Comprehensive overview of IRVAN syndrome: a structured review of Case Reports and Case Series

Hashim Ali Khan, Qaim Ali Khan, Muhammad Aamir Shahzad, Muhammad Amer Awan, Naeemullah Khan, Smaha Jahangir, Fiza Shaheen, Kamran Wali, Julie Rodman, Jozeph Pizzimenti and Ali Osman Saatci

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***Abstract*:** Idiopathic retinal vasculitis, aneurysms, and neuroretinitis (IRVAN) syndrome is a rare spectrum of retinal vasculitis, aneurysms, and neuroretinitis affecting young individuals in their third decade. Most of our current knowledge is based on case reports, case series, and a handful of collaborative studies. There is much diversity in treatment approaches and outcomes in the reported literature. We have aggregated published case reports and case series into quantitative and narrative synthesis to draw evidence-based conclusions toward clinical features, atypical and rare findings, systemic associations, disease course, and treatment outcomes. The analysis suggested the disease mostly affects young individuals with a female predilection. Anterior chamber and vitreous inflammation are common than previously believed. The most prevalent pattern of retinal vasculitis in IRVAN eyes is mixed vasculitis, followed by arteritis and phlebitis. Most eyes at the time of presentation have capillary nonperfusion and require treatment. Most eyes retain good visual acuity; however, treatment is required to maintain visual function. Intravitreal antivascular endothelial growth factors administered as an adjunct to retinal laser photocoagulation are more likely to improve visual outcomes. Besides, we have discussed the different hypotheses on the etiopathogenesis of the disease and stronger evidence suggests an inflammatory origin of the disease.

Keywords: anti-VEGF, IRVAN syndrome, neuroretinitis, posterior uveitis, retinal aneurysms, retinal vasculitis

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Correspondence to:
Hashim Ali Khan
Department of Ophthalmology, SEHHAT Foundation Hospital, Danyor, Gilgit 15100, Pakistan

School of Optometry, The University of Faisalabad, Faisalabad, Pakistan

Advance Eye Care, Gilgit, Pakistan
retinadr.hashimalikhan@gmail.com; @Hashim_FAAO

Qaim Ali Khan
Ophthalmology Department, Agha Khan Health Services, Gilgit, Pakistan

Muhammad Aamir Shahzad
Ophthalmology Department, Aziz Fatimah Medical & Dental College, Faisalabad, Pakistan

Muhammad Amer Awan
Ophthalmology Department, Shifa International Hospital and Shifa College of Medicine, Islamabad, Pakistan

Naeemullah Khan
Kamran Wali
Advance Eye Care, Gilgit, Pakistan

Smaha Jahangir
School of Optometry, The University of Faisalabad, Faisalabad, Pakistan

Fiza Shaheen
Al-Shifa Trust Eye Hospital, Rawalpindi, Pakistan

Julie Rodman
Broward Eye Care Institute, Nova Southeastern University, Fort Lauderdale, FL, USA

Joseph Pizzimenti
Rosenberg School of Optometry, University of the Incarnate Word, San Antonio, TX, USA

Ali Osman Saatci
Department of Ophthalmology, Dokuz Eylul University, İzmir, Turkey

Introduction

Idiopathic retinal vasculitis, aneurysms, and neuroretinitis (IRVAN) is a rare spectrum of ocular changes characterized by retinal vasculitis, disk and/or retinal macroaneurysms, and optic disk hyperemia with macular exudation.[1] Most of our current understanding is based on case reports and small case series, and there are only a few multicenter collaborative studies on IRVAN syndrome. The published data show great diversity in presentation, clinical features, associations, and treatment approaches. Authors have described both systemic and ocular therapies. Systemic treatments include oral and intravenous corticosteroids, disease-modifying antirheumatic drugs (DMARDs), and biologics. Ocular treatments involve laser photocoagulation to aneurysms and areas of capillary nonperfusion (CNP), intravitreal antivascular endothelial growth factor (VEGF) injections, intravitreal steroid implants, pars plana vitrectomy, and medical/surgical management of neovascular glaucoma.

Stage I disease is characterized by the classical triad of retinal changes. Many authors believe administering systemic corticosteroids may provide visual and anatomical benefits, while others advocate observation. Stage II disease is characterized by the

presence of CNP and requires laser photocoagulation. While many practitioners recommend systemic steroids with laser, others consider them unnecessary. Recent reports suggest the use of intravitreal anti-VEGF injections as an adjunct to the laser for better visual outcomes. The results are confounded by many factors including disease severity, comorbid conditions, different combinations of treatments and no studies, yet, have compared the different treatments due to the rarity of the disease.

By providing detailed information about individual cases, case reports offer a rich source of primary data. When well-designed studies are not possible, aggregating case reports into secondary quantitative and narrative synthesis can help understand better about rare disease entities and draw better conclusions.[2–4]

In the current article, we have aggregated the case reports to quantitative and narrative synthesis to evaluate the clinical features, visual outcomes, and effects of treatments on IRVAN syndrome.

Methods

The terms 'idiopathic retinal vasculitis aneurysm and neuroretinitis' were used to search Medline and Google Scholar for relevant literature. All results were exported to EndNote X8 software (Clarivate Analytics, Philadelphia, PA, USA). We identified and included only case reports and case series after removing duplicates. From the studies included, we extracted demographics, clinical features, treatments, and outcomes data. The extracted data included (1) age, (2) gender, (3) laterality, (4) baseline visual acuity, (5) final visual acuity, (6) anterior chamber status, (7) vitreous status, (8) extent and distribution of macroaneurysms, (9) presence and location of capillary nonperfusion, (10) neovascularization on disk, (11) neovascularization elsewhere on retina (NVE), (12) neovascularization on iris (NVI), (13) presence of neovascular glaucoma (NVG), (14) type of vasculitis, (15) Treatment(s) given, (16) follow up duration, (17) visual outcomes, and (18) additional ocular and systemic findings.

Visual acuity was averaged and converted to decimal notation following the method proposed by Holladay JT.[5] Anterior chamber and vitreous status were noted if reported by authors in the case description. Type of retinal vasculitis was labeled by two independent masked expert graders from provided clinical photographs or fundus fluorescein angiograms as (1) arteritis, (2) phlebitis, or (3) mixed. Distribution of macroaneurysms was recorded as (1) disk, (2) elsewhere, or (3) both as (1) few when there were less than five aneurysms or (2) multiple for more than 5. Fluorescein angiograms were used to look for the presence and location of retinal capillary nonperfusion (CNP). CNP was recorded as present *versus* absent and central, peripheral, or combined. The parameters CNP and vasculitis were labeled 'unknown' if an image or descriptive text was not provided for the given eye. Visual outcome was defined as 'stable' for equal baseline and final visual acuities. One line drop or gain in visual acuity was classified as 'deteriorated' or 'improved,' respectively.

Statistical analysis

All categorical data were presented as counts (percentages) and measures were displayed as mean or median according to the normality of distribution. All data were non-normally distributed and evaluated using nonparametric tests in statistical software (SPSS software Version 28; SPSS, Chicago, IL).

For analysis of the effect of systemic and ocular treatments and other baseline parameters on visual outcomes, binary logistic regression was performed. Only eyes with complete baseline and follow-up visual acuity, follow-up duration, and ocular treatment data were included in this analysis.

Results

Demographics and Clinical Features

Total 116 eyes from 60 patients, 35 (58.3%) females, were included for baseline and demographic analysis. Mean ± SD age was 30.284 ± 15.28 years. Table 1 shows baseline clinical features across genders.

Baseline visual acuity ranged from hand motion to 20/12. There was no difference between genders in terms of visual acuity. Fifty-five patients, 33 females, had bilateral disease, while four patients (two females) had unilateral disease. Of 116 eyes, there were mild cells and/or flare in 23 (19.2%) and the anterior chamber (AC) was quiet in 90 (75%) eyes. While the status of AC was not reported for three eyes, anterior chamber

Table 1. Distribution of baseline parameters across genders.

Parameters	Overall	Male	Female	Sig
Patients (eyes)	60 (116)	25 (48)	35 (68)	
Age, years, mean ± SD	30.28 ± 15.28	30.67 ± 18.02	30.01 ± 13.14	0.6
Baseline vision				
Mean ± SD	0.6 ± 0.41, 0.67	0.63 ± 0.47, 0.67	0.58 ± 0.38, 0.67	0.6
Median	0.001 to 1.54	0.01 to 1.54	0.001 to	
Min-Max			1.25	
CNP, Present/Absent. *N* Eyes	103/11	40/9	63/2	OR, *p* (male/female) 7.09, 0.009
Vasculitis. *N* eyes Mixed/phlebitis/arteritis	62/10/16	23/2/10	39/8/6	0.07
NVD, eyes Present/absent	14/106	7/43	7/63	0.3
NVE, present/absent	21/99	8/42	13/53	0.3
NVI, present/absent	8/112	1/49	7/63	0.3
NVG, present/absent	5/115	1/49	4/66	0.3

CNP, capillary nonperfusion; NVD, neovascularization on disk; NVE, neovascularization elsewhere; NVG, neovascular glaucoma; NVI, neovascularization on iris; OR, odds ratio; SD, standard deviation.

inflammation did not have any effect on initial and final visual acuities (p = all >0.05). Vitreous status was reported for total of 98 eyes. Vitreous was quiet in 34 (34.7%) eyes. Vitreous cells were reported in 46 (46.9%) eyes. Vitreous cells with scattered micro-hemorrhages involved 11 (11.2%) eyes, while vitreous hemorrhage obscuring retinal view was present in 7 (7.1% eyes).

Seventy-five (64.7%) eyes had multiple (more than 5) and 28 (24.1%) had few (less than 5) aneurysms. Only two eyes, of two patients, did not have any aneurysmal changes. Aneurysm count could not be ascertained for 11 (9.5%) eyes due to vitreous hemorrhage or unavailability of data in published reports. Aneurysms were more frequently distributed along the disk and elsewhere in the retina ($N = 50$), followed by retinal aneurysms ($N = 43$) and limited to disk only ($N = 10$). The distribution of aneurysms in the retina was dependent on the count. Multiple aneurysms were more likely to occur on disk and elsewhere or elsewhere in the retina while optic disks tended to have few aneurysms ($p < 0.001$, Fisher Exact).

Retinal vasculitis manifested as mixed vasculitis in 62 (53.4%) eyes, arteritis in 16 (13.8%) eyes, and phlebitis in 10 (8.6%) eyes. Two eyes did not have any vasculitis, while it was unknown for 26 (22.4) eyes either because of hazy media or lack of gradable data from reports.

Of 116 eyes, capillary nonperfusion (CNP) was present in 103 (88.8%) eyes and absent in 10 (8.6%) eyes and unknown for the rest. CNP was present in the peripheral retina in 90 (87.4%) eyes, while there was simultaneous central and peripheral CNP in 13 (12.6%) eyes. Baseline visual acuity in eyes without CNP (median = 1.00) was better than those with CNP (median = 0.53) as indicated by Mann–Whitney U test ($U = 224$, $p = 0.003$, $r = 0.88$). Nonetheless, the distribution of CNP did not affect visual acuity ($H = 0.01$, $df = 2$, $p = 0.99$).

Optic disk neovascularization (NVD) and retinal neovascularization (NVE) were present in 14 (12.1%) and 21 (18.1%) eyes, respectively, while iris neovascularization (NVI) was seen in nine (7.8%) eyes. Simultaneous NVD and NVE were present in four eyes while isolated NVD and

Table 2. Relationship between baseline VA and clinical parameters.

Parameter	VA, median (IQR)	*p*
Male/female	0.67 (0.21–1.0)/0.67 (0.18–1.0)	0.49
OD/OS	0.73/0.50	0.41
AC quite/cells	0.67 (0.21–1.0)/0.50 (0.2–1.00)	0.41
NVG present/absent	0.67 (0.2–1.0)/0.67 (0.1–0.8)	0.53
Vitreous NR/Q/Cells/Cells&Hem/Hem	0.33 (0.13–0.67)/0.8(0.5–1.0)/0.8(0.31–1.0)/0.04 (0.01–0.50)/0.01 (0.01–0.9)	**0.002***
Aneurysms few/multiple	0.8 (0.3–1.0)/0.67 (0.2–1.0)	0.14
Aneurysm location Disk/disk elsewhere/elsewhere	0.73 (0.25–0.95)/0.58 (0.21–1.0)/0.8 (0.31–1.0)	0.65
Vasculitis Uncertain/phlebitis/arteritis/mixed	0.8 (0.45–1.0)/1.0 (0.85–1.0)/0.2 (0.06–0.63)/0.50 (0.18–0.80)	**0.007****
CNP present/absent, $n = 111$	0.5 (0.17–1.0)/1.0 (0.75–1.0)	**0.03**
CNP location, $n = 101$ Peripheral/P&C/	0.5 (0.2–1.0)/0.58 (0.1–1.0)	0.99
NVD +/–	0.8 (0.58–1.0)/0.67 (0.37–1.0)	0.22
NVE +/–	0.67 (0.3–1.0)/0.8 (0.5–1)	0.7
NVI +/–	0.8 (0.05–1)/0.67 (0.23–1)	0.7

AC, anterior chamber; CNP, capillary nonperfusion; IQR, interquartile range; NVD, neovascularization on disk; NVE, neovascularization elsewhere; NVG, neovascular glaucoma; NVI, neovascularization on iris; VA, visual acuity. Bold values show statistical significance.

isolated NVE were present in 17 and 10 eyes, respectively. The presence of NVD and NVI was independent of each other in our data ($p = 0.357$, Fisher's exact). None of eyes without CNP had NVD, NVE, or NVI. The odds for NVD in eyes with CNP was 3.73 ($Z = 0.89$, $p = 0.3$), for NVE 5.65 ($Z = 1.18$, $p = 0.2$) and for NVI 2.04 ($Z = 0.48$, $p = 0.6$).

Of nine eyes with NVI, neovascular glaucoma was present in five eyes (55.6%). The association between NVI and glaucoma was significant and ($\chi^2(1, N = 116) = 62$, $p < 0.001$) and odds of NVG was 1.7 times higher in eyes with NVI.

Some of the baseline parameters, including vitreous status, the pattern of vasculitis, and capillary nonperfusion had an effect on the initial visual acuities of the patients (Table 2).

Eyes with quiet vitreous and those with vitreous cells had better median visual acuities than those with vitreous cells and scattered hemorrhage and those with vitreous hemorrhage obscuring fundi. Pairwise comparison showed the difference was significant between cells&hem-cells ($p = 0.03$), cells&hem-Quite ($p < 0.001$), Hem-Quiet ($p = 0.036$), and undefined vitreous status-quiet ($p = 0.027$) pairs. Interestingly, the difference between eyes with quiet vitreous and vitreous with cells was not significant ($p = 0.386$), and there was no relationship between initial visual acuity and age (Spearman Correlation Coefficient = 0.135, $p = 0.21$).

Additional retinal findings

Microaneurysms were seen in 11 eyes of eight patients (6 females). All eyes except one had few (<10) microaneurysms on the posterior pole, whereas one eye had multiple peripheral microaneurysms. Nonetheless, all 11 eyes had CNP adjacent to or isolated from microaneurysms. ERM was reported in eight eyes of six patients. Other retinal findings included branch retinal artery

occlusion (five eyes), microvascular occlusions (three eyes), neurosensory serous macular detachments (seven eyes), vitreomacular traction/tractional retinal detachment (four eyes), and outer retinal degeneration (three eyes). In addition, branch retinal vein occlusion, optic atrophy, and choroidal neovascularization each occurred singly.

Systemic Associations: two patients were reported to have raised P-ANCA levels. Raised serum homocysteine levels, positive tuberculin skin test, microcytic erythrocytes, and fungal sinusitis were encountered in one individual each.

Visual outcomes

For visual outcome analysis, only those cases were included where, in addition to all baseline parameters, treatment type, visual outcomes, and follow-up duration were clearly reported. A total 58 eyes of 38 patients were included in the final outcome analysis.

Median (IQR) age was 29 (21–36) years. The median (IQR) final and baseline visual acuities were 0.8 (0.175–1.0) and 0.8 (0.5–1.0). A Wilcoxon signed-rank test showed the final visual acuity was better than baseline visual acuity ($Z = 3.086$, $p = 0.002$, $r = 0.4$). Over a median (IQR) period of 10 (5.25–33) months, visual acuity in 28 (48.3%) eyes remained stable, while improved in 25 (43.1%) and deteriorated in 5 (8.6%) eyes. The distribution of age and follow-up durations were not significantly different between the three outcome groups (p all > 0.5)

Patients had been observed or managed with systemic or ocular therapies or a combination of both. Of 35 patients (58 eyes), 13 patients (20 eyes) did not receive any systemic treatment, while 16 (27 eyes) received oral steroids, 4 (8 eyes) were treated with oral steroids and DMARDs and 2 (3 eyes) were treated initially with intravenous steroids and maintained on oral steroids. Among ocular treatments, 17 (29.3%) eyes received no treatment, whereas 27(46.6%) received single or multiple sessions of retinal laser and 14 (24.1%) received both laser and intravitreal injections of antivascular endothelial growth factor as combination therapy. All (58) eyes except 1 eye had CNP and 4 eyes with CNP did not receive any treatment of any kind.

Neither systemic nor ocular treatment had an effect on visual outcome ($p = 0.33$ & $p = 0.13$; *Fisher's exact)*. However, when tested after adjusting for baseline vision, follow-up duration, ocular and systemic treatments and retinal ischemia, ocular combination therapy (i.e. Laser and Anti-VEGF) seem to result in an improved visual function. Logistic regression was used to ascertain the effect of baseline VA, follow-up duration, and systemic and ocular treatment on visual outcomes. The model was statistically significant, $\chi^2 = 54.6$, 7, $p < 0.001$. The model explained 85% (Nagelkerke R^2) of the variability and correctly classified 92.5% of the outcome. Eyes receiving combined Laser and Anti-VEGF were 8.8 times more likely to have improved visual outcomes, while systemic treatment or combination of systemic and ocular treatments did not have an effect on visual outcomes (Stable *versus* Improvement). Follow-up duration did not have a significant effect on visual outcomes when compared across improved or stable.

Discussion

Retinal vasculitis, aneurysms, and neuroretinitis are key features of IRVAN syndrome. All three classical signs may be seen in most eyes at the time of diagnosis. However, in some eyes, one feature may precede the other by many months. In our study, there were few patients who did not have all the three features present. With the progression of the disease, these eyes develop progressive capillary nonperfusion with subsequent retinal and iris neovascularization and neovascular glaucoma (Figure 1).

Young individuals, in their third decade, are mostly affected with a female preponderance. However, cases, as young as 7 years, have been reported. It reflects symptomatic macular involvement earlier in the course of disease, prompting patients to seek medical advice.

Pathogenesis

Despite the etiopathogenesis of IRVAN syndrome is not well understood, it is widely accepted that the spectrum is a consequence of intraocular inflammation due to presence of mild intraocular inflammation, vasculitis, and formation of epiretinal membranes. It is believed that migratory, segmented retinal vascular inflammation leads to a arterial wall weakening and consequent formation of aneurysms, vascular leakage, and capillary nonperfusion over time. Possible VEGF expression in response to retinal ischemia may further

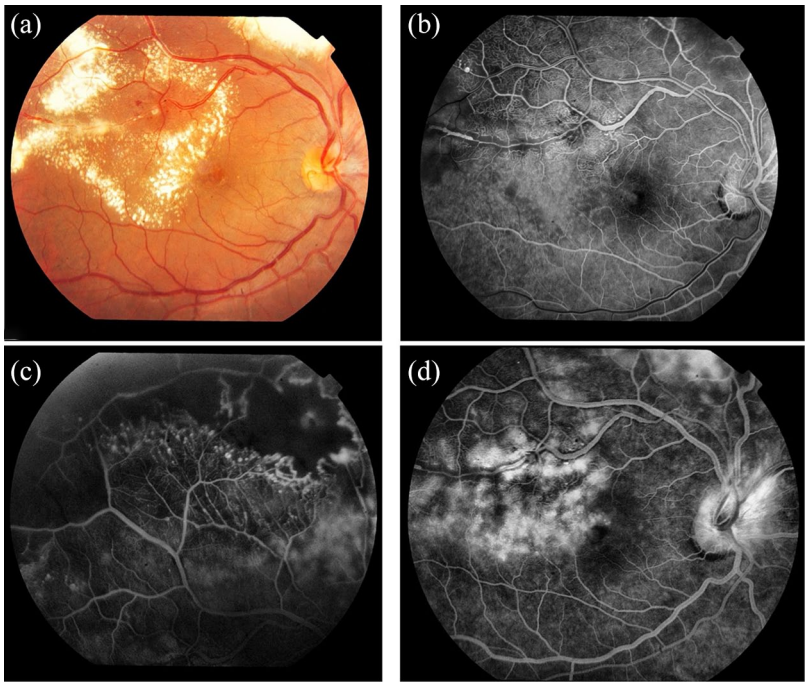

Figure 1. A typical case of IRVAN syndrome. (a) Color fundus image showing disk hyperemia and exudative maculopathy. (b) Aneurysmal dilatations enhance arterial wall staining, and focal narrowing of artery and vascular remodeling are seen on FA. (c) Peripheral CNP on FA and (d) leaking disk with macular edema.

increase the vascular permeability and hence retinal exudation and edema.

Recently, Chawla *et al.*[6] proposed that the aneurysmal changes are congenital or of developmental origin, disrupting the retinal hemodynamics and give rise to retinal ischemia and consequent VEGF release. Their hypothesis is based on the observation of two cases with disk aneuyrsms and macular exudates. They authors believed the cases lacked true vasculitis and attributed enhanced vessel wall staining to VEGF mediated vascular hyper-permeability. However, congenital/developmental origin of IRVAN is contradicted by several observations. Gharbiya *et al.*[7] examined the parents and a twin sister of 47-year-old patient with IRVAN syndrome and the results were unremarkable. Balaratnasingam *et al.*[8] reviewed 6-year-old retinal photographs of an IRVAN patient and found no abnormalities. It indicates an acquired nature of the disease. Rarely, authors have reported unilateral involvement.[9–11] These observations do not support a congenital/ developmental origin of IRVAN syndrome. Presence of low-degree intraocular inflammation and rapid visual improvement after intravenous pulse methylprednisolone all emphasize an inflammatory origin of the disease.[12–14]

Visual function

Depending on the severity of ocular involvement, the visual acuity may range between 20/13 to Hand Motion. However, most eyes, at the time of presentation, have VA around 20/40 and maintain a visual acuity of 20/40 or better. Visual acuity tends to improve over many months with or without treatment. Visual acuity reduction is usually secondary to vascular leakage and macular edema, epiretinal membrane, retinal ischemia, vitreous hemorrhage, and glaucoma.

Ocular inflammation

Mild intraocular inflammation characterized by inflammatory cells/flare or haze in the anterior chamber and/or vitreous is a common feature. Most eyes have mild ocular inflammation either in the anterior chamber or vitreous cavity or both at some point in the disease course. The mild ocular inflammation does not seem to have an effect on initial or final visual function. Nonetheless, it supports an inflammatory origin of the disease itself. Anterior segment inflammation in these eyes responds well to topical steroids.[1]

Vasculitis

It is characterized by inflammation and necrosis of blood vessels. Vasculitis manifests as perivascular exudation in acute phases and subsequent weakening of vessel walls with the formation of arterial/ capillary aneurysmal changes. In chronic stages, there may be retinal hypoxia, vascular sheathing, and pigmentary changes.[15,16] Among retinal vasculitides, phlebitis is most frequently encountered. Previously, arteritis has been assumed as the most prevalent type of retinal vasculitis in eyes with IRVAN syndrome.[1] But the current analysis demonstrated a mixed pattern is the predominant type followed by arteritis. Phlebitis appears to be the least frequent vasculitis type in IRVAN syndrome. The retinal vasculitis may improve over time or in response to treatment or may progress to vascular sheathing (Figure 2).

Aneurysms

Retinal arterial aneurysms are a key feature of IRVAN syndrome. While they frequently appear along the vascular bifurcations of first and second-order arterioles, the presence of optic disk aneurysms are pathognomonic of IRVAN syndrome. The current analysis demonstrated that the most common distribution pattern of aneurysms is their presence on both optic disk and retina, while isolated disk aneurysms are least commonly encountered. Aneurysms in IRVAN syndrome show extreme dynamics and may regress, enlarge, or resolve spontaneously during the disease course or in response to treatment.[17–19] While the aneurysms tend to regress or resolve, there may develop newer aneurysms adjacent to the site of previous aneurysms.[20,21] Different mechanisms behind the development of macroaneurysms in IRVAN syndrome have been discussed. Most authors believe segmental retinal vascular inflammation may cause vessel wall weakening and subsequent ectatic changes at the site of weakened vessels. We reviewed the fluorescein angiograms from cases that reported aneurysms dynamics and found weakened vessel wall segments and enhanced differential segmented vessel wall staining at the sites of new aneurysm formation.[20,21] Nonetheless, this observation may be time-dependent and needs further validation. Liu *et al.*[22] demonstrated a positive relationship between the aneurysms count and CNP area. Although not specifically described in literature, we identified 11 eyes having capillary microaneurysms in the posterior pole or areas adjacent to CNP. Microaneurysms also suggest focal vascular insults from a migratory inflammatory process or may develop in response to long-standing retinal ischemia.

Retinal ischemia and sequelae

Most eyes with IRVAN syndrome, at the time of diagnosis, have retinal ischemia. In our analysis, only 11 eyes had preserved retinal perfusion. CNP might be an outcome of vasculitis, compromised flow, peripheral microvascular occlusions, and perhaps vascular endothelial growth factor (VEGF) expression. Vascular remodeling is usually evident as intraretinal microvascular abnormalities (IRMA) around regions of CNP. With subsequent progression, CNP leads to further complications including retinal vascular proliferation and neovascular glaucoma as the end-stage disease. CNP is associated with poorer vision and a higher incidence of complications in eyes with IRVAN as demonstrated in the current analysis and past studies.[23,24] NVD, NVE, and iris rubeosis are always associated with long-standing retinal ischemia and CNP is invariably present in eyes with these serious vision-threatening complications.

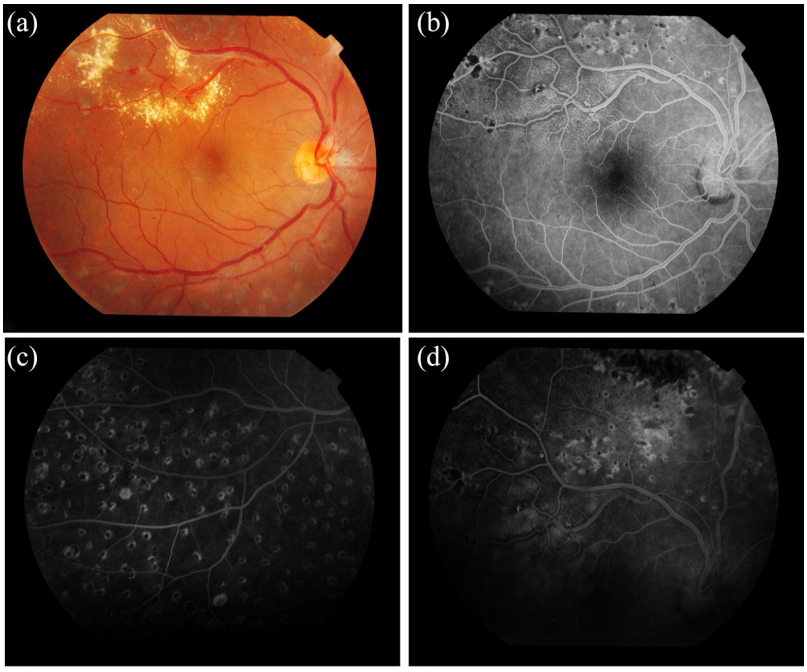

Figure 2. Same case as Figure 1. Two weeks after retinal laser photocoagulation to CNP and aneurysms. (a) Color fundus and (b–d) fluorescein angiograms.

Other retinal findings

Among nonclassic manifestations of IRVAN syndrome, vitreous hemorrhage and ERM are common findings.[12,18,25–33] Vitreous hemorrhage occurs when NVE or NVD complexes bleed. Subsequent fibrovascular proliferation may lead to tractional retinal detachment.[6] Other less frequent retinal associations/coincidental findings include branch retinal artery occlusion,[29,34–36] branch retinal vein occlusion,[27,29] peripheral or midperipheral microvascular occlusions,[13,37,38] serous neurosensory detachments,[6,33,39] vitreomacular traction,[28] and rarely retinal degeneration,[18,40] optic atrophy,[40] and choroidal neovascularization[41] (Figure 3).

Systemic findings

Although the spectrum is idiopathic, rarely authors have reported certain systemic associations including raised p-ANCA,[40,42] allergic

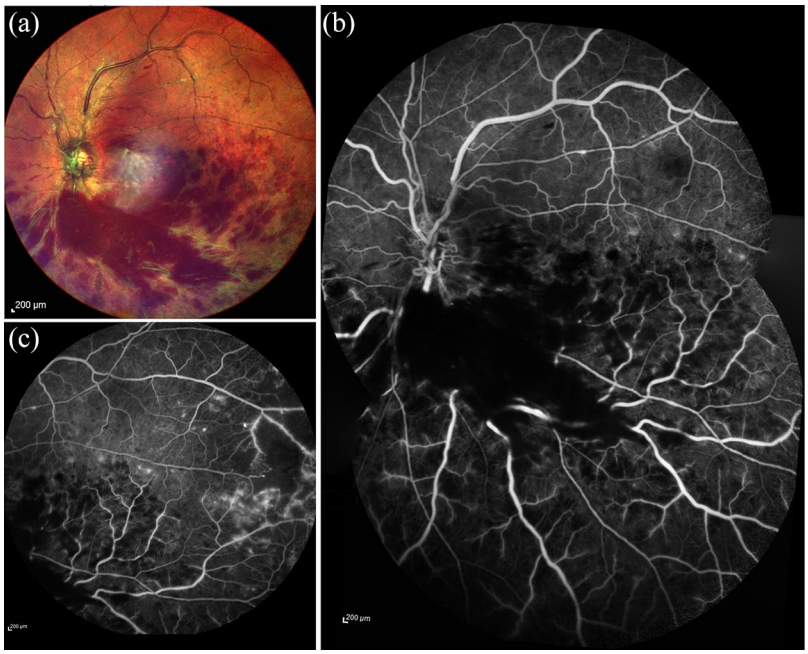

Figure 3. (a) Dense preretinal and intraretinal hemorrhage in an IRVAN eye with BRVO. (b) Aneurysmal changes, enhanced vascular wall staining and (c) peripheral CNP can be seen on FA.

fungal sinusitis,[43] hyperhomocysteinemia,[35] and raised intracranial pressure.[44]

Classification and severity staging

Samuel *et al.*[23] proposed a five-stage severity scale which has been subsequently used by clinicians consecutively in gauging disease severity and guiding treatment decisions. The five stages of the disease include the following:

1. Macroaneurysms, exudation, neuroretinitis, retinal vasculitis
2. CNP evidenced by angiography
3. Posterior segment neovascularization and/or vitreous hemorrhage
4. Iris rubeosis
5. Neovascular glaucoma

Recently, Qi *et al.*[24] have proposed a modified five-stage severity scale to the Samuel *et al.*[23] scheme. The first three stages are the same in both schemes; however, fourth stage in the modified scheme includes vitreoretinal fibrovascular proliferation and/or retinal detachment, while iris rubeosis and neovascular glaucoma have been assigned to fifth stage. The modified staging system is more inclusive and can be used for clinical staging and guiding treatments.

Atypical cases

IRVAN presents bilateral disease with all three classic findings including vasculitis, neuroretinitis, and aneurysms. Unilateral involvement is rare and only nine cases with unilateral involvement have been reported.[1,6,9,10,45] Garcia Vilaro *et al.*[46] reported a case with classic IRVAN features in one eye and the fellow eye had disk and retinal macroaneurysms only. There are cases with IRVAN features in the absence of aneurysms.[28,47]

Ancillary testing and imaging

Retinal fluorescein angiography (FA) has remained a gold standard in vascular imaging of the retina and most authors have used FA for enhanced visualization of vasculitis and retinal aneurysms as well as to detect and delineate the capillary nonperfusion, NVD, NVE, and other vascular alteration. On FA, aneurysms appear as saccular outpouchings of retinal arterial and arteriolar walls at the disk and elsewhere, while vasculitis manifests as enhanced vessel wall staining and leakage in later phase of angiogram. FA can be used to monitor the progression/regression of retinal ischemia, neovascularization, aneurysms, vasculitis, and guide treatment decisions as well as gauging response to treatment. Macular exudation and edema are the main cause of visual disturbance in eyes with IRVAN syndrome. Optical coherence tomography (OCT) is an invaluable tool for evaluating macular thickness and morphology during diagnosis and response to treatment. It provides both qualitative as well as quantitative metrics to gauge treatment response.

OCT-angio (OCTA) is a recently introduced retinochoroidal vascular imaging modality that provides depth-resolved high-resolution flow information without the need for a contrasting agent. Authors have used OCTA to evaluate disk, posterior pole macroaneurysms, and in some cases, CNP.[6,27,34,48] It can clearly demonstrate vascular changes, including hypoperfusion,[27] aneurysmal changes, retinal neovascularization, and vascular remodeling which can be sometimes obscured by leakage and edema on FA.[6,27,34,48] It is particularly helpful in cases with disk aneurysms which are hard to discern on FA due to leakage and overlying neuroretinitis. OCTA provides a clear visualization of aneurysmal changes in such cases.

OCTA can delineate CNP areas with sensitivity equal to or better than FA; however, a smaller

field of view limits its ability to detect peripheral CNP.[48] It can be compensated by obtaining scans from multiple areas and montaging multiple views. Nonetheless, some newer devices with updated software can provide up to 200° field of view and can be used for peripheral retina as well.[49]

Treatment approaches and visual outcomes

The primary goal of treatment is to prevent permanent visual loss from progressive ischemia and related complications including retinal neovascularization, fibrovascular proliferation, and neovascular glaucoma. The main cause of visual disturbance in stage 1 IRVAN eyes is neuroretinitis, macular edema, and lipid maculopathy. While there is no consensus on the standard of care for IRVAN syndrome, different modes of delivery are reported including systemic and ocular treatments. Systemic drugs include corticosteroids, DMARDs, and biologics, while ocular treatments include laser photocoagulation, intravitreal anti-VEGF injections, ocular steroids, surgery, and ablative procedures.[12–14,28,30,31,33,37,39,46,47,50,51]

For stage 1 IRVAN, some advocated the observation, while others administer systemic steroids and/or DMARDs.[30] Initial treatment with corticosteroids is assumed to improve retinal vasculitis, leakage, and macular edema. When treated with systemic steroids, stage I and II IRVAN eyes, either improve or maintain visual acuity. Intravenous administration of methylprednisolone has shown rapid improvement in visual acuity and macular exudation.[14,32] Eyes that require long-term immunosuppression are maintained on DMARDs for stable visual outcome in the long term.[12,41,47,52] Stage II and III eyes are usually treated with laser photocoagulation alone or in combination with systemic steroids to avoid permanent vision loss from progressive ischemia and its sequelae. Some authors demonstrated combination therapy with laser photocoagulation and intravitreal anti-VEGF injections.

It is interesting that four eyes (three patients) with stage II disease were not treated at all despite capillary nonperfusion but maintained visual acuity over a median (IQR) period of 14 (11.3–11.8) months.[26,31,44] It implies a variable time course of the disease progression and self-limiting nature.

In the current analysis, only 5 (8.6%) eyes had visual deterioration despite treatment, while 28 (48.3%) remained stable and 25 (43.1%) had improvement in visual acuities. When adjusted for baseline vision, retinal ischemia, and follow-up duration, all eyes regardless of treatment type (observation, systemic steroids, laser or combined systemic steroids, and ocular laser) had equal chances for improvement or maintaining stable vision. However, eyes treated with combined laser photocoagulation and intravitreal anti-VEGF injections were eight times more likely to have an improvement in visual acuities over a mean period of 19.9 ± 8 months compared to eyes treated with laser alone, a combination of laser and systemic steroids, systemic steroids alone, or no treatment.

Recent reports have demonstrated the role of intravitreal slow-release dexamethasone implant in improving the visual function and macular anatomy in eyes with IRVAN syndrome.[26,31,32,50,52] Most of the reported eyes had already received multiple treatments, including retinal laser photocoagulation, anti-VEGF injections, and pars plana vitrectomy. Dexamethasone implant resulted in a slight improvement in visual acuity but a substantial reduction in macular exudation in most eyes.[26,31,32,50,52]

Eyes with retinal and iris neovascularization need pan-retinal photocoagulation to avoid glaucoma. Pars plana vitrectomy is performed in eyes with tractional retinal detachment and vitreous hemorrhage, whereas NVG needs medical and surgical management.

Despite a variable response to described treatments, the treatment of IRVAN syndrome should involve control of ocular inflammation and treatment of ocular ischemia to avoid related complications and disease progression to advanced stages and permanent vision loss.

Author contributions

Hashim Ali Khan: Conceptualization; Data curation; Formal analysis; Methodology; Writing – original draft; Writing – review and editing. Qaim Ali Khan: Conceptualization; Data curation; Formal analysis; Investigation; Writing – review and editing. Muhammad Aamir Shahzad: Conceptualization; Formal analysis; Validation. Muhammad Amer Awan: Conceptualization; Formal analysis; Writing – review and editing. Naeemullah Khan: Data curation; Methodology; Writing – review and editing. Smaha Jahangir: Data curation; Formal analysis; Writing – review

and editing. Fiza Shaheen: Data curation; Formal analysis; Investigation; Writing – review and editing. Kamran Wali: Data curation; Formal analysis; Writing – review and editing. Julie Rodman: Conceptualization; Methodology; Supervision; Writing – review and editing. Joseph Pizzimenti: Conceptualization; Methodology; Supervision; Writing – review and editing. Ali Osman Saatci: Conceptualization; Writing – review and editing.

Conflict of interest statement

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ORCID iDs

Hashim Ali Khan https://orcid.org/0000-0002-6538-2033

Ali Osman Saatci https://orcid.org/0000-0001-6848-7239

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