

# Long-term Observation of Chinese Idiopathic Retinitis, Vasculitis, Aneurysms, and Neuroretinitis (IRVAN) Patients and suggestion of a Revised Staging System

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## Research article

**Keywords:** Retinitis, vasculitis, aneurysms, and neuroretinitis, Proliferative vitreoretinopathy, Exudative maculopathy, Intra-retinal microvascular abnormality, Acute macular neuroretinopathy, Pan-retinal photocoagulation, Fundus fluorescein angiography

**Posted Date:** March 4th, 2020

**DOI:** <https://doi.org/10.21203/rs.3.rs-16027/v1>

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# Abstract

**Background** To investigate the clinical characteristics and intervention effects on Chinese patients with idiopathic retinitis, vasculitis, aneurysms, and neuroretinitis (IRVAN).

**Methods** The consecutive series patients received eye examinations including fundus fluorescein angiography (FFA), optical coherence tomography (OCT) and systemic testing. Laser, including pan-retinal photocoagulation (PRP), oral corticosteroid and Pars plana vitrectomy (PPV) were used during the investigation period.

**Results** Forty-two eyes of 21 patients aged 15-58 years old, 19 females and 2 males, initial decimal BCVA NP  $\sim 1.5$  ( $0.55 \pm 0.38$ ), were included. Eighteen eyes reached Stage 2; 21 eyes with neovascularization of disc or elsewhere and/or vitreous hemorrhage (VH) reached Stage 3; one eye had neovascular glaucoma (NVG) at Stage 5. Two eyes had proliferative vitroretinopathy (PVR). Thirty-four eyes of 20 patients of stage 2 and 3 accepted retinal photocoagulation. 27 eyes completed PRP. PPV was performed for 3 eyes at the first visit due to VH or PVR. Three eyes developed to Stage 3 from Stage 2. One eye of Stage 3 developed to PDR with retinal detachment. Additional 5 eyes, 3 heavy VH, 1 PVR and 1 macular epiretinal membrane eye, received PPV during the follow-up. Intra-retinal microvascular abnormality (IRMA) was found in 7 eyes. Aneurysms on the optic nerve head and artery bifurcations disappeared in 8 eyes and decreased in number in 2 eyes after one year of photocoagulation. Seven eyes were found with BCVA  $\leq 0.1$ , of which 3 experienced PVR, 2 exudative maculopathy, 1 acute macular neuroretinopathy (AMN) eye and 1 eye due to NVG. The BCVA of the last visit was NLP  $\sim 1.2$  ( $0.53 \pm 0.38$ ), no significant difference was found with initial BCVA.

**Conclusions** Female is more susceptible to IRVAN. IRMA and AMN are firstly described in IRVAN patients. PVR and exudative maculopathy, the major causes for severe visual impairment, are suggested in the revised staging system.

## Background

Idiopathic retinitis, vasculitis, aneurysms, and neuroretinitis (IRVAN) may lead to blindness due to the development of proliferative vitroretinopathy (PVR) and neovascular glaucoma (NVG) [1, 2]. IRVAN is considered to be diagnosed by three major criteria (retinal vasculitis, aneurismal dilatations at arterial bifurcations and neuroretinitis) and three minor criteria (peripheral capillary nonperfusion, retinal neovascularization, and macular exudation) [1, 2]. As IRVAN is rare, the condition was often misdiagnosed as peripheral retinal vasculitis or Eales disease until Chang et al [1] described the clinical features of IRVAN in ten patients and Samuel et al [2] published a paper with observations of twenty-two IRVAN patients, including the above-mentioned ten patients. A stage system was also proposed by Samuel et al [2] in 2007. However, the diagnosis and management of IRVAN is still a challenge to ophthalmologists.

We firstly noticed a young girl with typical characteristics of IRVAN over 10 years ago. Her condition was diagnosed according to the criteria suggested by Chang et al [1]. Since then more IRVAN cases have been recognized and diagnosed in our outpatient department. We would like to present our long time observation outcomes of our series of Chinese IRVAN in this paper.

## Methods

We conducted a retrospective study of 21 consecutive cases of patients diagnosed as IRVAN at the outpatient department of the Eye & ENT Hospital of Fudan University between April 2003 and March 2018. The diagnoses were made according to IRVAN's three major criteria [2]. The diagnosis was considered for both eyes if one eye of the patients met the three major criteria even the fundus of the other eye could not be seen due to vitreous hemorrhage (VH) and/or PVR.

Patients underwent full clinical and imaging assessments, including medical history, decimal best corrected visual acuity (BCVA), anterior segment slit lamp examination and fundus ophthalmoscopy, fundus examination with color fundus photography (Topcon TRC50LX, Japan, or Optos 200Tx scanning laser ophthalmoscope, UK), B-scan ultrasonography, fundus fluorescein angiography (FFA) (Topcon TRC50DX, Japan, or Optos 200Tx scanning laser ophthalmoscope, UK) and B-ultrasound scanning. Optical coherence tomography (OCT) (Heidelberg Engineering, Heidelberg, Germany) was also performed for patients when it was available.

Patients were classified to different stages according to the system suggested by Samuel et al [2] at the first and last visits: Stage 1 includes macroaneurysms, exudation, neuroretinitis and retinal vasculitis; Stage 2 FFA evidenced peripheral capillary nonperfusion; Stage 3 neovascularization of the disc or elsewhere and/or VH; Stage 4 anterior segment neovascularization; Stage 5 NVG (Table 1).

The methods of the initial management and subsequent treatments were reviewed. The final clinical manifestation features and reasons for poor visual acuity ( $\leq 0.1$ ) were assessed.

The BCVA at first and last visit and between eyes of different stages (Stage 2 and Stage 3) or groups was analyzed using paired t test or t test with 95% confidence intervals. P values  $< .05$  were considered statistically significant. Statistical analysis was performed using commercially available software (SPSS software for Windows, Version 16.0; SPSS Inc, Chicago, Illinois, USA).

## Results

Twenty-one Chinese patients (19 female and 2 male) aged between 15-58 (mean  $37 \pm 11$ ) years old were included in this study. The presenting symptoms were usually floaters, blur vision and even lost vision of one eye for 1 to 6 months. One patient had no symptoms and was found retinal vascular abnormality and hemorrhage during health examination. The initial mean decimal BCVA was  $0.55 \pm 0.38$  (LP  $\sim 1.5$ ). All the patients were FFA proved IRVAN bilaterally at the first visit except 4 patients who had one eye with VH (2 eyes) and/or PVR (2 eyes). Two eyes with VH were proved with typical IRVAN by FFA after pars plana

vitrectomy (PPV). Two PVR eyes did not have FFA examination, although one of the eyes accepted PPV. Two patients were lost follow-up including the patient with a NVG eye. The follow-up time of the rest 19 patients 38 eyes was 6-120 ( $70\pm 36.4$ ) months. The demographic information and clinical features are summarized in Table 2.

No eye in this series cases agreed with Stage 1. Eighteen eyes (18/42) with FFA evidenced peripheral capillary non-perfusion (Fig. 1) that agreed with Stage 2, BCVA 0.04-1.2 ( $0.59\pm 0.32$ ). Twenty-one eyes (21/42) with neovascularization peripherally at the posterior edge of the non-perfusion, one eye with macular and two eyes with papillary neovascularization and/or VH reached Stage 3, BCVA 0.01-1.5 ( $0.57\pm 0.33$ ). One eye (1/42) had NVG at Stage 5 (BCVA 0.05) although scattered photocoagulation was performed before the patient came to the authors. The staging of the eyes is illustrated in Table 3. Two eyes (2/42) (BCVA 0.02 and LP respectively) had an obscuring view of the fundus and B-ultrasound scanning revealed a whole RD 2-4mm in the LP eye, with severe PVR in both eyes. These two eyes did not agree with any stages suggested by Samuel et al [2] (see Table 1).

Laser photocoagulation of non-perfusion areas were intended to be performed in eyes only with capillary non-perfusion of stage 2. Pan-retinal photocoagulation (PRP) for stage 3 or more severe eyes was indicated. Direct photocoagulation of the aneurysms was forbidden. For younger patients with obvious vessel leakage elucidated by FFA, oral corticosteroid was prescribed according to the doctor's judgment. With heavy VH and PVR or if the VH developed and did not resolved within at least two weeks at the initial visit or during the follow-up period, PPV was performed according to the clinical manifestation and doctor's consideration.

Retinal photocoagulations were performed by several doctors including doctors of other hospitals. Ten eyes (10/18) received photocoagulation of the non-perfusion areas only (Figure 2) and pan-retinal photocoagulations (PRP) were fulfilled in 8 eyes of stage 2 (8/18) finally (Figure 3). Nineteen eyes (19/21) of stage 3 accepted PRP. Two VH eyes of stage 3 and 1 PVR eye were indicated to PPV at the first visit and had PRP during the operation. Patient 4, with whole RD of the left eye, refused to accept any operation. Seven eyes had recurrent VH during or after photocoagulation, 4 eyes recovered spontaneously, 3 eyes with heavy VH received PPV. Among them, case 3 had PRP completed in both eyes but her left eye had fog-like blurred vision now and then due to VH and when the recurrent VH decreased the vision to 0.5 and persisted for 2 weeks, PPV was performed for the eye. The vision recovered to 1.0 and VH then did not appear till the last visit.

Overall, 34 eyes accepted retinal photocoagulation, 27 eyes completed PRP. Three eyes developed to Stage 3 from Stage 2. One eye of Stage 3 developed to PDR with retinal detachment, which had not been classified in any of the stage by Samuel et al [2] system. PPV was performed for 3 eyes at the first visit due to VH or PVR. Additional 5 eyes, 3 heavy VH, 1 PVR and 1 macular epiretinal membrane eye, received PPV during the follow-up (Table 2).

The BCVA was NLP~1.2 (mean decimal  $0.53\pm 0.38$ ) at the last visit. There was no significant change in BCVA between the initial and last visit of the patients. The final mean decimal BCVA of Stage 2 and Stage

3 eyes was  $0.58\pm 0.33$  and  $0.55\pm 0.41$  respectively. There was no significant difference between the initial and the final vision either (Table 3).

Severe visual impairment ( $BCVA\leq 0.1$ ) was estimated and found in 7 eyes (7/42) (Table 4). One eye (lost follow-up) was found at the first visit due to NVG. Three eyes experienced RD or/and PVR (among them 2 eyes had no light perception at the last visit) and 2 eyes due to exudative maculopathy with dense macular lesion and 1 eye had macular atrophy due to acute macular neuroretinopathy (AMN) which was 0.4 at baseline and 0.05 at the last visit.

## **Special Fundus Findings and Evolution**

### **Aneurysms on optic disc head and artery bifurcations**

Forty-one eyes of twenty-one patients were found aneurysms on the optic disc head and artery bifurcations at the baseline which were illustrated more clearly with FFA. During the follow-up visits, aneurysms on the optic nerve head and artery bifurcations disappeared in eight eyes of four patients (Figure 3). The aneurysms were found decreased in number and size in both eyes in one case. The shortest time observed for this phenomenon was one year. All these patients had received laser photocoagulations. However there was no significant difference in BCVA between the initial and last visit in these eyes (Table 3).

### **Intra-Retinal Microvascular Abnormality (IRMA)**

IRMA was found in the macular area, or nearby, in 7 eyes (Figure 3). Macular neovascularization was also found in the right eye of case 14. One eye with IRMA developed macular neovascularization in the later visit. IRMA was not found to retreat in any of the eyes during the follow-up time. No significant difference was found in BCVA between IRMA group and non-IRMA group, neither between the initial and last visit in eyes with IRMA (Table 3).

### **Venous abnormality**

Thirty eyes of 15 patients demonstrated mild to moderate venous fluorescein leakage either as segmented on the main branch of veins and/or peripheral venules at the first visit. Fluorescein leakage usually disappeared after photocoagulation in all the patients at the last visit.

### **Exudates, edema of maculae and exudative maculopathy**

Exudates were found in 28 eyes at the first visit. The exudate varied in amount from several dots or radiant stars to heavy yellow exudates and as well as in area from peri-papillary or involved the macular area. Massive macular and foveal exudates with macular edema were found in 2 eyes of 2 cases and dense ovoid lesions developed in these heavily exudate eyes and eventually led to severe damage to vision due to maculopathy ( $BCVA\leq 0.1$ ) (2/42). The exudates of other eyes reduced gradually during the observation period.

Exudates did not found in the posterior area of 11 eyes of 7 patients; unknown in three eyes because VH or PVR meant that fundus could not been seen. One patient had obvious exudates in the right eye, while the left eye had no exudates at all (Figure 3).

### **Macular epiretinal membrane maculae**

Macular epiretinal membrane developed in 8 eyes (8/42) during the follow-up and one eye was operated on.

### **AMN**

AMN developed four months after the diagnosis in the left eye of case 18 (1/42), a female patient less than 40 year- old. The FFA demonstrated a delay of a ciliary artery perfusion with a corresponding macular triangular edema. OCT illustrated a macular nasal edema and hyper-reflective band involved the deeper layers of inner retina at the same time and local retina hypertrophy 4 months later. The vision significantly decreased from 0.4 at the first visit to 0.05 at the last visit.

## **Discussion**

Although the syndrome was first described by Kincaid and Schatz [3], it was named IRVAN by Chang et al [1] and a stage system was proposed by Samuel et al [2] after observation of 22 patients. Several papers about IRVAN patients, describing one to seven cases (mostly one case) for short-term observation were published subsequently [4–10]. However the diagnosis of IRVAN remains a challenge to ophthalmologists as the disputed diagnoses of IRVAN cases can even be found in published papers. The etiology of the disease is still not clear. There are no obvious inflammatory cells in the anterior segment and vitreous as well as the corticosteroids does not give a definite control of the disease [2], the inflammatory and immunopathogenesis of the disease is not so convinced. Arterial involvement is also rarely seen in vasculitis [11]. The macroaneurysms on the optic disc and artery, particularly capillary non-perfusion are more suggestive for ischemia origin close to Coates disease and diabetic retinopathy with an arising of vascular endothelial Growth factor (VEGF) [10].

The number of patients in this series (21 cases) are similar to the Samuel et al [2] (22 cases), although ours were Chinese while theirs were including mainly Caucasian (13/22) and other races, but no Chinese. The average age of this group at diagnosis time was 37 (15–54) year-old which is comparable to that of the patients (average 31.5, 9–60 years old) reported by Samuel et al [2]. Most patients in our group were female 90.5% (19/21) and it was 68.2% (15/22) in the report of Samuel et al [2]. The follow-up time was also comparable; ours was  $70 \pm 36.4$  (6-120) months while theirs was 50 (2-132) months.

There was no systemic finding in our group of patients as Samuel et al [2] reported.

It seems young female are more susceptible to IRVAN as shown both in our group and Samuel et al [2]. Young females have been considered to have higher risk in many vascular retinopathies such as AMN

[12] and diabetic retinopathy [13] due to the narrower venule calibers and lower ratio of arterial length to diameter than males.

Patients in our group usually came to the clinic because of floating or even severe visual decrease. We also had patients exhibiting no symptoms but found retinal hemorrhage due to routine health examination. The diagnosis of all the patients was confirmed by FFA evidence of large extant areas of capillary non-perfusion and even peripheral neovascularization in all eyes except 2 eyes with PVR. We had patients who came with VH in one eye and were found to have IRVAN by FFA in both eyes after PPV. As IRVAN is usually considered bilaterally [1–2], therefore we diagnosed bilateral IRVAN in these patients even when the fundus of one eye could be seen as in case 4 who did not accept PPV due to PVR and complete RD.

The natural course of IRVAN is now believed to be severe or even devastating if without proper intervention [1–2]. The eyes with severe visual impairment in our group were 16.7% (7/42) which is less than that of Samuel et al [2] (8/32). The reasons for severe visual impairment are also assessed in this group of IRVAN patients. PVR, maculopathy caused by macular exudates and NVG which agreed with Samuel et al [2] and AMN which has not been described in IRVAN patients before, contributed to severe damage to vision in this group of eyes. The eyes undergoing PPV at the first visit with vision remained stable even improved. During the follow-up period, many eyes with recurrent VH during or after photocoagulation recovered spontaneously. Three eyes developed heavy VH and received PPV and stabled ever after. PPV is believed to remove the elevated vascular endothelial growing factor (VEGF) and other inflammation factors and early PPV for persisted VH may ease the proliferative or leakage of the retinal vessels of IRVAN.

IRMA which has not been reported in IRVAN patients was found in 7 eyes of our IRVAN patients. One eye was already and the other eye developed with macular neovascularization. IRMA is considered an indication of the severity of retinal vascular disease and the precursor of the neovascularization as described in diabetic retinopathy [14].

Laser photocoagulation, corticosteroid systemically and/or intra-vitreally have been tried in treatment for IRVAN [1–9]. Systemic corticosteroid was also used on younger patients of our group of patients for months, but no obvious effect was observed as many previous papers [1, 2] reported. The method of laser photocoagulation is also controversial. In our group of patients, those with peripheral capillary non-perfusion and neovascularization received pan-retinal photocoagulation. Patients only with peripheral capillary non-perfusion (stage 2) were suggested to be coagulated on the non-perfusion area and under close follow-up.

Samuel et al [2] proposed a function-staging system including five stages as described previously and in Table 1. According to this staging system, initial stage of the eyes were classified into Stage 2 (18/42 eyes); Stage 3 (21/42 eyes) with neovascularization of the disc or elsewhere and/or VH, and one eye had NVG at Stage 5. However two eyes which had PVR and RD (BCVA20/1,000-NLP) did not match any of the

five stages. In order to solve this dilemma, we suggest increasing a stage of PVR and RD to reflect the natural course of IRVAN (Table 1).

The exudates and edema at the macular area, particularly involving fovea, were found as important factors impairing visual acuity [2]. The staging systems of familial exudative vitreoretinopathy (FEVR) [15] and Coats' disease [16], both retinal vascular diseases, give a detailed presentation of involvement of the exudates and RD and a guide for proper treatment. In diabetic retinopathy, another retinal vascular disease, macular exudates are also considered seriously as a factor for impairment of vision [14], although they were not included in the staging. So we would strongly suggest that macular exudates should also be considered in the revised staging system. Therefore, according to the staging criteria of Samuel et al [2] for IRVAN, Kashani et al [15] for FEVR, and Shields et al [16] for Coats disease, our suggestion for the revised stage system is proposed (Table 1).

## Study Limitation

This study included the second largest reported and the largest of Chinese IRVAN patients in number. However, as IRVAN is a rare disease, it is difficult to collect larger cohort of patients for evaluate the patients. Our group of patients takes more than a decade to include and the examination methods varied even FFA experienced film, data and finally wide field images in recent cases. OCT was only performed in part of the cases and do not mention about the optical coherence angiography because of only available in recent years. Treatment was performed by the judgment of different doctors and patients' willingness. These may all influence the estimation and final outcome of the patients.

## Conclusions

In this study, 90.5% patients are female. IRMA and AMN are firstly described in IRVAN patients. PVR and maculopathy are found to be the major reasons for visual impairment, so that a revised staging system with an increase of the PVR and retinal detachment stage and macular exudates are recommended. We suggest that bilateral diagnosis of IRVAN could be made if one eye with VH or PVR blocks the fundus and the contra-lateral eye agrees with the IRVAN diagnosis. Earlier laser photocoagulation and PPV for heavy VH are recommended for better prognosis.

## Abbreviations

AMN: Acute macular neuroretinopathy; BCVA: Best corrected visual acuity; FEVR: Familial exudative vitreoretinopathy; FFA: Fundus fluorescein angiography; IRVAN: Idiopathic retinitis, vasculitis, aneurysms, and neuroretinitis; IRMA: Intra-Retinal Microvascular Abnormality; NVG: Neovascular glaucoma; OCT: Optical coherence tomography; PPV: Pars plana vitrectomy; PRP: Pan-retinal photocoagulation; PVR: Proliferative vitreoretinopathy; RD: Retinal detachment; VH: Vitreous hemorrhage

## Declarations

## **Acknowledgements**

The authors would like to acknowledge all of the participants and staff for their contributions to this research.

## **Funding**

This work was supported by Grant from the Science and Technology Commission of Shanghai Municipality (No. SHDC12016116). The funding organization had no role in the design and conduct of this research.

## **Availability of data and materials**

Transcripts of this study are available from the corresponding author on reasonable request; however all the identifying and confidential information of the participants would be removed.

## **Authors' contributions**

QY and ZY designed, analyzed, interpreted the patients' data and wrote the manuscript; ZY and XG reviewed the manuscript; LW, LL, YX, CQ, WM, XY and GJ collected the patients' data. ZY, XG, LW, LL, YX and CQ performed the medical treatment including laser photocoagulation and pars plana vitrectomy. All the authors read and approved the final manuscript.

## **Ethics approval and consent to participate**

This study was approved by the Institutional Review Board of the Eye and ENT Hospital of Fudan University. The principles of the Declaration of Helsinki were followed in all procedures. Written informed consent was obtained from all participants or their guardians.

## **Consent for publication**

Not Applicable

## **Competing interests**

None of the authors has any financial/ competing interests to disclose.

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## Tables

Table 1. Description of the Previous and Revised Idiopathic Retinitis, Vasculitis, Aneurysms, and Neuroretinitis (IRVAN) Clinical Staging System.

Stage	Description
<b>Samuel et al (2007) proposed a function staging system including 5 stages:</b>	
Stage 1	macroaneurysms, exudates, neuroretinitis and vasculitis
Stage 2	fluorescein angiographic evidence of capillary non-perfusion
Stage 3	neovascularization on optic disc or elsewhere and/or vitreous hemorrhage
Stage 4	rubeosis iridis
Stage 5	neovascular glaucoma
<b>Suggested staging system including 6 stages:</b>	
Stage 1:	macroaneurysms of retinal artery and/or on optic disc, neuroretinitis and vasculitis
stage 2	macroaneurysms, neuroretinitis, vasculitis and exudation 2A: extrafoveal exudation 2B: foveal exudation
Stage 3	fluorescein angiographic evidence of capillary non-perfusion
Stage 4	neovascularization on optic disc or elsewhere and/or vitreous hemorrhage
Stage 5	proliferative vitreoretinopathy with or without retinal detachment
Stage 6	rubeosis iridis / neovascular glaucoma

Table 2. Demographics and clinical characteristics of Chinese Idiopathic Retinitis, Vasculitis, Aneurysms, and Neuroretinitis (IRVAN) patients (21patients, 42 eyes).

Characteristics	Mean $\pm$ SD or number
Age (year)	37.1 $\pm$ 11.6 (range 15-58)
Male, n (%)	2 (10%)
Female, n (%)	19 (90%)
Follow-up time (months)	73.4 $\pm$ 34.4 (range 6-120) 2 patients lost follow-up
Initial BCVA (decimal)	0.55 $\pm$ 0.38 (range LP-1.2, 42 eyes)
Final BCVA (decimal)	0.53 $\pm$ 0.38 (range NLP-1.2, 38 eyes)
Laser	34 eyes (81%)
PRP	27 eyes (64%)
PPV	8 eyes (19%)
IRMA	7 eyes (17%)
Decreased aneurysm	10 eyes (24%)
Exudates	19 eyes (45%)
Venous leakage	30 eyes (71%)
Epimembrane maculae	8 eyes (19%)
AMN	1 (2%)

SD=standard deviation; BCVA=best corrected visual acuity; LP=light perception; NLP=No light perception; PRP= pan-retinal photocoagulation; PPV=pars plana vitrectomy; IRMA= intra-retinal microvascular abnormality;AMN= acute macular neuroretinopathy.

Table 3. Data analysis for the Chinese Idiopathic Retinitis, Vasculitis, Aneurysms, and Neuroretinitis (IRVAN) Patients.

	No. of (eyes)	Initial BCVA	Final BCVA	Paired-t test (P value)
	42	0.55±0.38	0.53±0.38	0.534
Initial stage 2	18	0.59±0.33	0.59±0.33	0.977
Initial stage 3	21	0.58±0.44	0.55±0.41	0.726
Initial stage 5	1	0.05	Lost follow-up	
PVR	1	LP	NLP	
IRMA	7	0.33±0.76	0.27±0.15	0.326
Aneurysm Decreased	10	0.86±0.47	0.81±0.44	0.343
PPV	8	0.27±0.24	0.42±0.41	0.411

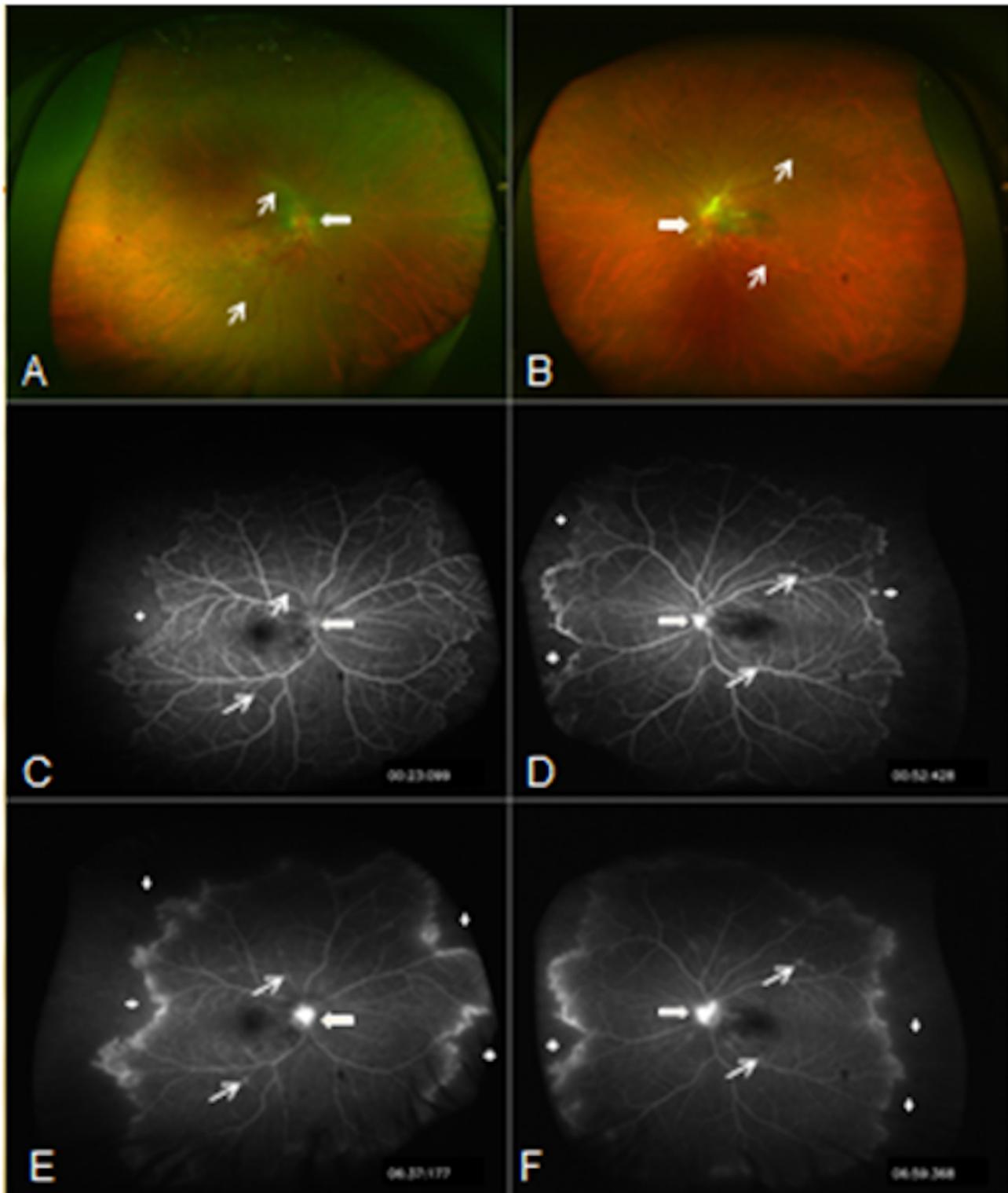
BCVA=best corrected visual acuity; LP =light perception; NLP=no light perception; VH=vitreous hemorrhage; PVR=Retinal detachment and Vitreoretinopathy; IRMA=intra-retinal microvascular abnormality; PPV=pars plana vitrectomy.

Table 4. Reasons for the Final Severe Impaired Visual Acuity ( $\leq 20/200$ ) of the Chinese Idiopathic Retinitis, Vasculitis, Aneurysms, and Neuroretinitis (IRVAN) Patients.

Reasons	Number of eyes(n=42)	Initial VA	Final VA
Retinal detachment and vitreoretinopathy	3	LP 20/40 20/1,000	NLP 20/200 NLP
Macular dense yellow-gray lesion (fibrosis)	2	20/666 20/500	20/200 20/2,000
Para-central Acute Middle maculopathy	1	20/50	20/400
Neovascular glaucoma	1	20/400	Lost follow-up
Overall	7		

LP, light perception; NLP, no light perception

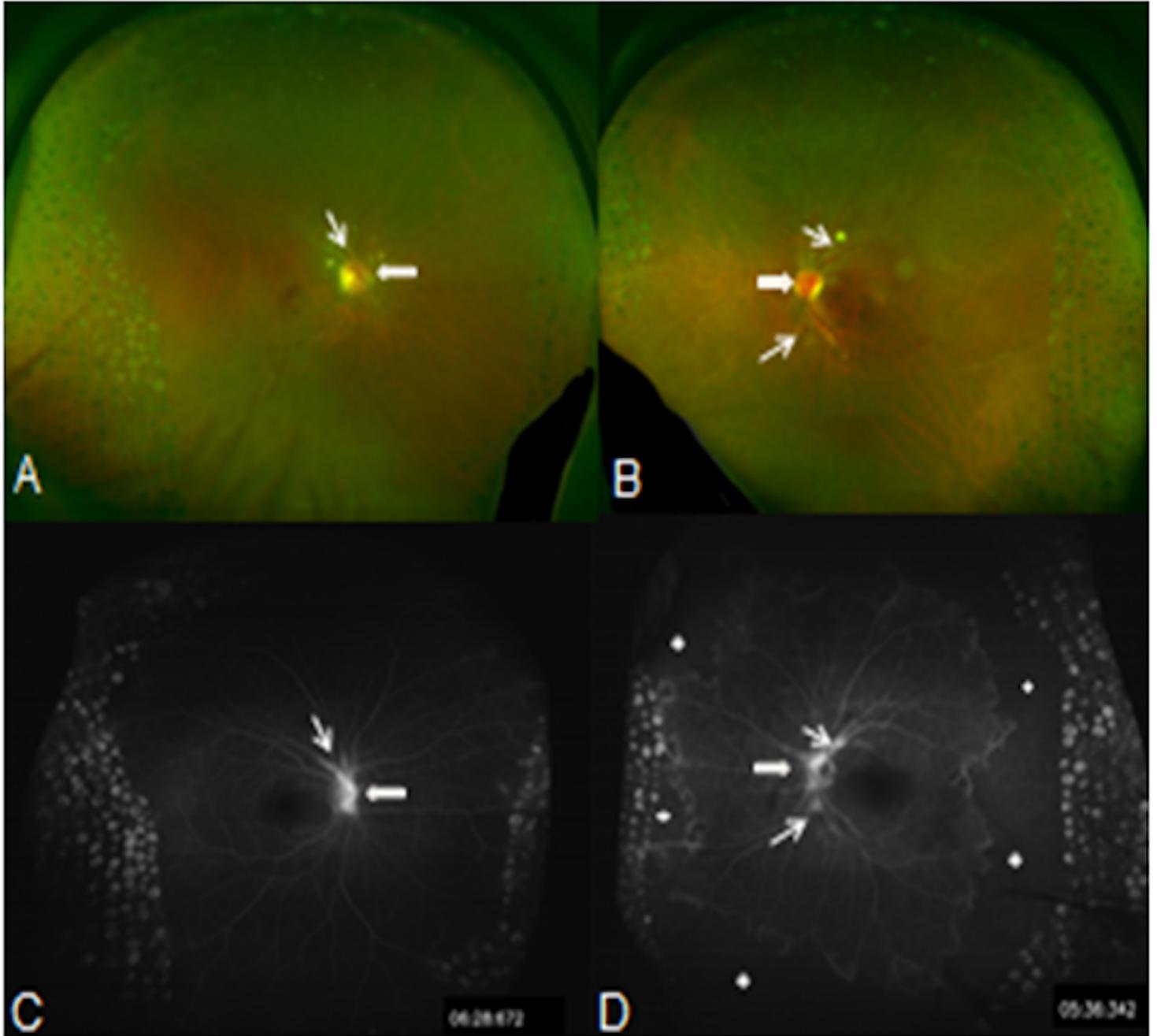
# Figures



**Figure 1**

Images of case 20, a female about 40-year-old. Ultra-wide field fundus color photographs of right eye (A) and left eye (B) show several hemorrhage dots, aneurysms on the optic disc (big arrows) and arterial bifurcations (small arrows) and peripheral vascular occlusion in white lines. Photographs of early phase

fundus fluorescein angiography (FFA) of right eye (C) and left eye (D) illustrate higher fluorescein on the optic disc head (big arrows) and arterial bifurcations (small arrows) and peripheral large area of capillary nonperfusion (stars). Photographs of late phase FFA of right eye (E) and left eye (F) show severe fluorescein leakage on the optic disc head (big arrows) and arterial bifurcations (small arrows) and vessels close to the peripheral large area of capillary nonperfusion (stars).



**Figure 2**

Images of case 18, a female patient less than 40-year-old. Ultra-wide field color fundus photographs of right eye (A) and left eye (B) show several hemorrhage dots, hard exudates, aneurysms on the optic disc (big arrows) and arterial bifurcations (small arrows) and laser scars in the peripheral area. Fluorescein angiography images of right eye (C) and left eye (D) show obvious fluorescein leakage on the optic disc (big arrows) and arterial bifurcations (small arrows) and vessels close to the peripheral large area of capillary nonperfusion (stars).

head (big arrows) and arterial bifurcations (small arrows). Peripheral laser scars in both eyes and a large area of capillary nonperfusion remnant posterior to the laser scars in the left eye (stars) illustrated.



**Figure 3**

Images of case 11, a young girl. Right fundus color photograph (A) shows arterial aneurysms on the optic disc (big arrow) and along the artery (small arrows) with hemorrhage, exudates, intra-retinal microvascular abnormality (IRMA) (long arrow) near the upper temporal vascular arcade. B. fundus fluorescein angiography (FFA) image of the right eye illustrates severe fluorescein leakage of the optic disc head and arterial aneurysms, no leakage of IRMA (long arrow). C. Right fundus color photograph 58 months later illustrates laser spots, fewer aneurysms on the optic disc (big arrow), no arterial aneurysms (small arrows) and no hemorrhage and exudates, IRMA (long arrow) remain near the upper temporal vascular arcade. D. FFA image of the right eye 58 months later shows only one large aneurysm (big arrow) but no obvious fluorescein leakage on the optic disc head, the arterial aneurysms disappearance (small arrows), fluorescein stain of IRMA but no leakage (long arrow). E. Mosaic FFA image 58 months later shows laser scar of pan-retinal photocoagulation (PRP), stain of the remained large aneurysm wall (washout of fluorescein) (big arrow), fluorescein stain of IRMA but no leakage (long arrow). F. Left fundus color photograph of case 11 reveals aneurysms on the optic disc (big arrow) and aneurysmal dilations along arterial (small arrows) with posterior hemorrhage, IRMA (long arrow) near the upper temporal vascular arcade, but no obvious exudate. G. Mosaic FFA image of the left eye shows severe fluorescein

leakage on the optic disc head (big arrow), mild leakage of arterial aneurysms and venules, no leakage of IRMA (long arrow), and large area of capillary non-perfusion located peripherally (stars). H. Left fundus color photograph 58 months later shows laser spots, fewer and smaller aneurysms on the optic disc (big arrow), no arterial aneurysmal dilatations and no posterior hemorrhage, IRMA still near the upper temporal vascular arcade (long arrow). I. Mosaic FA image of the right eye 58 months later illustrates large amount of laser scar (pattern laser), no obvious aneurysm and no fluorescein leakage of the optic disc head (big arrow), arterioles, venules and IRMA (long arrow).