance Unit

SD= Standard Deviation, PDT= Photodynamic Therapy

AS= angioid streaks

RCT= Randomised Controlled Trial

VA= Visual Acuity

FFA= Fundus fluorescein angiography

OCT= optical coherence tomography

CF= Counting Fingers

VEGF= Vascular Endothelial Growth Factor

Materials And Methods

Patients with newly diagnosed AS-associated CNV were identified prospectively through active surveillance by the British Ophthalmological Surveillance Unit (BOSU) during a 14-month period from January 2009 to March 2010. BOSU operates a monthly active surveillance scheme throughout the United Kingdom (UK) [30]; it was developed to assist in the investigation of uncommon ocular conditions that are of public health or scientific importance. The surveillance scheme involves all permanently employed ophthalmologists in the UK with clinical autonomy (consultants and associate specialists) who form the reporting base. Before the initiation of a study, BOSU informs all ophthalmologists about the new ocular condition under investigation, including the specific case definition. At the end of each month, a report card is sent to each ophthalmologist, who then returns it specifying whether a new case had been seen that month or whether no cases were seen. After case notification, incident and follow-up questionnaires are sent by the investigators to reporting ophthalmologists.

The baseline incident questionnaire collected data on demographics (age, gender, and ethnicity), ocular history, visual acuity (VA), systemic associations, family history of AS, CNV location, and investigations used for diagnosis. The 12-month follow-up questionnaire collected data on VA, treatment(s) performed, complications of treatment, status of the CNV (active/inactive), whether new CNVs developed during the 12 month follow-up period in the affected and fellow eye, investigations used to assess CNV activity, and whether the case was discharged or continued to followed. Paired t-tests were used to compare visual acuity at baseline and at follow-up.

This study was conducted in accordance with the tenets of the Declaration of Helsinki. Approval was granted by the North East of Scotland Multi-centre Research Ethics and Research and Development committees.

Results

During the study period, the response rate to BOSU was 77%. The investigators received 56 case reports, 12 were duplicates, leaving 44 cases of AS-associated CNV. Based on the 2009 population of UK (Available at: United Kingdom Office for National Statistics http://www.statistics.gov.uk/cci/nugget.asp?id=6), these 44 cases gave an annual incidence of 0.057 cases (95% CI: 0.040-0.074) per 100,000 population. For 35 (79.5%) of these 44 cases, baseline questionnaires were completed by reporting ophthalmologists and received by the investigators; 12 month data questionnaires were completed for 30 of these 35 patients.

There were 20 males and 13 females (gender not available in two) with a mean age of 47 years (range: 24-62 years). Thirty-three patients were of British white origin; two were Caribbean. The right eye was affected in 18 patients. AS were associated with pseudoxanthoma elasticum in 22 patients (63%) and sickle cell in one; in 12 patients (34%), AS seemed to be idiopathic. A family history of AS was present in five patients. The AS-associated CNV was subfoveal in 18 eyes, juxtafoveal in 10, and extrafoveal in seven.

Fundus fluorescein angiography (FFA) was used to diagnose AS-associated CNV in all cases. Other imaging techniques were used to evaluate these patients, including optical coherence tomography (OCT) in 32/35 cases (91%), autofluorescence (AF) in 4/35 cases (11%), and indocyanine green angiography (ICG) in 1/35 cases (3%).

At baseline, the mean LogMAR VA (SD) was 0.53 (0.51) (Snellen equivalent 6/18) (n=35). At one-year follow-up (FU), the mean LogMAR VA was 0.73 (0.59) (Snellen equivalent 6/36) (n=30). Figure *1* illustrates the change of VA from baseline to last follow-up. No statistically significant difference in VA between baseline and one-year follow up was detected (p=0.053, 95% confidence interval of -0.66 to -0.9, paired t-test). VA improved by 0.2 LogMAR (>2 Snellen lines) in six eyes (21%) and deteriorated by 0.2 LogMAR (>2 Snellen lines) in 13 cases (41%). At the end of the follow-up period, 21 patients (70%) maintained driving vision (>6/12) in their affected eye(s).

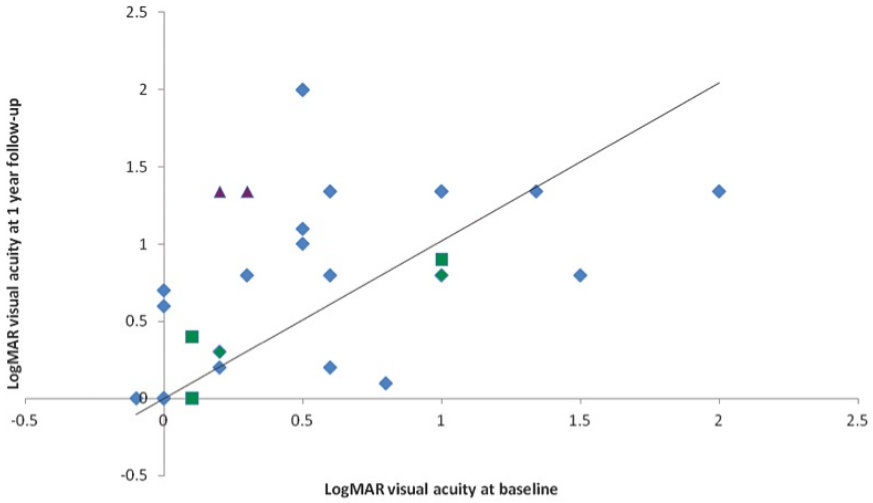

FIGURE 1: Visual acuity (LogMAR) at presentation and at one year follow-up

Visual acuity (LogMAR) at presentation and at one year follow-up in patients with angioid-streak associated choroidal neovascular membranes. Diamonds = eyes treated with anti-vascular endothelial growth factor therapy; squares = eyes observed; triangles = eyes treated with PDT.

New CNV developed in the affected eye at a different location in five eyes (17%) and in the fellow eye in two (7%) during the follow-up. At last follow-up, 10 patients (33.3%) had bilateral CNVs. Treatments used included anti-VEGF therapy in 25 eyes (83%) [bevacizumab in seven (23%) average four injections; and ranibizumab in 18 (60%), average five injections], photodynamic therapy (PDT) in two (7%), and observation in three (10%). No complications related to the treatment were reported. In the subgroup of patients treated with anti-VEGF, the mean baseline vision was 0.55 (0.54) (Snellen equivalent ~6/18), and it was reduced at

one year to 0.72 (0.57) (Snellen equivalent ~6/30). This difference was not, however, statistically significant (p=0.15). In this group, VA improved by 0.2 LogMAR (> 2 lines) in five cases (20%) and deteriorated by 0.2 LogMAR (> 2 lines) in 11 cases (44%). Patients managed by observation included one patient with extrafoveal CNV that maintained 6/6 vision at last follow-up, and two others with juxtafoveal and subfoveal CNVs that had initial VA of 6/18 and 6/12 and deteriorated to counting fingers (CF) at the 12-month follow-up. The two cases that were treated with PDT had 6/12 and 6/18 vision at baseline, both deteriorated to CF at one year.

At 12 months, the CNV remained active in seven eyes (23%), and it was inactive in 23 (77%); treatment was still ongoing in eight eyes (27%) and it had been stopped in 18 (68%). All but one patient remained under follow-up after one year.

Discussion

To our knowledge, this represents the first prospective, population-based study on the epidemiology of AS-associated CNV undertaken in the UK. Based on this study, the annual incidence of AS-associated CNV is estimated ~ 0.057 cases per 100,000 individuals, confirming the rarity of this condition. This study, which represents one of the largest prospective, consecutive cohorts of patients with AS-associated CNV, provides important information with regards to baseline characteristics and outcomes following treatment.

AS-associated CNV affects young individuals, and despite of treatment, many experienced marked visual loss. In keeping with data previously reported [10, 20, 31-32], visual outcomes following PDT were poor; the two patients that received PDT in the current study had vision of CF at the 12 month follow-up visit. Given that visual results following laser and PDT are often disappointing [19-20], anti-VEGF therapies would appear to be the treatment of choice at present time for AS-associated CNV [27, 33-40]. Table *1* summarises currently available studies (presenting > five cases) on the use of anti-VEGF in patients with AS-associated CNV. Some of these studies reported favourable visual outcomes following treatment with stabilisation or improvement of VA in 78-100% of cases (Table *1*). However, the majority of these studies were retrospective case series with numbers ranging between four and 27 patients, and some had received previous treatments prior to the one investigated. Others, however, have reported less favourable visual results similar to those presented herein (Table *1*). Artunay and colleagues [41] investigated the use of combined intravitreal ranibizumab and reduced fluence PDT in a prospective case series which included 10 treatment-naïve cases. At 12 months, they achieved stable (within two Snellen lines from baseline) or improved VA (> two Snellen lines) in 90% of cases.

Authors	Year	# of Eyes	# of Patients	FU (Months)	Design	Drug	Average # of Injections	Mean / Baseline VA	Mean / FU VA	Sig	Stable (%)	> 2 Lines Improvement (%)	> 2 Lines Deterioration (%
Shah & Amouko [42]	2012	12	9	21.7	Pet	Ran	5.7	6/15	6/12	No (p=0.6)	92	25	8
Finger et al [33]	2011	7	7	12	Pro	Ran	12	20/63	20/32	Yes (p=0.012)	N/A	N/A	N/A
Finger et al [43]	2011	16	14	28	Ret	Bev	6.5	20/80	20/40	Yes (p=0.04)	94	50	6
Ladas et al [44]	2010	15	14	12	Pro	Ran	7	20/100	20/50	Yes (p=0.006)	93.3	N/A	6.7
Vadala et al [45]	2010	9	9	14	Pro	Ran	5	20/60	20/40	Yes (p=0.014)	100%	78%	0%
El Matri et al [34]	2010	18	17	13	Ret	Bev	4.8	20/80	20/44	Yes (p=0.014)	100	66	0
Mimoun et al [35]	2010	35	27	24	Ret	Ran	5.7	20/43	20/46	No (p=0.73)	85.7	14.3	14.3
Sawa et al [36]*	2009	15	13	19	Ret	Bev	4.5	6/15	6/18	No (p=0.35)	87	33	13
Neri et al [37] *	2009	11	11	23.8	Pro	Bev	3.5	6/24	6/12	Yes (p=0.018)	100	N/A	0
Bhatnagar et al [27]	2007	9	9	6	Ret	Bev	1.8	20/368	20/289	No (p=0.056)	100	22	0
Wiegand et al [39]	2009	9	6	19	Ret	Bev	4.4	20/50	20/50	No (p N/A)	78	55.5	22
Noda et al [40]	2010	5	4	12	N/A	Bev	N/A	N/A	N/A	No (p N/A)	60	20	40
Myung et al [38]	2010	9	9	28.6	Ret	Bev	8.4	20/368	20/281	No (p=0.14)	100	30	0

TABLE 1: Summary of the studies (with n > 5 cases) reporting the results of anti-VEGF therapy for angioid streaks-associated choroidal neovascular membranes.

#= number, FU= follow up, VA= visual acuity, FU VA= visual acuity at last follow up, Sig= statistically significant difference between baseline and last observed visual acuity, stable= stable or improved VA, > 2 = VA improvement by > 2 Snellen lines, > 2 = VA reduction by > 2 Snellen lines, Ret = retrospective case series, Pro= prospective case series, Bev = bevacizumab, Ran = ranibizumab, *= treatment naïve. N/A= not available.

In the current study, stabilisation or improvement of VA was achieved in 56% of eyes treated with anti-VEGF (n=25) with only 20% experiencing a > two Snellen lines of visual acuity improvement. This is in keeping with findings by Noda, et al. [40] and Bhatnagar, et al. [27] in their small case series, and slightly more favourable that outcomes reported by Mimoun, et al. [35], the largest series, although retrospective, published prior to the current study.

Although this study has several limitations, including the small number of patients included, missing data (in 35/44 cases data available at baseline and in 30/44 cases data was available at 12 months), the short follow-up period, and the inherent limitation of any surveillance study, namely incomplete ascertainment, it provides important epidemiological data and useful information for the management and counselling of

patients with this rare retinal disease.

Conclusions

Patients with AS-associated CNV have now a more favourable visual prognosis with the use of anti-VEGF therapies. Early diagnosis and treatment are essential to restore and maintain vision. Despite of anti-VEGF treatment, in a proportion of patients visual deterioration still occurs and, hence, new therapeutic options are much needed.

Additional Information

Disclosures

Human subjects: Consent was obtained by all participants in this study. The North of Scotland Research Ethics Committees on 27/05/2008 issued approval # 08/S0802/66. This study was conducted in accordance with the tenets of the Declaration of Helsinki. The ethics committee waived the need for informed consent for this study. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

Acknowledgements

Author's contributions: EA participated in designing the study and obtaining ethical approval, collected the data, and drafted the manuscript. NS performed the statistical analysis. NL designed the study, reviewed the manuscript, and supervised the whole work. All authors read and approved the final manuscript. Acknowledgements: The authors would like to thank the British Ophthalmological Surveillance Unit (BOSU), and especially Dr. Barny Foot, research coordinator for BOSU, for their help to undertake this study. We are also very grateful to the WH Ross Foundation for the Prevention of Blindness (Scotland) for supporting this study, Dr. S. Mustafa for his help, and to the reporting ophthalmologists who assisted us reporting cases and collecting data for this study: M.S. Mustafa, D.A. Mulholland, Y.C. Yang, M. Minihan, N. Davies, S.T.D. Roxburgh, G. Menon, C. Blythe, N. Lois, D. Jones, P.L. Atkinson, S. Sengopta, R.J. Antcliff, Y. Osoba, D. Steel, B. Matthews, S. Mahmood, S. Webber, R. Gupta, B. Musthtaq, N. Acharya, R. Gale, P. Tesha, A. Nestel, N. Beare, Y.F. Yang, N. Dhingra, M. Gibson, S. Dinakaran, C. Brand, C. Dayan, and Laidlaw. The study was supported by the WH Ross Foundation for the Prevention of Blindness (Scotland). The funding organization had no role in the design or conduct of this research.

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