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Visual prognosis based staging for retinal capillary hemangioma

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Purpose. *To analyze the literature to determine the visual prognosis of eyes affected by retinal angiomatosis of Von-Hippel Lindau disease (VHL).* ***Study Type****. Retrospective literature analysis.* ***Methods.*** *Medline and PubMed searches were performed for publications on retinal capillary hemangioma (CRH). Data was collected on patient age of presentation, CRH laterality, location, treatment, and progression. Statistical analyses using Pearson Chi-Square test, likelihood ratio, and Fischer's exact tests were performed for the effect of these characteristics on visual acuity outcomes.* ***Results.*** *Vision outcomes need to be based on current technology to be clinically relevant. Therefore, only significant publications from 1960 to 2019 were included. Of these, 5 clinical case series included, a total of 427 cases. Of these 69.4 % (58–94.1 %) cases were unilateral CRH, 30.6 % (5.9–42 %) were bilateral, 18.1 % (10.9–23.5 %) were juxtapapillary in location. Major factors affecting visual acuity were age at onset ($p = 0.03$), location ($p < 0.0001$) and multifocality ($p = 0.0005$). Of interest, CRH-related vision loss was independent of the presence of VHL disease ($p = 0.157$).* ***Conclusion.*** *In this study, age at onset, location, multifocality of CRH were the most important predictors of vision loss, which were used to create a vision-outcome based classification system. This information can be used to counsel patients and for informed consent.*

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Классификация капиллярной гемангиомы сетчатки на основе визуального прогноза

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Цель *— провести анализ данных литературы для определения зрительного прогноза при ретинальном ангиоматозе (болезни Гиппеля — Линдау).* ***Тип исследования****: ретроспективный анализ литературы.* ***Методы.*** *Проанализирована литература, посвященная капиллярной гемангиоме сетчатки (КГС), в базах Medline и Pubmed. Собирались данные, касающиеся возраста обращения пациента к врачу, латеральности КГС, локализации, лечения и прогрессирования заболевания. В статистическом анализе для оценки влияния этих параметров на остроту зрения использовался критерий согласия Пирсона Хи-квадрат, критерий отношения правдоподобия и точный тест Фишера.* ***Результаты.*** *Клинически релевантная оценка результирующей остроты зрения должна основываться на тех исследованиях, в которых применялась современная технология. Соответственно, мы учитывали только значимые публикации за период с 1960 по 2019 г. Из этих публикаций было выделено 5 клинических серий общей численностью в 427 случаев. 69,4 % (58–94,1 %) случаев приходилось на одностороннюю КГС, 30,6 % (5,9–42 %) на двустороннюю, 18,1% (10,9–23,5 %) КГС имели юкстапапиллярную локализацию. Основными факторами, влияющими на остроту зрения, являлись возраст, в котором наступила болезнь ($p = 0,03$), локализация ($p < 0,0001$) и мультифокальность ($p = 0,0005$). Интересно, что потеря зрения, связанная с КГС, не зависела от наличия болезни Гиппеля — Линдау ($p = 0.157$).* ***Заключение.*** *Самыми значимыми предикторами потери зрения при КГС являются возраст начала заболевания,*

локализация и мультифокальность. Эти факторы и были использованы для создания классификации, основанной на визуальном исходе. Данная информация может быть использована при консультировании пациентов и оформлении информированного согласия.

Ключевые слова: острота зрения; капилляр; сетчатка; зрение; прогноз; болезнь Гиппеля — Линдау
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Von Hippel — Lindau (VHL) disease has been found to be a progressive, familial, autosomal dominant, multi-systemic phacomatosis with retinal capillary hemangioblastoma (CRH) as the most common manifestation [1]. CRH are benign, well-circumscribed, vascular and progressive neoplasm arising from inner, mid-peripheral retina [2, 3]. These tumors are sporadic or found in association with systemic manifestations . Sporadic CRH are indistinguishable from those associated with VHL [4]. However, CRH associated with VHL tends to occur at an earlier age and is more likely to be multifocal [5]. They can remain stable without leakage, regress spontaneously, grow, induce high-flow state retinal angiopathy with exudation of vascular components [3, 6, 7]. CRH have been found to be unilateral or bilateral; solitary or multifocal; stable or progressive with new lesions appearing over time. While 46 % of solitary CRH without systemic disease have been associated with VHL, 100 % of multifocal CRH patients had VHL disease [8].

Various modalities have been used to treat CRH. Treatments typically included observation, laser, cryotherapy for CRH < 5 millimeters (mm) base whereas plaque brachytherapy and vitreoretinal surgery for larger CRHs and their complications. With the advancement in knowledge about VHL protein and its relationship with vascular endothelial growth factor (VEGF), current research has focused on pharmaceutical intravitreal therapy.

Close ocular surveillance and thus early CRH detection have led to earlier intervention and a better prognosis for eye and vision retention. Similarly, close VHL-related systemic surveillance has led to earlier treatment and life preservation [9]. The average life span of VHL patients is 40 to 50 years [10].

METHODS

No identifiable patient records were used in this study. Therefore, the internal review board of the New York Eye Cancer Center did not require submission. The Health Insurance Portability and Privacy Act and the Declaration of Helsinki were not relevant.

Literature Search

A review of the literature was performed using Medline and PubMed databases. Keywords included: visual function, vision, visual acuity, visual prognosis, ocular angiomatosis, retinal angiomas, retinal capillary hemangioma, RCH, CRH, Von-Hippel Lindau disease, vision, visual acuity, outcomes, complications and retinal angiomatosis in VHL patients. For this, study selection criteria included: longitudinal studies, those including visual acuity as well as an association between visual acuity and CRH. We also looked for data on the relationship with VHL and its long-term outcomes, including the effect on the prognosis for vision. Though 10 publications contained the aforementioned data, we chose 5 major studies containing 427 patients to collect and analyze visual acuity outcome results for comparison and statistical significance [10–14]. These 5 studies contained the foundational data for our vision-prognosis-based staging classification for CRH (Table 1).

Statistical analyses were performed utilizing the Pearson Chi-Square test, likelihood ratio, Fischer's exact test and linear regression by linear association tests to prove the statistical significance of age at onset, location, laterality, gender, multifocality on visual outcomes (SPSS Statistics 20 software, New York City, New York, United States).

METHODS OF TREATMENT

Each institution used them as monotherapy, synergistically with others, sequentially or in combination as needed for local tumor control. In this study, we presumed the best possible care from each eye tumor specialist and thus, did not analyze the relative efficacy of each treatment.

Observation. Observation as treatment is typically used for peripheral CRH smaller than 0.5 mm or juxtapapillary CRH without any signs of progression, exudation or loss of visual function [15]. The risks of treatment are weighed against the risks of tumor-related vision loss. Observation is more preferred in juxtapapillary tumors, which are slightly more stable than extrapapillary CRH, 86 % and 81 % respectively [16].

Laser Photocoagulation. Laser photocoagulation is typically used for 1.5 to 4.5 mm thick CRH [16]. Success rates of 91–100 % have been reported [17–19]. Dr. Finger suggests photo-coagulation of the feeder vessels to scar, then the posterior 180 degrees are demarcated. Lastly, if the tumor vascular pattern persists, direct tumor laser can close any residual blood vessels [15]. A. Singh et al. noted peripheral CRH does better than Juxtapapillary CRH with laser treatment with a success rate of 74 % [16].

Cryotherapy. Cryotherapy is used when CRH are larger than 3 mm and have significant sub-retinal fluid making laser photocoagulation difficult or impossible. CRH In general, double freeze thaw cryotherapy is employed to cover the tumor as viewed by indirect ophthalmoscopy [20]. A. Singh, et al. noted 74 % of success rate with cryotherapy of less than 3.75 mm base CRH [16].

Radiation Therapy. Radiation therapy plaque and proton beam have been used for CRH [4]. Ocular morbidity and vision outcomes have been dependent on tumor location, the radiation dose and thus the incidence of radiation retinopathy and optic neuropathy. Siebel et al. noted that there were successful anatomical outcomes after proton beam radiation whereas there was a significant drop in vision from 20/100 to 20/125 ($p = 0.071$) [21]. K. Kreusel, et al. published their experience with ruthenium-106 plaque brachytherapy in 24 patients showing a slight improvement from 20/60 ± 20/60 to 20/50 ± 20/40 post-treatment [22].

Anti-Vascular Endothelial Growth Factor therapy. Anti-VEGF treatment has been used to treat CRH with exudation [23]. In VHL, chromosome 3p25-26 is affected by germline mutations leading to inactivation of VHL protein [6, 24]. VHL protein is needed for normal retina vessels and ocular structures. In its absence or deficit, VEGF levels increase [25]. Drugs like bevacizumab, ranibizumab, and aflibercept are now commonly used for reducing VEGF produc-

Table 1. Visual function associated with retinal capillary hemangioma
Таблица 1. Нарушения зрения, ассоциированные с капиллярной гемангиомой сетчатки (КГС)

Parameters Показатели	A. Webster, et al. [11][a]	M. Niemelä, et al. [10]	C. McCabe, et al. [12]	K.-M. Kreusel, et al. [13]	B. Toy, et al. [14]	Mean
Sample size Количество пациентов	17	36	68 (72 eyes)	57	249	85.4
Age, years Возраст, лет	30.9	40	36	20.3	33.3	32.1
Male: Female Муж.: Жен.	1:2.4	1:2.6	1:0.9	N/A	1:1	1:1.07
Bilaterally Билатерально	N/A	16.7 % (6)	5.9 % (4)	42 % (24)	33 % (82/249)	30.7 %[b]
VHL disease Болезнь ГЛ	N/A	30.0 % (11)	33.9 % 23 (27 eyes)	100 % (57)	100 %	32.0 %
Mean Follow up, years Средний срок наблюдения, лет	8.7	5	5.4	7.3	7.7	6.8
Visually symptomatic at presentation among VHL patients Зрительная симптоматика у пациентов с ГЛ	N/A	45.4 % (5/11)	74.1 % (20/27 eyes)	63.0 % (36/57)	16.1 % (80/498 eyes)	49.7 %
Visually symptomatic at presentation among non-VHL patients Зрительная симптоматика у пациентов без ГЛ	41.1 % (7/17)	68.0 % (17/25)	88.9 % (40/45 eyes)	N/A	N/A	49.5 %
Vision worsening during follow-up Снижение зрения в период наблюдения	64.7 % (11/17)	30.6 % (11/36)	37.5 % (27/72 eyes)	63 % (36/57)	41.8 % (208/498)	47.5 %
Juxtapapillary angioma Юкстапапиллярная ангиома	23.5 % (4/17)	N/M	100 % (72 eyes)	10.9 % (11/105 eyes)	20 % (100/498 eyes)	18.1 %[c]
Vision (≤ 20/200) at the end of follow up Зрение (≤ 20/200) в конце наблюдения	64.7 % (11/17)	16.7 % (6/36)	25.0 % (18/72 eyes)	25.7 % (27 eyes of 21 patients)	N/M	33.0 %
Painful blind eye Слепой болящий глаз	11.8 % (2/17)	5.6 % (2/36)	4.4 % (3/68)	5.3 % (3/57)	5.6 % (14/249)	6.5 %

Note. N/A — data not applicable, N/M — Data not mentioned, VHL — Von-Hippel Lindau disease, [a] — A. Webster, et al. [11] were based on the unilateral sporadic CRH tumor with no VHL disease, [b] — for mean bilateral data, C. McCabe, et al. [12] was not considered. It was a study limited to juxtapapillary tumors which typically present unilaterally, [c] — for mean juxtapapillary tumor, C. McCabe, et al. [12] was not considered as it was 100 % juxtapapillary tumors.
Примечание. N/A — нет данных, N/M — не упомянуто, ГЛ — болезнь Гиппеля — Линдау, [a] — исследование A. Webster, et al. [11] описывает одностороннюю спорадическую КГС без болезни Гиппеля — Линдау, [b] — при расчете средних билатеральных данных результаты работы C. McCabe,et al. [12] не учитывались, поскольку в ней рассматривались только юкстакапиллярные опухоли, которые обычно бывают односторонними, [c] — при расчете средних данных по юкстакапиллярным опухолям результаты работы C. McCabe, et al. [12] не учитывались, поскольку в ней рассматривались только (100 %) такие опухоли.

tion, thereby reducing the formation of new vessels and exudation [26–28]. W. Wong, et al. published a case series of 5 patients showing the outcomes of intravitreal ranibizumab therapy for CRH [29]. With their results, they concluded that intravitreal ranibizumab as monotherapy at a 4 weekly interval had minimal beneficial effects on VHL-related CRH and needs to be used in combination with other modality of treatment. Though it can be efficacious in case of small CRH with minimal exudation [29].

Other Laser-Based Treatments. Photodynamic Therapy (PDT) and Transpupillary thermotherapy (TTT) have been tried [30, 31]. U. Schmidt-Erfurth, et al have concluded a drop in visual acuity from 20/40–20/500 pretreatment to 20/50–20/2000 after treatment with PDT. They are not commonly used widely due to their lack of efficacy [32].

Summary. While each center employed what they considered the "best possible treatment" for each CRH. This study examines the published results from the literature to classify risk factors for vision loss related to CRH and their treatment.

RESULTS

In this review, the choice of CRH treatment modality depended on the size, amount of exudation, retinal detachment as well as the tumor's proximity to optic disc and fovea. Though treatment can prevent vision loss, and 67 % of patients retain better than 20/200 vision, despite treatment 33 % become legally blind in the affected eye.

Our search revealed 5 studies that met our inclusion criteria (Table 1). Thus, we were able to study the visual acuity results of 427 treated patients. Of this 32 % had VHL and rest had spontaneous or new mutations. There was no sexual predilection for CRH ($p = 0.47$) in that 48.2 % ($n = 206$) were males, 51.8 % ($n = 221$) females with a mean follow up of 6.8 years.

There was no significant patient-age difference among the studies ($p = 0.929$). Overall, there were 69.4 % (58–94.1 %) unilateral CRH, 30.6 % (5.9–42 %) bilateral and 18.1 % (10.9–23.5 %) juxtapapillary tumors. Tumor-related vision loss was noted at presentation in 38.6 % ($n = 165/427$) of patients. Censoring vision loss related to mortality; CRH-related vision loss was found independent of the presence of VHL disease ($p = 0.157$).

Age at onset. Both K.-M. Kreusel, et al. and H. Dollfus, et al. found that younger age of onset is associated with poor visual prognosis. K.-M. Kreusel, et al. noted an average of vision ≤ 20/1000 in the younger age of manifestation ($p = 0.03$) and H. Dollfus, et al. defined 15–25 years as a critical age group [13, 33]. Webster et al. also concluded that patients presenting with symptoms were younger ($p = 0.02$) [11].

CRH location. According to B. Toy, et al., using ETDRS noted that there was a loss of 7.6 ± 1.2 letters from baseline visual

acuity in VHL in comparison to 2.8 ± 0.6 in non-VHL patients (p = 0.0003). Patients with new peripheral involvement or juxtapapillary tumor had 2.3 ± 1.2 or 12.5 ± 5.2 letters lost respectively. Individuals with VHL disease having no new CRH lost 6.6 ± 1.2 letters in comparison to eyes that developed new CRH had 21.6 ± 7.8 (p = 0.08). Patients with baseline juxtapapillary tumors with the development of new peripheral CRH had a maximum drop of 49.5 ± 30.5 letters. On comparing the patients having baseline VHL disease with no progression to severe progression there was 7.4 ± 1.2 and 26.1 ± 9.0 letters drop respectively (p = 0.05). They concluded that peripheral CRH that is non-exudative, distant from posterior pole and amenable to treatment can have stable visual acuity with least impact on central vision whereas Juxtapapillary CRHs which affects the central vision and are difficult to treat. From this analysis, patients with progression (p = 0.05) are at the highest risk of losing vision [14].

Laterality and Focality. C. McCabe, et al. in their series of 57 juxtapapillary patients, concluded that visual prognosis was more guarded in bilateral tumors (p = 0.019) and in association with peripheral tumors (p < 0.0001). They also inferred that multifocal CRH or progressive CRHs whether it is the increase in number and/or extent of peripheral CRH with/out in combination with juxtapapillary tumors can progress to visual loss [12]. K.-M. Kreusel, et al. reported that the symptomatic eyes presented with larger angiomas in comparison of asymptomatic eyes (p < 0.0001) and have a higher chance of developing new angiomas making it as multifocal on subsequent follow-up (p = 0.0005), which will more readily progress to vision loss (p < 0.0001) [13].

Risk Factors. According to B. Toy, et al, risk factors for anatomical CRH progression include (1) age at presentation, (2) age of onset of VHL ocular manifestation and (3) involvement of fellow eye. Whereas loss of vision is dependent on (1) anatomical progression, (2) increase in peripheral extent or a number and (3) presence of exudation, retinal detachment, and macular involvement. They also found that the presence of extraocular VHL manifestations and anatomical progression are not correlated. They also concluded gender, BMI and smoking status have no role in the visual prognosis of CRH [14]. While McCabe et al. defined age and peripheral tumors in one or both eyes as independent risk factors for poor visual acuity at initial presentation, while CRH growth pattern was not [12].

Garg-Finger CRH Classification. In order to be useful for the CRH specialist, this study's classification was based on anatomical presentation with a secondary focus on progression and its pathological effects. This data was derived from the multicenter, published data on visual acuity outcomes published in the studies seen in Table 2.

DISCUSSION

Both A.Webster, et al. and K.-M. Kreusel, et al. suggest that the cumulative probability of a permanent visual deficit in CRH is 60% [11, 13]. K.-M. Kreusel, et al. also proved that VHL patients who are symptomatic before 20 years of age are more likely to lose vision [13]. R. Toy, et al. published the largest cohort study providing the details on ocular manifestations, vision, and factors leading to the progression of the disease. They have inferred that with early treatment CRH can remain stable but in the long term, the impact of ocular manifestations and its complications were cumulative. They described visual function, its course and its dependency on anatomical phenotype, and progression over time [14].

CRH size and number. K.-M. Kreusel, et al. reported significant difference (p < 0.0001) in size of CRH 1.1 ± 0.2 mm in visually asymptomatic and 3.8 ± 0.3 mm in symptomatic with number of angiomas 2.6 ± 0.9 and 7.2 ± 0.9 respectively (p = 0.0005) [13]. R. Toy, et al. noted a drop in visual acuity of 3.6 ± 1.3 letters in patients with CRH ≤ 2 and 11.1 ± 3.9 letters drop in patients with CRH ≥ 3 in number (p = 0.07). They also found a drop of 4.4 ± 1.2 letters in patients with CRH involving ≤ 1 quadrant and 7.7 ± 2.6 letters drop in CRH involving ≥ 1 quadrant (p = 0.021) [14].

CRH Location. CRH are more frequently located in the peripheral retina. The prevalence of juxtapapillary CRH has been found to be 11–15 % among VHL patients with a higher incidence

Table 2. Visual prognosis based staging system for retinal angiomatosis
Таблица 2. Классификация ретинального ангиоматоза на основе визуального прогноза

Stage Стадия	Retinal angiomatosis Ретинальный ангиоматоз
I a	Peripheral CRH with age of onset > 20 years old with no progression* Периферическая КГС с возрастом начала > 20 лет, непрогрессирующая*
I b	Peripheral CRH with either age of onset < 20 years or progression* Периферическая КГС либо с возрастом начала < 20 лет, либо прогрессирующая*
I c	Peripheral CRH with age of onset < 20 years and progression* Периферическая КГС с возрастом начала < 20 лет, прогрессирующая*
II a	Juxtapapillary CRH with age of onset > 20 years with no progression* Юкстапапиллярная КГС с возрастом начала > 20 лет, непрогрессирующая*
II b	Juxtapapillary CRH with either age of onset < 20 years or progression* Юкстапапиллярная КГС либо с возрастом начала < 20 лет, либо прогрессирующая*
II c	Juxtapapillary CRH with age of onset < 20 years and progression* Юкстапапиллярная КГС с возрастом начала < 20 лет, прогрессирующая*
III a	Juxtapapillary and peripheral CRH with age of onset > 20 years with no progression* Юкстапапиллярная и периферическая КГС с возрастом начала > 20 лет, непрогрессирующая*
III b	Juxtapapillary and peripheral CRH with either age of onset < 20 years or progression* Юкстапапиллярная и периферическая КГС либо с возрастом начала < 20 лет, либо прогрессирующая*
III c	Juxtapapillary and peripheral CRH with age of onset < 20 years and progression* Юкстапапиллярная и периферическая КГС с возрастом начала < 20 лет, прогрессирующая*

Note. * — progression: 1) increase in number of Peripheral CRH (> 2); 2) increase in the extent of Peripheral CRH (> 1 quadrant); 3) involvement of fellow eye; 4) presence or development of retinal detachment, exudation, vitreous hemorrhage or neovascularization.
Примечание. * — прогрессирование: 1) увеличение числа периферических КГС (> 2); 2) увеличение зоны периферической КГС (> 1 квадранта); 3) вовлечение парного глаза; 4) наличие или прогрессирование отслойки сетчатки, экcудации, витреального кровоизлияния или неоваскуляризации.

in younger patients [12, 34]. In our meta-analysis, it was higher at 18.1 %. Juxtapapillary CRH were more commonly associated with VHL disease [25]. Because of their location and less clearly defined efferent and afferent feeder vessels, they are more difficult to treat leading to a poor prognosis for vision. Typically presenting early, as small tumors, they gradually enlarge over time, with vascular leakage leading to loss of vision as a result of retinal edema, epiretinal membranes, hard exudates, and retinal detachment. McCabe et al. reported a general decline in visual acuity over the follow up of ≥ 6 months from 43 eyes (61 %) having vision ≥ 20/40 to only 21 eyes (35 %) retaining vision ≥ 20/40 [12].

VHL disease Association. In this study, we found that there was no significant difference in the risk of CRH-related vision loss if suffering from spontaneous versus VHL-related tumors, similar to webster et al. [11]. Though this finding contrasts with that of M. Niemelä, et al. where vision outcomes were better in cases of patients with no VHL [10]. Our review found that VHL disease was present in 32 % of patients presenting with CRH and this was not associated with age, gender or laterality of CRH. Overall, 42 % of CRHs presented as unilateral whereas 58 % presented bilaterally [35].

Various systems have been used in the past to classify CRH are described in Table 3.

Effects of CRH are (1) exudative (25 %) or (2) tractional (9 %). The exudation can present as either intraretinal fluid (10 %) or subretinal fluid (16 %) [3, 36]. D. Vail [37] has classified based on the development of complications (Table 4).

Whereas J. Sigelman [38] has classified the CRH based on their presentation (Table 5).

Table 3. Systems used to classify retinal capillary hemangioma [4]
Таблица 3. Принятые системы классификации капиллярной гемангиомы сетчатки [4]

	Basis Основа	Classification Классификация
1	Retinal Distribution Расположение на сетчатке	Peripheral Периферическое Juxtapapillary Юкстапапиллярное
2	Morphology Морфология	Endophytic Эндофитная Sessile На широком основании Exophytic Экзофитная
3	Effects on Retina Реакция сетчатки	Exudative Экссудативная Vitreoretinal Traction Витреоретинальная тракция
4	Systemic Features Системные особенности	Without VHL Болезни ГЛ нет With VHL Болезнь ГЛ есть

Table 4. D. Vail's Classification [37]
Таблица 4. Классификация D. Vail [37]

Stages Стадия	Complications Осложнения
I	Early stage with dilatation of feeding artery and draining vein and angioma formation Ранняя стадия с расширением питающей артерии и дренирующей вены и формированием ангиомы
II	Development of hemorrhages and exudation Развитие кровоизлияний и экссудации
III	Massive exudation and retinal detachment (RD) Массивная экссудация и отслойка сетчатки
IV	Uveitis, absolute glaucoma, and loss of the eye Увеит, абсолютная глаукома и потеря глаза

Table 5. J. Sigelman's Classification [38]
Таблица 5. Классификация J. Sigelman [38]

Stages Стадия	CRH presentation Вид КГС
I	Very small CRH without any feeder vessels КГС очень маленького размера без питающих сосудов
II	CRH appears as a small red nodule with the prominence of only the draining vein КГС в виде небольшого красного узла с проминенцией только дренирующей вены
III	CRH both feeding artery and draining vein are present ± retinal exudates КГС с питающей артерией и дренирующей веной ± ретинальный экссудат
IV	Partial exudative RD Частичная экссудативная отслойка сетчатки
V	Total exudative RD Тотальная экссудативная отслойка сетчатки

It is quite evident that both D.Vail's and Sigelman's classification were based on the anatomical presentation of CRH instead of its effect on the visual functions of an individual.

Screening should be mandated in VHL patients as CRH can be treated at an early stage and prevent the progression [39–41]. Present screening guidelines are based on prevalence data and initial presentation with no mention of progression and its effects [34, 42–45].

Herein, we have performed a meta-analysis for the risk factors associated with vision loss at diagnosis. Patient age at onset ($p = 0.03$), CRH location ($p < 0.0001$), and multifocality ($p = 0.0005$) were the strongest predictors for vision loss. Additional factors included the involvement of fellow eye, progression, and macular involvement. The current study provides an overview of visual prognosis, factors affecting and a new staging system to prognosticate visual system. This information provides medical evidence for both patients and ophthalmologists to decide on timing of treatment and likely outcomes. However, in our review, we found a lack of large studies and no multicentric prospective data collection to describe the visual prognosis in CRH and VHL patients. This paper encourages such studies on visual function and offers a vision-outc ome based classification to assess its inapplicability in follow up, prognostication and treatment of retinal angiomatosis (Table 2).

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