Active surveillance of choroidal neovascularisation in children; Incidence, aetiology and management findings from a national study in the United Kingdom

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Synopsis

This prospective national surveillance study identifies the incidence (0.21 per 100,000 in age ≤16), aetiology, management and visual outcome in children with choroidal neovascularization. Visual prognosis was poor irrespective of CNV location and use of anti-VEGF therapy.

Abstract

Background/Aims: To determine the United Kingdom (UK) incidence, demographics, aetiology, management and visual outcome for children developing choroidal neovascularization (CNV).

Methods: A prospective population-based observational study of routine practice via theBritish Ophthalmological Surveillance Unit (BOSU) between January 2012 to December 2013 with subsequent1 year follow-up in children under 16 years old with newly diagnosed CNV.

Results: Twenty-seven children with CNV were reported. The UK estimated annual incidence for those aged 16 and under was 0.21 per 100,000 (95% CI: 0.133-0.299). Mean age 11.1 years (SD 3.9, range 4-16). Fourteen were female. Seventy-seven per cent (22 patients) were Caucasian British. Twenty-three children (85%) had unilateral disease. The most common aetiology included inflammatory retinochoroidopathy (n=9), optic disc abnormalities (n=9), and idiopathic (n=5). Optical coherence tomography (OCT) was performed in all cases and fundus fluorescein angiography (FFA) in 61%. Management included observation only (n=10), anti-vascular endothelial growth factor (VEGF) injection of bevacizumab (n=14) or ranibizumab (n=2) or both (n=1), and additional use of oral (n=1) and local (periocular n=2 and intravitreal n=2) steroids in five children with inflammatory retinochoroidopathy. The mean number of anti-VEGF injections was 2±1, with eight patients receiving only one injection. The mean (SD) best corrected visual acuity (BCVA) in LogMAR was 0.91 (0.53) at presentation and 0.74(0.53) at 1 year follow-up (p=0.09).

Conclusion: This is the first population-based prospective study of CNV in children. This is a rare disorder with a poor visual prognosis irrespective of CNV location and the use of anti-

VEGF therapy.

Introduction

In the paediatric population, choroidal neovascularisation (CNV)has been reported in association with infection, inflammation, optic disc anomalies, retinal dystrophies, trauma and may also be idiopathic[1].Although causes of CNV have been reviewed before[1 2], the incidence of CNV in children is unknown; there have been no reported prospective epidemiological studies. The management of CNV in the paediatric setting is challenging, there are a number of options such as observation, photodynamic therapy (PDT), laser photocoagulation, sub-macular surgery and anti-vascular endothelial growth factor (VEGF) agents, all yielding variable visualoutcomes.[3-6]Theuseofanti-VEGFagentsremainscontroversialassuppressingthephysiological role of VEGF may have deleterious effects in children.[3]This British Ophthalmological Surveillance Unit (BOSU) study is the first prospective epidemiological study providing national data on the incidence, aetiology, treatment and visual outcome of CNV in a paediatric population.

Methods

This was a prospective population-based study performed in association with the BOSU monthly reporting system.[7 8] All ophthalmologists with clinical autonomy (consultant and associate specialist grade, however we did not ascertain their subspecialty) in the United Kingdom (UK) receive a monthly reporting card with definitions of the conditions currently under surveillance and they indicate how many new cases are seen each month. For the 24-month study period between January 2012 to December 2013, ophthalmologists were asked to report any case of new CNV in patients ≤16 years old. Every ophthalmologist who notified a patient to BOSU was sent an initial questionnaire requesting information regarding demographics, aetiology, presenting features and first-line management. A one year follow-up questionnaire was also sent to ascertain subsequent management and visual outcome.

Ophthalmologists who did not return a questionnaire were sent a reminder letter. Questionnaires are available as supplementary materials. The protocol of this study adhered to the provisions of the Declaration of Helsinki and was approved by the local ethics committee of Moorfields Eye Hospital and BOSU.

Statistical analyses

All statistical analyses were performed using the Statistical Package for the Social Sciences (version 21.0; SPSS Inc., an IBM Company, Chicago, IL). Continuous variables (BCVA baseline, BCVA follow up, and age are presented as the mean (standard deviation, SD) after assessing for normality by inspection of histograms. Categorical variables were compared using Chi squared test. Differences between BCVA baseline and BCVA follow-up were compared using the paired t-test. For comparison of BCVA at baseline and follow-up amongst the different CNV locations and management groups, the ANOVA test was used. A *P* value <0.05 was considered statistically significant. Details of all affected eyes (n=31) were reported in the table 1, however, information of only 27 eyes were used for the statistical analysis. Bilateral cases were not simultaneous and, in the statistical analysis, we included only the eye that was treated or the most recent diagnosed. In addition, only 16 unaffected eyes were reported on by the respondents. As this is a rare condition, numbers are small and so the power of this study to detect associations was limited.

Results

Reports to BOSU leading to estimates of the UK incidence of CNV

During the study period, the BOSU used a reporting base of 1245 ophthalmologists. Between January 2012 to December 2013 inclusive, BOSU received 39 reports of patients with CNV

(card return rate 75%), of these only 32 incident questionnaires were returned; one patient was older than 16, thus excluded; and there were three duplicates and one triplicate (this constituted the same patient referred to other ophthalmologists within the UK for further management, hence the patient was over-reported), each one was only counted once to ensure accurate incidence calculations but with full collection of management data. This left 27 children with the accurately reported target disorder. After 12 months, 96.2% of reporting ophthalmologists returned the 1year follow-up questionnaire providing follow up data on 26 out of 27cases.The mid-year population for 2013was estimated to be approximately64.1 million, with a denominator of 12.8 million for children aged 16 and under (the UK Statistic Authority website: http://www.statistics.gov.uk/). The UK estimated annual incidence for those aged 16 and under was 0.21 per 100,000 (95% CI: 0.133-0.299).

Patient characteristics and presenting details

Based on the 27 patients initially reported, themean age at presentation was11.1 years (SD 3.9, range 4-16). Fourteen were female. Seventy-seven percent (22 patients) were Caucasian British, 2 Caucasian non-British, 1 Indian, 1 African and 1 mixed Caucasian and Black Caribbean. Main sources of referral are reported in Fig. 1A. Five patients (19%) were asymptomatic at diagnosis, identified through regular hospital surveillance of their pre-existing ophthalmic condition (n=3) and routine vision check with optometrists (n=2). Median duration of symptoms (reduced vision, positive scotoma) was 31 days (range 1-252). The clinical findings are summarized in Table 1.

Unilateral presentation was most common, found in 23 children (85%). Four patients had bilateral presentation; 2 patients with inflammatory retinochoroidopathy; 1 with Best disease macular dystrophy; and 1 with bilateral chorioretinal coloboma. In patients with bilateral

disease, the localization of the CNV was the same in both eyes. Nearly half (48%) of cases (n=13) had a subfoveal CNV, 7 patients (26%) had peripapillary CNV and in the remaining 7 (26%) it extended from the peripapillary region to the macula.

The most common aetiology included inflammatory retinochoroidopathy (n=9), of which five cases were secondary to multifocal choroiditis), optic disc abnormalities (n=9), of which five cases were secondary to optic disc drusen), Best disease (n=2), high myopia (n=1), idiopathic (n=5) and one associated with laser toy injury (Fig 1B). Twenty-two patients did not have any systemic diseases, however, four patients had a medical history of epilepsy, vitiligo, ventricular septal defect or sarcoidosis.All patients had an OCT, FFA was performed in 16 patients (61%), three cases had indocyanine green angiography (8%). Ultrasound, electrodiagnostic testing and autofluorescence was performed together in one case.

Management included observation only (n=10), anti-VEGF intravitreal injection of bevacizumab (n=14) or ranibizumab (n=2), and both in one case. Eight patients received only one injection, four patients two injections, two patients three injections and two patients (one with optic disc drusen and the other with toxocara uveitis) had four injections. Additional steroid treatment was reported in five patients with inflammation; 2 patients received a biodegradable intravitreal implant of 700 μg of preservative-free dexamethasone (Ozurdex®; Allergan, Inc, Irvine, CA, USA); 2 patients had periocular triamcinolone acetonide (4 mg) injection; and one patient was treated with oral prednisolone.

A total of twenty-one patients did not have any complications following treatment. There were no complications amongst those who received anti-VEGF injections. Two patients with inflammatory CNV treated with anti-VEGF and steroid intravitreal implant reported raised intra ocular pressure (patient 16 and 27), and cataract formation (patient 16). For 3 cases, this information was missing and one respondent failed to send back the 1 year follow-up questionnaire.

The mean (SD) spherical equivalent refraction at presentation in the affected eye was 0.30 (2.55), range −9.25 to 5.00. The presenting mean (SD) BCVA in LogMAR of affected eyes was 0.91 (0.53) and at 1 year was 0.74 (0.53), there was a mild improvement in overall vision compared to the presenting BCVA, although not significant (p=0.09). The distribution of BCVA from baseline to the end of follow-up was similar across the different locations of CNV (ANOVA p=0.46 and p=0.09 respectively). In the macula only group, BCVA baseline in LogMAR was 0.98 (0.61) and at one-year follow-up 0.72 (0.61) (p=0.14); in the peripapillary extending to macula region, BCVA baseline was 0.85 (0.42) and at one-year follow-up 0.64 (0.37) (p=0.12); and in the peripapillary area only BCVA baseline was 0.99 (0.38) and at one-year follow-up 1.0 (0.42) LogMAR (p=0.77, Fig 1C). Overall, during the follow-up, five patients (19%) maintained the same BCVA, 15 (58%) reported a slight improvement and six patients (23%) a reduction. One patient did not have visual acuity follow-up. There was no statistical significant difference in the BCVA at the end of follow-up between the different management groups (ANOVA=0.43). Patients treated with anti-VEGF had a baseline BCVA in LogMAR of 1.0 (0.58) and one-year follow-up of 0.70 (0.56) (p=0.14). Patients treated with a combination of anti-VEGF and steroids had a baseline BCVA in LogMAR of 0.76 (0.47) and one-year follow-up of 0.69 (0.85) (p=0.82). Patients without any treatment had a baseline BCVA of 1.0 (0.14) and one-year follow-up of

0.86(0.38) (p=0.13). One patient was treated with immunosuppressants only and her worse eye deteriorated from 0.30 LogMAR to 1.0 LogMAR at one-year follow-up (Fig. 1D). No statistical significance difference was identified between different treatments at each CNV location. (Supplementary Fig 2). No difference amongst gender was identified for the visual acuity outcome (chi-square=0.1, p=0.92) and no significant correlation was identified between the age at diagnosis and the BCVA at the end of follow-up (r=-0.11, p=0.58). Presenting mean (SD) BCVA in LogMAR of unaffected eyes (n=16) was 0.06 (0.17) and at one-year was 0.10 (0.22), there was no statistical significant difference (p=0.90) in unaffected eyes over this follow-up period.

Discussion

This is the first population-based prospective study of CNV in children. The disorder is rare with an annual incidence in the UK for those aged 16 and under of 0.21 per 100,000. Two retrospective studies of CNV in children younger than 18 years[2 9]reported opposing gender preponderance with Barth *et al.*[9] reporting a strong female predominance (80%), in contrast to Rishi *et al.*[2]who described a higher male preponderance (63%).This result may be due to the different ethnic background and access to healthcare facilities. In our study, no gender preference was identified and the visual acuity outcome was the same in both groups. CNV in the paediatric age group is generally seen in older children[2 9] although it has been reported in a 4 month old[10] with congenital toxoplasmosis, and a 3 year-old with North Carolina macular dystrophy.[11]In our study, the youngest presentation was seen in two female4 year-olds with optic disc anomalies but the majority of cases were in older children with a mean age at presentation of 11 years. The most common aetiologies were inflammatory disease, particularly multifocal choroiditis and optic disc anomalies, which is in concordance with

Rishi and colleagues. Whereas Barth *et al*.[9]reported choroidal osteoma followed by hereditary macular dystrophy as the most common causes. Both studies reported that most CNV was subfoveal. There was an equal divide with half our patients developing subfoveal CNV with the other half having extrafoveal CNV extending from or solely involving in the peripapillary region.

Before the advent of anti-VEGF therapy most cases of CNV in children were managed by observation but there were a few reports of the outcome of sub-macular surgery [4 12]or PDT.[6 13] The lack of calcification, thickening of Bruch's membrane and a solitary ingrowth site were better candidates for surgery.[14]The visual outcomes of 35 children with CNV that underwent surgery revealed ninety percent had a preoperative visual acuity of 0.6 LogMAR or worse and seventy-five per cent gained two or more Snellen lines in visual acuity post-surgery.[4 5]Mateo and colleagues[12]reported 2 cases of sub-macular surgery for CNV in children associated with optic disc drusen; a 16-year-old boy whose visual acuity improved from 1.0LogMAR to 0.09 LogMAR at 26 months follow-up, and a 12 year-old boy with an improvement from 0.40to 0.09 LogMAR at 24 months follow-up without any evidence of recurrence. However, a 9-year-old girl with bilateral peripapillary CNV with subfoveal extension in the left eye secondary to optic disc drusen underwent sub-macular surgery and her visual acuity worsened from 0.05 to 0.3 in the left eye but did not change from 0.3 in the right eye during the 6-month post-operative period.[15]The results of PDT in paediatric CNV are also encouraging.[6 13]Twelve patients with age range4 -15 years underwent PDT for CNV associated with toxoplasma, Best disease or idiopathic causes. Follow-up ranged from 7-77 months, and PDT was able to reduce leakage in 10 out of 12 cases with an improvement in visual acuity in nine cases. The treatment was safe and

effective but there was an intrinsic risk of the regressed membrane leaving a scar causing a reduction in visual acuity over time.

The most common treatment for CNV in children reported in our survey was intravitreal anti-VEGF injection, and steroids in inflammatory cases. There were no cases of PDT, focal laser and sub-macular surgery reported. There are no randomized prospective clinical trials that assess the interventions for CNV in childhood, but anti-VEGF treatment seems to have become the preferred first line approach. Several case reports reported in the literature describe the treatment of CNV associated with optic disc drusen with anti-VEGF agents.[16 17].Anti-VEGF agents do not appear to be associated with any ocular toxicity in the developing eye in humans and this is supported from experimental studies in animals.[18]However, some authors considered treatment with bevacizumab in infants with retinopathy of prematurity (ROP) a significant risk for retinal function and the development of the retinal vasculature.[19] A more serious concern is whether leakage of anti-VEGF agents into the circulation after intravitreal injection may interact with VEGF receptors in other tissues such as the developing brain. A recent observational study found that infants with ROP who were treated with bevacizumab had greater risk of neurodevelopmental disabilities, such as motor delay, compared with those who had laser (but the group of infants who received bevacizumab also a more severe form of ROP).[20]There are no clinical studies that are large enough to evaluate the systemic effects of intravitreal anti-VEGF drugs in children. A multicentre retrospective study reported no ocular or systemic side effects relating to anti-VEGF treatment for CNV, Coats disease, familial exudative vitreoretinopathy and cystoid macular oedema at 1 year follow-up[3] in 90 children, in concordance with no reported side effects in our survey. Avery *et al*[21] suggested that ranibizumab may be more appropriate for children due to its shorter serum half-life. Regarding the dosage, some studies

use a standard adult dose of 1.25 mg/0.05ml of bevacizumab or 0.5 mg/0.05ml of ranibizumab[22] as there is little difference in ocular volume between older children and adult eyes, preterm infants with a smaller ocular size require a lower dosage.[23]The number of injections required to control the disease was lower compared to adults[3], and this was supported by the favourable course of CNV in younger subjects reported by Spaide *et al*[24], attributed to the better health of the RPE pump.[2]

In our cohort, steroid use was required in combination with anti-VEGF injections in five children affected by inflammatory retinochoroidopathy. The anti-angiogenic approach for inflammatory CNV has already been described and identified to be effective when the inflammation is controlled.[25]

Observation remains an important management option. Previous papers report spontaneous regression in 58%[26]and 41.7%[2] of eyes. A characteristic finding that may be predictive of regression is a pigmented ring or encapsulation around the lesion.[27]In our cohort, amongst the observation group, 7 out of 10 cases had a spontaneous improvement in visual acuity, although overall, the visual outcome remained poor. Subfoveal location of the CNV complex, exudative detachment, subretinal pigment epithelial hemorrhage and cystoid degenerative changes of the neurosensory retina may strongly compromise the visual outcome.[27] Ninety percent of patients in a case series with initial visual acuity of less than 1.0 LogMAR remained unchanged.[26] In our sample, almost half of the patients did not report any significant subjective changes in visual acuity during the follow-up, but 33% showed a slight objective improvement.

A potential limitation of this study could be the under-ascertainment of CNV from referring UK ophthalmologists. The high card return rate and previous evaluation of the methodology suggest good levels of compliance, but the incidence of CNV in children in this study is a minimum estimation. The study was not designed to evaluate different methods of treatment and can only give a snapshot of treatment modalities used in current UK practice and the general visual outcomes.

In conclusion, inflammatory retinochoroidopathies and optic disc abnormalities are the commonest associations with CNV in the paediatric population. Most affected eyes will have a subfoveal CNV location. However, we found no evidence of a relationship between CNV location and baseline VA. Eyes treated with anti-VEGF with a macula or peripapillary CNV extending to macula resulted in a slight improvement in VA; but the observation-only group reported a similar VA improvement. Patients with peripapillary CNV did not show any improvement using anti-VEGF or steroids whereas a slight improvement was found if they were observed. It should be noted, however, that because this is a rare condition, numbers are small and thus power to detect differences is low. Ocular co-morbidities play an important role in deciding the choice of treatment and they have an important impact on the visual outcome. No particular treatment has been validated, but laser coagulation, photodynamic therapy, and submacular surgery are not being employed in the UK for this condition.

Legends:

Fig 1(A) Pie chart showing the main source of referral for paediatric CNV in the UK. (B) Pie chart reporting the aetiologies associated with CNV. (C) Bar graph showing the distribution of BCVA in LogMAR at baseline and at the end of follow-up according to the CNV location and (D) within the different management groups. Mean (SD) BCVA value is reported. No statistical significant difference was found across the different locations of CNV nor management groups. * indicates the patient without follow-up.

Supplementary figure 1. Bar graph showing the distribution of BCVA in LogMAR at baseline and at the end of follow-up according to the CNV locations and treatments. No statistical significant difference was found across the different locations of CNV nor management groups. * indicates the patient without follow-up.

Table 1 Clinical data and treatment details of 27 children with choroidal neovascularization

Patient N.	Gender	Age *Years*	BCVA Baseline *LogMAR*	BCVA Follow-up *LogMAR*	CNV location	Ocular comorbidity	Treatment	No. of injections (or dose)
Unilateral cases								
1	M	14	1.77	1.47	Macula only	Laser toy injury	Observation	
2	M	14	0.73	0.60	Macula only	Multifocal choroiditis	Bevacizumab/Ranibizumab	1/2
3	F	6	0.96	0.52	Peripapillary extending to macula	Optic disc drusen	Observation	
4	F	16	2.00	2.00	Macula only	Idiopathic	Bevacizumab	2
5	M	10	1.30	1.20	Macula only	Idiopathic	Observation	
6	F	12	1.30	1.10	Peripapillary extending to macula	Multifocalchoroiditis	Ranibizumab	1
7	F	13	1.30	0.00	Macula only	High myopia	Bevacizumab	2
8	M	15	0.44	0.02	Macula only	Multifocal choroiditis	Bevacizumab/Prednisolone	1/(20mg)
9	M	15	0.32	0.12	Macula only	Best disease	Observation	
10	F	13	0.60	0.77	Macula only	Toxoplasmosis	Bevacizumab	1
11	F	4	0.77	0.17	Peripapillary extending to macula	Optic disc coloboma	Bevacizumab	1
12	M	12	0.74	0.80	Peripapillary only	Congenital optic disc harmatoma	Bevacizumab	1
13	M	15	0.00	0.30	Peripapillary extending to macula	Optic disc drusen	Bevacizumab	4
14	M	7	1.00	1.00	Macula only	Multifocal choroiditis	Bevacizumab	1
15	F	9	0.30	0.17	Macula only	Panuveitis	Bevacizumab/ periocular triamcinolone	1

16	M	15	1.00	0.70	Peripapillary extending to macula	Toxocara uveitis	Ranibizumab/triamcinolone/ dexamethasone intravitreal implant	4/1/1
17	M	11	1.15	1.15	Peripapillary extending to macula	Idiopathic	Observation	
18	M	8	0.60	1.00	Peripapillary only	Optic nerve hypoplasia	Observation	
19	M	16	1.60	0.87	Peripapillary only	Optic disc drusen	Observation	
20	F	18	0.90	0.90	Peripapillary only	Idiopathic	Observation	
21	F	4	0.80	0.80	Peripapillary only	Optic disc drusen	Bevacizumab	2
22	F	13	1.90	0.17	Macula only	Idiopathic	Bevacizumab	1
23	F	13	0.00	----------	Peripapillary only	Optic disc drusen	Bevacizumab	3
Bilateral cases								
24	M	8	RE 0.58 LE 0.86	0.38 0.84	Macula only	Best disease	Observation	
25	F	16	RE 0.77 LE 1.00	0.60 1.00	Peripapillary extending to macula	Bilateral retinal coloboma and left iris coloboma	Observation	
26	F	5	RE 0.30 LE 0.30	1.00 0.00	Macula only	Vogt-Koyanagi- Harada syndrome	Oral steroids and methotrexate	
27	F	6	RE 1.30 LE 0.17	1.90 0.39	Peripapillary only	Multifocal choroiditis	Bevacizumab/dexamethasone intravitreal implant	RE 1 LE 1

F= Female, M=Male, BCVA= Best corrected Visual Acuity, CNV= choroidal neovascularization, RE=Right eye, LE=Left

References:

1. Sivaprasad S, Moore AT. Choroidal neovascularisation in children. The British journal of ophthalmology 2008;**92**(4):451-4 doi: 10.1136/bjo.2007.124586[published Online First: Epub Date]|.
2. Rishi P, Gupta A, Rishi E, Shah BJ. Choroidal neovascularization in 36 eyes of children and adolescents. Eye 2013;**27**(10):1158-68 doi: 10.1038/eye.2013.155[published Online First: Epub Date]|.
3. Henry CR, Sisk RA, Tzu JH, et al. Long-term follow-up of intravitreal bevacizumab for the treatment of pediatric retinal and choroidal diseases. Journal of AAPOS : the official publication of the American Association for Pediatric Ophthalmology and Strabismus / American Association for Pediatric Ophthalmology and Strabismus 2015;**19**(6):541-8 doi: 10.1016/j.jaapos.2015.09.006[published Online First: Epub Date]|.
4. Uemura A, Thomas MA. Visual outcome after surgical removal of choroidal neovascularization in pediatric patients. Archives of ophthalmology 2000;**118**(10):1373-8
5. Sears J, Capone A, Jr., Aaberg T, Sr., et al. Surgical management of subfoveal neovascularization in children. Ophthalmology 1999;**106**(5):920-4 doi: 10.1016/S0161-6420(99)00510-2[published Online First: Epub Date]|.
6. Mimouni KF, Bressler SB, Bressler NM. Photodynamic therapy with verteporfin for subfoveal choroidal neovascularization in children. American journal of ophthalmology 2003;**135**(6):900-2
7. Foot B, Stanford M, Rahi J, Thompson J, British Ophthalmological Surveillance Unit Steering C. The British Ophthalmological Surveillance Unit: an evaluation of the first 3 years. Eye 2003;**17**(1):9-15 doi: 10.1038/sj.eye.6700233[published Online First: Epub Date]|.
8. Nicoll A, Lynn R, Rahi J, Verity C, Haines L. Public health outputs from the British Paediatric Surveillance Unit and similar clinician-based systems. Journal of the Royal Society of Medicine 2000;**93**(11):580-5 doi: 10.1177/014107680009301107[published Online First: Epub Date]|.
9. Barth T, Zeman F, Helbig H, Oberacher-Velten I. Etiology and treatment of choroidal neovascularization in pediatric patients. European journal of ophthalmology 2016;**26**(5):388-93 doi: 10.5301/ejo.5000820[published Online First: Epub Date]|.
10. Mavrikakis E, Levin AV, Lam WC. Choroidal neovascularization secondary to congenital toxoplasmosis in an infant. Canadian journal of ophthalmology. Journal canadien d'ophtalmologie 2010;**45**(6):e11-2 doi: 10.3129/i10-087[published Online First: Epub Date]|.
11. Rhee DY, Reichel E, Rogers A, Strominger M. Subfoveal choroidal neovascularization in a 3-year-old child with North Carolina macular dystrophy. Journal of AAPOS : the official publication of the American Association for Pediatric Ophthalmology and Strabismus / American Association for Pediatric Ophthalmology and Strabismus 2007;**11**(6):614-5 doi: 10.1016/j.jaapos.2007.06.010[published Online First: Epub Date]|.
12. Mateo C, Moreno JG, Lechuga M, Adan A, Corcostegui B. Surgical removal of peripapillary choroidal neovascularization associated with optic nerve drusen. Retina 2004;**24**(5):739-45
13. Giansanti F, Virgili G, Varano M, et al. Photodynamic therapy for choroidal neovascularization in pediatric patients. Retina 2005;**25**(5):590-6
14. Grossniklaus H, Gass JD. Clinicopathologic correlations of surgically excised type 1 and type 2 submacular choroidal neovascular membranes. American journal of ophthalmology 1998;**126**(1):59-69
15. Sullu Y, Yildiz L, Erkan D. Submacular surgery for choroidal neovascularization secondary to optic nerve drusen. American journal of ophthalmology 2003;**136**(2):367-70

16. Baillif S, Nguyen E, Colleville-El Hayek A, Betis F. Long term follow-up after a single intravitreal ranibizumab injection for choroidal neovascularisation secondary to optic nerve head drusen in a 5-year-old child. Graefe's archive for clinical and experimental ophthalmology = Albrecht von Graefes Archiv fur klinische und experimentelle Ophthalmologie 2013;**251**(6):1657-9 doi: 10.1007/s00417-012-2180-8[published Online First: Epub Date]|.
17. Gregory-Evans K, Rai P, Patterson J. Successful Treatment of Subretinal Neovascularization with Intravitreal Ranibizumab in a Child with Optic Nerve Head Drusen. Journal of pediatric ophthalmology and strabismus 2009 doi: 10.3928/01913913-20090818-03[published Online First: Epub Date]|.
18. Wu WC, Lai CC, Chen KJ, et al. Long-term tolerability and serum concentration of bevacizumab (avastin) when injected in newborn rabbit eyes. Investigative ophthalmology & visual science 2010;**51**(7):3701-8 doi: 10.1167/iovs.09-4425[published Online First: Epub Date]|.
19. Lepore D, Quinn GE, Molle F, et al. Intravitreal bevacizumab versus laser treatment in type 1 retinopathy of prematurity: report on fluorescein angiographic findings. Ophthalmology 2014;**121**(11):2212-9 doi: 10.1016/j.ophtha.2014.05.015[published Online First: Epub Date]|.
20. Morin J, Luu TM, Superstein R, et al. Neurodevelopmental Outcomes Following Bevacizumab Injections for Retinopathy of Prematurity. Pediatrics 2016;**137**(4) doi: 10.1542/peds.2015-3218[published Online First: Epub Date]|.
21. Avery RL. Extrapolating anti-vascular endothelial growth factor therapy into pediatric ophthalmology: promise and concern. Journal of AAPOS : the official publication of the American Association for Pediatric Ophthalmology and Strabismus / American Association for Pediatric Ophthalmology and Strabismus 2009;**13**(4):329-31 doi: 10.1016/j.jaapos.2009.06.003[published Online First: Epub Date]|.
22. Kozak I, Mansour A, Diaz RI, et al. Outcomes of treatment of pediatric choroidal neovascularization with intravitreal antiangiogenic agents: the results of the KKESH International Collaborative Retina Study Group. Retina 2014;**34**(10):2044-52 doi: 10.1097/IAE.0000000000000200[published Online First: Epub Date]|.
23. Mintz-Hittner HA, Kennedy KA, Chuang AZ, Group B-RC. Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. N Engl J Med 2011;**364**(7):603-15 doi: 10.1056/NEJMoa1007374[published Online First: Epub Date]|.
24. Spaide RF. Choroidal neovascularization in younger patients. Current opinion in ophthalmology 1999;**10**(3):177-81
25. Chaudhary KM, Mititelu M, Lieberman RM. An evidence-based review of vascular endothelial growth factor inhibition in pediatric retinal diseases: part 2. Coats' disease, best disease, and uveitis with childhood neovascularization. Journal of pediatric ophthalmology and strabismus 2013;**50**(1):11-9 doi: 10.3928/01913913-20120821-02[published Online First: Epub Date]|.
26. Goshorn EB, Hoover DL, Eller AW, Friberg TR, Jarrett WH, 2nd, Sorr EM. Subretinal neovascularization in children and adolescents. Journal of pediatric ophthalmology and strabismus 1995;**32**(3):178-82
27. Sears JE. Macular Choroidal Neovascularization and Defects in Bruch's Membrane in Children. Pediatric Retina: Springer, 2011:345-49.