Original Article

Insights into retinal hemangioblastoma using ultra widefield imaging

Pradeep Kumar, Raghav Ravani, Sahil Agarwal, Suman Dhanda, Vinod Kumar

Purpose: Retinal hemangioblastomas (RHs) are characteristic of von Hippel-Lindau (VHL) disease. Early diagnosis of retinal lesions may aid in systemic diagnosis. Early identification of VHL is life-saving and also prevents vision loss. Fundus fluorescein angiography (FFA) is a useful tool in the diagnosis and management of RHs. The aim of this study is to report FFA features of RH using ultra-widefield (UWF) imaging. **Methods:** A retrospective cross-sectional study of consecutive patients of RH who underwent UWF FFA at a tertiary eye care center. Images were analyzed and assessed by authors. The main outcome measures were (a) the number and size of RH in each eye and (b) vascular characteristics of the retina. UWF-FFA characteristics in each eye were tabulated. The number of clock hours involved by these characteristics and their correlation with the number and size of RH were analyzed. **Results:** The study evaluated 24 eyes of 13 patients. The mean age was 28.4 years. The median number of RHs in an eye was 3.5 (range 1–16), and the size of RHs varied from 0.1 to 4 disc diameters. Novel UWF-FFA findings noted in this study were the presence of abnormal capillary network in 22 of 24 eyes (91.7%), capillary leakage in 15 of 24 eyes (62.5%), and capillary telangiectasia in 7 of 24 eyes (29.2%). In addition, feeder arterioles and venules showed bulbous projections in 8 of 24 eyes (33.3%). **Conclusion:** The UWF-FFA characteristics of RH, which have not been described before, were identified. These add to our understanding of the pathogenesis of the disease and may pave the way for future therapeutic targets.

Key words: Abnormal capillary network, fundus fluorescein angiography, retinal hemangioblastoma, ultra-widefield imaging, von Hippel–Lindau disease

Access this article online

Website: www.ijo.in

DOI: 10.4103/ijo.IJO_802_19

Quick Response Code:

Retinal hemangioblastomas (RHs) are benign neoplasms of the eye that originate from the neurosensory retina or the optic disc.[1] Typically, these occur in the setting of von Hippel-Lindau (VHL) disease and the pathogenesis is attributed to mutations in the VHL tumor suppressor gene.[2] Loss of heterozygosity at the *VHL* locus leads to the production of abnormal VHL protein (pVHL), and subsequently upregulation of hypoxia-inducible factor (HIF) pathway.[3] Histologically, RH consists of capillary-like fenestrated vascular channels surrounded by "foamy" stromal vacuolated cells.[4] RH may be classified as extrapapillary or juxtapapillary and their size may vary from few hundred micrometers to few millimeters.

While a large RH with typical dilated feeder and draining vessels may be easy to diagnose, the clinical features of a small RH may overlap with several entities (macroaneurysm or intraretinal hemorrhage). Fundus fluorescein angiography (FFA) provides valuable information in such cases and may aid in the diagnosis. Typical FFA features of RH include prominent early hyperfluorescence that persists till late stages and is often associated with leakage.[5] Importance of early diagnosis lies in the life-threatening nature of VHL disease and management of retinal lesions, which can lead to vision loss if left untreated.[6]

Widefield imaging refers to the field of acquisition of 100° or more in a single click.[7] Ultra-widefield fundus fluorescence angiography (UWF-FFA) can capture up to 200° of the retina in a single click. The advent of UWF-FFA has helped in the diagnosis and management of diseases affecting the peripheral retina.[8] The role of UWF-FFA has been established in several vascular disorders such as diabetic retinopathy, venous occlusions, Coats' disease, Eales disease, and even in macular disorders such as Stargardt disease.[9,10] Our study aims to report the retinal vascular features of RH with the help of UWF-FFA.

Methods

It was a retrospective, cross-sectional study of consecutive patients with RH presenting to the retina clinic of a tertiary eye care hospital in urban India from the period of March 2016 to August 2017. The study was conducted in accordance with the Declaration of Helsinki and adheres to the tenets of institutional research guidelines. Informed consent was obtained from all the patients. All patients with RH in at least one eye and having media clear enough to provide good quality images were included in the study. The patients with an inability to undergo FFA were excluded.

Dr. Rajendra Prasad Centre for Ophthalmic Sciences, All India Institute of Medical Sciences, New Delhi, India

Correspondence to: Dr. Vinod Kumar, Dr. Rajendra Prasad Centre for Ophthalmic Sciences, All India Institute of Medical Sciences, New Delhi, India. E-mail: drvinod_agg@yahoo.com

Received: 23-Apr-2019 Revision: 30-May-2019
Accepted: 21-Aug-2019 Published: 22-Nov-2019

Cite this article as: Kumar P, Ravani R, Agarwal S, Dhanda S, Kumar V. Insights into retinal hemangioblastoma using ultra widefield imaging. Indian J Ophthalmol 2019;67:2029-34.

Evaluation

Detailed history was obtained, and all patients underwent clinical examination involving best-corrected visual acuity, slit-lamp examination, and indirect ophthalmoscopy. In addition, neurology, endocrinology, and gastroenterology review was done for assessment of systemic features of VHL disease. Any history or clinical evidence of undergoing prior retinal laser therapy or intravitreal injections was noted. After obtaining informed consent, UWF-FFA (Optos TX200; Optos PLC, Dunfermline, Scotland, UK) was conducted with the acquisition of the pseudo-color image and early-, mid-, and late-phase fluorescein angiography images of both eyes.

The UWF images were analyzed and assessed to identify the FFA changes. The RHs were studied for their number, size, and location in the retina. The retinal vasculature was studied for the presence of vessel wall changes and the presence of telangiectasia. Capillary telangiectasias of the brain have been defined as irregular clusters of dilated capillaries intermixed with normal brain parenchyma.[11] We extrapolated the same definition as retinal capillary telangiectasia to define the new finding of a cluster of dilated capillaries seen in the peripheral retina. The capillary network was studied for leakage and abnormalities if any. Macular changes were studied for any exudation, leakage, or ischemic changes. The optic nerve head (ONH) was studied for involvement with RH and disc leakage.

The observational data were tabulated using Microsoft Excel. Statistical analysis was conducted using EpiInfo™ Version 7.2.2.2, developed by the Centre of Disease Control and Prevention, Atlanta. Tests applied include Pearson's correlation coefficient (for the extent of the abnormal capillary network (ACN) with number and size of RH) and *T*-test (for the association of capillary leakage and capillary telangiectasia with number and size of RH).

Results

Twenty-four eyes of 13 patients were analyzed for the UWF-FFA changes [one patient had phthisis bulbi in one eye (phthisis occurred after open globe injury in childhood) and one patient had unilateral involvement with RH]. There were nine males and four females. The mean age was 28.4 years (range 19–38 years). Evidence of prior laser photocoagulation therapy was seen in five of these eyes. None of the eyes had received intravitreal antivascular endothelial growth factors or steroids. While bilateral involvement was seen in 9 of 12 (75%) patients on clinical examination (one patient being one-eyed was not considered for bilateral affection), UWF-FFA revealed bilateral involvement in 11 of 12 patients (91.7%) [Fig. 1a-d] (small RH could be picked in two additional eyes). Nine patients underwent systemic evaluation for VHL disease and five of these (55.5%) were found to have features of VHL disease.

The number of RHs in each eye varied from 1 to 16 (median of 3.5, mean of 5.13 with standard deviation of 4.12). The total number of RHs identified in all 24 eyes was 123. The size of RH varied from 0.1 to 4 disc diameters (DDs). The most common affected quadrant was inferotemporal (83%), followed by superotemporal (67%) and inferonasal (63%).

The UWF-FFA showed prominent early hyperfluorescence in all lesions of RH. While the intensity of hyperfluorescence increased with time in all cases, the size of hyperfluorescence increased only in 108 of 123 RHs [Fig. 2a and b]. Blocked hyperfluorescence was seen in cases with subretinal exudation (7 of 24 eyes) (29.2%) [Fig. 2c]. Exudative retinal detachment (RD) was seen in 3 of 24 eyes (12.5%). The RD was total in one eye and partial in two eyes. RH involving the ONH, showing an increase in size and intensity of hyperfluorescence, was seen in only one eye [Fig. 3a and b]. ONH hyperfluorescence in the absence of ONH involvement by RH lesion was seen in 7 of 24 eyes (29.2%) [Fig. 3c and d].

The feeder arterioles and drainage venules of the RH were dilated and tortuous [Fig. 4a] when the size of RH was more than one DD in size (34 of 123RHs were more than one DD in size). Veins were always more dilated than arteries. The origin of these feeder vessels was from the same quadrant as the origin of RH. The feeder arterioles to these RH showed bulbous projections (8 of 24 eyes) (33.3%) [Fig. 4b and c].

An ACN was seen in the retinal periphery in 22 of 24 eyes (91.7%). This abnormal network showed the presence of a well-defined but sparse capillary network with the absence of a typical fine capillary network between these capillaries [Fig. 5a-d]. The posterior extent of such capillary abnormality was usually limited till equator (18 of 22 eyes) (81.8%). The extent of retinal involvement by capillary network abnormality ranged from 1 to 12 clock hours (median of 6 clock hours of the retina being involved by ACN). The extent of ACN did not correlate either with the number (Pearson's correlation coefficient: $r^2 = 0.00$) or the size (Pearson's correlation coefficient: $r^2 = 0.03$) of the largest RH. The ACN was not always in the vicinity of RH and was noted to involve retina up to 1 to 6 clock hours away from the RH [Fig. 5e]. ACN was seen even in the paramacular region in two eyes [Fig. 5f].

The capillary leakage was present in 15 of 24 eyes (62.5%) [Fig. 6a, b, and e, f]. This leakage was localized to the peripheral retina. The capillary leakage was located 1 to 4 clock hours away from the nearest RH. The presence of capillary leakage in a particular case did not correlate with the total number of RH (*T*-test *P* value = 0.15) but showed significant statistical association with the size of the largest RH (*T*-test *P* value = 0.01). The capillary leakage was also not associated with localized exudates or subretinal deposits.

Retinal capillary telangiectasias were noted in 7 of 24 eyes (29.2%) [Fig. 6c-f]. These telangiectasias were located in the retinal periphery and located 1 to 3 clock hours away from the nearest RH. The presence of capillary telangiectasia in a particular case did not correlate with total number (*T*-test *P* value = 0.10) or the size of the largest RH (*T*-test *P* value = 0.48). The telangiectasia, when present, corresponded with areas of ACN.

Macular leakage was noted in 5 of 24 eyes (20.8%), with the size and intensity of hyperfluorescence increasing from the early to late phase [Fig. 3b]. The presence of macular leakage correlated with the number of clock hours of the peripheral retina demonstrating ACN (*T*-test *P* value = 0.02). The presence of macular leakage did not correlate with the number of RH (*T*-test *P* value = 0.31) or the size of the largest RH (*T*-test *P* value = 0.46) in the affected eye.

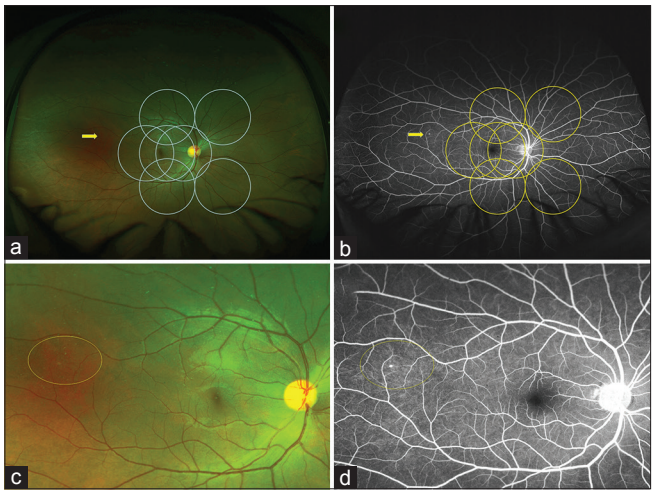

Figure 1: (a) Ultra-widefield (UWF) pseudocolor picture of the right eye of a patient with a retinal hemangioblastoma (RH) (white arrow), which is barely visible. (b) UWF angiography (UWF-FFA) confirmed a small RH (yellow arrow), which would have been missed even on ETDRS 7 field FFA. (c) The yellow circle gives a magnified view of RH in Fig. 1a. (d) The yellow circle gives a magnified view of UWF-FFA

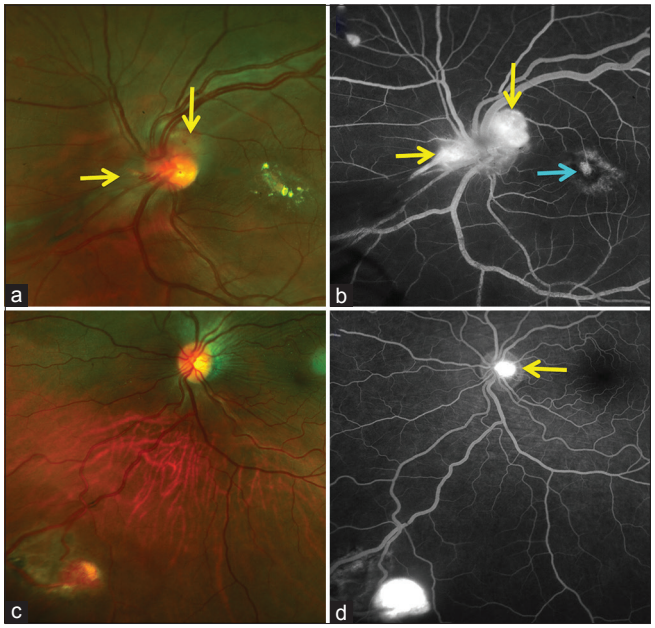

Figure 3: (a) RH involving optic nerve head with fullness of temporal (horizontal yellow arrow) and superior (vertical yellow arrow) disc margins. (b) Ultra-widefield angiography (UWF-FFA) shows hyperfluorescence of the temporal disc RH (horizontal yellow arrow) and superior disc RH (vertical yellow arrow) with leakage into surrounding peripapillary retina. Macular leakage without RH involvement is also seen (blue arrow). (c) Pseudocolor image shows an inferior RH and a normal looking optic disc (d) UWF-FFA shows leakage at the optic disc without the involvement of optic disc by RH

Discussion

FFA is an indispensable tool in the diagnosis and management of RH.[12] Welch RB first described the FFA features of RH.[5] The typical features of RH on FFA include rapid and intense hyperfluorescence that persists or changes to late leakage.[5,13]

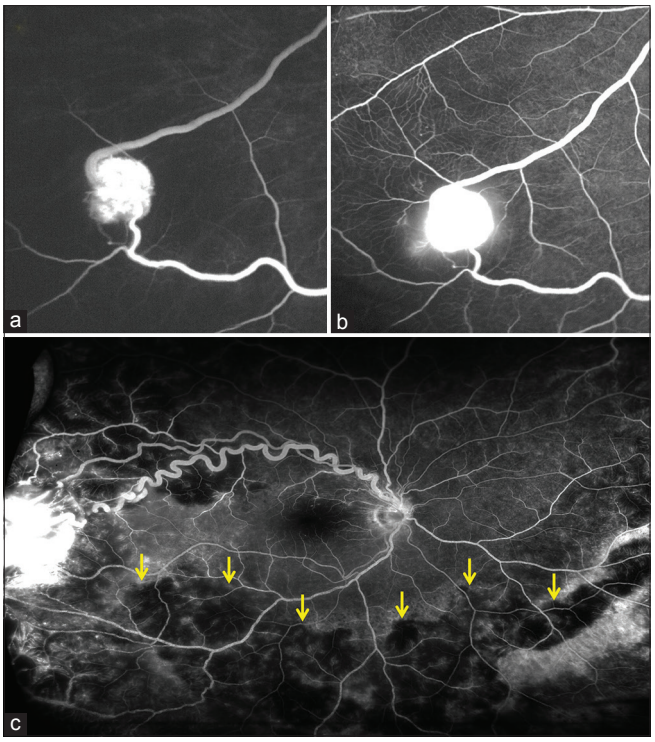

Figure 2: (a) Early-phase ultra-wide field angiography (UWF-FFA) of a typical retinal hemangioblastoma (RH) with feeder vessels shows hyperfluorescence, (b) hyperfluorescence increases in intensity and size in the late phase. (c) Subretinal exudation was seen as blocked hyperfluorescence on UWF-FFA (yellow arrows mark the upper border of exudation)

Though prominent afferent vessels to RH, hard exudates, and leakage from the optic disc (when involved by RH) have been described,[13] peripheral vascular abnormalities and capillary nonperfusion have been described infrequently.[14] Even in cases with macular exudation due to extramacular RH, macular leakage on FFA is uncommon.[5]

UWF imaging using Optos (Optos PLC, Dunfermline, Scotland, UK) was described nearly a decade ago. The applicability of this technique in the management of peripheral retinal diseases is well-established.[15] UWF-FFA has revealed novel lesions in pathologies such as diabetic retinopathy, vascular occlusions, Coats' disease, Eales disease, and Stargardt disease.[10] However, UWF-FFA in the setting of RH has been described infrequently.[16,17]

It is known that FFA may be able to pick RHs which are otherwise undetectable on clinical examination.[12,14,15] In a recent study by Chen *et al*., UWF-FFA may be able to pick even peripheral RH, which could be missed on conventional and seven standard fields of FFA [Fig. 1a-d].[17] In this study, we could detect RH in seemingly normal eyes (2 of 24 eyes). UWF-FFA may thus be used in the screening of these individuals as the risk–benefit ratio of performing FFA outweighs the benefit of early diagnosis of VHL.[6] However, high cost and limited availability of the equipment are major issues.

The observation of feeder vessels indicates increased blood flow into the tumor. The dilatation of vessels correlated with

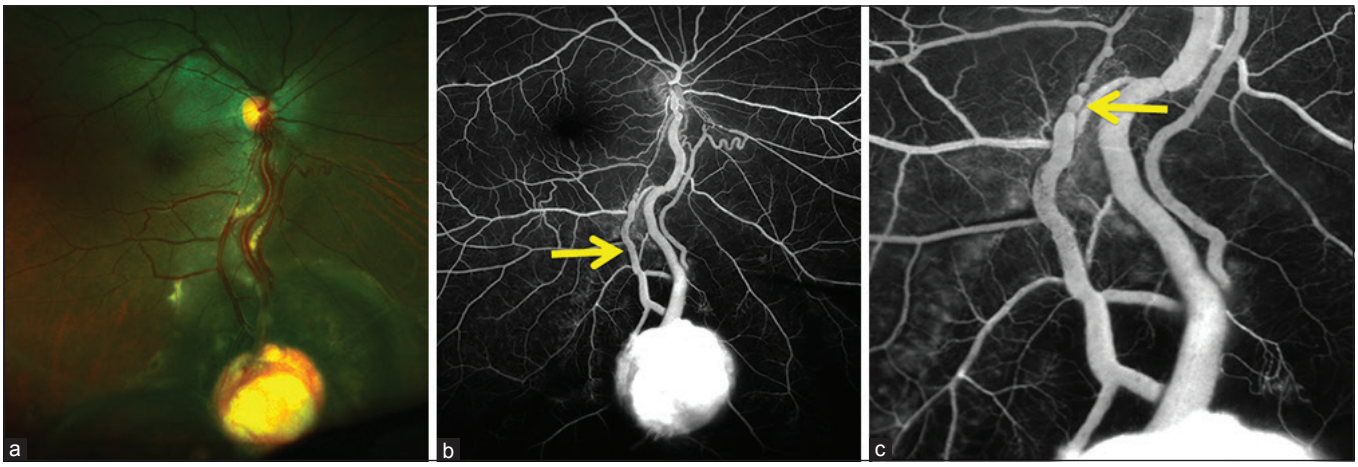

Figure 4: (a) A large retinal hemangioblastoma (RH) inferiorly with the dilated and tortuous artery and vein. (b) The artery shows the fine bulbous appearance of the feeder artery (yellow arrow) on ultra-widefield angiography. (c) Magnified view of Fig. 2f better delineates the bulbous appearance of the arterial wall (yellow arrow)

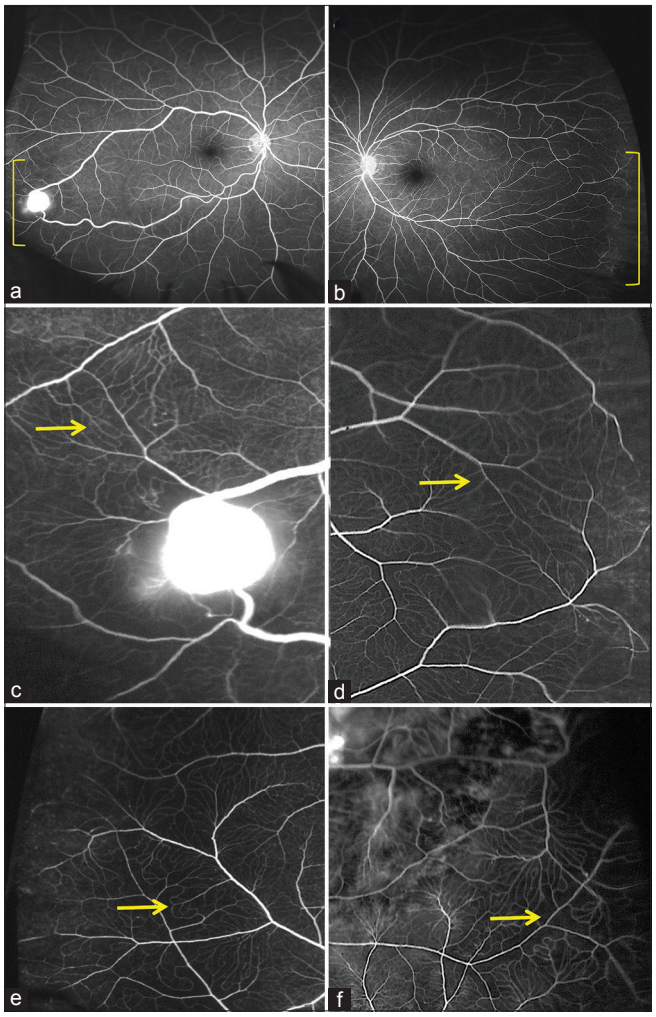

Figure 5: (a) Ultra-widefield angiography (UWF-FFA) shows abnormal capillary network (ACN) in temporal retina (yellow bracket) around the retinal hemangioblastoma (RH). (b) The fellow eye with no RH seen clinically or on UWF-FFA; it also shows ACN marked by yellow bracket. (c and d) Magnified view of 3a and 3b shows the sparse capillary network (yellow arrow). (e and f) Similar ACN was identified in other cases of RH. Yellow arrows show the sparse capillary distribution

the size of RH and smaller RH did not demonstrate any such feeder vessels [Fig. 1b-d]. An important observation in this study was the presence of bulbous dilatations of the feeding artery. This may point toward adaptation of arteries to the increased blood supply demand from the RH and may aid in the differentiation of feeding arteriole and draining venule. Identification of arteriole is of paramount importance for laser treatment, as accidental laser photocoagulation to venule may lead to occlusion of venule and subsequent hemorrhage from the RH.[18]

We observed a novel finding of ACNs in association with the RH. The ACN consisted of dilated capillary vessels and loss of perfusion in the intervening capillary bed. This may be explained by the "vascular steal" phenomenon where the RH draws the major portion of blood inflow into the affected retinal region. The similar capillary bed abnormalities have also been described in cases of arteriovenous malformations where steal phenomenon is well-known.[19] Though Shah *et al*. have reported the similar findings (occurrence of terminal networks, the absence of details of the capillary bed, ground-glass hyperfluorescence, and microaneurysms) in the normal peripheral retina, these findings in their study were restricted to the retinal periphery and were uniformly distributed in all clock hours of the retina.[20] The ACNs in our study, however, were predominantly located around the RHs and were seen even in the postequatorial retina.

Pan-retinal affection has been hypothesized in patients with VHL disease even in the absence of RH.[21] The effect of pVHL on the retinal capillaries outside the RH is unknown and we hypothesize that it may also contribute to this phenomenon. The ACN may exist even in absence of RH, as demonstrated by the presence of large ACN in the fellow eye of a patient with RH [Fig. 4b and d]. In addition, ACN was observed in regions of the peripheral retina up to 6 clock hours away from RH whose size was less than ½ DD. These observations support a more global effect of pVHL on the entire retinal vasculature.

Furthermore, these ACNs may indicate areas of relative ischemia in the capillary bed. Pulido *et al*. recently described a case of RH in VHL with peripheral nonperfusion with the help of UWF-FFA. This correlates with previous studies which

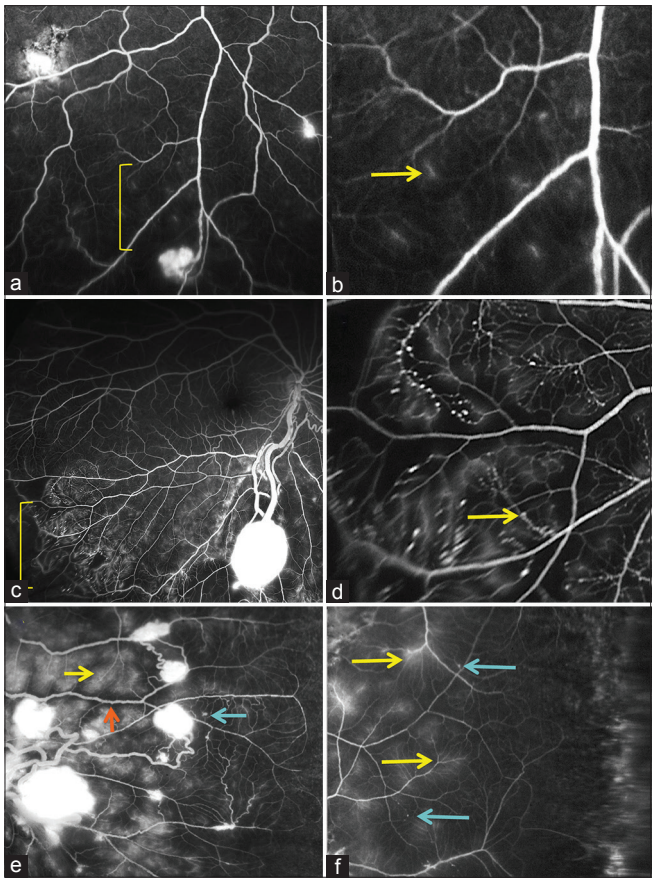

Figure 6: (a) Diffuse capillary leakage in arteriovenous phase marked by yellow bracket. (b) Magnified view of 6a shows capillary leakage (yellow arrow). (c) Temporal periphery (yellow bracket) shows telangiectasias. (d) Magnified view of 6c shows multiple telangiectasias; yellow arrow depicts capillary telangiectasia. (e) Temporal periphery shows ACN in RH with diffuse capillary leakage (yellow arrow), bulbous dilatations of arteriolar wall (orange arrow) and capillary telangiectasias (blue arrow). (f) ACN in the periphery with capillary leakage (yellow arrow) and telangiectasias (blue arrows)

show role of hypoxic stress in the formation of RH and vascular endothelial growth factor as the key mediator in the expression of ocular VHL disease.[22,23]

Another observation was the presence of vascular telangiectasia. They were seen as focal dilatation of the capillaries and were associated with areas of ACN in all the cases (7 of 24 eyes) (29.2%) [Fig. 5c-f]. Retinal capillary leakage was seen in 62.5% of eyes. All these eyes had concurrent areas of ACN exceeding 6 clock hours and RH more than one DD in diameter. These indicate an attempt by the vascular bed toward angiogenesis in the presence of hypoxia.[24] The consequent VEGF production results in leaky capillaries [Fig. 5].

Conclusion

To conclude, we report novel angiographic features of RH using UWF-FFA. These include the presence of abnormal peripheral retinal capillary networks (91.7%), capillary telangiectasia (29.2%), and capillary leakage (62.5%). This adds to our understanding of the pathogenesis of RH and provides a possible therapeutic target to preserve ocular function in patients with VHL disease.

Ethical approval

All procedures performed in this report were in accordance with the institutional guidelines and with the 1964 Declaration of Helsinki and its later amendments. Consent from each patient was taken for each investigation as well as their participation in study.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

All authors certify that they have no affiliationswith or involvement in any organization or entity with any financial interest (Such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

References

1. Şahin Atik S, Solmaz AE, Öztaş Z, Eğrilmez ED, Uğurlu Ş, Atik T, *et al*. Von Hippel-Lindau disease: The importance of retinal hemangioblastomas in diagnosis. Turk J Ophthalmol 2017;47:180-3.
2. Frantzen C, Klasson TD, Links TP, Giles RH. Von Hippel-Lindau syndrome. In: Pagon RA, Adam MP, ArdingerHH, Wallace SE, Amemiya A, Bean LJ, *et al*., editors. GeneReviews(®) [Internet]. Seattle (WA): University of Washington, Seattle; 1993. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1463/. [Last cited on 2017 Sep 16].
3. Wang Y, Abu-Asab MS, Shen D, Zhuang Z, Chew EY, Chan CC. Upregulation of hypoxia-inducible factors and autophagy in von Hippel-Lindau-associated retinal hemangioblastoma. Graefes Arch Clin Exp Ophthalmol 2014;252:1319-27.
4. Grossniklaus HE, Thomas JW, Vignesavaran N, Jarrett WH. Retinal hemangioblastoma: A histologic, immunohistochemical, and ultrastructural evaluation. Ophthalmology 1992;99:140-5.
5. Welch RB. Fluorescein angiography in sickle-cell retinopathy and von Hippel-Lindau disease. Int Ophthalmol Clin 1977;17:137-54.
6. Haddad NMN, Cavallerano JD, Silva PS. Von Hippel-Lindau disease: Agenetic and clinical review. Semin Ophthalmol 2013;28:377-86.
7. Diabetic Retinopathy Clinical Research Network. Peripheral diabetic retinopathy (dr) lesions on ultrawide-field fundus images and risk of dr worsening over time [Internet]. DRCR.net; [cited 2017 Nov 11]. Available from: http://drcrnet.jaeb.org/Studies.aspx?RecID=239.
8. Nagiel A, Lalane RA, Sadda SR, Schwartz SD. Ultra-widefield fundus imaging: A review of clinical applications and future trends. Retina J Retin Vitr Dis 2016;36:660-78.

9. Ghasemi Falavarjani K, Tsui I, Sadda SR. Ultra-wide-field imaging in diabetic retinopathy. Vision Res 2017;139:187-90.
10. Kumar V. Insights into autofluorescence patterns in Stargardt macular dystrophy using ultra-wide-field imaging. Graefes Arch Clin Exp Ophthalmol 2017;255:1917-22.
11. Scaglione C, Salvi F, Riguzzi P, Vergelli M, Tassinari CA, Mascalchi M. Symptomatic unruptured capillary telangiectasia of the brain stem: Report of three cases and review of the literature. J Neurol Neurosurg Psychiatry 2001;71:390-3.
12. Schoen MA, Shields CL, Say EAT, Douglass AM, Shields JA, Jampol LM. Clinically invisible retinal hemangioblastomas detected by spectral domain optical coherence tomography and fluorescein angiography in twins. Retin Cases Brief Rep 2016.
13. Beroud C. Retinal hemangioblastoma in von Hippel-Lindau disease: A clinical and molecular study. Invest Ophthalmol Vis Sci 2002;43:3067-74.
14. Schachat AP. Ryan's Retina. 6th ed, vol. 1. Cleveland, USA: Elsevier. 2018. p. 294.
15. Ehlers JP, Wang K, Vasanji A, Ming Hu, Srivastava SK. Automated quantitative characterisation of retinal vascular leakage and microaneurysms in ultrawidefield fluorescein angiography. Br J Ophthalmol 2017;101:696-9.
16. Pulido JS, Dalvin LA, Olsen TW, Mano F, Yu M, Shields CL. Peripheral retinal nonperfusion using widefield imaging with von Hippel-Lindau disease. Int J Retina Vitr 2018;4:36.
17. Chen X, Sanfilippo CJ, Nagiel A, Hosseini H, Mitchell D, McCannel CA, *et al*. Early detection of retinal hemangioblastomas in von Hippel-Lindau disease using ultra-widefield fluorescein angiography. Retina Phila Pa 2018;38:748-54.
18. Schmidt D, Natt E, Neumann HP. Long-term results of laser treatment for retinal angiomatosis in von Hippel-Lindau disease. Eur J Med Res 2000;5:47-58.
19. Bandyopadhyay S, Sheth RD. Acute spinal cord infarction: Vascular steal in arteriovenous malformation. J Child Neurol 1999;14:685-7.
20. Shah AR, Abbey AM, Yonekawa Y, Khandan S, Wolfe JD, Trese MT, *et al*. Widefield fluorescein angiography in patients without peripheral disease: A study of normal peripheral findings. Retina Phila Pa 2016;36:1087-92.
21. Lubiński W, Krzystolik K, Cybulski C, Szych Z, Penkala K, Palacz O, *et al*. Retinal function in the von Hippel-Lindau disease. Doc Ophthalmol Adv Ophthalmol 2003;106:271-80.
22. Mottow-Lippa L, Tso MO, Peyman GA, Chejfec G. von Hippel angiomatosis. A light, electron microscopic, and immunoperoxidase characterization. Ophthalmology 1983;90:848-55.
23. van Rooijen E, Voest EE, Logister I, Bussmann J, Korving J, van Eeden FJ, *et al*. von Hippel-Lindau tumor suppressor mutants faithfully model pathological hypoxia-driven angiogenesis and vascular retinopathies in zebrafish. Dis Model Mech 2010;3:343-53.
24. Fruttiger M. What do retinal telangiectasia tell us about the control of vasculature in the retina? Acta Ophthalmol (Copenh). 2014;92(s253).